DOCTOR OF PHILOSOPHY

Diagnostic journeys in Myeloma: How long does it take to diagnose what factors influence the diagnostic journey and how can timelier diagnosis be achieved

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Diagnostic Journeys in Myeloma: How long does it take to diagnose, what factors influence the diagnostic journey and how can timelier diagnosis be achieved?

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North Wales Centre for Primary Care Research, School of Healthcare Sciences

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Dedication and Acknowledgements

To

Dawn, my Mum, who unexpectedly died just before I commenced my studentship

and

all the myeloma patients, who over the years, I have been involved in the care of. You have filled my thoughts on this journey and I sincerely hope this helps future myeloma patients with their diagnoses.

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manuscript. Also, a big thanks to my sister, Max, for the help with formatting presentations, guidance and crisis counselling in weak moments.

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Finally, my thanks to the patients and clinicians who, so willingly, gave their time and shared their experiences and who, without their contribution, this thesis would not have been a reality.

Abstract
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Doctor of Philosophy

Diagnostic Journeys in Myeloma: How long does it take to diagnose, what factors influence the diagnostic journey and how can timelier diagnosis be achieved?

Summary:

Background:

Myeloma is a rare, destructive bone marrow cancer, recognised as 'hard to diagnose'. Timelier diagnosis may have potential to lead to earlier stage diagnosis and prolonged survival. The aims of this thesis were to:

- Calculate intervals to diagnosis/treatment;
- Determine factors contributing to journey length; and
- Determine how timelier diagnosis may be achieved.

Methods:

Systematic Review: Standard techniques were used to map the myeloma diagnostic journey. This informed:

Phase I: Quantitative survey of newly diagnosed myeloma patients, their GPs, and their haematologists;

Phase II: Qualitative interview study with patients and their GPs

Phase III: Synthesis of findings to make recommendations for policy and practice.

Results:

Systematic review: Longer primary care and diagnostic intervals occurred. Early symptoms were vague, with multiple GP consultations and more emergency presentations. Later stage diagnosis, greater numbers of complications and poorer outcomes occurred with longer intervals. Evidence was limited and unable to inform policy and practice.

Phase I: The patient, primary care and total intervals were longer than any other cancer type. The secondary care interval was longer than the primary care interval. The three most important symptoms were muscle/joint pain, fatigue and bone pain. >80% participants initially presented to primary care, a median of three consultations occurred. Longer intervals were associated with consulting different GPs. There was low use of physical examination, radiography of symptomatic areas and protein-electrophoresis. Patients were referred to multiple secondary care teams (n=15), <50% had an urgent suspected cancer referral. Longer secondary care intervals were associated with routine referrals.

Phase II: All patients initially blamed symptoms on ageing. Delayed help-seeking resulted in rapid deterioration and unscheduled presentation to secondary care. GPs did not recognise symptoms were sinister, and delayed investigation. Patients were not encouraged to come back if symptoms persisted. Overall GPs failed to suspect myeloma.

Discussion:

A fragile and complex diagnostic journey was seen for myeloma.

Recommendations from this thesis:

GPs should:

- Suspect myeloma in patients presenting with fatigue or pain in muscles, joints or bones; and
- Have a lower threshold for examining patients and ordering radiographs and protein electrophoresis of serum or urine.

Table of Contents

List of Tables

List of Figures

List of Boxes

Thesis overview

This thesis comprises of a series of chapters, as follows:

Chapter One: Introduction

This chapter provides a background understanding of the disease myeloma. It reviews the context of early diagnosis of cancer policy initiatives to improve its timely diagnosis. The evidence of the difficulties diagnosing cancer early and timely, at the conception of this research, is then reported. The chapter concludes with the review of the problems specifically faced in the early diagnosis of myeloma which provides the rationale for undertaking the study.

Chapter Two: Systematic review of the literature

This chapter reports the systematic review of the evidence base of diagnostic journeys in myeloma at the outset of the study. Firstly, the chapter reports the scoping reviewing methods used as an approach to explore and identify the evidence which was regarded as likely to be scarce. The chapter then reports the evidence identified and used to map the timing and influences across the journey to diagnosis of myeloma. The chapter concludes with the review's overall findings and recommendations, as follows:

- There is a dearth of literature on the topic which cannot inform policy and practice;
- There is a need for an in-depth prospective study of journeys to diagnosis in myeloma patients to quantify the entire journey and determine the factors of influences across this journey;
- The behavioural and contextual experiences affecting the diagnostic journey in myeloma requires exploration;
- There is a need to assess the pre-diagnostic symptoms in myeloma; and
- There is a need to understand the interactions in the primary care interval, which may contribute to the long primary care and diagnostic intervals identified.

Chapter Three: Methodology and methods

This chapter outlines the methodological approach chosen to answer the research questions, namely the explanatory sequential research design.

Firstly, the chapter reviews the research questions to identify what data is required to inform or answer these. The chapter then discusses the explanatory sequential programme of research and how this complements the research questions and the collection of data required to answer these. There is a report of the exploration of the stance of the student researcher and the areas of her epistemology and ontology that could impact the implementation of the chosen methods and a discussion of how these will be managed.

The second half of the chapter discusses the chosen methods for the quantitative assessment of journeys to diagnosis of myeloma, the first phase of the explanatory sequential method of enquiry. This includes a report on the designing of the questionnaires to elicit the required responses and face validity checking. The recruitment strategy implemented is detailed along with a rationale for its choice. The quantitative analysis plan is detailed, and rationales for the choice of descriptive statistics to describe the observed journeys and statistical testing with correlation and regression modelling adds, for the first time, the ability to demonstrate associations of the measured phenomena.

The third part of the chapter discusses the methods adopted in the qualitative assessment, the second phase of the explanatory sequential programme of research. The rationale for the chosen approaches in both qualitative interview studies with patients and their diagnosing GPs is discussed. The analysis plan is reviewed and the rationales for the Framework approach to analysing data given in the context of the research setting.

The fourth part of the chapter reports the methods undertaken to integrate the findings from the quantitative and qualitative studies to produce a final report and explanation of the recorded phenomena of the quantified journey. This is the final interpretation phase of the explanatory sequential research design.

Chapter Four: Results from the quantitative study

This chapter reports the results from the quantitative study.

The chapter first reports recruitment activity and questionnaire returns (the intervention) for transparency and then the categorised findings from the questionnaires completed by three participant groups: the patient, the GP and diagnosing haematologist. The variances collected are reported using descriptive statistics, detailing case numbers, frequencies and percentages. A correlation analysis is reported of all the numerical variances and their associations with the intervals to diagnosis and treatment, followed by a regression analysis using multiple models of the collected variables and their associations with the intervals to diagnosis and treatment.

The chapter concludes with: a summary of the results from the quantitative study; a report on how they compare with other literature on the topic; details of strengths and limitations of the approach; and recommendations for policy and practice and further research. The chapter ends with a report of the conclusions drawn from the results of the quantitative study. These included:

- There is a need for greater awareness of symptoms in both the patient and GP group;
- There is a low level of specific and targeted investigation in primary care; and
- The use of optimal referrals into secondary care is poor.

Chapter Five: Findings from the patient interview study

This chapter reports the findings from the interview study with purposively sampled patients from the phase I study.

The chapter firstly reports the experiences of the implementation of the semi-structured interview design, reporting the dynamics and success of exploring diagnostic journeys in myeloma through this approach. The themed findings are then reported as 'meta themes' and then individually discussed in an in-depth narrative review of the patient's experiences and perception. Individual quotes taken from patient participant transcriptions are used to illuminate these themes. The chapter concludes with a discussion of the findings, which summarises the main findings, compares findings to the known literature, reports strengths and limitations of the approach, and makes recommendations for policy and practice and further research. The section closes with a report of conclusions drawn from these qualitative findings. These included:

- The findings in this qualitative study inform the understanding of why some of the observed phenomena in the quantitative study exist;
- Multiple behavioural and contextual influences are identified that contribute to delayed help-seeking in myeloma diagnostic journeys which culminate in patients normalising symptoms to ageing; and
- There are consequences that occur when there is a delay in help-seeking and progression through primary care that result in non-linear and sometimes tortuous routes to a diagnosis for myeloma patients.

Chapter Six: Findings from the GP interview study

This chapter reports the qualitative interview study with GPs which contributes to the second phase of the qualitative assessment.

The chapter first reports the experiences of implementing the semi-structured interviews with GPs of patients interviewed in the patient interview study and how these explored their perception and experiences of diagnosing myeloma and the success in providing understanding of the influences within individual pathways. The chapter then reports the major emergent themes from analysis and then individually reports these in a narrative in-depth description. These narratives are supported with quotes from GP transcripts to illuminate the understandings of the opinions and experiences of the GPs in the study. The chapter concludes with a discussion of the main findings, how these compare to the literature, the strengths and limitations of the study, and the recommendations for policy and practice and further research and offers conclusions drawn from the qualitative assessment. These were:

- There is a lack of understanding in GPs of the early symptoms of myeloma and the suspicion of myeloma in primary care is not timely. Greater appreciation of early symptoms is required by GPs; and
- GPs have higher thresholds for commencing specific testing for myeloma based on their low suspicion of sinister symptoms and lowering thresholds may help the identification of myeloma earlier in primary care.

Chapter Seven: Synthesis of the overall findings and final discussion and recommendations

This final chapter reports the synthesis of the quantitative and qualitative findings in this explanatory sequential research design to provide an overall report for this thesis and answers the research questions determined from the systematic review. The chapter first reports the organisation of the synthesis into categorised areas from the quantitative study. Results are then synthesised through the integration of all dataset findings and explanation provided of the observed phenomena in the categorised results from phase I. The chapter concludes with an overall discussion of the findings in a final summary of the synthesised data. The discussion then compares the overall findings in this report to other literature and discusses the strengths and limitations observed in implementing this study design and answering the research questions. Finally, recommendations are made for policy and practice for the early or timely diagnosis of myeloma and further research required. The final conclusions of the thesis are drawn together to conclude that:

- The programme of research has successfully investigated and informed the understanding of how long it takes to diagnose myeloma and the influences which contribute to this. Particularly, the design has allowed the explanation of the quantified phenomena observed in the Phase I study by informing this with the findings from the phase II qualitative study;
- Patients with myeloma take a long time to present their symptoms and this is because of low levels of awareness which may be improved by awareness campaigns that the symptoms identified reported in the quantified study could contribute to;
- GPs have a low level of suspicion of myeloma in primary care and this is rooted in their misunderstanding or low knowledge of the early symptoms of myeloma. It is possible, through knowledge transfer, that symptoms in the pre-diagnostic patient identified from this study could contribute to this knowledge transfer and improve the identification of symptom seriousness or myeloma in primary care;
- Earlier specific investigations would be likely to identify myeloma earlier and help target referral to the optimal specialist team in secondary care, possibly preventing progressive disease and emergency presentation; and

- There are opportunities to influence the intervals to diagnosis and treatment in myeloma.

Where does this thesis fit in?

At the conception of this study there were no studies that had quantified the diagnostic journey in myeloma or attempted to determine and measure the influences across the journey. Additionally, no studies had explored the behavioural or contextual experiences of the journeys to diagnosis from patients or explored the difficulties experienced by GPs when diagnosing myeloma. This was observed despite UK-wide cancer policy to improve the timely diagnosis of all cancers. This thesis has been able to quantify the entire diagnostic journey in myeloma and gives insights into the relative contribution of the different intervals within the total interval. It has, additionally, provided important insights into the factors associated with altering these individual intervals. This greatly contributes to knowledge in the field of early diagnosis of cancer and to the timely diagnosis of myeloma more specifically. The thesis is able to also provide insights into how the diagnosis of myeloma may be improved through greater understanding of early symptoms and earlier specific investigation of myeloma patients in primary care.

Referencing:

The Harvard referencing system is used in the test, and the author cites up to two names consecutively. Where there are two authors both authors names will be cited. If there are more than two authors the lead authors names will use cited followed by *et al.*

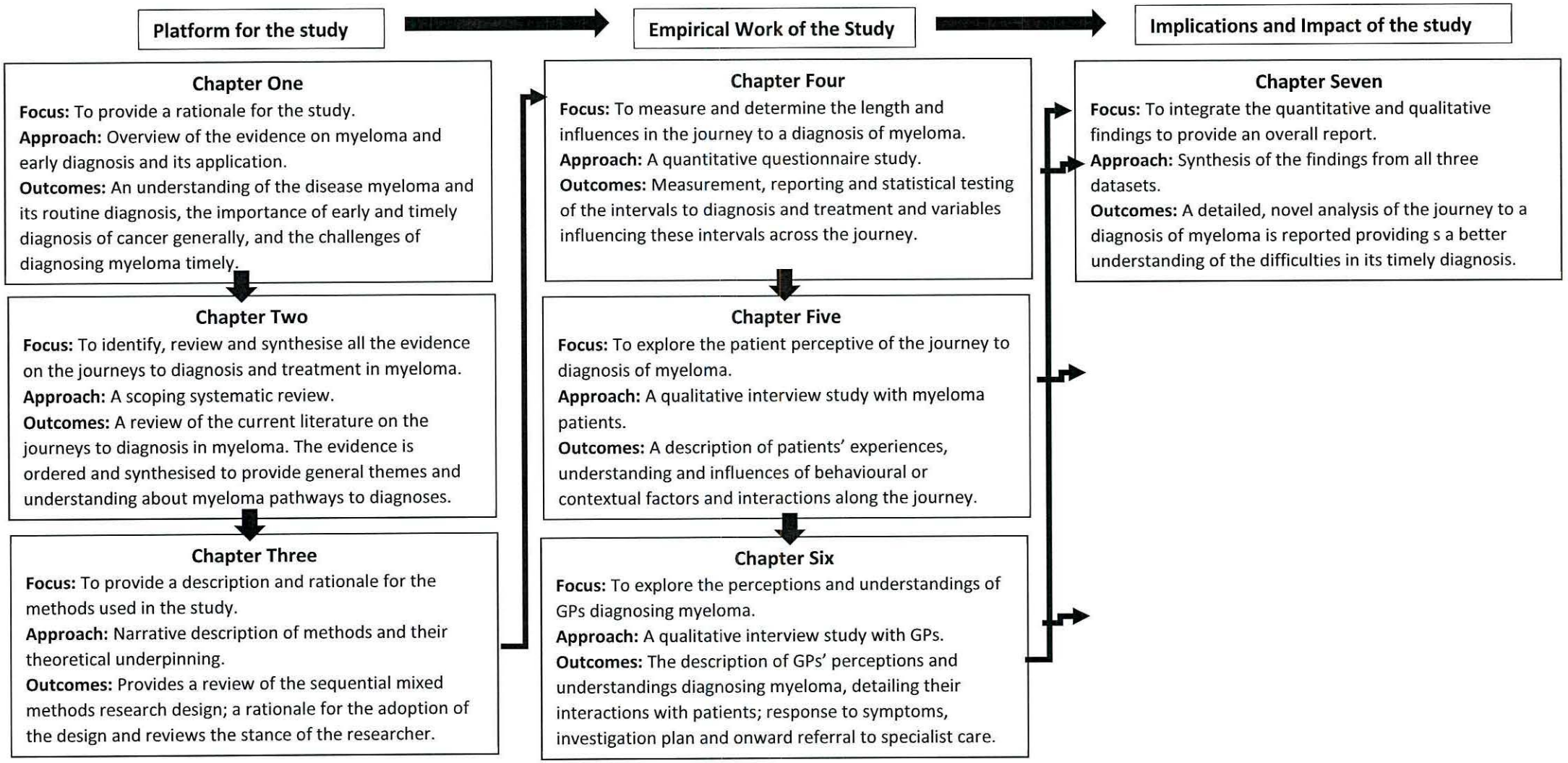

Figure 1: Diagnostic Journeys in Myeloma: PhD thesis outline

List of Abbreviations

Abbreviation	Full meaning
ACE	Accelerate, Coordinate, Evaluate
AML	Acute Myeloid Leukaemia
ASCT	Autologous Stem Cell Transplant
BMA	British Medical Association
BSH	British Society of Haematology
BM	Bone Marrow
CART	Completeness, Accuracy, Relevance and Timeliness
CASP	Critical Appraisal Skills Programme
CIG	Cancer Implementation Group
COSMIN	Consensus-based Standards for the selection of health status Measures INstruments
COTE	Care of the Elderly
CPD	Cancer Delivery Plan
CRF	Clinical Research Form
CRP	C-Reactive Protein
CRPD	Clinical Practice Research Datalink
CT	Computer Tomography
CTIMP	Clinical Trial of Investigational Medicinal Product
DEXA	Dual Energy X-ray Absorptiometry
ED	Emergency Department
EP	Emergency Presentation
ENT	Ear Nose and Throat

ESR	Erythrocyte Sedimentation rate
FBC	Full Blood Count
GRPD	General Practice Research Database
GP	General Practitioner
HES	Hospital Episodes Statistics
ICD	International Disease Classification of Neoplasms
ICBP	International Cancer Benchmarking Partnership
ICBPM4	International Cancer Benchmarking Partnership Module 4
ID	Identity
Ig	Immunoglobulin
ISS	The International Staging System
IQR	Inter Quartile Range
LFT	Liver Function Test
LHB	Local Health Boards
MDT	Multi-Disciplinary Meeting
MGUS	Monoclonal Gammopathy of Undetermined Significance
MMAT	Mixed Methods Appraisal Tool
MREC	Main research and Ethics Committee
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
N	Number
NAEDI	National Awareness and early Diagnosis Initiative
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NSAG	National Specialist Advisory group for Cancer

NWORTH	North Wales Organisation for Randomised Trials in Health
ONS	Office of National Statistics
SPE	Serum Protein Electrophoresis
PC	Primary Care
PhD	Doctor of Philosophy
PPI	Patient and Public Involvement
PV	Plasma Viscosity
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
R&D	Research and Development
ROTI	Related Organ and Tissue Impairment
SC	Secondary Care
SFLC/BJP	Serum Free Light Chain/Bence Jones Protein
SOP	Standard Operating Procedure
TWW	Two Week Wait
U&E	Urine and Electrolyte
UK	United Kingdom
WCISU	Welsh Cancer Intelligence Surveillance Unit
WHO	World Health organisation

1 Chapter One: Diagnostic journeys in myeloma: why do we need to understand them better?

1.1 Chapter summary

Chapter One aims to set the context for the research undertaken in this thesis, which investigates the timelier diagnosis of myeloma. The chapter logically takes the reader through a process of understanding the disease myeloma, the particular nuances and complexities associated with it and its diagnosis. The chapter considers policy initiatives promoting early diagnosis of cancer, and how this has led to the generation of a body of research to inform further policy initiatives and practice on timelier diagnosis. The parallels between the diagnosis of myeloma and early diagnosis of cancer research are detailed, providing a rationale for the programme of research undertaken.

1.2 Overview of the disease: What is Myeloma?

Myeloma is one of over 100 different cancer types (National Cancer Institute, 2017). The disease is heterogeneous in its molecular and clinical presentations. Appreciating these nuances is necessary to understand the diagnostic procedures required to identify and determine its presence.

1.2.1 Origin of the disease

Myeloma originates in the immunoglobulin-producing plasma cell of the bone marrow and results from genetic changes in the terminal differentiation of B lymphocytes into plasma cells (Figure 1-1).

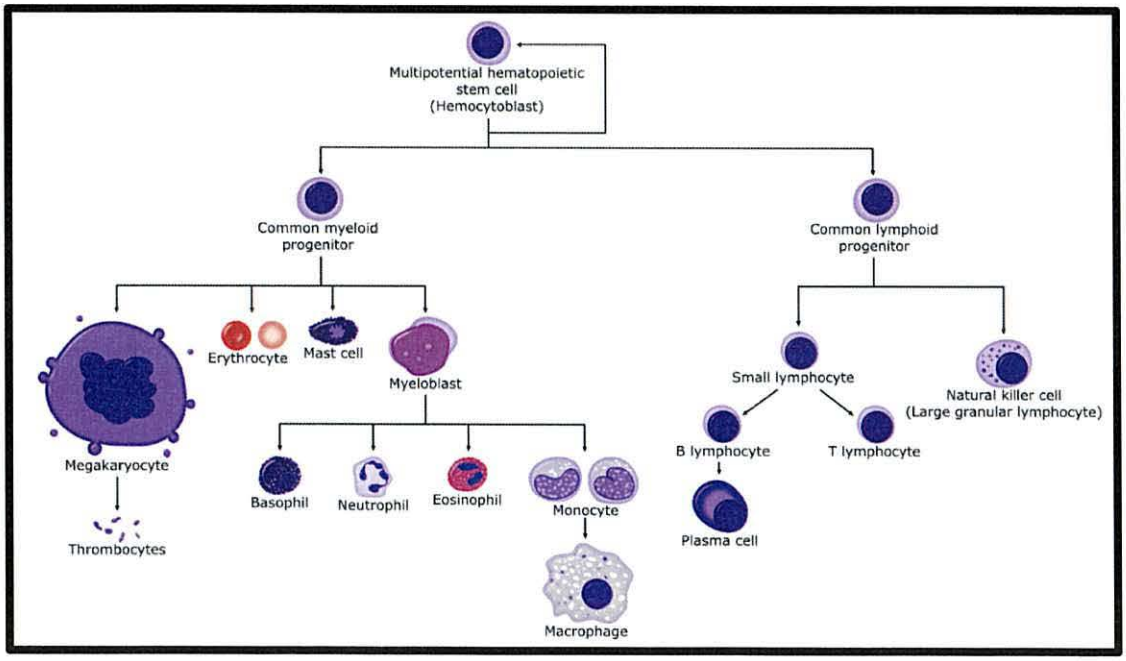

Figure 1-1: Haemaopoeisis in the bone marrow

(http://www.allthingsstemcell.com/wp-content/uploads/2009/02/hematopoiesis_simple1.png)

1.2.2 Plasma cells

B cells are involved in the humoral immune response by developing into either mature plasma cells or memory cells. B cells undergo maturation into mature B cells independent of interactions with antigen. Mature B cells leave the bone marrow and express a membrane bound immunoglobulin with a specific antigen specificity. These cells circulate in the blood and lymph and are carried to the secondary lymph organs such as the spleen and lymph nodes. When the B cell has an interaction with antigen, for which it has specificity within its membrane bound immunoglobulin (antibody), the cell undergoes a clonal proliferation and differentiation, producing a population of antibody-secreting plasma cells and memory cells (Kuby, 1997). Antibodies secreted by plasma cells bind with antigen enabling their removal by other cells. An individual plasma cell only secretes an antibody with specificity for a single antigen.

The antibody structure consists of two pairs of polypeptide chains (chain of amino acids linked by peptide bonds) that form a Y shape (Figure 1-2). The bottom 'stem' of the structure consists of one end of two identical 'heavy chains'. Each arm of the structure contains the other end of the heavy chain and smaller portions of 'light chains'. The bottom region and lower ends of the arms are similar in all antibodies and are known as the 'constant' region. The tip of the antibody is where variability in sequencing occurs, and specificity of binding to antigen is seen (Kuby, 1997).

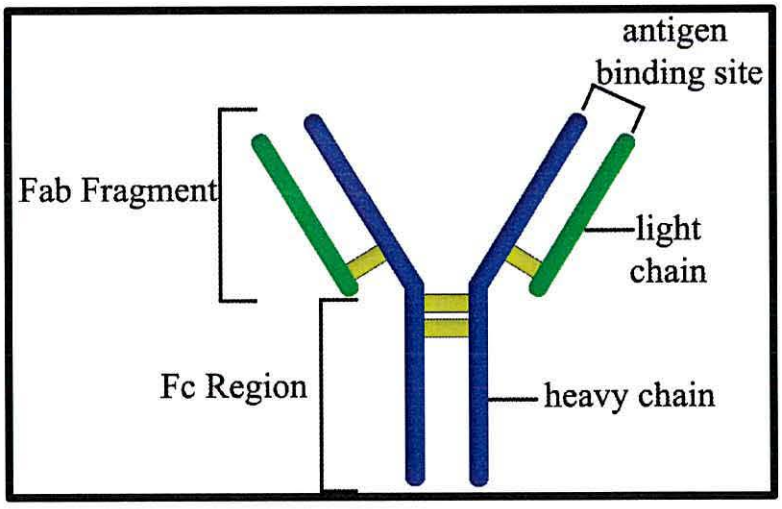

Figure 1-2: Basic antibody structure: Example - Immunoglobulin G

(https://www.searchlock.com/search?safe=&tbm=isch&sr=sb-serp&q=structure+of+antibody+immunoglobulin)

There are five classes of antibodies and these are grouped by the constant regions within the structure. Classes of antibody have a designated letter that follows an

abbreviation of the word immunoglobulin (Ig): IgG, IgM, IgA, IgD, and IgE. IgG is the most commonly occurring immunoglobulin.

1.2.2.1 The malignant plasma cell

The malignant plasma cell, in most cases, produces a monoclonal antibody, known as a paraprotein. Most commonly, the monoclonal immunoglobulin produced is IgG. The paraprotein produced is detectable in serum or urine through protein electrophoresis examination. Around 20% of patients with myeloma produce only light chains in the urine and about 2% produce neither light chains nor paraproteins and are termed non-secretors or non-secretory myeloma. Uncontrolled proliferation of the malignant plasma cells and the excreted paraprotein invade and populate the bone marrow and other organs (Smith and Yong, 2013).

It is now generally accepted that almost all cases of myeloma are preceded by an asymptomatic state, Monoclonal Gammopathy of Undetermined Significance (MGUS) (Weiss et al., 2009; Ludwig et al., 2010).

1.2.3 Incidence of myeloma

Myeloma accounts for 2% of newly diagnosed cases of cancer in the UK, (Cancer Research UK, 2017a). It is the second most common haematological malignancy accounting for 10-15% of new diagnoses (Group IMW, 2003). The number of new cases of myeloma diagnosed in the United Kingdom (UK) in 2014 was 5,500, with 269 of these in Wales. Myeloma is the 15th most common cancer for men, with 3,100 of the 5,500 cases in 2014 being diagnosed in males. In females, it is the 17th most common cancer with 2,400 of the 5,500 cases diagnosed in females (Cancer Research UK, 2017a).

Myeloma predominantly affects older people with incidence rates highest for the age group 85-89 for the period 2012-2014 (Cancer Research UK 2017a). The median age of diagnosis is 70 years. Only 15% of myeloma is diagnosed in adults under 60 years of age, and 2% in adults under 40 years (Bird et al., 2011). The incidence is two times greater in Afro-Caribbeans and African-Americans (Waxman et al., 2010; Alexander et al., 2007).

Myeloma incidence rates have increased by 15% in the last decade, with the level of rise similar for both males (15%) and females (13%). The rates are projected to rise further between 2014 and 2035 by 11%, increasing the incidence to 12 cases per 100,000 (Cancer Research UK, 2017a).

Death from myeloma accounts for 2% of all deaths from cancer in the UK, and 15-20% of deaths related to haematological malignancy (Group IMW, 2003).

The median reported survival for myeloma is five years (Bergsagel et al., 2013). A third of people diagnosed with myeloma in England and Wales survive their disease for ten years or more (2010-2011) (Cancer Research UK, 2017a).

1.2.4 Categorisation of myeloma

Two distinct forms of myeloma are described; asymptomatic (smouldering or indolent) and symptomatic myeloma. The distinction between these two forms and MGUS is made by measuring the level of disease present in terms of: percentage of plasma cells; level of paraprotein; and the presence of organ and tissue damage (Table 1-1 & 1-2 & 1-3). The distinction and differentiation of these groups of disorders is necessary in order to determine clinical management of the disease (Bird et al., 2011). Treatment options range from paraprotein surveillance for MGUS, to systemic chemotherapy treatment for symptomatic myeloma (Bird et al., 2011).

An important distinction should be made between asymptomatic myeloma as a condition and myeloma that has an asymptomatic presentation. Asymptomatic myeloma is distinguished from symptomatic myeloma by the level of measurable paraprotein and the extent of organ and tissue damage. Symptomatic myeloma that has an asymptomatic presentation will have a paraprotein level to achieve a diagnosis of myeloma or end organ disease such as renal failure, but the patient does not report symptoms.

Table 1-1: Differential Diagnosis for Monoclonal Gammopathy of Undetermined Significance (MGUS), smouldering myeloma (SMM) (asymptomatic), and symptomatic myeloma (MM)

Feature	MGUS	SMM	Multiple Myeloma
BMPC, %	<10	≥10	≥ 10
Serum monoclonal protein, g/L	< 3	≥ 3	≥ 30
	and	and/or	and/or
Clinical manifestation	Absent	Absent	Present

From the International Myeloma Working Group.

Clinical features may include increased serum calcium concentrations, renal failure, anaemia, skeletal involvement (lytic lesions), and recurrent bacterial infections.

(Blade et al., 2009)

Table 1-2: Diagnostic criteria for MGUS, asymptomatic myeloma and symptomatic myeloma (adapted from International Myeloma Working Group, 2003)

MGUS	Asymptomatic myeloma	Symptomatic myeloma
M-protein in serum <30 g/L	M-protein in serum ≥30 g/L And/or	M protein in serum and/or urine*
Bone marrow clonal plasma cells <10% and low level of plasma cell infiltration in a plasma cells or biopsy trephine biopsy (if done)	Bone marrow clonal plasma cells ≥10%	Bone marrow (clonal) plasma cells † or biopsy proven plasmacytoma
No related organ or tissue impairment (no end organ damage including bone lesions)	No related organ or tissue impairment (no related end organ damage including bone lesions or symptoms)	Myeloma-related organ or tissue impairment (including bone lesions)

**No specific concentration required for diagnosis. A small percentage of patients have no detectable M-protein in serum or urine but do have myeloma-related organ impairment (ROTI) and increased bone marrow plasma cells (non-secretory myeloma).*

† If flow cytometry is performed, most plasma cells (≥90%) will show a 'neoplastic' phenotype. Some patients may have no symptoms but have related organ or tissue impairment.

(Blade et al., 2009)

Table 1-3: Myeloma-Related Organ or Tissue Impairment (ROTI), adapted from International Myeloma Working Group, 2003

Clinical effects due to myeloma	Definition
*Increased calcium levels	Corrected serum calcium >0.25 mmol/l above the upper limit of normal or >2.75 mmol/l
Renal insufficiency	Creatinine >173 mmol/l
*Anaemia	Haemoglobin 20 g/L below the lower limit of normal or haemoglobin <100 g/L
Bone lesions	Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other	Symptomatic hyper-viscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

MRI, Magnetic resonance imaging; CT, Computerized tomography.

**CRAB (calcium, renal insufficiency and anaemia or bone lesions).*

(Bird et al., 2011)

1.2.5 Pathophysiology of myeloma

A progressive systemic disease is seen in symptomatic myeloma, where the uncontrolled proliferation of the plasma cell leads to bone marrow failure with associated anaemia, thrombocytopenia and leukopenia. Production of the monoclonal paraprotein leads to hyper-viscosity, renal impairment, lytic bone lesions, pathological fractures and hypercalcaemia. Cytokine secretion and osteoclast activation leads to osteoporosis, lytic bone lesions and pathological fractures (Smith and Yong, 2013). Due to the combination of leukopenia and immune paresis of normal antibody production, there is a significant risk of infection and early mortality (Augusten et al., 2005).

Osteoclasts, which have a role in bone resorption and osteoblasts which synthesise new bone, are affected by cytokines produced by the myeloma cell. These cytokines inhibit osteoblast differentiation and increase osteoclast activity, resulting in bone breakdown. This osteolysis then results in hypercalcaemia (Smith and Yong, 2013).

Renal failure occurs when the light chains, filtered through the glomeruli precipitate out as casts in the distal tubules, resulting in tubular obstruction and tubule-interstitial inflammation leading to acute renal injury. Cast nephropathy is said to cause 90% of renal damage in myeloma. Additionally, renal impairment can be attributed to amyloid deposits, dehydration, hypercalcaemia, hyper-viscosity and nephrotoxic drugs such as non-steroidal anti-inflammatories (Smith and Yong, 2013).

In the absence of treatment, the prognosis is very poor (Bird et al., 2011).

1.2.6 Symptoms

The extent and diversity of the disease process leads to a wide range of symptoms. Searching the literature for symptoms of myeloma (Table 1-4) reveals that the symptoms reported were generally obtained from data collected at the secondary care diagnosis of myeloma and not those seen in the earlier stages of disease development.

Table 1-4: Myeloma symptoms at presentation from scoping literature

Symptom	Rate of occurrence reported in study	Author and year of publication
Bone disease (lytic bone lesions, vertebral fractures, long bone (femur and radius)	79%	Kyle et al., 2003
Osteoporosis	20%	Kyle et al., 2003
Bone pain	48% 67%	Kariyawasan et al., 2007 Kyle et al., 2003
Hypercalcaemia	13%	Kyle et al., 2003
Renal impairment	36%	Kariyawasan et al., 2007
Anaemia	73% 53%	Kyle et al., 2003 Kariyawasan et al., 2007

Howell et al., (2013) reported the first comprehensive assessment of symptoms in myeloma prior to the diagnosis of the disease. The authors concluded that myeloma did not have a symptom signature, based on the diverse range of symptoms reported by myeloma patients to have occurred prior to the diagnosis of their disease.

1.2.7 Staging/Prognosis myeloma

Myeloma is a heterogeneous disorder. Whilst it is reported that a third of patients survive with myeloma for ten years or more (Cancer Research UK, 2017a), others suffer a rapidly progressing disease and die within 24 months of their diagnosis (Bergsagel et al., 2013). Disease burden at diagnosis (higher beta 2 microglobulin levels), age, performance status and early infection are considered to be major predictors for early death (Augusten et al., 2005). The staging system for myeloma, the International Staging System (ISS), (Greipp., et al 2005) measures risk categories in myeloma to assess disease burden and predict prognosis: serum concentrations of albumin, Beta 2 microglobulin (β^2), (Table 1-5).

Table 1-5: International staging system for myeloma

Stage	Criteria	Median survival (months)
I	Serum β2 microglobulin <3.5 mg/L and albumin ≥35 g/L	62
II	Does not fit criteria for stage I or II	44
III	Serum β2 microglobulin ≥5.5 mg/L (regardless of albumin level)	29

(Greipp et al., 2005)

Further prognostic evaluations of myeloma can be made through cytogenetic assessments, with specific genetic lesions now known to have associations with worse outcomes. Immunoglobulin heavy chain locus (IgH) translocation involving chromosomes 4 and 16, termed t(4;14) and t(14;16) are associated with a poor prognosis. Deletion of the short arm of chromosome 17 (del 17p), where the tumour suppressor gene P53 is located, is also associated with worse outcomes. Patients who have the t(11;14) or t(6;14) IgH translocation are considered to have a standard risk (prognostic risk is not increased by their cytogenetic profile), as they are hyperdiploid and this is associated with better prognosis across many cancer types (Bergsagel et al., 2013).

Age is considered to be an independent prognostic risk factor with older patients experiencing worse outcomes and reduced five-year survival (Cancer Research UK, 2017a). Limitations in treatment options for the older patient, such as the reduced tolerance of high intensity stem cell transplant programmes, is thought to contribute to these worse outcomes (Bird et al., 2011).

Patients who achieve a complete response to induction treatment have better prognosis and longer progression free survival, whilst poor response to induction treatment is associated with a worse prognosis (Brenner et al., 2008).

1.3 Diagnosis of myeloma

A clear set of guidance for the clinical investigations of myeloma exists. This details how identification and diagnosis of the disease should be made (Bird et al., 2011). Tests are separated into two categories: those performed to 'screen' for the disease, which may be performed in primary care, as the patient presents with symptoms; and those used to determine and categorise the disease within specialist care (Table 1-6). Guidelines do not, however, specify where tests should be performed, or in what order they should be completed.

The screening investigations recommended, i.e. full blood count, electrophoresis of serum and urine, are available to primary care clinicians. Other tests used to establish the diagnosis of myeloma are conducted in secondary care, with some tests specialist to haematology services i.e. bone marrow aspirate, skeletal survey. Therefore, to complete a diagnosis of myeloma, a referral to a haematologist is necessary.

In February 2016, new National Institute for Health and Care Excellence (NICE) guidance (NICE, 2016a), was issued for the diagnosis and management of myeloma.

This guidance aimed to expedite a diagnosis of myeloma for the patient referred into secondary care. Recommendations were made for the use of serum free light chains (SFLC) to replace the Bence Jones Protein test (electrophoresis of urine) for identifying the paraprotein, as greater sensitivity was reported (Pratt, 2008). Immediate whole body Magnetic Resonance Imaging (MRI) was recommended, where identification of discrete changes could prompt earlier intervention. No recommendations were made for primary care as the guidance was focused on secondary care identification, but it possibly raises a question of whether these new strategies might have a place in expediting a diagnosis of myeloma from primary care.

Table 1-6: Initial investigations in patients with myeloma

Screening tests	Tests to establish diagnosis	Tests to establish tumour burden and prognosis	Test to assess myeloma-related organ impairment	Special tests indicated in some patients
FBC, ESR or plasma viscosity	Bone marrow aspirate + trephine with plasma cell phenotyping	FISH analysis	FBC	
Urea, creatinine, calcium and albumin Electrophoresis of serum and concentrated urine Quantification of non-isotypic immunoglobulins	Immuno-fixation of serum and urine	Quantification of Monoclonal protein in serum and urine Albumin B_{2}-microblobulin	Serum urea and creatinine Creatinine clearance (measured or calculated) Calcium Albumin Plasma viscosity Tissue Biopsy (or fat pad aspirate) for amyloid (if suspected) Quantification of non-isotypic immunoglobulins	SFLC assay in olio-secretary, light chain and non-secretory disease
X-rays of symptomatic areas	Skeletal survey	Skeletal survey	Skeletal survey	MRI/CT scan

FBC: full blood count; ESR: erythrocyte sedimentation rate; FISH: Fluorescence in situ hybridization; SFLC: serum-free light chain: MRI: Magnetic resonance imaging; CT, computerised tomography *(Bird et al., 2011)*

1.4 Treatment of myeloma

The treatment of myeloma is based on the categorisation of the disease at diagnosis i.e. MGUS, asymptomatic or symptomatic myeloma (Table 1-2). MGUS and asymptomatic myeloma are followed up within surveillance programs, where the aim is to detect evolving symptomatic myeloma, allowing early commencement of treatment (Bird et al., 2011). Guidelines recommend asymptomatic myeloma surveillance is carried out at three-monthly intervals, by a consultant haematologist (Bird et al., 2011). This reflects the higher progression rate of asymptomatic myeloma to symptomatic myeloma (10% per year for the first 5 years (Bird et al., 2011); 78% in 20 years (Kyle, et al 2007)). The 2016 new NICE guidance for diagnosing and managing myeloma (NICE, 2016a) confirms this approach by recommending monitoring for the first five years following the diagnosis of asymptomatic myeloma. A group of asymptomatic myeloma patients are described to have an increased 'risk' for progression to symptomatic myeloma based on SFLC ratio, monoclonal paraprotein and bone marrow plasma cell concentrations and flow cytometry (Witzig et al., 1994, Dimopoulous et al., 2000, Weber et al., 1997). It is not known whether early intervention with treatment in these patients can improve survival, but current guidelines (Bird et al., 2011) recommend surveillance for asymptomatic myeloma, with the initiation of cytotoxic chemotherapy when organ and tissue damage are diagnosed and the criteria for symptomatic myeloma is met (Table 1-4). The guidelines do encourage recruitment into clinical trials to assess the survival benefit of early intervention for this group (Bird et al., 2011). This is supported by newer research evidence for the management of asymptomatic myeloma with novel therapies and reports of increased survival for the high risk of progression groups (Mateos et al., 2013).

Symptomatic myeloma requires treatment with systemic chemotherapy, as well as correction or treatment of any consequent pathology such as renal impairment, hyper-viscosity, hypercalcaemia, pathological fractures, spinal cord compression or early infection (Bird et al., 2011). Early mortality is reported with 10% of newly diagnosed myeloma patients dying within the first 60 days of the commencement of treatment (Augusten et al., 2005). This is probably a consequence of the high burden of disease at diagnosis.

Chemotherapeutic advances have been made in the last ten years, with the development and introduction of agents such as bortezomib (Velcade – a protease

inhibitor), thalidomide and lenolidamide (immunomodulatory drugs), which are now considered to be the mainstay of treatment (Smith and Yong, 2013).

Younger, fitter patients are treated following induction regimens with autologous stem cell transplants, which increase the depth of response and longevity of disease free and overall survival (Child et al., 2003).

1.5 Outcomes in myeloma

1.5.1 Survival

Myeloma remains an incurable disease, but is treatable. Improvements in treatment options and outcomes mean that there is now a median predicted survival of five years (Bergsagel et al., 2013; Cancer Research UK, 2017a). Survival is said to have quadrupled over the last 40 years. Previously, five in every 1,000 people newly diagnosed with myeloma survived for 10 years; now a third live beyond 10 years.

Autologous stem cell transplant programs (ASCT) for younger, fitter patients has led to increased progression-free and overall survival (Child et al., 2003). These are now the mainstay of treatment plans for patients able to withstand the intensity of the treatment (Bird et al., 2011; NICE, 2016a).

The availability of 'novel' therapies (Velcade and Lenolidomide) has also improved survival (Kumar et al., 2008). Improvements are expected to continue further with the development of second and third generation protease inhibitors and immunomodulatory drugs: Carfilzomab (Siegel et al., 2009; Jakubowiak et al., 2012); Vorinostat (Campbell et al., 2010; Bandros et al., 2004); Pomlidamide (Lacy et al., 2009; Escoubet-Lozach et al., 2009).

Despite the availability of novel agents and stem cell transplant programmes, survival outcomes have only improved in the younger, fitter patient group. Survival and treatment options in those aged over 70 years, the largest proportion of the myeloma population, have not seen significant improvements (Brenner et al., 2008).

1.5.2 Mortality and morbidity

A number of clinical and laboratory interventions have been cited as reasons for the improvements in morbidity and mortality in myeloma patients. Improvements include: the identification of the genetic basis and variants in myeloma; and the development of targeted treatment pathways (Bergsagel et al., 2013; Kumar et al., 2012). Greater understanding and development of supportive care programmes such as

bisphosphonate treatment, growth factor support, radiotherapy and improved access to specialist departments are also reported as important (Snowden et al., 2011).

Patients with myeloma will relapse following cytotoxic chemotherapy or stem cell transplantation, in a cyclical pattern until a refractory disease state occurs and myeloma progresses, or complications of the treatment or disease cause death (Smith and Yong, 2013).

The disease, "myeloma", is clearly complex and heterogeneous. Despite well recognised improvements in care and treatment, survival benefits are seen mainly for the younger, fitter patient group. This means overall survival for the majority of the myeloma population have seen only limited improvements. It is possible that the outcomes for myeloma patients are relatively unchanged in this older age group because they are rooted in a failure to identify the disease early, before complications develop and outcomes are worse. Would timelier diagnosis of the disease be possible and beneficial? Work undertaken in other cancer types may offer insights.

1.5.3 Earlier diagnosis of cancer

1.5.3.1 Early diagnosis policy

Interest in the early diagnosis of cancer followed reports that the United Kingdom's (UK) figures for one and five-year survival were worse than other European countries with comparable healthcare systems, and that these worse outcomes were related to the late diagnosis of cancer (Berrino et al., 2007). It was estimated that if UK survival figures matched those of other European nations, between 6,600 and 7,500 premature cancer deaths could be avoided (Abdel-Rahman et al., 2009). Over the last decade or more, initiatives to improve cancer outcomes through better understanding the factors that influence timelier diagnosis have been introduced at a national level. This has led to the generation of a large body of evidence informing the practice of timelier diagnosis of cancer which provides a framework for future research.

1.5.3.2 Policy development for early diagnosis of cancer

In England, the NHS Cancer Plan (Department of Health, 2000), launched in 2000 was the first comprehensive review of national cancer programmes. However, the plan was limited in its recommendations for early diagnosis initiatives. The Cancer Reform Strategy (Department of Health, 2007) built on progress made by the Cancer Plan, adding 'Diagnosing cancer early' as one of its six action points. This plan also set up the National Awareness and Early Diagnosis of Cancer Initiative (Cancer Research UK, 2017b), which supported early cancer diagnosis with programmes such as:

- The 'Be clear on cancer' campaign, January 2011. This increased the public's awareness and understanding of signs and symptoms of cancer, encouraging prompt help-seeking from GPs when a symptom of possible cancer was first noticed;
- Optimising clinical practice and systems. This brought together a range of relevant cancer data in the primary care setting, allowing comparisons between practices;
- Improving GP access to diagnostics. Accelerate, Coordinate, Evaluate (ACE) Programme June 2014. This was an NHS England initiative supported by Cancer Research UK and MacMillan Cancer Support. It addressed system delays including the development and evaluation of new streamlined diagnostic pathways to encourage future service improvements; and
- Early diagnosis research conferences. These conferences showcase the early diagnosis of cancer research and brings together researchers, clinicians, patients and policy makers for the wide dissemination of the outcomes.

These initiatives are mirrored in the devolved nations' policies for cancer care. NHS Scotland implemented policy for early diagnosis governed by 'Better Cancer Care, an Action Plan' (Scottish Government, 2008) and 'Beating cancer: Ambition and Action' (Scottish Government, 2016); and in Wales through the implementation of 'Together for Health, Cancer Delivery Plan' (Welsh Government, 2012). Whilst the strategies vary, their overall aims are the same, namely to improve the prevention, detection, diagnosis and treatment of cancer.

This body of work initially reported outcomes for commonly occurring cancers such as breast, colorectal and gynaecological cancers. This developed a framework which informs early diagnosis work more generally, and can be used as a benchmark for less common cancers that are more difficult to diagnose, such as myeloma.

1.6 What has the research in 'the early diagnosis of cancer' told us?

The journey to a cancer diagnosis is full of complexity and can be influenced by a number of individuals, events or interactions occurring across a time interval that may not be continuous (Walter et al., 2012). This complexity is visually depicted in the pathways to treatment model (Figure 1-3), which clearly demonstrates how the process may be disrupted by multiple factors across a timeline.

The total time to diagnosis and treatment has been sub-divided into domains: patient, primary care, secondary care, diagnostic, time to diagnosis, treatment interval, and the total interval to treatment (Figure 1-4). In order to standardise the definition and reporting of intervals for comparison and quality, the Aarhus statement has made recommendations for consistent measurement of individual and total intervals (Weller et al., 2012).

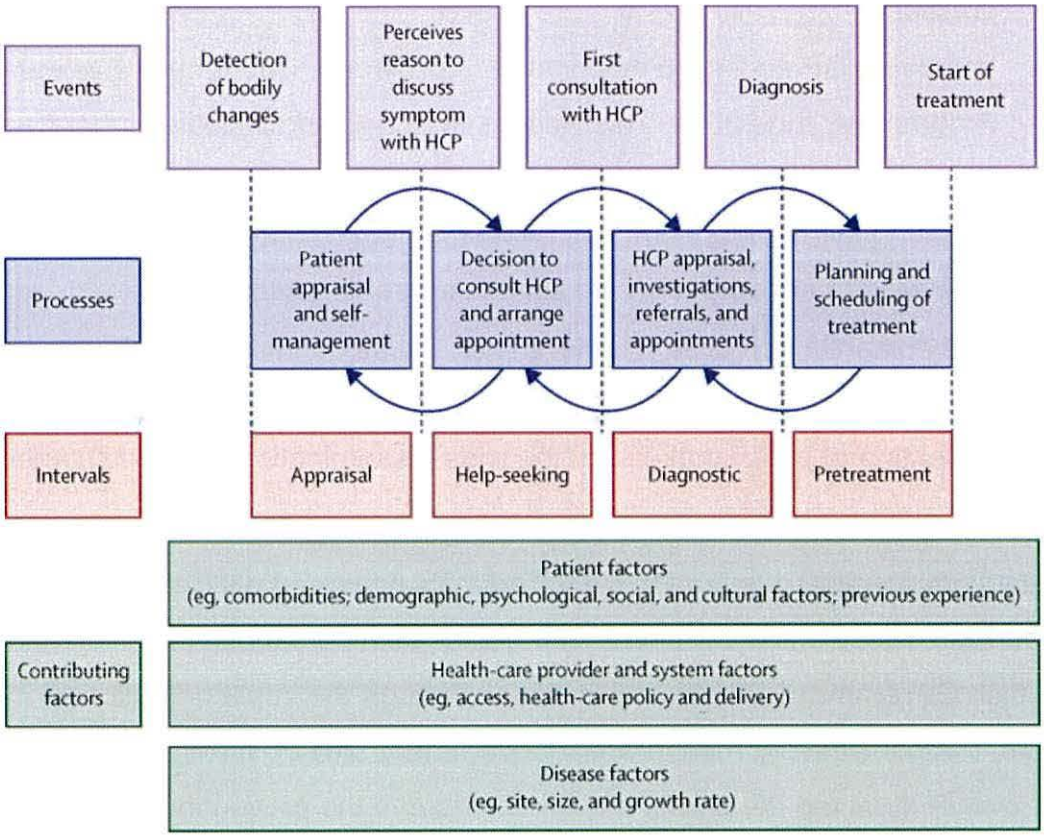

Figure 1-3: Pathways to treatment

(Walter et al., 2012 reproduced in Rubin et al., 2015, reproduced by kind permission)

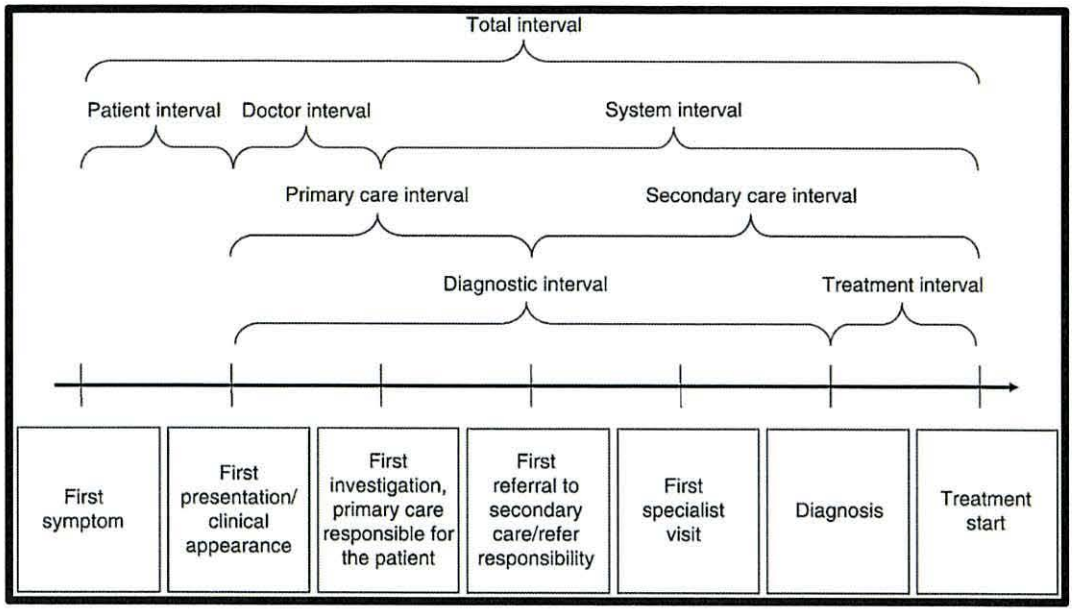

Figure 1-4: Intervals to diagnosis and treatment

(University of Aarhus General Practice Research Department cited Weller et al., 2012 reproduce by kind permission)

Reporting these intervals to diagnosis allows comparisons between different cancer types, and cancers with timelier intervals to diagnosis and better outcomes become benchmarks for good diagnostic practices.

The influences that affect the duration of these intervals have been reported to be: patient generated; behavioural or demographic; related to doctors' investigations; interactions; referral routes; cancer site specific or disease and stage specific (Figure 1-4). NAEDI formed a hypothesis to depict how these influences occur in the journey to a diagnosis. This hypothesis has underpinned research development (Figure 1-5), and was modified and updated as new evidence became available (Hiom, 2015).

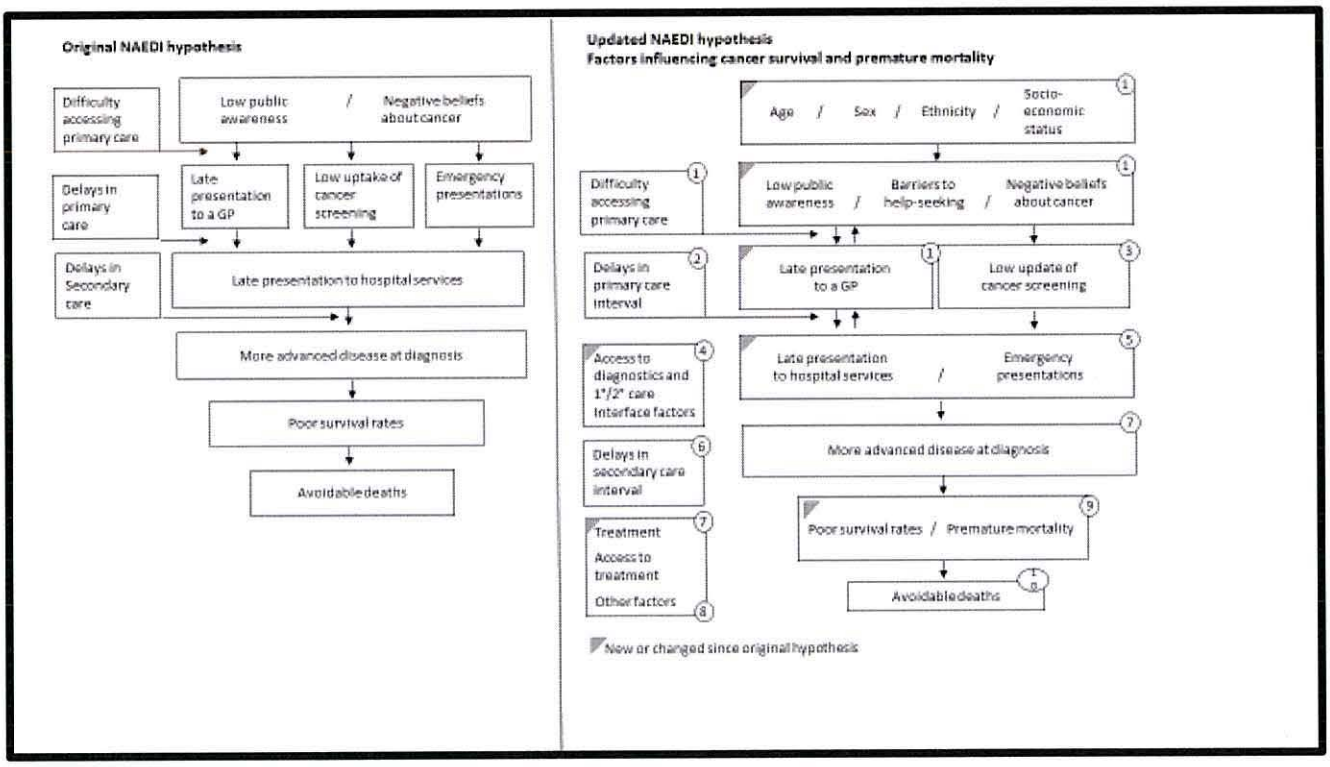

Figure 1-5: The NAEDI hypothesis

(Modified from Hiom, 2015)

Further understanding of the differences in influences in patients' responses to the symptoms experienced and the need to seek help have been characterised through the understanding of health belief theories (Scott, et al. 2013). Scott, et al. (2013) offers an explanation for the dynamic changes in the Appraisal and Help Seeking intervals within the Model to Treatment Pathway (Walter, et al., 2012) by detailing a reciprocal relationship between the environment, personal and social determinants of the individual patient. Scott, et al. (2013) describes these as being explained by existing psychological theories such as Leventhal's Common Sense Model of Illness Self-regulation and Bandura's Social Cognitive Theory. These provide a systemic approach to understanding the health behaviour and build knowledge allowing hypotheses to develop.

1.6.1 Early diagnosis knowledge related to individual intervals

1.6.1.1 Patient interval

This interval is defined as the period between the first symptom or bodily change experienced by the patient, to the presentation to a health professional (Weller et al., 2012).

Reporting this interval is challenging, as it requires the subjective assessment of the date that the symptom/s was/were first experienced. Analysis from coded data within primary care databases, such as the General Practice Research Database (GPRD) (now renamed as the Clinical Practice Research Datalink (CRPD)), allows large cohorts of cases to be examined for research, but will not adequately capture the patient experience and assessment. To do this requires the collection of data directly from the patient, close to the diagnostic date, in order to reduce recall bias or prospective collection (Keeble et al., 2014). This is challenging ethically, as it further burdens the patient at the time of diagnosis and is resource heavy, requiring increased research resource to collect the self-reported symptom data form participants. This type of self-reported data collection can limit recruitment and the number of cases for analysis (Keeble et al., 2014; Weller et al., 2012).

This patient interval consists of both the appraisal of symptoms by the patient and the prompt to seek help. Therefore, there are both behavioural and contextual influences that affect it. These influences are recognised in the NAEDI hypothesis (Hiom, 2015), and have been explored in different cancer types. It is, possibly, the most complex of the intervals, involving widespread and varied influences associated with the presentation of the symptomatic patient.

1.6.1.2 Appraisal of symptoms

How symptoms are appraised is affected by individual attitudes (Robb et al., 2009; Whitaker et al., 2015a). Patients are reported to have a reluctance to access GP services based on fears of an impending cancer diagnosis or 'bothering' or 'wasting' GPs' time. Power and Wardle (2015) confirmed this 'fear' factor when evaluating the "Be Clear on Cancer" campaign, although no evidence of participant concern about wasting GP services or time was reported. Whitaker et al. (2015a) reported that delays in help-seeking were associated with attitudes of trivialising or normalising symptoms or stoicism in the face of symptoms.

1.6.1.3 Awareness of symptoms

Low public awareness and poor recall of cancer symptoms are reported to be associated with longer patient intervals. This gap in patients' knowledge of symptoms leads to a failure to recognise the need to access GP services for assessment (Stubbings et al., 2009; Robb et al., 2009). An example of this is the greater symptom awareness in breast cancer being associated with earlier help-seeking and shorter patient intervals (Keeble et al., 2014).

1.6.1.4 Socio-economic status

Disparities are reported and associated with different outcomes and routes to diagnosis for different demographic groups. Groups with lower educational attainment have associations with longer help-seeking intervals, this being influenced by the way the risk of cancer is assessed (Wardle et al., 2001; Quaife et al., 2014). Health literacy, expectation biases and life experiences in lower socio-economic groups are associated with negative impacts on help-seeking. Conversely social sanctioning in higher socioeconomic groups is associated with positive influences and timely help-seeking (Whitaker et al., 2015).

1.6.1.5 Patient factors

Age, sex and deprivation influences are associated with differences in the interval duration, stage of disease at diagnosis, and, in turn, outcomes in survival (Rutherford et al., 2015a; Rutherford et al., 2015b). Rubin (2011) discussed an interplay between demographics, patients and outcomes in terms of age, ethnicity and socioeconomic status and appraisal periods. Abel, et al. (2015) reported differences in age, sex and deprivation beyond tumour biology, associated with emergency presentation for a diagnosis of cancer. Emergency route presentation is associated with psychosocial processes and factors negatively influencing help-seeking behaviour. Multi-morbidities in patients and the cancer journey, are associated with failure to appraise symptoms, resulting in missed opportunities to diagnose, longer intervals and a need for repeated presentation of the patient in primary care (Kostopoulou, et al 2008; Lyratzopoulos et al., 2012).

1.6.1.6 Interval to diagnosis

In the journey to a cancer diagnosis of symptomatic cancer, there are a number of intervals that represent the period when a cancer diagnosis is being made following the presentation of the patient with symptoms. These intervals are sub-divided, giving greater clarity and reporting of the difficulties associated with the individual intervals (Figure 1-4) (Weller et al., 2012). The diagnostic interval is the period of time between the presentation of the patient to a health professional and the histological confirmation of the diagnosis of a cancer. The diagnostic interval can be incorporated into the time to diagnosis interval, by the inclusion of the patient interval, and this then measures the journey from first symptoms to the cancer diagnosis. The primary care interval is a sub division of the diagnostic interval. It is the period from the first presentation of the patient to the GP and ends at the transfer of care to secondary care services, through a

referral by the GP or self-referral by the patient as an emergency (Figure 1-4). The secondary care interval is not fully incorporated into this interval, as the interval commences with the referral of the patient from the GP or self-referral to secondary care, and ends at the commencement of treatment for the diagnosed cancer. This then extends beyond the calculation of the diagnostic interval. However, it still remains possible for the diagnostic interval to be influenced by the length of time it takes to investigate and make a diagnosis of a cancer in secondary care.

1.6.1.7 Primary care interval

Eighty-five percent of cancers are diagnosed following the presentation of symptoms to GPs, making the interaction in primary care crucial to the process of timely diagnosis (Rubin et al., 2015). However, GPs in England see approximately only seven or eight new cases of cancer each year (Richards, 2009), but will have consultations related to hundreds of other conditions. The low incidence of cancer in primary care places unique challenges on GPs when investigating and referring potential cancer patients in a timely manner. The assessment and measurement of the primary care interval has been a rich area of investigation in response to policy initiatives for the early diagnosis of cancer. However, the transparency and quality of studies measuring this interval has been variable, making comparison of the reported intervals across cancer types difficult (Weller et al., 2012). The introduction of clear definitions of individual intervals has led to more unified reporting and easier comparison across studies and cancer types (Figure 1-4).

Over the last decade, there has been substantial evidence for primary care difficulties and missed opportunities for diagnosing cancer early (Allgar and Neal , 2005; Rubin et al., 2011; Rubin et al., 2015; Lyratzopoulos et al., 2015a). Missed opportunities may be influenced by the presence of multi-morbidities; a lack of alert symptoms at presentation to the GP (a set of recognised symptoms that lead to a suspicion of serious disease) at presentation to GP; the rarity of the cancer; primary care doctors' inexperience; or asymptomatic or atypical presentation of the cancer (Neal, 2009; Round et al., 2013; Corner et al., 2005; Tørring et al., 2011; Kostopoulou et al., 2008).

1.6.1.8 Measurement of primary care intervals

This interval has shown variations in its lengths across cancer types, with intervals for breast cancer generally being shorter than the rarer cancers or cancers with less well-defined symptoms (Neal et al., 2015; Tørring et al., 2013; Din et al., 2015; Lyratzopoulos et al., 2013).

1.6.1.9 Recognition of symptoms

How symptoms in different cancer types influence diagnostic time intervals has been investigated widely (Corner et al., 2005; Moffat et al., 2015; Walter et al., 2015; Walter et al., 2016). When symptoms associated with the cancer are vague and non-specific, increased primary care intervals are reported, with associated delays in a referral to specialist care services (Allgar and Neal, 2005; Torring et al., 2011; Round et al., 2013). A symptom signature for a cancer is a single symptom or set of symptoms that 'alert' the GP to the possibility of cancer or serious pathology, such as lump in breast cancer or bleeding per rectum in colorectal cancer. Cancers that have a poor 'symptom signature' are associated with longer intervals to diagnosis (Lyratzopoulos et al., 2014; Rubin et al., 2015). GPs have guidance to help the recognition of symptoms relating to a cancer in the NICE referral guidelines for alert symptoms of cancer (NICE, 2005). This guidance was updated (NICE, 2015), following the publication of many 'symptom' studies to provide a more comprehensive guidance in 2015, the impact of the update has yet to be evaluated (Hamilton, 2009; Howell et al., 2013; Shephard et al., 2015; Walter et al., 2015; Walter et al., 2016).

1.6.1.10 GP consultations

There is a large variation across cancer types in terms of the number of consultations required with a GP before a referral to specialist care is made for a cancer diagnosis (Lyratzopoulos et al., 2012). This is least for breast cancer, where the proportion of patients with three or more visits was 10%, and most for pancreatic cancer and myeloma, where the proportion rose to 40% and 50% respectively. Rubin et al., (2015) reported that, overall, 90% of cancers with characteristic symptoms, such as breast or melanoma, are referred after one or two consultations. These differences across cancer types are hypothesised to occur because of the difficulties in identifying certain cancer types due to their non-specific symptom profiles (Rubin et al., 2015).

Multi-morbidities are associated with difficulties in the recognition of symptoms in primary care as serious or relating to a cancer, and lead to missed opportunities to diagnose cancer in a timely way (Kostopoulou et al., 2008; Lyratzopoulos et al., 2015a).

1.6.1.11 Systems

The diagnostic interval is affected by system difficulties. The UK healthcare structure of 'GP gatekeeping', where access to specialist tests or cancer services is made via a referral from a GP, is associated with difficulties progressing through the pathway/system (Rubin et al., 2015; Round et al., 2013). This is also reported as

problematic in other European healthcare systems with similar structures to the UK, such as Denmark (Olesen et al., 2009). Vedsted and Olesen (2011) reported that GP gatekeeping was associated with reduced one-year survival for cancer. They described pressures for gatekeepers to use resource correctly, impacting on the responsiveness of GPs to patients' needs and concerns. In the authors' opinion, the gatekeeper system was "too rigid" for cancer care, and a need was seen for more interplay between primary and secondary care services in the early diagnosis of cancer. This was supported by Allgar and Neal (2005), who reported associations of patients who bypassed their GPs having faster diagnoses. Round et al. (2013) discussed fragmented services, seen in the current primary care provision, making the GP gatekeeper role even more challenging. The fragmentation of services was also reported to increase the burden on early cancer diagnosis when GPs were interviewed about their practice (Green et al., 2015). The increasing numbers of sessional and part-time workers in UK primary care services has been associated with loss of continuity and poor communication, making gatekeeper roles more difficult (Round et al., 2013; Rubin et al., 2015). Rubin et al. (2015) reported that greater continuity in primary care can influence better and earlier recognition of cancer. Round et al. (2013) commented that sessional doctors in general practice reported greater difficulty with accessing training, resulting in these clinicians being isolated from professional services which might impact their education and diagnostic potential (Round et al., 2013). Neal (2009) discussed how difficulties with accessing diagnostic investigations for primary care doctors can be associated with longer diagnostic intervals, either through the access being dependant on secondary care referral or there being waiting lists. Rubin et al. (2015) discussed the role of 'false negative' investigations in delaying diagnosis, especially for rarer or difficult to diagnose cancers. Another barrier for patients presenting to GPs was difficulty obtaining an appointment at their surgeries (Robb et al., 2009). Longer diagnostic pathways in secondary care were associated with referrals being sent to the wrong speciality groups (Neal, 2009). However, changes have been made to improve cancer referral pathways and access to services, with the introduction of target timelines and dedicated referral routes for suspected cancers (Richards, 2009).

1.6.1.12 Emergency presentation for a diagnosis

In 2012, it was reported that, overall, 24% of cancers were diagnosed following emergency presentation (EP), but variances between cancer types existed. The percentage EP presentations were: 3% melanoma; 5% breast; 50% pancreas; 62%

central nervous system) (Elliss-Brookes et al., 2012). Further evaluation of the patient factors associated with emergency presentation have been discussed previously in the 'patient factors - sex/age/deprivation' of this chapter section 1.6.1.5 (Abel et al., 2015). Patients who receive a diagnosis of cancer following an emergency presentation are also reported to have associations with worse outcomes, with lower one-year survival rates (Elliss-Brookes et al., 2012). This is typified by breast cancer survival rates which at one year were reported at 100% for screen detected and 98% for urgent suspected cancer two-week referrals, but only 54% following an EP for a diagnosis. This was further investigated by McPhail et al. (2013), who reported EP was predictive of early mortality at one year and associated with worse outcomes within the first month of diagnosis. McPhail et al. (2013) additionally reported that excess mortality was strongly associated with EP independent of the case mix factors of age, stage, gender and deprivation factors. There are criticisms that the current system for diagnosing cancer does not provide the structure required to facilitate timely and seamless referral to specialist oncology services but it has been argued by McCartney (2013), from a primary care perspective, that analysis of data referencing EP presentation was incomplete, without reference to concurrent GP consultations. Abel et al. (2017) recently published further data on the associations between increased frequency of consultations in primary care and EP presentation, reporting that a third of all EPs had not had consultations with their GP prior to their presentation in secondary care. The authors concluded that missed opportunities for diagnosis are not the only factors affecting the overall frequency of EP for a cancer diagnosis. Abel et al. (2017) does, however, report variations across cancer sites with more difficult to suspect cancers having different profiles. The new NAEDI hypothesis (Hiom, 2015) equates emergency presentation with late presentation and more advanced disease at diagnosis, which ultimately leads to worse outcomes and avoidable deaths. Cancers that are associated with higher emergency presentation rates clearly require greater understanding of the influences on symptom development and the pathway to diagnosis.

1.6.2 Effect on outcomes

Longer diagnostic intervals are reported to be associated with worse outcomes (Neal et al., 2014; Tørring et al., 2013). However, contradictory evidence supported that some cancer types had shorter intervals to diagnosis but were associated with worse outcomes (Crawford et al., 2002). Where these shorter intervals and worse outcomes occurred, it was hypothesised that this was a result of underlying tumour pathology

(Neal, 2009). This 'waiting time paradox' relates to the aggressive nature of these tumours, making them more easily and rapidly detected with shorter diagnostic intervals. However, the rapid tumour growth and aggressive nature of the cancer type also leads to worse outcomes and reduced survival rates. Paradoxically, tumours that grow at a slower rate take longer to diagnose but due to slower tumour development they are less aggressive and have a lower burden of disease and better outcomes.

Emergency presentation for a diagnosis of cancer is seen in a quarter of patients and is associated with worse short-term survival across all cancer groups (Elliss-Brookes et al., 2012). However, there are variations in cancer type for emergency presentation and associations with gender, age socioeconomic status (Abel et al., 2015). Compared to men, women had a higher risk of emergency presentation for bladder, brain, rectal, liver, stomach, colon and lung cancer. This was the opposite for oral/oropharyngeal cancer, lymphoma and melanoma. Younger people were at a higher risk of emergency presentation for acute leukaemia, colon, stomach, and oesophageal cancers; older people for laryngeal, melanoma, thyroid, oral and Hodgkin's lymphoma. Inequalities by deprivation group, were greatest for oral/oropharyngeal, anal, laryngeal and small intestine caner.

The consequence of longer diagnostic intervals and associations with survival, morbidity and stage of disease at diagnosis were investigated in a systematic review (Neal et al., 2015). It was concluded that expediting a cancer diagnosis was likely to improve all three outcome measurements, but that there were differences in the extent of the benefits across cancer types. The cancer types of breast, colorectal, head and neck and melanoma were associated with shorter intervals to diagnosis and more favourable outcomes. However, these cancer types were seen to make the largest contribution of evidence to the review and evidence for some cancers was very limited.

1.6.3 Diagnosing cancer in Wales – the landscape and context

The Welsh Government is responsible for health provision in Wales. From 2012, cancer care in Wales has been driven by the policy outlined in the "Cancer Delivery Plan" (CDP) (Welsh Government, 2012). This plan took cancer care forward to the year 2016, and was built on the previous policy Designed to Tackle Cancer in Wales (2006). The policy aimed to improve cancer incidence and survival in Wales to match the best In Europe. The CDP was focused on promoting patient centred care which delivered equally across the Welsh population. It tackled the increasing burden of cancer by

focusing on cancer prevention and early diagnosis. In 2016, cancer policy was renewed with the production of a new Cancer Delivery Plan, which extends policy from 2016 to the year 2020. Early diagnosis of cancer remains a key objective within the plan (Welsh Government, 2016).

Cancer care structure and delivery in Wales is led by The Cancer Implementation Group (CIG). Their role is to strategically oversee the implementation of the CDP. Alongside them, the National Specialist Advisory Group for Cancer (NSAG) has clinical input responsibility and Local Health Boards (LHBs) deliver services at a local level. A regional cancer network facilitates coordination between LHBs and trusts (Cancer Research UK, 2017c)

The structure and management of the delivery of cancer care across Wales has been recently reviewed and recommendations for better outcomes in cancer provision made (Cancer Research UK, 2017c). Early diagnosis of cancer has its own specific recommendations, as the report acknowledges the need to diagnose early to improve patient outcomes. The report highlights Welsh Government as being less proactive with implementation of public awareness campaigns in cancer, compared to its neighbouring countries. Recommendations were to evaluate the lung cancer awareness campaign in 2016, so as to consider the appropriateness of further campaigns in Wales. Access to primary care systems was said to be problematic, with reports of difficulty organising GP appointments and disparity in access across affluent and non-affluent areas. The report recognised difficulties for GPs accessing direct diagnostic testing and recommended an urgent review of the resources available to GPs to enable them to lower thresholds for investigation and referral of potential cancer symptoms to secondary care.

All these recommendations were made in a climate of austerity with demands for the delivery of healthcare that was equitable and cost-efficient, as detailed in the Bevan Report on prudent healthcare (Bevan Commission, 2017). This adds another dimension to diagnosing cancer earlier, demanding that new initiatives are cost effective.

1.6.4 Gap in the knowledge

Myeloma has a non-specific symptom profile and this lack of a 'symptom signature' may influence its recognition by both the patient and the GP. Behavioural and contextual issues may influence the appraisal and timely presentation of the myeloma patient in the same manner as for other cancer types. The myeloma population is older and

influences associated with age and longer intervals to diagnosis may be relevant to this group. Additionally, the older population will have increased multi-morbidities, which adds to the potential for missed opportunities for early recognition of cancer symptoms. There is a complex process of investigation leading to the identification and diagnosis of myeloma. The process of initiating and conducting these investigations may influence the diagnostic processes though the availability and timeliness of testing. Patients with myeloma experience multiple complications such as renal failure, hypercalcaemia, pathological fractures, anaemia and infection. Referral to secondary care may be influenced more by the management of these complications by referral to secondary care departments, including emergency referrals, which may delay referral to a haematologist and the identification of the underlying disease with subsequent lengthening of the intervals to diagnosis and treatment.

The preliminary scoping of the literature comparing timely diagnosis of other cancer types and myeloma showed a relative dearth of information on the diagnosis of myeloma, although myeloma was identified as a difficult to diagnose cancer (Rubin et al., 2015). The primary care intervals in myeloma are reported to be longer than other cancer types (Lyratzopoulos et al., 2013), and myeloma patients are reported to have multiple GP consultations before referral to secondary care (Lyratzopoulos et al., 2012). Additionally, myeloma patients had higher frequency of emergency presentation associated with worse outcomes at one-year survival compared to other cancer types (Elliss-Brookes et al., 2012). The longer journeys for myeloma patients were associated with higher numbers of complications at disease diagnosis and reduced survival (Kariyawasan et al., 2007). The preliminary scoping of the literature could not determine if any behavioural or contextual influences affected the journey to a diagnosis in myeloma and found only limited evidence for the significance testing of influences reported across the intervals to diagnosis and treatment.

Given that clear policy exists which aims to improve outcomes by diagnosing cancers earlier, assessment of the diagnostic journeys of newly diagnosed myeloma patients is relevant and pertinent.

1.7 Aims of the research

The overall aims were to determine how diagnostic journeys in myeloma occur in newly diagnosed patients across Wales and to identify the factors which facilitate timelier diagnosis. The specific aims were:

- To undertake a systematic review of the literature to identify and explore what is known of the pathways to diagnosis in myeloma and the consequences of longer intervals in diagnostic pathways;
- To prospectively demonstrate how long it takes for patients with myeloma to be diagnosed in Wales, by measuring their various intervals to diagnosis and treatment and influences affecting these intervals;
- To assess the views and opinions of patients regarding their individual journeys to diagnosis and treatment, and to describe the important personal, social and contextual factors;
- To explore the experiences and perceptions of GPs diagnosing myeloma in primary care and the barriers and difficulties of achieving this;
- To determine the factors which contribute to prompt and longer diagnostic journeys; and
- To make clinical and policy recommendations based on the evidence collected, to facilitate timelier diagnosis of myeloma.

The study adopted the theoretical models discussed in this chapter (Section 1-6) to conceptualise and theorise the findings. The 'Pathway to Treatment' (Walter, et al., 2012) and the 'Aarhus Statement' (Weller, et al., 2012) conceptualised the findings in the journey to a diagnosis of myeloma and the 'NAEDI hypothesis' (Hiom, 2015) was used to theorise the factors of influence on the journey. The study used mixed methods to collect both quantitative and qualitative data to close the gap in knowledge. However, because the evidence in myeloma is limited, the study adopted a sequential research design (Creswell, 2014) to allowing the building of evidence and understanding as the study progressed. Firstly, data was collected to determine the length and variation of diagnostic journeys. Findings from this initial quantitative study were then used to inform second phase qualitative studies. These qualitative studies described the behavioural and contextual factors affecting the journey to diagnosis in myeloma and examined the interactions between patient and GP in primary care. The research design then culminated in a synthesis of data from all datasets. This synthesis provides a detailed explanation of the influences in the diagnostic journey in myeloma. The method chosen to facilitate this complex process was the mixed methods 'Explanatory sequential research design' described by Creswell, (2014) and portrayed in Figure 1-6. This research design is fully described in Chapter 3.

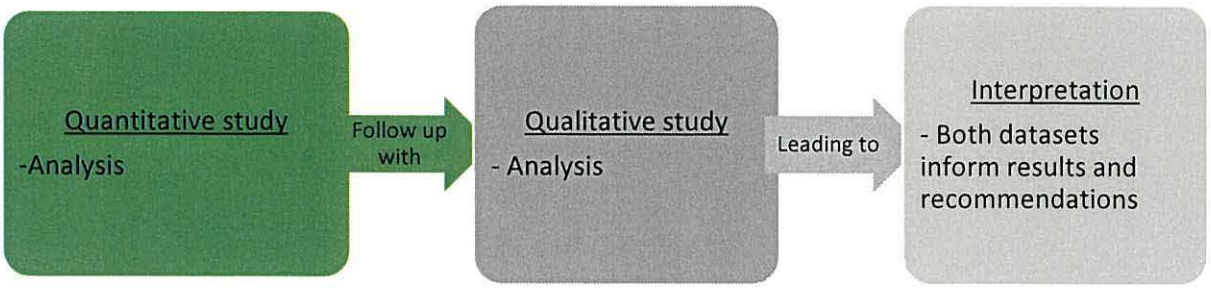

Figure 1-6: Diagram of Explanatory Sequential Research Program

(Adapted from Creswell, 2014)

2 Chapter Two: How long does it take to diagnose myeloma, what influences diagnostic complexity and length of interval from first symptom to diagnosis and treatment? A scoping systematic review.

2.1 Chapter summary

This chapter reports the systematic and rigorous review of the evidence to understand the diagnostic processes, time intervals and difficulties in the pathway to diagnosis of myeloma. Evidence is reported in categorised themes to produce a detailed account to better understand these difficulties. All evidence is collated to make recommendations for a study to explore diagnostic journeys in myeloma and, where possible, to inform policy and practice to achieve timelier diagnosis.

2.2 Background

Chapter One (section 1.2) provided an overview of the disease myeloma and discussed the rationale for assessing its diagnostic journeys to better understand how timelier diagnosis of the disease may be made.

The evidence identified to scope the topic for Chapter One was meagre (section 1.6.4), and the literature identified was mediocre in quality. The evidence was generated mainly from retrospective reviews of small cohorts or case studies within single centres (Kyle et al., 2003; Kariyawasan et al., 2007; Ong, et al 1995). Studies reported individual intervals within the journey to a diagnosis, or single factors alongside these intervals. The assessment of single factors reduced the ability to measure their relative contribution or significance across the whole journey to diagnosis. Evidence from the scoping exercise was considered insufficient to inform policy and practice on expediting a diagnosis of myeloma, or the development of further research. As the scoping procedures used were non-comprehensive, it was considered possible that identifying more evidence through comprehensive searching with a systematic review could better-inform research, policy and practice.

A systematic review was planned to identify all the evidence, collate this and allow the comparison of individual study outcomes to generate themed evidence from the combined results. The theme development would allow the areas of consensus, divergence and gaps in the literature to be displayed, adding depth and understanding of the topic.

2.2.1 Objectives of the review

The objectives of the review were to explore and identify all literature relating to the journeys to diagnosis of myeloma. The review would report measured intervals to diagnosis, the factors affecting these intervals and processes, and the characteristics of the sub groups within the identified populations reported in studies. This aimed to then lead to recommendations to improve the timeliness in the diagnosis of myeloma and develop research to answer the gaps in knowledge identified.

2.2.1.1 Objectives:

- To report the intervals to diagnosis, with given start and end points in the diagnosis of myeloma;
- To describe routes of presentation and referral pathways in primary and secondary care for myeloma cases;
- To determine barriers and facilitators to prompt diagnostic pathways in the diagnosis of myeloma;
- To determine the factors that characterise the sub-groups of patients with myeloma who experience prompt and longer diagnostic journeys e.g. age, gender, socio-economic status, comorbidities, performance scores;
- To report measurement of the stage of disease and complications reported in groups with measured intervals to diagnosis for myeloma cases; and
- To report survival outcomes reported in groups with measured intervals to diagnosis for myeloma cases.

2.3 Methods

2.3.1 Design and scope of the review

The systematic review followed a configurative reviewing process as described by Gough et al, (2012; Gough et al., (2012a). This scoping style of review generates themes of evidence by arranging and interpreting data through an inductive, evolving process. This evolving process was considered important as there was a likelihood of identifying new themes of evidence from comprehensive efforts to identify all the literature on the topic. This was considered the most appropriate method to inform on a poorly understood topic and was therefore complementary to the findings from the scoping of the literature for Chapter One (section 1.6.1 and 1.7) (Gough et al., 2012; Gough et al., 2012a).

Through scoping the literature, it was considered likely that relevant literature would report single or multiple factors within the diagnostic journey of myeloma cases.

Reported outcomes were likely to cross the patient, primary or secondary care domains. To best identify these multiple factors and intervals, an 'exhaustive' literature search strategy, using multiple 'terms', was developed. This was characteristic of scoping reviewing styles, and was in contrast to the traditional aggregate style search strategy, where defined search terms are used to narrow the literature field rather than expand it (Gough et al., 2012; Gough et al., 2012a).

The scoping exercise recognised that literature informing the review would sit within multiple data sources, policy documents, reviews, editorials and reports. Given that the anticipated yield of literature was likely to be small, comprehensive searching was adopted across multiple databases and websites. This was, again, in contrast to the narrower source searching adopted for aggregate reviews, where principally only peer-reviewed literature is sought (Gough et al., 2012; Gough et al., 2012a).

Multiple study designs were identified in the scoping exercise. Therefore, in an attempt to include further relevant myeloma literature, no exclusion of study design was added for the scope of the review. The inclusion of study designs not demonstrating homogeneity was a move away from more traditional systematic reviewing methods. The scoping reviewing process, and the development of themes of evidence across the literature, made it possible to conduct the review in this way (Gough et al., 2012; Gough et al., 2012a).

The loss of homogeneity was considered inevitable due to the wide searching and inclusion criteria adopted for this explorative style review (Dalziel et al., 2005). The diversity of the included studies, was likely to make measurement of quality more challenging. It was recognised that criticism of reviews which do not use aggregate style, tightly defined search strategies and inclusion criteria exist because of the difficulty assessing quality across a diverse, non-homogeneous group of studies (Hemingway, 2009). Aggregate style reviews that use these narrowly defined search strategies and inclusion criteria are more in keeping with the classic Cochrane style review (Gough et al., 2012a), and their objectives are in contrast to the descriptive nature of the scoping review. Overall the desire to maintain an exploratory review was considered the most significant element of this myeloma review, which made scoping reviewing the most appropriate method despite challenges of reviewing quality of included studies. Efforts were made to identify a quality measurement tool that would

allow the simultaneous assessment of a range of study designs that would compensate for any loss of homogeneity.

2.3.2 Searches

The search strategy comprised of:

- Searching of electronic databases
- Review of cancer information web based sites
- Backwards and forwards citation searching of included studies
- Pearl growing
- Contact with experts in the field (when considered appropriate following supplementary search strategies)

2.3.2.1 Databases interrogated:

MEDLINE, MEDLINE in process, EMBASE, CINAHL, Cochrane Library/Cochrane database of systematic reviews, Health Technology Assessment (HTA), Cochrane Central Registry of Controlled Trials (CENTRAL), Health Economic NHS EED/HEED, Web of Science, Psychinfo

These databases were selected to complement the exhaustive search strategy. These databases allowed identification of literature from medical and allied health, psychology, health economics, systematic reviews and literature awaiting publication. The search strategy was adapted from a prominent systematic review for interval assessments in cancer diagnosis (Neal et al., 2015). Advice was additionally sought on the expansive search strategy from experienced systematic reviewers within Bangor University and the SURE unit at Cardiff University. A search strategy was developed for the MEDLINE database (Table 2-1) and reviewed and endorsed by these two groups, before it was then adapted for the other bibliographic databases.

Website searches were made. These included searches of Cancer Research UK, Myeloma UK, Department of Health, International Myeloma Forum, International Myeloma Working Group, Agency for Health Research and Quality, UKCRN (NCRI) Portfolio database, British Society of Haematology, The American Society of Hematology, policy documents, guidelines and audits from NHS and representative professional bodies for NICE and searching for policy documents from the NHS through Google search using key words 'myeloma', 'diagnosis', and 'guidelines'.

Table 2-1: Search strategy for MEDLNE (Ovid)

1	*Multiple Myeloma/ or myeloma.mp.
2	(asymptomatic myeloma or smouldering myeloma or indolent myeloma or smouldering myeloma).mp.
3	1 or 2
4	(interval* adj4 diagnos*).ti,ab.
5	(interval* adj4 consult*).ti,ab.
6	(interval* adj4 treat*).ti,ab.
7	(interval* adj4 refer*).ti,ab.
8	(interval* adj4 present*).ti,ab.
9	(interval* adj4 therap*).ti,ab.
10	(interval* adj4 primary care*).ti,ab.
11	(interval* adj4 secondary care*).ti,ab.
12	(interval* adj4 reduc*).ti,ab
13	(interval* adj4 improve*).ti,ab.
14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	(time adj4 diagnos*).ti,ab.
16	(time adj4 consult*).ti,ab.
17	(time adj4 treat*).ti,ab.
18	(time adj4 refer*).ti,ab.
19	(time adj4 present*).ti,ab.
20	(time adj4 interv*).ti,ab.
21	(time adj4 therap*).ti,ab.
22	(time adj4 delay*).ti,ab.
23	(time adj4 prompt*).ti,ab.
24	(time adj4 late*).ti,ab.
25	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	(diagnos* adj4 prompt).ti,ab.
27	(diagnos* adj4 late).ti,ab.
28	(diagnos* adj4 delay*).ti,ab
29	(diagnos* adj4 demography).ti,ab.
30	(diagnos* adj4 symptom*).ti,ab.
31	(diagnos* adj4 manifest*).ti,ab.
32	26 or 27 or 28 or 29 or 30 or 31
33	(outcome* adj4 therap*).ti,ab.
34	(outcome* adj4 diagnos*).ti,ab.
35	(outcome* adj4 interval*).ti,ab.
36	33 or 34 or 35
37	14 or 25 or 32 or 36
38	3 and 37

2.3.3 Secondary searches

Secondary search strategies were implemented to allow higher levels of identification of evidence (Papaionnou. et al. 2009).

Forward and backward citation searching was implemented from bibliographies of included studies. This process involved reviewing referenced articles of included studies in order to identify further relevant literature (backward citation searching); then searching for articles where the authors of included studies had been cited after publication (forward citation searching) (Papaionnou. et al. 2009).

Pearl Growing was additionally implemented for the critical articles (Elliss-Brookes et al., 2012; Friese et al., 2009; Howell et al., 2013; Kariyawasan et al., 2007; Lyratzopoulos et al., 2012; Lyrazopoulos et al., 2013). This process involved compiling criterial articles, and logging their indexed terms. These terms and databases were interrogated with the logged terms to further identify relevant articles. As the relevance was lost in identified articles, the strategy was discontinued (Schlosser et al., 2006).

No language restrictions were applied to the search criteria. Non-English language published articles would have English abstracts available, allowing assessment of their relevance. Articles identified as relevant would be translated using Google Translate to assess their relevance and inclusion for synthesis. English language restrictions are not considered to restrict the conduct of reviews, but given that the objectives for this review were exploratory, this search practise was adopted to allow a higher level of identification of evidence (Morrison et al., 2012)

To check that the wide and exclusive search criteria would identify correctly themed literature, the first 500 citations were reviewed before running the search across all databases. Consideration was made of the ability of the search strategy to be inclusive enough to ensure the relevance of articles identified, but not too burdensome in the number of articles identified with no relevance (Gough et al., 2012). On review of the first 500 identified studies by two reviewers, abstract and titles were considered to be specific enough to myeloma and diagnosis. The search criteria were, therefore, run in full across all databases selected.

2.3.4 Review inclusion/exclusion criteria

Inclusion:

- Any study, of any design, related to the diagnostic pathways or intervals in the diagnosis of myeloma;
- Studies reporting diagnostic pathways in asymptomatic and symptomatic myeloma participants;
- Literature generating from any institute or healthcare provider in any country; and
- Unpublished reports, guidelines and audits.

Exclusion:

- Studies reporting survival outcomes correlated with treatment and treatment choice. Survival outcomes, related to choice of treatment or treatment pathway i.e. intensive (Autologous Stem Cell Transplants) or non-intensive, novel agents. The intention of the review was to report survival outcomes correlated directly to the intervals to diagnosis.
- Studies reporting efficacy of diagnostic techniques, used in the diagnosis of myeloma. The intention of the review was to report tests performed in response to treatments and not the efficacy of diagnostic techniques e.g. cytogenetic analysis, MRI signal density analysis.
- Studies reporting diagnosis of MGUS (Monoclonal Gammopathy of Undetermined Significance). The intention of the review was to report pathways for participants with asymptomatic and symptomatic myeloma.
- Studies reporting clinical presentation features and stages reported in isolation of 'time to diagnosis/total interval to diagnosis and treatment', pre-diagnosis symptoms or routes of diagnosis.

Editorials were to be included when relevance to the topic was identified. It was considered that editorials were likely to be written by experts in the field who are knowledgeable on the topic. Therefore, they could have relevance to the review. Editorials identified would be reviewed and, if relevant, included in synthesis but reported separately from peer-reviewed literature. Conference abstracts were scrutinised for relevance to the topic as these could identify work currently being undertaken or awaiting publication. In relevant identified abstracts, a policy of

approaching named authors was adopted to gain further information on the study's publication.

2.3.5 Assessing the relevance of included studies

Two reviewers independently screened titles and abstracts, with disagreements resolved by discussion and consensus. Potentially relevant studies were retrieved in full, then assessed for inclusion by two independent reviewers. Disagreements were resolved by discussion, or, when necessary, by a third reviewer.

Included articles were judged for relevance, firstly, on the primary outcomes for the review, then secondly, on an interpretive basis by reviewer agreement. This interpretative review was in line with scoping reviewing (Gough et al., 2012; Gough et al., 2012a) and allowed the identification of new or unexplored themes in the literature, to influence the inclusion of additional studies.

The wide search and inclusive criteria allowed identification of all literature related to the topic. Despite the review of the first 500 citations, a large number of irrelevant and less-relevant studies were anticipated. To further define and achieve a greater level of relevance to the topic, a CART (Completeness, Accuracy, Relevance and Timeliness) criteria was developed and implemented based on the model described by Tennison et al. (2006) and implemented, with reported success, by Whitaker et al. (2013). This tool is a method of systemising studies to identify the most in-depth data to answer the research questions, focusing resources towards the most fruitful areas of evidence. Studies were assessed on four categories: Completeness, Accuracy, Relevance and Timeliness, against the review questions. These categories were modified from the Whitaker et al. (2013) version and made specific to this review through assessment and modification of a group of systematic reviewers from Bangor University and clinicians from the supervisory team (Appendix 1).

2.3.6 Data extraction

Included studies were data-extracted into bespoke data-extraction forms. The bespoke forms were piloted against a random sample of studies of different designs that were identified as critical from the scoping exercise in Chapter One (section 1.7) (Friese et al., 2009; Kariyawasan et al., 2007; Lyratzopoulos et al., 2012; Howell et al., 2013). This allowed the assessment of the suitability of the forms to accommodate the design of the review, and the heterogeneity of the study designs anticipated (Elamin et al., 2009). Piloted Microsoft ACCESS database (Version 2013) forms were found to be too

cumbersome for the low level of homogeneity between studies, and therefore a simpler to use design was formulated. The new forms were formulated in Microsoft Word (Version 2013) tables (Appendix 2), which accommodated the need for expansion of particular data categories to capture the diversity of evidence.

Data extraction was conducted in line with the project aims and objectives. Any unknown or unexpected categories were acknowledged and incorporated for further exploration (Gough et al., 2012). All new categories were described and mapped through an iterative, interpretive approach. Data were extracted from each included study and included: study characteristics (design, sample type, sample size); study outcome measures (interval times, symptoms experienced, presentation route, and multi-morbidities); contextual factors in the study setting; postulated theories by authors; rationale for study and summary discussion. Data were extracted by one reviewer and checked by a second independent reviewer. Disagreements were resolved by consensus and, when necessary, a third reviewer.

2.3.7 Assessment of quality

The methodological quality of each included study was assessed by one reviewer and then checked by a second reviewer. Disagreements were resolved by consensus or, when necessary, through a third reviewer. Assessment of quality of the included studies, was carried out using the MMAT (Mixed Methods Appraisal Tool) Version 2011, developed by Pace et al. (2012). The MMAT was principally chosen as it allowed quality appraisal of multiple study designs (qualitative, RCT, non-RCT, observation and mixed methods) and had been piloted and reported as reliable (Pace et al., 2012). The tool, therefore, was unlike other quality assessment tools recommended by CASP (Critical Appraisal Skills Programme) (http://www.casp-uk.net), where appraisal of quality was limited to studies of singular designs i.e. randomised controlled trials or observational studies, making the tools unsuitable to this review. For documents the MMAT did not facilitate appraisal of, but that were included for synthesis (e.g. case studies, editorials, audits), the intention was to comment on their reliability rather than exclude from analysis.

2.3.8 Data synthesis

In order to accommodate the range of data, as well as the aims and objectives of the review, the chosen synthesis method had to be inductively responsive to the process of theme identification within a diverse dataset included for synthesis. A textual response was considered which allowed detailed description of the synthesised evidence. A

narrative synthesis method was implemented allowing textual descriptive exploration of the patterns of evidence identified across the studies (the interpretive synthesis), and visual representation of data (the descriptive synthesis) (Popay et al., 2006).

The four main elements of the framework were:

- Developing a theory of how myeloma is diagnosed;
- Developing a preliminary synthesis of findings of included studies;
- Exploring relationships in the data; and
- Assessing the robustness of the synthesis.

A range of individual tools were described in the framework, which were considered to identify the best tools to facilitate each section of the synthesis. This flexibility was likely to assist the scoping review process, as themes evolved as the review progressed and required description (Gough et al., 2012). A combination of grouping and clustering, tabulation and thematic analysis were used to synthesise data (Popay et al., 2006). Initial clustering or grouping, assisted organisation and identification of patterns across these data. The number of studies included for synthesis was not likely to be large, but the breadth and range of data was likely to make the process extensive. Tabulation was used to further organise and visually portray data. This was a natural progression from grouping and clustering, and was undertaken to identify patterns in data. Finally, thematic analysis was used to summarise the clustered and tabulated evidence. This method, although more often associated with qualitative analysis, allowed the diversely reported evidence to be explored and reported (Popay et al., 2006) and complemented the inductive theme development desired for this review (Gough et al., 2012; Gough et al., 2012a). Thematic analysis was conducted, primarily, through seeking prevalence of themes across clustered groups. Prevalence was judged inductively against the frequency of reporting of a theme, along with the relevance to the research question, and the depth of explanation of the theme (Braun and Clarke, 2006).

2.4 Results

Searches were conducted in May 2014, initially to underpin the research study design, and updated in May 2015 as analysis of data continued in the study.

Search results are displayed in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram in Figure 2-1 (Moher et al., 2009).

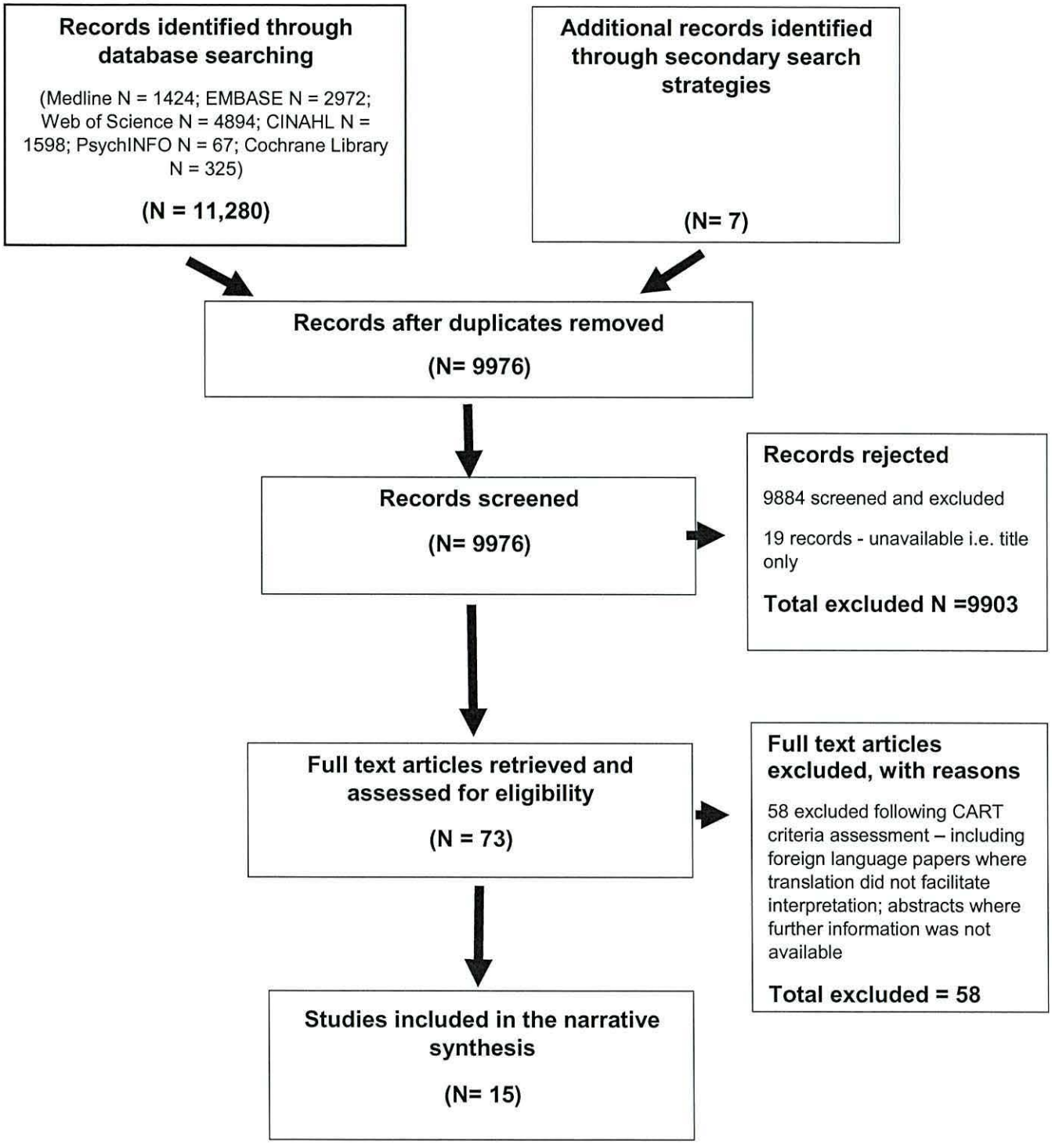

Figure 2-1: PRISMA flow diagram

A number of studies were excluded by the CART criteria. These included:

- Foreign language articles, where translation via Google translate services did not allow full interpretation of evidence due to the quality of the translation of the scientific content (N=5);
- Abstracts of interest, where attempts to contact authors failed (N=5); and
- Studies reporting the diagnosis of myeloma where either methods or relevance to early diagnosis did not allow full reporting e.g. case study reports.

No studies were excluded based on quality alone.

2.4.1 Summary of included data

Fifteen studies fulfilled the inclusion criteria and were included for synthesis (Table 2-2). Included studies were published between 1995 and 2015. The majority of studies (12/15) were undertaken in the United Kingdom; the remainder were from the United States, China and the Netherlands. Heterogeneity was seen for both study design and reported outcomes. Database or registry data collection formed the largest category of studies (Abel et al., 2015; Din et al., 2015; Elliss-Brookes et al., 2012; Howell et al., 2013; Lyratzopoulos et al.; 2013, Lyratzopopulos et al., 2015a; Neal et al., 2014; Ong et al., 1995; Shephard et al., 2015). The Howell et al. (2013) study added to registry dated by the inclusion of a recruited cohort of participants to a survey study, where questions relating to symptoms and help-seeking behaviour were collected. Survey data were accessed from The National Patient Experience Survey audit (Keeble et al., 2014; Lyratzopoulos et al., 2012) or directly through surveys to participants (Howell et al., 2015). The remaining studies used either hospital records, reviewed retrospectively (Kariyawasan et al., 2007; Li et al., 2012), or review of medical insurance claims for a myeloma diagnosis (Friese et al., 2009). The population of myeloma cases analysed within individual studies varied from 59 to 11,221 cases. All outcomes reported in the 15 studies were considered in the process of theme development for synthesis.

2.4.2 Quality appraisal for synthesised studies

The MMAT was not easily applied to the range of studies included in synthesis. The anticipated methodological variations (Dalziel et al., 2005) made application of the tool

variable in its ability to assess and interpret quality. Due to the difficulty in the tools application, and the plan to not exclude studies based on quality assessment, a decision was made by the reviewers to analyse each section of the tool against all 15 synthesised studies, category by category. This principally allowed the description of quality and an appreciation of the variance of quality between studies. An additional 'interpretive assessment' by the reviewers was added which consisted of discussion between the two reviewers of their opinion of how fully the study answered the research questions. This was considered to not be out of keeping with the scoping methods of the review (Gough et al., 2015), and as no study was to be excluded based on quality, it was an exercise aimed at providing greater assessment of the quality of studies. It was accepted that this was a pragmatic approach that would be complementary to the formal assessment of quality.

The reviewer's interpretation of quality was seen to be in conflict with the MMAT in two areas of quality appraisal. Older studies, the reviewers judged, were generally found to be of poorer methodological design and rigour, with transparency in reporting not adequately made. It was found that the MMAT did not highlight these variances, with the majority of studies being judged at a similar level of quality. In studies where a number of cancer types were analysed collectively, the reviewer's assessment found that in the reporting of the collective group of cancers studied, individual cancer type relevance against reported recommendations was lost, as most of the recommendations and some outcomes were reported as a collective group. This was not highlighted by the MMAT, but did limit relevance of evidence for the review.

The assessment with the MMAT reported no study was 'poor' in quality; three studies were assessed as 'good' (Din et al., 2015; Howell et al., 2013; Shephard et al., 2015), with the remaining studies assessed as 'moderate' (full MMAT assessment is detailed in Appendix 3).

Table 2-2: Characteristics of synthesised studies

Study: author/year of publication/ location	**Study methods and aims**	**Study period**	**Study population: Number myeloma cases reported in study**	**Quality assessment: Good (G), Moderate (M), Poor (P)**
Abel et al., 2015. UK	Secondary analysis of data collected for 'Routes to Diagnosis' project (HES (Hospital Episodes Statistics)) and linked data from Cancer Waiting Times and Cancer Screening Programmes and Cancer Registration data for 27 cancers. Crude proportions and crude and adjusted ratios calculated for emergency presentation; interactions between sex, age and deprivation.	2006-2010	6693	M
Din et al., 2015. UK	Analysis of CPRD data routinely collected in primary care for 15 cancers. Analysis of the relationship of the diagnostic interval and the predictors: age, gender and symptom type.	2007-2010	1158	G
Elliss-Brookes et al., 2012. UK	Routinely collected data from HES data and linked data from Cancer Waiting Times and Cancer Screening Programmes and Cancer Registration data for 15 cancers. Analysis of the relationship between routes to diagnosis and survival.	2006-2008	11221	M
Friese et al., 2009. USA	Review of MEDICARE insurance claims data, Parts A and B for myeloma diagnosis and linked to tumour registries in the Surveillance and Epidemiology and End Results Programme. Calculation of the interval between initial visits for anaemia and back pain and myeloma diagnosis and assessment of the predictors for delay.	1992 - 2002	5483	M

Howell et al., 2013. UK	Analysis of routinely collected data via a research registry and additional consent to collect, via survey from patients, parameters relating to help-seeking symptoms and circumstances of diagnosis in 19 haematological cancers.	2004 – 2011	152	G
Howell et al., 2015. UK	Analysis of survey data collected from patient participants relating to symptoms and barriers to help-seeking for 5 haematological cancer groups.	2010-2010	150	M
Kariyawasan et al., 2007. UK	Analysis of routinely collected hospital records for a secondary care myeloma clinic, to examine and analyse the causes and consequences of delay in the diagnosis of myeloma.	2001-2006	103	M
Keeble et al., 2014. UK	Analysis of primary care data collected from patient records from GPs or other health professionals as part of the National Audit of Cancer Diagnosis in Primary Care. Variations in the promptness of presentation were assessed for 18 different subsequent cancer diagnoses.	2009-2010	127	M
Li et al., 2012. China	Review of single institute hospital records for myeloma patients. Analysis of routes of presentation via nephrologist or haematologist and the causes of a delayed diagnosis and raise in level of early diagnosis of atypical myeloma.	1999-2007	Total 109 Group 1: 29 Group 2: 62	M
Lyratzopoulos et al., 2012. UK	Analysis of data collected as part of the National Cancer Patient Experience in England with 24 different cancers. Variations in the number of GP consultations with cancer symptoms prior to hospital referral were examined. Assessment for three or more consultations adjusted for age, sex, deprivation quintile and ethnicity.	2010	1854	M

Lyratzopoulos et al., 2013. UK	Analysis of data collected for the National Audit of Cancer Diagnosis in primary care for 18 cancers. The association between interval from first symptomatic presentation to specialist referral (primary care interval) and the number of pre-referral consultations.	2009-2010	176	M
Lyratzopoulos et al., 2015b. UK	Analysis of data from the National Audit of Cancer Diagnosis in Primary care for 28 cancers. Measurement of the patient and primary care intervals and their ratio.	2009-2010	124	M
Neal et al.,2014. UK	Analysis of data from the GPRD for 15 cancers. Assessment of routine collected data to examine cancer diagnostic intervals before and after the implementation of the 2005 NICE referral guidelines for suspected cancer.	Cohort 1 2001-2002 Cohort 2 2007-2008	Cohort 1: 582 Cohort 2: 780	M
Ong et al., 1995. Netherlands	Analysis of medical histories collected from a population-based registry serving 15 hospitals within the Comprehensive Cancer Centre West. Comparison of two groups of participants, a delayed group (where myeloma was not in a differential diagnosis) with a group where the diagnosis was made immediately, with the examination of the differences in presentation.	1991 and 1993	127	M
Shephard et al., 2015. UK	Analysis of patient records from GPRD for patients aged over 40 with a diagnosis of myeloma with a control cohort. Qualification and quantification of the risk of myeloma from specific clinical features reported in primary care.	2000-2009	2730	G

2.4.3 Interpretive synthesis

Homogeneity in clustered data was examined to assess the ability to perform meta-analysis. Included studies displayed little homogeneity of outcomes; no randomised controlled trails were included for synthesis and studies did not look to primarily answer a clinical effectiveness question. Meta-analysis was therefore not carried out.

2.5 Themes of evidence

Five themes were developed from the clustered and ordered data.

2.5.1 Theme 1: Length of the intervals to diagnosis in myeloma and comparison with other cancer types measured

Time intervals to diagnosis measured were identified in line with the Aarhus statement (Weller et al., 2012 Figure 1-3), unless otherwise stated. Nine studies reported at least one interval to diagnosis for myeloma; these are listed in Figure 2-2 and 2-3 (Appendix 4 Table 1).

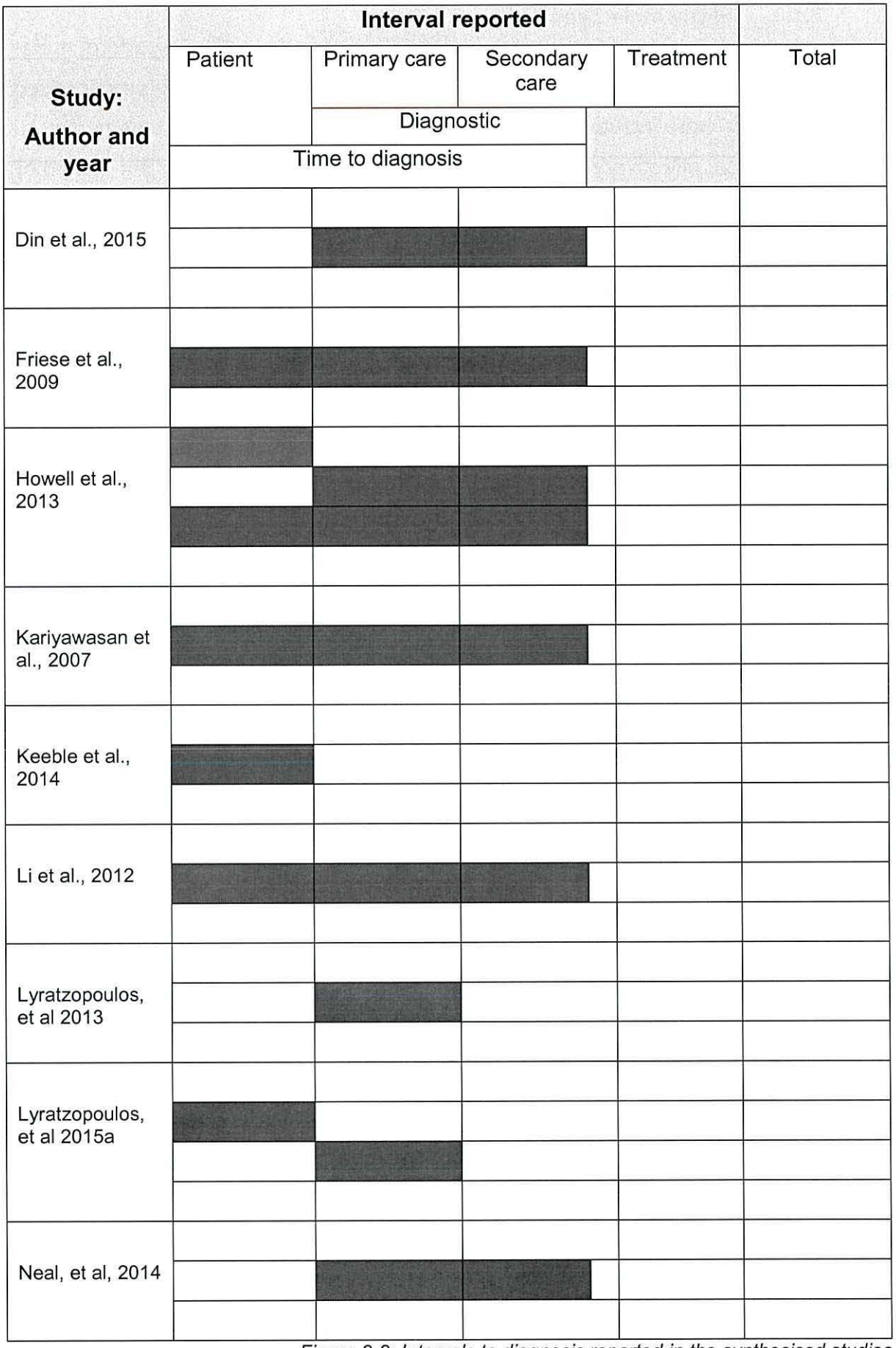

Figure 2-2: Intervals to diagnosis reported in the synthesised studies

Author and year of publication	Interval	Median (days)	IQR (days)	90th Centile (days)
Howell et al., 2013	Patient	31	1-122	NR*
Keeble et al., 2014	Patient	14	0 - 40	95
Lyratzopoulos, et al 2015	Patient	13.5	0 - 31	93
Lyratzopoulos, et al 2013	Primary care	21	5 – 55	NR*
Lyratzopoulos, et al 2015a	Primary care	20.5	5 – 62	134
Din et al., 2015	Diagnostic	149	54 - 263	334
Howell et al., 2013	Diagnostic	83	34 -167	NR*
Neal, et al, 2014	Diagnostic	Cohort 1: 144 (Pre-NICE guidance)	56 - 264	325
		Cohort II: 156 (Post NICE guidelines)	59 - 273	336
Howell et al., 2013	Time to diagnosis	163	84 - 306	NR*
Friese et al., 2009*	Time to diagnosis†	99	27 - 526	NR*
Li et al., 2012*	Time to diagnosis†	Median = 6 months for Group 1 (Presented via Nephrologist) Median =0.5 months for Group II (Presented to haematologist)		
Kariyawasan et al., 2007*	Time to diagnosis†	Group 1 = 30% diagnosed within 3 months of the first symptom. Group 2 = 70% took > 3 months to diagnose 41% patients' journeys >6 months		

Figure 2-3: Intervals to diagnosis reported in included studies

* not reported in line with the Aarhus statement (Weller et al., 2014)

2.5.1.1 The patient interval

The patient interval was reported by Keeble et al. (2014); Lyratzopoulos et al. (2015a); and Howell et al. (2013). The median patient intervals reported by Keeble et al. (2014) were 14 days and Lyratzopoulos et al. (2015a), 13.5 days, but a higher median was reported by Howell et al. (2013) of 31 days. A wider interquartile range was reported by Howell et al. (2013) of 1 -122 days, when compared with the other two studies: Keeble et al. (2014) reporting 0-40 days and Lyratzopoulos et al. (2015a) 0-31 days. Two studies, reported 90th percentiles, these were reported as Keeble et al. (2014) 95 days and Lyratzopoulos et al. (2015a) 93 days.

All three studies compared the median patient interval measured with other cancer types. Howell et al. (2013), reported that the patient interval in myeloma was above the median for a group of 19 haematological cancers. Keeble et al. (2014) and Lyratzopoulous et al. (2015a) reported mid-range median patient intervals for myeloma, when compared to 28 other cancer types.

Keeble et al. (2014) and Lyratzopoulos et al. (2015a) accessed the same dataset of participant information, the National Cancer Patient Experience Survey in England to make their calculations. Howell et al. (2013), calculated the patient interval start date from a symptom onset date in participant self-reported data. This shows that myeloma patient intervals are within the mid-range when compared to other cancer types. However, the measurement of the median and other intervals may be different when the methodological approach to the collection of symptom data is made from patient generated data. Evidence for the patient interval is limited.

2.5.1.2 The primary care interval

The primary care interval was reported by Lyratzopoulos et al. (2013) and Lyratzopoulos et al. (2015a). The median and interquartile ranges reported by Lyratzopoulos et al. (2013) were 21 days and 5-55 days respectively and Lyratzopoulos et al. (2015a) 20.5 days and 5-62 days. Lyratzopoulos et al. (2015a) additionally reported the 90th percentile at 134 days.

Lyratzopoulos, et al. (2013) reported primary care intervals were longest for myeloma when measured against 18 other cancer types, and Lyratzopoulos et al. (2015a) reported the intervals were the longest measured of the 28 other cancer types analysed.

The findings show that the primary care interval is longer for myeloma when compared to other cancer types. However, evidence for synthesis was limited to two studies.

2.5.1.3 The diagnostic interval

The diagnostic interval was reported by Din et al. (2015); Howell et al. (2013) and Neal et al. (2014). Neal et al. (2014) reported two separate cohort measurements within the same study, these were measured at different time periods before and after the implementation of the NICE referral guidance for suspected cancer (NICE, 2005). Medians reported by the authors were: Din et al. (2015) 149 days and Neal et al. (2014) cohort 1= 144 and cohort 2 = 156 days. Howell et al. (2013) reported a median significantly shorter of 83 days. Interquartile ranges reported showed a similar pattern of reporting: Din et al. (2015) reported a range of 54- 263 days and Neal et al. (2014) reported the two cohorts as cohort 1 = 56-264 and cohort 2 = 59-273 days. Howell et al. (2013) reported IQR as 34-167 days. The 90th percentile was reported in only two studies: Din et al. (2015) 334 days and Neal et al. (2014), cohort 1 = 352 and cohort 2 = 336.

All three studies compared diagnostic interval medians with other cancer types. Din, et al. (2015) and Neal et al. (2014), reported myeloma had the longest diagnostic intervals of the 15 cancer types analysed in their studies. Howell et al. (2013), reported that myeloma diagnostic interval ranked 7th out of 19 by length, when compared to 19 other haematological cancers. Howell, et al (2013) reported haematological malignancies which had longer diagnostic intervals than myeloma were the more indolent haematological cancers, such as myeloproliferative disease.

The two different time cohorts reported by Neal et al. (2014) reported the diagnostic interval for the myeloma group in the study was not shortened following the implementation of the NICE referral guidance (NICE, 2005) unlike the intervals measured for the other cancer types of kidney, head and neck, bladder, colorectal, oesophageal and pancreas.

Din et al. (2015) and Neal et al. (2014) reported diagnostic intervals from the same dataset with overlapping times periods which may account for the similar measurements reported.

The findings suggest that diagnostic intervals for myeloma are longer when compared with most other cancers. However, evidence for synthesis was limited.

2.5.1.4 Time to diagnosis interval

The time to diagnosis interval was reported by Friese et al. (2009); Howell et al. (2013); Kariyawasan, et al (2007) and Li et al. (2012). These four studies reported intervals in a variety of ways, both grouping and reporting in months or days (Karyawasan et al., 2007; Li et al., 2012) or, reporting medians and interquartile ranges (Friese, 2009; Howell et al., 2013). Where time to diagnosis was reported in days, Friese et al. (2009) reported a median of 99 days and Howell et al. (2013) reported a median of 163 days. Interquartile ranges reported by Friese et al. (2009) were 27– 526 days and Howell et al. (2013) 34 – 306 days. No 90th percentiles were reported in either study. The remaining studies reported intervals in months rather than days, with either percentages of participants in grouped intervals (Kariyawasan et al., 2009), or percentages of participants based on a referral pathway (direct referral to haematology or via nephrologist for Li et al. (2012)). Kariyawasan et al. (2007) reported 70% of participants were referred via an indirect route to haematology and took longer than three months to be diagnosed, with 41% of this group taking longer than six months to achieve a diagnosis. Li et al. (2012) reported a median of six months when referrals were made to a nephrologist first, comparing this to direct referrals to haematology where the median was 0.5 months.

Howell et al. (2013) compared time to diagnosis in myeloma with other haematological cancers. The myeloma interval was ranked 8th out of 19 by length, with indolent haematological cancers measuring longer intervals.

The cluster of studies reporting the time to diagnosis interval in myeloma contained studies with older publication dates. These studies were not seen to be compliant with the Aarhus statement (Weller et al., 2012). In this cluster, only one study reported time to diagnosis in line with the statement. This meant there were difficulties interpreting the start and end dates of the intervals, due to the way the measurements were reported i.e. months. This limited the ability to synthesise the intervals reported. The Friese et al. (2009) study defined time to diagnosis using Medicare data claims, which relied on patients surviving at least six months following a diagnosis in order to evaluate pathways. Given the known high proportion of early deaths (within 60 days of diagnosis) associated with the disease (Augusten et al.,

2005), there was a likely loss of these participants due to premature death. The Friese, et al (2009) study additionally defined the study period as commencing one year prior to the date of diagnosis. The inclusion of symptoms present or claimed before this period was excluded from analysis and is a potential loss of data. The Friese et al. (2009) study, also, identified a population of 8,735 eligible patients, with over one third being excluded from analysis (N= 2952). Two studies made analysis from retrospective reviews of hospital records (Kariyawasan et al., 2009; Li et al., 2012), which possibly reduced the ability to calculate accurate time to diagnosis intervals and inform synthesis. The study reporting the longest time to diagnosis intervals in days (Howell et al., 2013) used participant-reported symptom onset date to commence the calculation of the interval. A longer measurement of the interval was recorded with a methodological approach of this type.

These findings do not allow the complete assessment of this interval; comparability of studies is limited by heterogeneity of outcomes, interval reporting and methodological rigour.

2.5.1.5 Intervals not reported

No study reported the secondary care interval, the treatment interval or the total interval for myeloma. However, the Li et al. (2012) study did focus on secondary care presentation associated with in direct referral routes to haematology, but it did not measure the specific secondary care interval.

2.5.2 Theme 2: Symptoms experienced by myeloma participants

Seven studies reported symptoms experienced by myeloma participants (Din et al., 2015; Friese et al., 2009; Howell et al., 2013; Howell et al., 2015; Kariyawasan et al., 2007; Ong, et al; 1995; Shephard et al., 2015). (Appendix 4 Table 2).

This was a largely evidenced theme but there was heterogeneity in study design and reported outcomes. The heterogeneity in this group was greater than any other themed group in the review and this possibly reflects the difficulty and nuances of the disease, its diagnosis and the difficulty capturing the subjective understanding of symptoms for research evaluation (Chapter One section 1.6.1).

2.5.2.1 Study design

Din et al. (2015); Howell et al. (2013); Ong et al. (1995) and Shephard et al. (2015) reported from primary care or registry databases. Howell et al. (2013) and Howell et al. (2015), collected survey data from participates to provide self-reported symptom

data. Friese et al. (2009) and Kariyawasan et al. (2007) used routinely collected secondary care data, which as a method of collecting symptom data is considered helpful when validating other data gained from different sources, but is said to lack strength as a primary data source (Weller et al., 2012). This was considered in synthesising data and an intention was made to prioritise evidence from studies using registry database data or self-reported symptoms data. However, evidence was so limited that the evidence reported from these retrospective secondary care analysis data was seen to remain quite influential in synthesis

2.5.2.2 Subsets of the themes

2.5.2.3 Absence of symptoms

Howell et al. (2013); Howell et al. (2015); Ong et al. (1995), reported the number of participants diagnosed with myeloma in the absence of symptoms. Percentages across the studies varied and were reported as 21%, 31%, and 12% respectively. Studies using surveys to collect self-reported symptoms data (Howell et al., 2013; Howell et al., 2015) reported higher percentages of the 'no symptoms' groups. However, between the two studies reporting from self-reported symptoms data, there was a difference of 10%. Why the variance in reporting occurred is unclear in the evidence reported.

2.5.2.4 Symptoms experienced prior to diagnosis

Friese et al. (2009); Howell et al. (2013); Howell et al. (2015); Kariyawasan et al., (2007) and Shephard et al. (2015) reported the type of symptoms experienced prior to the diagnosis of myeloma. The clarity of pain-reporting in the included studies did not allow appreciation of whether the percentages given for symptoms related to a single symptom or part of a grouped number of symptoms. Additionally, the categories of symptoms reported were varied across studies. These factors made synthesis difficult. To best display the symptoms reported in myeloma patients prior to diagnosis, the symptoms reported were clustered into groups based on the frequency of occurrence reported across the studies i.e. most frequently reported, and synthesis was conducted through these groupings.

Pain was the most frequently reported symptom in all studies. Four out of the five studies reported pain in more than half the study population (Friese et al., 2009; Howell et al., 2013; Howell. et al. 2015; Kariyawasan et al., 2007). Three studies further defined pain by location. Friese et al. (2009) reported back pain in 50% of the

population of patients. Howell et al. (2015) reported 77% of participants had pain symptoms more generally, but qualified this to pain/discomfort in bones in 73% of the wider pain group. Kariyawasan et al. (2007) reported bone pain in 67% of participants with de novo (newly presented, not progressed from a previously diagnosed condition such as MGUS) diagnoses.

Table 2-3: Symptoms reported prior to the diagnosis of myeloma

Study author and year	Most frequently reported symptom	Second most frequently reported symptom	Third most frequently reported symptom	Fourth most frequently reported symptom	Fifth most frequently reported symptom	Sixth most frequently reported symptom	Seventh most frequently reported symptom
Friese et al. (2009)	Back pain	Anaemia	NR	NR	NR	NR	NR
Howell et al. (2013)	Pain	Fatigue	Joint problems/fractures	Itching/rash	Infection	Stomach/bowel problems	Other
Howell, et al (2015)	Pain symptoms – pain or discomfort in bones	Systemic symptoms – extreme fatigue or tiredness	Chest +symptoms – shortness of breath	Bleeding symptoms	Lump	Other symptoms	
Kariyawasan et al. (2007)	Bone pain	Asthenia	Fatigue	Dyspnoea	Weight loss	NR	NR
Shephard et al. (2015)	Back pain	Chest pain	Chest infection	Shortness of breath	Nausea	Fracture	Joint pain

NR= not reported

Fatigue, or reports of systemic symptoms, was the second most frequently reported symptom group. However, this was only reported in two of the six studies (Howell et al., 2013 and Howell et al., 2015). The studies reporting fatigue were studies where self-reported participant data had been collected and analysed. Beyond these two clustered groups, reporting was too diverse to make any synthesis.

Although Howell et al. (2013) and Howell et al. (2015) specifically reported symptoms in the pre-diagnostic phase of myeloma, the authors did not make any analysis of whether these symptoms had an effect on the help-seeking behaviour or the patient interval.

No studies reported symptoms in the context of the length of intervals to diagnosis i.e. patients with these symptoms, number or type, had longer or shorter journeys. The relevance of the symptoms reported and the intervals to diagnosis was not apparent in the evidence.

These findings are able to establish that pain is the most frequently reported symptom prior to the diagnosis of myeloma. However, the characterisation of pain was so varied across the studies that conclusions could not be definitively made about the location or type of pain most experienced in myeloma patients prior to a diagnosis. Fatigue was the second most frequently reported symptom across the studies, but this was not conclusively shown and beyond this second group of symptoms evidence was too varied to draw further conclusions about which type of symptoms are most frequently seen prior to a diagnosis of myeloma. Whilst there was a larger group of studies representing this clustered group within the 'symptom' theme, the heterogeneity of reporting outcomes is too limiting to make synthesis capable.

2.5.2.5 Symptoms and NICE referral guidance

Din et al. (2015) and Howell et al. (2013), reported symptoms and how they related to the NICE referral guidance for suspected cancer (NICE, 2005). Howell et al. (2013) reported that 10% of myeloma patients reported symptoms that were not listed within the NICE guidance, and Din et al. (2015) reported that myeloma diagnostic intervals saw non-association between non-NICE symptoms and longer diagnostic journeys. This was in contrast to 10 of the 15 cancer types analysed, where an association was seen for non-NICE symptoms and longer diagnostic

intervals. When all cancer types were pooled there was strong evidence reported of increased intervals in non-NICE symptoms.

These findings were unable to form a consensus about an association of NICE or non-NICE symptoms and the journey to diagnosis in myeloma. There appeared to be a relatively low level of non-NICE symptoms reported by Howell et al. (2013) in myeloma, which would not be in-keeping with the difficult diagnostic processes and longer primary care and diagnostic intervals reported. However, evidence is too limited to confirm this.

2.5.2.6 Predictive value of symptoms

The positive predictive value (PPV) of symptoms was reported by Shephard et al. (2015). Single or paired symptoms were reported to have a low PPV. Abnormal clinical investigations such as hypercalcaemia and leukopenia had a higher PPV. Hypercalcaemia with skeletal pain or fracture had a PPV of 10%. Leukopenia and fracture or nosebleeds also had a PPV of 10%.

No synthesis with other studies was possible. The limited findings show that myeloma is not likely to be identified from a single symptom and even combined symptoms have a limited predictive value. However, symptom evaluation alongside some clinical abnormalities has a stronger PPV.

2.5.2.7 Synthesis of the themed evidence

Overall the studies synthesised reported symptoms collected retrospectively, with some analysed data being from historically collected, not intended for research purposes (Friese et al., 2009; Kariyawasan et al., 2007). Kariyawasan et al. (2007). These data, collected at diagnosis by secondary care clinicians, relied on details being accurately and comprehensively collected at the diagnosis of the disease and are likely to be affected by recall bias. Only two studies (Howell et al., 2013; Howell et al., 2015) collected self-reported symptom data from participants; the vast majority of data, therefore, being generated from databases (Din et al., 2015; Ong et al., 1995; Shephard et al., 2015) or national survey data (Friese et al., 2009). The collection of data through database-held information could potentially lessen the relevance of data used in the synthesis due to the methodological limitations discussed above.

Overall synthesis of symptom data is restricted due to the diversity of outcomes measured and particular clustered outcomes being supported by minimal data. The

findings support that pain is the most frequent symptom but that there is a wide range of other symptoms additionally reported in myeloma patients. The findings also support that there is a proportion of patients who receive a diagnosis of myeloma without experiencing symptoms. Whether these patients are patients who have an earlier diagnosis of MGUS or asymptomatic myeloma and have progressed and been identified through surveillance, or whether these are patients who have received an earlier diagnosis of the disease is not clear.

2.5.3 Theme 3: How and where myeloma patients first present

Five studies reported the ways in which myeloma patients present for a diagnosis (Elliss-Brookes et al., 2012; Friese et al., 2009; Kariyawasan et al., 2007; Li et al., 2012; Lyratzopoulos et al., 2012) (Appendix 4 Table 3). The outcomes measured in the studies were varied and within the clustered themes, further subdivision for synthesis was necessary and demonstrated the complexity and diversity of access to healthcare for myeloma patients.

2.5.3.1 Primary care consultations

Friese et al. (2009); Kariyawasan et al. (2007) and Lyratzopoulos et al. (2012) reported aspects of primary care presentation. The outcomes measured across these studies were very varied. Friese et al. (2009), reported shorter time to diagnosis intervals when diagnosis was made during an inpatient stay. Kariyawasan et al. (2007) reported delays in the referral onto specialist care were associated with longer time to diagnosis intervals. Kariyawasan et al. (2007) descriptively reported the activity associated with longer time to diagnosis intervals and primary care consultation as: 65% of participants first presenting to a GP had a time to diagnosis interval of greater than six months.

Primary care consultations, were quantified and compared to other cancer types by Lyratzopoulos et al. (2012). Half of the myeloma population in this study, were reported to have three or more consultations before referral to specialist care. The number of consultations reported in the myeloma group were the highest for all 24 cancer types analysed.

The synthesised evidence shows increased consultation of the myeloma patient in primary care prior to presentation in secondary care.

2.5.3.2 Secondary care presentation

Elliss-Brookes et al. (2012); Kariyawasan et al. (2007) and Li et al. (2012), reported the type of presentation and variations of myeloma patients to specialist care. Li et al. (2012) reported referral to nephrology, compared to haematology, resulted in increased time to diagnosis intervals.

Elliss-Brookes et al. (2012) reported 37% of myeloma patients were diagnosed through an emergency presentation to secondary care, with myeloma being ranked fourth highest of the 15 cancer types studied. This study additionally reported a low-level use of the 'Two Week Urgent Suspected Cancer' (TWW) referral route for myeloma patients at 11%, compared to 43% for breast, 30% for bladder and 27% for colorectal cancers. Myeloma and pancreatic cancers had the second lowest reported use of the TWW referral.

Kariyawasan et al. (2007), reported 11 different referral routes into secondary care for the 103 myeloma participants in the study. More recognisable routes of GP referral and Accident and Emergency presentation were recorded, as well as less obvious routes, such a neurology. The diversity of these referral patterns suggests a haematological diagnosis was not suspected at referral to specialist care. Kariyawasan, et al. (2007) reported the longest intervals (greater than six months) were associated with GP, nephrology and orthopaedic referral.

These findings show the method of entry to specialist care for the myeloma patient is associated with longer intervals to diagnosis and affected by route, referral method and team. The direct referral to haematology is the optimal route but relies on suspicion of myeloma in primary care to ensure optimal pathway into secondary care for a timelier diagnosis.

2.5.3.3 Overall synthesis of the themed group

The overall findings for the theme were limited by study design, heterogeneity of outcomes and quality of data. Some studies benefited from larger cohort numbers (Elliss-Brookes et al., 2012; Friese et al., 2009; Lyratzopoulos et al., 2012), but these studies used secondary data for analysis. The remainder of the studies used retrospective review of secondary care data records for analysis. These studies reported from smaller numbers of participant's (Kariyawasan et al., 2007; Li et al., 2012). Making recommendations for policy and practice from data limited and

collected in less-robust manners is not possible. The topic area of secondary care referral and pathway, however, is worthy of further exploration.

2.5.4 Theme 4: Associations of stage of disease, complications present at diagnosis and survival

Five studies reported one or more association of stage, complications at diagnosis and survival for myeloma participants (Elliss-Brookes et al., 2012; Friese et al., 2009; Kariyawasan et al., 2007; Li et al., 2012; Ong et al.,1995). Due to heterogeneity of study outcomes this theme was further defined through organisation of sub themes to allow better synthesis and interpretation (Appendix 4 Table 4)

2.5.4.1 Stage of disease and intervals to diagnosis

Kariyawasan et al. (2007) and Ong et al. (1995) reported associations between intervals to diagnosis and stage of disease. Both studies reported stage of disease using now obsolete criteria: The Durie Salmon Staging (Greipp et al., 2005). Kariyawasan et al. (2007) reported higher stage disease at diagnosis in participants with a time to diagnosis interval greater than six months. Ong et al. (1995), reported no increase in disease stage in groupings of participants considered delayed, due to a failure to include myeloma within an initial differential diagnosis. Ong et al. (1995) did not qualify the time to diagnosis interval, but reported grouped participants based on a differential diagnosis being made (immediate group) or not made (delayed group).

The evidence for synthesis of this subgroup cannot be compared due to heterogeneity of reported outcomes and is limited by the numbers of studies.

2.5.4.2 Complications at diagnosis of myeloma

Friese et al. (2009); Kariyawasan et al. (2007); Li et al. (2012) and Ong; et al. (1995) reported associations between the diagnostic journey and the presence of complications of the disease at diagnosis in myeloma cases. Kariyawasan et al. (2007) reported complications were present in all participants whose time to diagnosis intervals were greater than six months; anaemia and bone disease were the most frequently recorded complications. Ong et al. (1995) reported higher levels of lytic bone lesions in the 'delayed' group of patients but reported other complications were present in the 'immediate' diagnosis group. Ong et al. (1995) suggested symptoms were more advanced in this 'immediate' group and more obvious because of the extent and burden of the disease. Li et al. (2012) reported participants with longer time to diagnosis intervals, due to an indirect referral to

haematology, had lower levels of bone complications but higher levels of raised serum calcium, renal failure, and proteinuria. Friese et al. (2009) reported predictors for complications in participants diagnosed as inpatients who had increased inpatient care measured by MEDICARE claims in the year preceding a diagnosis. These participants were also reported to require chemotherapy within six months of diagnoses suggesting a higher burden of disease was present at diagnosis.

Although synthesis was made difficult due to the heterogeneity of the outcomes, the findings show that higher complications exist at the diagnosis of myeloma for participants who had longer journeys or delayed identification of diagnoses.

2.5.4.3 Survival

Kariyawasan et al. (2007) and Elliss-Brookes et al. (2012) reported survival differences in relation to either the length of intervals or pathways followed. Kariyawasan et al. (2007) reported disease-free progression was reduced in patients with longer time to diagnosis intervals, but overall survival was unaffected. Elliss-Brookes et al. (2012) reported relative one-year survival in myeloma was reduced in patients whose diagnosis was made following an emergency presentation to secondary care.

The synthesis was limited in evidence. However, the findings show a reduction in disease-free survival for patients with longer time to diagnosis intervals. Additionally, the findings show an association between decreased overall survival for participants' whose diagnoses are made through an emergency presentation.

2.5.5 Theme 5: Factors associated with processes and intervals to diagnosis

This theme was generated from multiple sets of clustered data, relating to evidence for the factors which influenced the diagnostic journey in myeloma. Clustered data was varied, making the theme complex (extracted data, where possible, is visually displayed in Appendix 4 Tables 5-12)

2.5.5.1 Multi-morbidities

Friese et al. (2009) and Ong et al. (1995) reported associations of multi-morbidity. Friese et al. (2009) reported patients with one or more morbid features had a positive predictor for being in a "delayed diagnostic group"; (greater than six months) and Ong et al. (1995) reported the presence of multi-morbid factors was significantly higher in the 'delayed differential diagnosis' group.

Friese et al. (2009) measured multi-morbidities from MEDICARE claims but restricted this to the presence of anaemia, the recording of packed red cell blood (PRBC) transfusion and back pain. This limited analysis, as there was no consideration of claims for a wider grouping of conditions such as diabetes, cardiovascular disease or arthritis. Additionally, patients with claims for end-stage renal disease and disability were excluded from the study. There was a potential, therefore, that the contribution of multi-morbidities in these cases was lost. In the collection of symptom information related to any other conditions unrelated to myeloma, Ong et al. (1995) reported a higher number of patients in the delayed group had recorded 'other symptoms'. This was not further qualified or quantified.

Whilst these data were limited and methodological issues exist, the synthesis suggests there is an association between multi-morbid features and longer time to diagnosis intervals. However, neither study offers an understanding of how the multi-morbidities affects the intervals i.e. the way the multi-morbidities affects appraisal of symptoms in the patient or GP, or offer an understanding of the significance of individual multi-morbidities i.e. greater significance of diabetes and longer intervals. A greater understanding of the effect of multi-morbidity in the diagnosis of myeloma is required.

2.5.5.2 **Age**

Abel et al. (2015); Din et al. (2015); Friese et al. (2009); Howell et al. (2013); Keeble et al. (2014) and Ong et al. (1995) reported associations of age and the processes or intervals to a diagnosis of myeloma. Abel; et al. (2015) and Din et al. (2015) specifically reported the assessment of age as a planned outcome and gave full and detailed descriptions of the methods and statistical analysis. Din et al. (2015) reported no association of age with longer diagnostic intervals, and Ong et al. (1995) reported no association of age and myeloma being in an initial differential diagnosis. Friese et al. (2009); Howell et al. (2013) and Keeble et al. (2014) reported associations with age for subsets of patients with myeloma. Friese, at al. (2009) and Howell et al. (2013) reported older patients were associated with longer time to diagnosis intervals, whilst Keeble et al. (2014) reported younger patients were associated with shorter patient intervals.

Abel et al. (2015) reported an association of age increasing the risk of presenting as an emergency for a diagnosis of myeloma.

Three included studies reported the influence of age in multiple cancer types (Elliss-Brookes et al., 2012; Lyratzopoulos et al., 2012; Lyratzopoulos et al., 2013) which included an assessment of myeloma cases. Reporting in these studies were made for all cancer types analysed with no separate reporting of the myeloma group, and could not, therefore, be included in the synthesis.

The findings from synthesis supports that for certain subsets of the myeloma population, age is associated with longer or shorter intervals to diagnosis or emergency presentation.

2.5.5.3 Gender

Abel et al. (2015); Din et al. (2015); Friese et al. (2009) and Ong, (1995) reported associations between gender and diagnostic processes in myeloma. Friese et al. (2009) reported associations between longer time to diagnosis intervals and women. Din et al. (2015) and Ong et al. (1995) reported no associations between gender and diagnostic interval or being within a delayed group for diagnosis whilst Abel et al. (2015) reported no association of age and a risk of emergency presentation for a diagnosis of myeloma.

Two studies (Howell et al., 2013; Lyratzopoulos et al., 2012) reported results of gender and diagnostic journey associations but these were reported for all cancer types analysed, and synthesis and relevance to myeloma were not specifically made.

The synthesis shows gender differences appear not to be associated with diagnostic processes or length in myeloma.

2.5.5.4 Ethnicity

Friese et al. (2009) reported the association of longer journeys for non–white ethnic groups. Outcomes were crudely reported with no breakdown of ethnic groups and provided only rudimentary data on the influence of ethnicity.

Two additional studies reported the association of ethnicity on the myeloma patients' journeys within their studies (Howell, et al 2015; Lyratzopoulos et al., 2013). The influence of ethnicity was reported for all cancer types studied and synthesis for the review could not be made.

No synthesis of evidence was possible as only one study was identified and reported outcomes were not interpretable.

2.5.5.5 Deprivation

A positive association was reported by Abel et al. (2015) for the most deprived groups and an increased risk of presentation as an emergency prior to the diagnosis of myeloma, which was in keeping with the majority of other cancer types studied (24/27).

Synthesis was not possible, with deprivation association in myeloma reported in only one study.

2.5.5.6 Geographical association

Friese et al. (2009) reported findings related to geographical variations and diagnostic journeys in myeloma. In the narrative reporting of this study, the authors reported geographical variations were associated with longer time to diagnosis intervals. However, this was not substantiated by statistical evidence presented in the paper. This could potentially be a reporting error not picked up on peer or editorial review. The relevance of findings, due to the reporting error found, were not considered further for this review.

2.5.5.7 Diagnostic workup

Friese et al. (2009) and Ong et al. (1995) reported associations between the completeness of the diagnostic workup and the subsequent diagnosis of myeloma. These two studies had no homogeneity in the reported findings. Friese et al. (2009) reported less than a quarter of patients had a complete diagnostic workup recorded. Half of the cases had a claim for protein electrophoresis of urine or serum, 37% a recorded a claim for bone marrow biopsy (BM) and 42% a recorded claim for a bone scan or skeletal survey. Friese et al. (2009), additionally, reported patients who had electrophoresis and BM biopsy completed were significantly less likely to suffer a complication of the disease at diagnosis. Ong et al. (1995) reported on the reassessment of diagnostic testing for the study population 134/945 had an incomplete assessment and reported this to have a positive association for a missed diagnosis. Ong et al. (1995) reported that these 134 patients were unable to have a diagnosis established on reanalysis of their diagnostic testing, due to incomplete sampling.

Neither study aimed to report the observation of diagnostic workup in the original study objectives. Both studies reported from retrospective review of secondary data.

The synthesis, though limited, points to an association with incomplete testing at diagnostic workup, resulting in missed diagnoses and a greater frequency of complications.

2.5.5.8 Barriers to help-seeking

Howell et al. (2015) reported a range of factors influencing help-seeking behaviour in myeloma and other haematological cancers. The most frequently reported barrier was 'failure to recognise symptoms as serious', which was reported in over a quarter of the study population (25.4%). Less frequently seen barriers were: 'too many other things to worry about' (5.1%); 'not wanting to waste the GP's time' (3.4%); 'being worried what the doctor may find' (3.4%); 'too busy to go to the doctors' (2.5%) and 'the doctor was too difficult to talk to' (1.7%).

This study collected participant reported data on help-seeking barriers to assess whether there were risk factors associated with time to presentation in myeloma and four other haematological cancers. The most frequently reported barrier of "Did not realise symptom was serious" was reported for all cancer types and relevance of an association in myeloma more limited.

No synthesis was available as a single study available and reporting does not allow relevance to myeloma diagnostic journeys to be interpreted.

2.6 Major recommendations from the 13 synthesised studies

All the synthesised studies made recommendations as a result of their findings (Appendix 4 Table 13). However, the majority of studies made recommendations based on the overall findings for the collective group of cancers studied (Abel et al., 2015; Din et al., 2015; Elliss- Brookes et al., 2012; Howell et al., 2013; Howell et al., 2015; Keeble et al., 2014; Lyratzopoulos et al., 2012; Lyratzopoulos et al., 2013; Lyratzopoulos et al., 2015b; Neal et al., 2014).

The synthesised recommendations were assessed for relevance to myeloma diagnosis and clustered into four main themes: methodological, policy, research and practice.

2.6.1 Methodological recommendations

Elliss-Brookes et al. (2012); Howell et al. (2013); Keeble et al. (2014) endorsed the use of routinely collected health service data, applied in an automated computerised fashion, to understand the differences in variations in diagnostic journeys for various cancer groups, including myeloma. These methods benefit from using routinely

collected data that pre-exists, requiring no specific data collection processes, and facilitate the analysis of large numbers of cases. Howell, et al (2013) and Keeble et al. (2014) endorsed methodology to capture symptoms and define the patient interval directly from patient-reported data. Howell et al. (2013) described survey data as useful to capture the patient experience, whilst Keeble et al. (2014) advocated the review of case information collected alongside interviews in order to capture the patient experience and context.

These findings support the analysis of large datasets, and are useful in the demonstration of the variations across cancer types. This may be facilitated through analysis of routinely collected health service data. However, where there is a need to demonstrate the complexity and assessment of symptoms, the impact of the presentation of myeloma patients or the calculation of the patient interval, the use of self-reported participant information is preferable.

2.6.2 Policy recommendations

Friese et al. (2009); Howell et al. (2013); Howell et al. (2015); Kariyawasan et al. (2007); Keeble et al. (2014); Lyratzopoulos et al. (2012); Lyratzopoulos et al. (2013); Lyratzopoulos et al. (2015a); Neal et al. (2014); Shephard et al. (2015) made recommendations for policy changes.

Friese et al. (2009) recommended the development of diagnostic investigation guidelines for the diagnostic workup of myeloma patients to ensure all cases receive complete diagnostic testing.

Raising public awareness of cancer and its symptoms was frequently discussed as a policy recommendation, but this was general to all cancer types and lacked specific direction in many of the studies (Howell et al., 2015; Kariyawasan et al., 2007; Keeble et al., 2014; Lyratzopoulos et al., 2013). Howell et al. (2015) and Keeble et al. (2014), did discuss more specifically the need for public awareness campaigns, but added cautionary notes for the need to monitor the usefulness and cost effectiveness of any campaign implemented.

Howell et al. (2013) and Shephard et al. (2015) recommended a review of the NICE referral guidelines (NICE, 2005) in order to improve myeloma suspicion, identification and onward referral to secondary care. Howell et al. (2013) advocated haematological cancers be classified individually, not as a collective group, and

Shephard et al. (2015) recommended that the positive predictor values reported for symptoms and clinical tests inform a revision of the guidance. Neal et al. (2014) made positive recommendations for the use of the NICE referral guidance, acknowledging an impact on diagnostic intervals saying even a modest reduction impacts stage and survival. This recommendation was made for all cancer types, despite myeloma diagnostic intervals demonstrating no reduction following the implementation of the guidance.

Lyratzopoulos et al. (2012) and Lyratzopoulos et al. (2013) advocated system redesigns to allow more appropriate and timely use of specialist diagnostic tests to reduce the diagnostic interval. Lyratzopoulos et al. (2013) recommended a more liberal referral and investigation policy for cancer with non-specific symptoms, difficulties in suspecting or those which have longer primary care intervals. Although these recommendations were made more generally for all cancer types, other evidence in the review shows myeloma diagnosis to be associated with these nuances. It was cautioned by authors that a balance is required between the distress caused by increased investigation activity, and the resource needed to be respond to this demand and the benefit of earlier diagnosis. Neal et al. (2014) also highlighted associations of soft symptoms adversely affecting the diagnostic journey through a failure of the patients with these symptoms to fall into fast track criteria. Awareness of soft symptoms for certain cancer groups was recommended by the authors. Lyratzopoulos et al. (2015a) recommendations were for optimisation of community-based healthcare systems that would look to address those associations of longer primary care intervals contributing to the diagnostic pathway.

The findings from synthesis are limited as most recommendations are made for all cancer types studied and evidence for some recommendations limited. However, relevance for myeloma may be considered when recommendations made are based on associations reported elsewhere in this review specifically for myeloma, such as non-specific symptoms and longer primary care intervals. The findings support a need for better awareness of myeloma to help with the identification of symptoms in the patient group. The lowering of diagnostic thresholds and access to diagnostic testing supported through primary care initiatives, but specifics of these initiatives are not given. Recommendations for the updating of the NICE referral guidance for urgent suspected cancer were made (NICE, 2005) and these have been completed

with new guidance issued in 2015, which include a more detailed description of haematological malignancies and diagnostic testing in primary care recommendations (NICE, 2015). Recommendations for guidelines in diagnostic workup have similarly been developed since the recommendations were made and guidelines are now in place (Bird et al., 2011).

2.6.3 Research recommendations

Din et al. (2014); Friese et al. (2009); Howell et al. (2015); Kariyawasan et al. (2007); Lyratzopoulos et al. (2012) and Lyratzopoulos et al. (2013) made research recommendations but these were varied and diverse. Further research was recommended in particular population groups. Din et al. (2015) endorsed more research into variances related to age and gender. Keeble, et al (2014) advocated widening the population studied in the patient interval, and Lyratzopoulos et al. (2012) recommended further study of diagnostic delay in women and younger patients and ethnic minority groups. These recommendations related to all cancer types studied and relevance to myeloma and the ability to synthesise evidence was limited

Lyratzopoulos et al. (2012) and Lyratzopoulos et al. (2013) recommended research which would inform policy developments. Lyratzopoulos et al. (2012) sanctioned research that further explores and assesses physician level of education, interventions, point of care decision aids, and risk calculators as diagnostic tests. Lyratzopoulos et al. (2013) endorsed this wider expansion of primary care be assessed continuously, encompassing assessment of diagnostic testing; point of care diagnostic technologies to assess the effect of reducing the number of pre-referral GP consultations.

Friese, et al (2009) generally recommended research that allows the assessment of the clinical impact of delay, which was further defined by advocating the assessment of delay on survival by Kariyawasan et al. (2007) and Howell et al. (2013). Kariyawasan et al. (2007) also advocated the assessment of delay and consequences in larger cohorts of patients in future studies. Howell et al. (2015) called for the assessment of the relevance and association of individual subtypes and biological basis of individual cancers be considered in haematological malignancy.

Howell et al. (2015) recommended future research collaboration with primary care, where aims should be to identify mechanisms by which patients may be identified earlier, and referral routes made seamless.

The synthesis of evidence was made difficult by the diversity of the recommendations across the studies and the lack of recommendations specifically for myeloma. Overall these findings show a need for studies using larger populations and that assess the difficulties associated with the identification of myeloma in primary care. Additionally, the assessment of interventions to improve policy and practice changes require evaluation following implementation. There is a need to assess survival outcomes related to delay in the diagnostic journeys in myeloma.

2.6.4 Clinical practice recommendations

Abel et al. (2015); Din et al. (2015); Howell et al. (2013); Kariyawasan et al. (2007); Keeble et al. (2014); Li et al. (2012); Lyratzopoulos et al. (2012); Lyratzopoulos et al. (2013); Neal et al. (2014); Ong et al. (1995); Shephard et al. (2015) made recommendations for clinical practice developments. These recommendations for the improvement of practice were so varied in reporting clustering and displaying consensus across the evidence was difficult. Recommendations were made mostly for all cancer types studied and are interpreted for myeloma where evidence was given for associations of myeloma and the factors assessed.

The authors made recommendations for the improvement in the understanding of signs and symptoms of myeloma in primary care to improve suspicion and identification and reduce diagnostic delay. This was the largest of the clinical practice recommendation clusters (Din et al., 2015; Kariyawasan et al., 2007; Howell et al., 2015; Li et al., 2012; Keeble et al., 2014; Lyratzopoulos et al., 2012; Lyratzopoulos et al., 2013; Ong et al., 1995; Shephard et al., 2015). The more specific recommendations made were:

- Howell et al. (2015) recommended informing primary care practitioners of an absent 'symptom signature' in myeloma, to increase their surveillance of non-specific symptoms;
- Shephard et al. (2015) specified back pain/pain should prompt further investigation with clinical tests as this was likely to improve early detection;

- Li et al. (2012) recommended targeted areas for increasing understanding of symptoms and presentation of myeloma patients where non-direct referrals to haematology are made;
- Lyratzopoulos et al. (2013) recommended the use of decision making tools to improve and sensitise appraisal of symptoms by GPs;
- Lyratzopoulos et al. (2012) recommended increasing the awareness of a pattern of repeated consultation of myeloma patients in primary care to alert GPs of possible serious disease;
- Keeble et al. (2014) recommended GPs have increased vigilance based on the observed variations in presentations to help the development of interventions to aid the recognition of cancer;
- Abel et al. (2015) recommended knowledge transfer to GPs of the importance of sociodemographic influences and the risk of emergency presentation for a diagnosis of myeloma; and
- Li et al. (2012) and Ong et al. (1995) recommend emphasis on the importance of the diagnostic workup and laboratory investigations to promptly identify the clinical features of myeloma.

Overall findings show that the recommendations made mostly relate to the description of what needs to change rather than how to change.

2.7 Discussion

2.7.1 Summary of main findings

This is the first comprehensive review of the processes and time intervals in the diagnosis of myeloma. Importantly, this review demonstrates that the processes involved in diagnosing myeloma are complex, and intervals are longer than most other cancer types. In particular, the primary care interval in myeloma is the longest interval recorded when compared with all other cancer types. This implies that patients with myeloma experience symptoms, and present these symptoms to primary care, but that something relating to the type and nature of these symptoms hinders GPs in their prompt referral for specialist opinion or diagnostic evaluation. Hence, the design and evaluation of interventions aimed at reducing the primary care interval may be of value, if earlier stage diagnosis is to be achieved.

2.7.2 Discussion of the findings within the context of the literature

This review identified important areas of interest where evidence is limited. Behavioural aspects related to public awareness, appraisal of symptoms or help-seeking behaviour in myeloma were reported in only one study (Howell et al., 2015). Given significant interest in this area for other cancer types (Wardle et al., 2001; Whitaker et al., 2015a; Whitaker et al., 2015b; MacDonald et al., 2013), it is perhaps a failing that research into behavioural aspects of myeloma diagnosis is missing, and that more understanding in this area could inform timely diagnosis interventions. The influences of ethnicity and deprivation are insufficient to draw meaningful conclusions. The acknowledgement in the updated NAEDI hypothesis (Hiom, 2015) of the influence of ethnicity and deprivation affirms the importance of the assessment of these factors in the diagnosis of myeloma, and requires further investigation. Whilst slightly more evidence was available for the evaluation of emergency presentation, survival and stage of disease at diagnosis, interpretation of the combined meaning of studies is limited and is not reflective of the level of interest in other cancer types (McPhail et al., 2015).

Comparison of this systematic review with others in this field was limited as the reviews identified for myeloma more commonly evaluated treatment options and effectiveness in myeloma (Glassmacher et al., 2006; Koreth et al., 2007). Reviews that sought to understand the diagnostic processes of myeloma reviewed haematological cancer diagnoses together (Abel et al., 2008) and, therefore, were not specific to myeloma, which is clearly different in its presentation. The results for stage of disease and diagnostic intervals in this study were comparable to one other systematic review (Neal et al., 2015). Results from this review were comparable to in terms of stage of disease and intervals to diagnosis, but the scoping methods were able to identify one additional study.

2.7.3 Strengths and limitations

The main strength of this review is the use of systematic and robust reviewing methods (Gough et al., 2012; Gough et al., 2012a), allowing identification of all literature and theme development throughout the reviewing process. This has culminated in a rich and detailed description of the literature relating to diagnostic intervals and processes for myeloma, and contributes to a deeper understanding of the difficulties involved in its diagnosis.

The review was primarily conducted to inform the development of a national study exploring diagnostic journeys in myeloma. The review search was not updated once the study was in progress. It is therefore possible that there is now more recent literature that could inform this review, but this is not reported here. There are at least two studies that would be latterly included in synthesis (Abel et al., 2017; Lacey et al., 2016) and one awaiting publication (Howell et al., 2017) and future reporting of this chapter within a published paper would see an update of the search and inclusion of these relevant articles.

There were a number of conference abstracts identified that reported assessment of the difficulties diagnosing myeloma. Unfortunately, despite attempts to contact authors, no further information could be obtained. It is possible that there is more evidence available, but this evidence is unpublished and therefore not available for review.

The main limitation of the review is the quantity and quality of the included papers. Evidence is limited and there are gaps in knowledge. There was variation in the definition and reporting of the time to diagnosis interval and a complete absence of reporting the secondary care, treatment interval and total interval to treatment. Findings differed between studies reporting the patient interval, probably as a result of different methodological approaches. There was no exclusion date added to the search and inclusion criteria. This was intentional and related to the small body of evidence anticipated. This resulted in the inclusion of older studies, where methods were less rigorous.

2.8 The implications for policy, practice and research

2.8.1 Policy

Based upon this review, there are relatively few recommendations for policy, as more research is needed to inform policy developments.

2.8.2 Practice

There are several implications for clinical practice. Clinicians need to be aware that myeloma is 'hard to diagnose' and that time intervals in myeloma diagnosis are long compared with other cancers. However, patients with myeloma do have symptoms and do present these symptoms, so there are opportunities for diagnostic activity that may lead to timelier diagnosis. In particular, patients presenting with pain and

systemic-type symptoms probably warrant investigations to exclude myeloma (or other serious conditions), or refer for a specialist opinion.

2.8.3 Research

There is a clear need for more research to better understand symptoms in the pre-diagnostic stage, the complete and relative contributions of time intervals across the diagnostic journey; influences over diagnostic processes and the development; and evaluation of interventions to reduce time intervals, especially the primary care interval. Such studies need a strong theoretical underpinning and use high-quality methods, including self-reported participant symptom data. Qualitative work is needed to understand patients' perceptions and the role of clinicians in the diagnostic process. The general lack of evidence and age of many of the included studies supports the need to investigate and invest in further research to improve the long intervals measured. The lack of heterogeneity in the study designs and outcomes demonstrate a need for a coordinated approach to research in this area.

These recommendations were used to inform the development of a study to determine how long it takes to diagnose myeloma and what influences the intervals across the diagnostic journey. These recommendations have been presented as aims within Chapter 3, section 3.3. The recommendations also form a research hypothesis underpinning the quantitative study and the development of the research questions to be answered by both quantitative and qualitative studies. These are discussed in Chapter 3, sections 3.4 and 3.5.

2.9 Conclusion

Myeloma diagnostic journeys have been shown to be longer when compared to other cancer types. Multiple factors have been identified in this review which contribute to lengthening intervals along the diagnostic process. Whilst it is clear that there are significant difficulties in the pathway to diagnosis, ultimately the evidence is too limited to influence policy development.

3 Chapter Three: Methodology: the designing of research to explore the in-depth diagnostic journeys of newly diagnosed myeloma patients

3.1 Summary

This chapter describes the choice of methods and justifies the methodology underpinning these. The researcher's positioning in the study is defined through review of their experiences and perspectives, detailing their assumptions and understandings, and how these may influence the process of inquiry. A description of the methods is detailed and justified individually for the quantitative, qualitative and interpretation stages of the study. The efforts to establish validity, reliability and authenticity of the methods chosen are outlined in each methods section. Limitations of the design and possible difficulties implementing the research are discussed. Ethical and research and development applications are detailed.

3.2 The research hypothesis and questions

The systematic review (Chapter Two section 2.7) found that evidence for the early diagnosis of myeloma was limited, and there was insufficient understanding of the diagnostic processes to inform policy and practice. However, the findings helped inform a basic understanding of some of the difficulties when diagnosing myeloma. The review highlighted the benefits of examining diagnostic detail to provide evidence for how timelier diagnosis of myeloma could be achieved. The recommendations and observations identified in the review were used to inform a research hypothesis, research questions and research design.

3.3 Observations and recommendations from the review

To better understand earlier diagnosis of myeloma, research should:

- Recruit participants in a prospective manner, reducing recall bias in collection of data, following the diagnosis of myeloma
- Measure and define the diagnostic journey in individual participants, detailing the total interval to treatment and the interim intervals of patient, primary care, secondary care, diagnostic, time to diagnosis and treatment
- Determine and describe factors associated with these diagnostic journeys including: demographics; routes of access to healthcare services in primary and secondary care; frequency of access to primary care; influence of pre-diagnosis symptoms or multi-morbid diseases; investigations performed in response to symptoms in participants in primary and secondary care; stage of disease and disease profile at diagnosis; response to treatment; treatment choices and survival

- Describe the occurrence and prevalence of determined influences through descriptive statistics
- Measure the recorded factors of influence, determining their significance within intervals to diagnosis through statistical methods
- Explore the personal experience, perceptions, social and contextual meanings in order to identify behavioural and contextual influences on intervals to diagnosis
- Explore the perceptions and experiences within the clinical setting of diagnosing GPs relating to how they determine and understand symptoms, how they order investigations and their onward referral preferences
- Inform policy and practice, making recommendations for timelier diagnosis of myeloma.

3.4 The research hypothesis

The research hypothesis arising from the systematic review was:

There are potential improvements for the timelier diagnosis of myeloma through better understanding the factors that influence the intervals to diagnosis. Greater understanding of the appraisal of symptoms, and barriers to help-seeking, can lead to improvements in the patient interval. Greater understanding of the delays in the assessment, investigation of symptoms, and referral of myeloma patients into and through their secondary care journey may reduce diagnostic intervals by informing changes and recommendations for practice and health systems. Recommendations have the potential to improve patients' outcomes in survival.'

3.5 Research Questions

Research questions would need to capture the complexity of the processes and interactions when making a diagnosis of myeloma, and identify significant factors and influences contributing to longer intervals to diagnosis. Additionally, evidence would be required to produce changes in practice and policy to promote timelier diagnosis of myeloma.

Three research questions were formed:

- What is the range of diagnostic journeys in myeloma patients across Wales?
- What are the factors, interactions and experiences that influence the pathway to individual diagnosis?
- What factors may influence more timely diagnosis?

In order to understand the data requirements of the research questions, questions were added to a conceptual model, advocated by Creswell, (2014). The conceptual model deconstructs questions, allowing the researcher to develop an understanding of the context of the data required, and to facilitate appropriate choice of the research design.

Table 3-1: Conceptual model for research questions: A primer for research design

What we hope to learn:	Quantitative questions	Qualitative questions	Mixed methods questions
What is the range of diagnostic journeys in newly diagnosed myeloma patients in Wales? Timelines for total interval to diagnosis, patient, primary care, secondary care, diagnostic, time to diagnosis, treatment. Observed interactions between primary and secondary care and patient. Frequency of presentation and routes of presentation in primary and secondary care. Investigative response in primary and secondary care. Individual factors of age, ethnicity, geography, deprivation, presence of comorbidities. Symptoms experienced pre-diagnosis, awareness and attribution of symptoms, help-seeking barriers/prompts. Stage of disease, complications at diagnosis, response to treatment, survival. Effect and contribution of the length of the diagnostic journey. *Key words in questions:*	Probable cause and effect, relationships among variables, comparison among groups Factors, causes, measures, determinants, correlations, trends, level, magnitude	Individual experiences, personal meanings, individual perceptions Meaning, experiences, explorations, individual views	Combination of individual experiences and relationships among variables and between groups Combination of qualitative and quantitative terms

What are the influences, interactions and experiences that influence the pathway to individual diagnosis? Influences on help-seeking, awareness of symptoms, attribution of symptoms. Interactions in primary and secondary care. Attitudes to health and wellbeing, expectations of health. Effect, contribution and significance to the length of the diagnostic journey. *Key words in questions:*	Probable cause and effect, relationships among variables, comparison among groups Factors, causes, measures, determinants, correlations, trends, level, magnitude	Individual experiences, personal meanings, individual perceptions Meaning, experiences, explorations, individual views	Combination of individual experiences and relationships among variables and between groups Meaning, experiences, explorations, individual views
What factors may influence more timely diagnosis? Personal, contextual variables in patients, clinicians and interactions within primary and secondary care that influence the journey. *Key words in questions:*	Probable cause and effect, relationships among variables, comparison among groups Factors, causes, measures, determinants, correlations, trends, level, magnitude	Individual experiences, personal meanings, individual perceptions Meaning, experiences, explorations, individual views	Combination of individual experiences and relationships among variables and between groups Meaning, experiences, explorations, individual views

The conceptual table highlights that the research questions require both quantitative, qualitative or a mix of both data types in order to generate answers and develop understanding (Creswell et al., 2004; Pope et al., 2000). Research questions that require the measurement of an objective phenomena, and require collection of numerical or ordered categories of data, will be answered through quantitative data and statistical testing. Questions that aim to answer why or how a phenomenon exists, and are rooted in personal experiences, meanings and perceptions, require qualitative data through immersion in the narrative of the words and meanings (Creswell, 2014). An appropriate research design, for this study, would therefore require collection and analysis of both quantitative and qualitative data. This may be collected as standalone separate datasets, but when the datasets are collected and analysed in a sequential or integrated design they are considered mixed methods studies (Creswell, 2014). These studies are said to provide a greater depth and understanding of the phenomena of poorly understood processes. Mixed method study designs require the adaptation of different techniques and philosophical worldviews, with traditional scientific or service topics required, as well as encompassing behavioural and contextual topics (Creswell et al., 2004; Őstlund et al., 2011; Pope et al., 2000; Mertens, 2010). However, theoretical perspectives for mixed methods research are less well established (Evans, et al., 2011). It is for these reasons mixed methods studies are considered to be inherently more difficult to implement.

3.6 Research design

3.6.1 Choice of study design

An explanatory sequential research design (Figure 3-1) was chosen as a mixed methods design. This type of mixed methods research was considered appropriate as it allowed the testing of the study hypothesis and the theory generated from this hypothesis testing (Creswell, 2014). Additionally, John Creswell is considered to be a leader in the field of mixed methods studies and the research designs described in his books allow the organisation and guiding of the phases of inquiry, facilitating implementation of the research design along with transparency and reproducibility. This guiding or structure was considered advantageous for a less experienced researcher such as the student researcher. An initial quantitative study was undertaken, which described the numerical and categorical topic area and allowed statistical testing. The adapted theoretical perspective described by Creswell, (2014)

for the quantitative study was 'theoretical rationale'. This was first described by Lebovitz and Hagedorn, (1971). Creswell, (2014) defines this theory as specifying how and why variables and the relational statements measured are interrelated. This study tested the hypothesis that diagnostic journeys in myeloma were longer because: symptoms are vague and non-specific; patients present late to their health care provider; patients present more frequently as an acute presentation; patients have higher frequencies of GP consultations before referral and this extends the primary care intervals. These observations were made from conducting a systematic review of the available literature and, therefore, allowed a deductive approach to the quantitative study. Creswell, (2014) describes this deductive approach as a researcher verifying theory (conducting a review of the literature); testing the hypothesis or research questions generated from the theory; defining and operationalising variables derived from the theory and measuring or observing variables using an instrument to obtain scores. The theory generated from the testing and measuring of the diagnostic journey in myeloma was then explored in qualitative studies. Theory was tested within the qualitative study to provide an explanation of the evidence identified in the first phase of the research (Creswell, 2014). The qualitative research theoretical perspective was based on 'critical theory'. As Creswell, (2014) describes, this is theory that underpins inquiry looking to empower human beings to transcend the constraints of race, class and gender. Using inductive logic, Creswell (2014) describes a process of the researcher gathering information through methods that are open and engaging, encouraging the development of themes and priorities determined by the research subjects. The researcher records this information and in analysis forms themes or categories emergent from these data. Broad patterns or generalisations are made across these themes and categories which leads the researcher to form generalisations or theories from past experiences or the literature. Both phases of inquiry were analysed and reported independently, and findings were interpreted from all datasets to produce an overall report with recommendations for policy and practice. This structure was facilitated by the chosen research design the explanatory sequential research program.

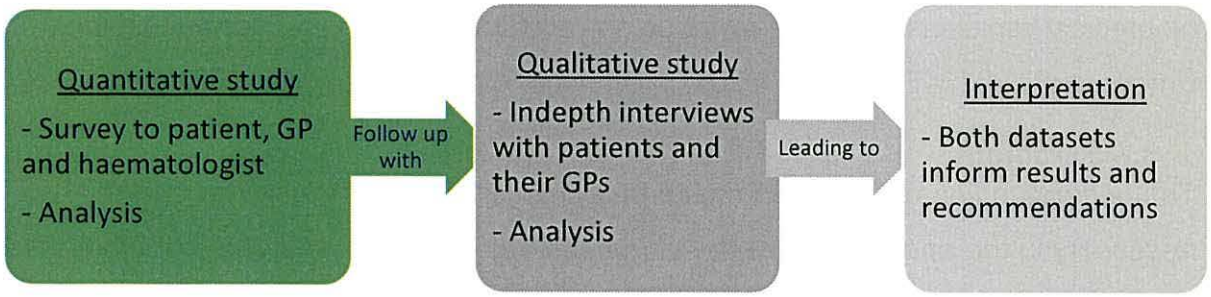

Figure 3-1: Diagram of Explanatory Sequential Research Program

(Adapted from Creswell, 2014)

Importantly, the research design followed a sequential pattern which gave the flexibility to include, for further exploration in the qualitative study, newly identified factors as they emerged from the analysis of the quantitative data. The sample population for the qualitative phase was sampled from the larger population of patients in the quantitative study, linking the two datasets and the findings to create a deeper understanding of the processes by which myeloma is diagnosed.

3.6.2 Previous use of the research design

Previous studies have used mixed methods to understand cancer diagnostic journeys (Emery et al., 2013; Jones et al., 2010; Place et al., 2011) providing a precedence for the use of the chosen design. Although these mixed methods designs are relatively new, the last decade has seen their more frequent application. Mixed methods designs have also been strengthened in rigour as evidence has emerged on how to apply methods, maintain quality, and interpret the results to make recommendations for health service policy and practice (Creswell et al., 2004; Östlund et al., 2011; Pope et al., 2000).

3.6.3 Dissemination and the study design

The dissemination of the research findings was planned and proposed in a dissemination protocol (Appendix 5). The target audiences identified were:

- Policy makers in cancer care;
- Primary care clinicians/academics;
- Secondary clinicians/academics; and
- Haematologists and third-sector parties.

These 'target' audiences were prioritised in the plan for the dissemination of findings and recommendations. The research design was considered suitable to this group of

biomedical clinicians, who largely focus on quantitative findings (Creswell, 2014; Emery et al., 2013; Place et al., 2011).

3.7 Paradigm

The understanding of the researcher's paradigm is widely acknowledged as necessary in the appreciation of the effect and balance the researcher contributes to the inquiry (Guba and Lincoln, 1994; Joubish et al., 2011; Creswell, 2003; Creswell, 2014). The explanatory sequential program required the researcher to apply both quantitative and qualitative research methods with a paradigm shift recognised as being necessary but challenging for a researcher (Creswell, 2014).

3.7.1 Theoretical stance of the student researcher

In acknowledging that the researcher brings a set of assumptions and understandings that can affect the collection and analysis of data within a mixed methods study (Guba and Lincoln, 1994; Joubish et al., 2011; Creswell, 2003; Creswell, 2014), a personal statement of the student researcher is offered. The aim of this statement is to provide the reader with a picture of who the researcher is; what drives their motivation to complete the project; what their expectations of the project are; what experiences and prejudices they may bring to the project. The statement is written in the first person as it is a personal reflection by the student researcher.

What drew me to the topic 'early diagnosis of myeloma' was my interest and experience of blood cancer and myeloma specifically. I have over 20 years' experience of working with patients who have haematological malignancies. Many of these years were spent nursing patients at different stages of their disease: diagnosis, treatment, relapse and survivorship. I have also spent over 10 years supporting NHS research with seven of these specifically working on national haematology clinical trials. In all the years working in these areas, myeloma is the one disease that I have found is repeatedly discussed by patients and clinicians as difficult to diagnose. Importantly, it is also a disease where the diagnostic pathway does not seem to have improved greatly. Although there have been advances in treatment, I have heard numerous stories from patients who presented with late stage disease with high levels of morbid complications. This, for me, made the project seem valid and important.

What drew me to completing a PhD was a desire to move beyond supporting research, to develop skills of study design, methodology, data analysis and presentation. These have allowed me to develop as an independent researcher.

I appreciate I came to the project with a knowledge base that may give me assumptions of how the diagnostic journey in myeloma occurs. Acknowledging these assumptions early in the development of the project allowed me to guard against possible biases. However, it was also true that some of these previous experiences have benefited the project.

My background was beneficial to the qualitative methods because of my highly developed interpersonal skills. These skills helped me to engage with patients and develop an ease of communication. This led to a discursive exploratory dialogue which illuminated the qualitative findings. My background as a research facilitator benefitted the process of rigorous study data collection and management, strengthening the design, implementation and analysis of data.

I have a rich, varied and long nursing history. My nursing background has allowed me to gain a deep understanding of how individual the engagement and management of health and wellbeing can be. I am able to reflect on how different the individuals I have cared for over the years are, based on their social, intellectual and contextual differences. This benefitted my appreciation of the qualitative work undertaken within this project.

Overall, I would say I have a drive and commitment that ensured the project's success. My mixed background made me flexible to the required shift of perspectives and approaches in a mixed methods study.

3.8 Methods

3.8.1 Quantitative study

3.8.1.1 Tool Choice

The first phase of the research design collected quantitative data to describe the diagnostic journeys of newly diagnosed myeloma cases and measure their intervals to diagnosis. This addressed the research question, 'What is the range of diagnostic journeys in myeloma patients across Wales?'

This quantitative phase of the study aimed to identify and define the important factors that influenced each of the intervals to diagnosis. This addressed the second research question, 'What are the factors, interactions and experiences that influence the pathway to individual diagnosis?' The results from analysis from this phase of the study would also be used to provide observations to respond to the third research question; 'What factors may influence more timely diagnosis?'

The International Cancer Benchmarking Partnership (ICBP) Module 4 (ICBPM4) (Cancer Research UK, 2017d, Weller et al., 2016) named "root causes of diagnosis and treatment delay" was used as a benchmark for the design of the quantitative

phase. The ICBPM4 was an international comparative study which built on previous exploratory work related to epidemiology, awareness, beliefs and behavioural aspects of cancer diagnosis. The aim of the module four programme was to examine and test the hypothesis that delay in diagnosis and extended pathways are related to poorer outcomes. The study collected time intervals across the diagnostic journey through a robust examination of the patient pathway. The project was recruiting successfully in Wales (personal communication Neal) at the conception of the myeloma study. ICBPM4 was embedded in a larger programme of research and conceived and run by some leading researchers in early diagnosis of cancer; Professor Peter Vedsted (Aarhus University, Denmark), Professor Usha Menon (University College London, UK) and Professor David Weller (Edinburgh University, UK). Similar methods to ICBPM4 were used but adapted for myeloma, using evidence from the systematic review.

3.8.2 Questionnaire design

The questionnaires used for the ICPBM4 facilitated the collection of data from the patient, their GP and their diagnosing hospital doctor. Within these three questionnaires, the collection of data allowed the depiction of the diagnostic journey from the three main contributors. These questionnaires have been demonstrated, to be valuable, usable and reliable (Weller et al., 2016). The questionnaires allowed the calculation of the intervals to diagnosis measured according to the Aarhus statement (Table 3-3). This ensured that valid methods were used producing results that were comparable across studies, with transparent reporting (Weller et al., 2012; Andersen et al., 2009).

Table 3-2: *Time point definitions based on 'Aarhus Statement' used for ICBPM4 questionnaires (Weller et al., 2016)*

Date of first symptom	The time point when first bodily changes and/or symptoms are noticed. Should encompass several key components: the date when the first bodily change was noticed, the date when the first symptom was noticed, the date when the person perceives a reason to discuss the symptom with a healthcare professional and the date when the first 'alarm' or 'high-risk' symptom was noticed.
Date of the first presentation	The time point at which, given the presenting signs, symptoms, history and other risk factors, it would be at least possible for the clinician

	seeing the patient to have started investigation or referral for possible important pathology, including cancer.
Date of referral	The time point at which there is a transfer of responsibility from one healthcare provider to another (typically, in 'gatekeeper' healthcare systems, from a primary care provider to a doctor/service specialising in cancer diagnosis and management) for further clinical diagnostic and management activity, relating to the patient's suspected cancer. Patients may be referred more than once or between specialists.
Date of diagnosis	Studies should be explicit about how the date is measured, and should consult the well-developed hierarchical rationales available in the public domain in choosing their definition of date of diagnosis.

Questionnaires within the ICBPM4 study collected data related to the diagnosis of breast, colorectal, ovarian and lung cancers. Items collected detailed information about the presentation, interactions, investigations, referral routes and processes and diagnosis and treatment (Table 3-3), allowing the in-depth description of the complex process.

Table 3-3: Areas of enquiry, numbers of items and extracts of questions used to elicit time points (example from breast cancer questionnaires) (Weller et al., 2016)

Patient	PCP	CTS
▸ Background (1) ▸ Route to diagnosis (e.g. via PCP, A&E) (1) ▸ Description of symptoms and date first noticed (2) ▸ Time taken to consult doctor (1) ▸ Time to get an appointment and date seen (2) ▸ Number of health professional visits (1) ▸ Time taken to get CTS appointment (2) ▸ Date of diagnosis (1) ▸ Description of treatments received (1) ▸ Details of CTS (1) ▸ General health and comorbidity (2) ▸ Socio-demographics (3) ▸ Smoking status (3)	▸ Duration of symptoms prior to presentation (1) ▸ Route to diagnosis (1) ▸ Investigations ordered and dates (1) ▸ Date of referral to CTS, and details of referral (3) ▸ Date of diagnosis (1) ▸ Comorbidity information (1)	▸ Date of first attendance for specialist services (1) ▸ Route of referral (1) ▸ Where patient seen (1) ▸ Date of diagnosis (1) ▸ Date cancer treatment started (1) ▸ Tumour information (2)
Date of first symptom (patient questionnaire) Please write down your best estimate of the date you noticed ... any symptom(s) you may have had before contacting a doctor or taking part in screening Date of first presentation to primary care (patient questionnaire) What was the date you first saw your doctor about your health concern(s) or symptom(s)? Date of first presentation to primary care (PCP questionnaire)		

Through what route did the patient first present? (If your patient first presented to primary care, either in-hours or out-of-hours). Can you please provide your best approximation of the date of his primary care visit? Date of referral (PCP questionnaire) At what date did you first refer the patient to hospital or another specialist, thereby transferring the responsibility for ongoing investigation/treatment to other medical services? Date of diagnosis (patient questionnaire) What was the date you were told you had cancer? Date of diagnosis (PCP and CTS questionnaires) Please indicate date of diagnosis: This can be decided in different ways; please tick and complete as many of the following dates as possible: Date of histological confirmation; date of results of investigation confirming cancer; date patient was told; date of biopsy; date patient was first admitted to hospital because of the malignancy; date of MDT confirmation of diagnosis; other (please specify)
A&E, accident and emergency; CTS, cancer treatment specialists; MDT, multidisciplinary team; PCP, primary care physician.

These questionnaires were reviewed and adapted for myeloma using data from the systematic review or from clinicians' consensus where appropriate.

The amended patient questionnaire was assessed for face validity by two Patient and Public Involvement (PPI) groups (6 PPI reviewers). The primary care questionnaire was assessed by a random sample of three GPs from North Wales. The secondary care questionnaire was assessed by a random selection of five consultant haematologists across Wales. The PPI groups used were the Involving People Network (hosted by Health and Social Care Research Wales) (https://www.healthandcareresearch.gov.wales/involving-people-network) and the North Wales Cancer Patient Forum Group (www.northwalescancerforum.co.uk). Both groups have recognised expertise in reviewing research documentation for usability, applicability and appropriateness. The random sample of GPs and haematologists were thought to be representative of possible participants within the study and, therefore, felt to be a representative group. The reviewing groups were asked to review the questionnaires for face validity (Streiner and Norman, 2008), and give an opinion as to whether the questionnaire was assessing the areas of interest. Although this relies on subjective assessment, the groups of reviewers were considered to be 'experts' within their fields, therefore, their opinions were valid and worthy (Streiner and Norman, 2008). Observations made by the two PPI groups, GPs and haematologists were collated and reviewed by the student researcher. These were presented to supervisors, with a plan for modifications and rationale for changes. Concerns were raised by the PPI groups in several areas of the patient

questionnaire and these were amended and are detailed below with rationales (Box 3-1). There were very few observations made by GPs or haematologists about the usability, structure or applicability of the relevant questionnaires, therefore, only minor modifications were made to questionnaires and these are detailed (Boxes 3-2 and 3-3). Comments from clinicians were made regarding the length of time required to complete the questionnaire. A balance was considered with the amount of detail required in questionnaires to display the complexity of diagnostic journeys in myeloma and fill in the missing gaps in the knowledge. A decision was taken to keep the detail and number of questions in the questionnaires, to allow the depth of the diagnostic processes to be displayed, and reflect the exploratory nature of the study design. It was acknowledged, though, that this may be a deterrent to some clinicians completing the questionnaire.

Although Wales is a bilingual nation, patient questionnaires were not translated into Welsh. Questionnaires had not been validated in their English format and ethical approval required only validated material to be translated (Roberts personal communication).

Modifications and additional items in myeloma questionnaires (Appendix 6):

Box 3-1: Modification to the patient questionnaire

Introduction and consent:

The introduction was made specific to myeloma with an explanation of the study purpose. A revised time to complete questionnaires was added to reflect the additional questions.

Identification questions

Name, address, date of birth, gender, contact details – telephone and e-mail.

Primary care doctor details – details were requested to be given of the doctor most involved in the diagnosis of myeloma to ensure that the GP most likely to have detailed knowledge of diagnostic journey was approached.

Identification of the route to diagnosis – patient perspective

Participants were requested to fill in one box of a series of possible scenarios leading to the identification of myeloma. Modifications included: surveillance programs for MGUS and plasmacytoma; and removal of the screening option, as this was not applicable to myeloma. All modifications complied with processes reported in the British Society of Haematology (BSH) Guidelines (Bird et al., 2011).

Symptoms

Participants were requested to complete a table with a suggestion of seven symptoms associated with myeloma, and asked to tick any that were applicable to their symptoms prior to their diagnosis. Seven commonly reported symptom categories

were offered, which reflected those reported in data identified from the systematic review (Friese et al., 2009; Kariyawasan et al., 2007; Howell et al., 2013). Participants were requested to tick as many symptoms as they experienced. A free text box was also added for participants to detail any further symptoms experienced but not included in the table, this was added to reflect the diversity of symptom reported in Howell et al. (2013).

Date of first symptom and first symptom experienced

The date of first symptom was collected to allow the measurement of the patient, time to diagnosis and total interval (Weller et al., 2012). The participant was asked to complete the full date i.e. date/month/year. It was anticipated this may be difficult for the participant and so participants were asked to report to the nearest month or year, as in the ICBPM4 study questionnaire. Participants were additionally asked to report which, of all the first symptoms they reported, was the first symptom experienced. This was added to allow the description of early symptoms of myeloma.

Time to help-seeking

Participants were requested to tick one box which reflected the length of time they had symptoms before consulting. Categories were the same as the ICBPM4 questionnaire with the addition of two categories added for 1 ½ - 2 years and more than 2 years. These extra categories were included because it was expected that symptom duration would be longer in myeloma (Howell et al., 2013).

Length of time to make an appointment at the doctors

Participants were asked to complete a tick in one category recording the length of time it took to secure an appointment with their GP. The categories reflected those in ICBPM4 questionnaires with the addition of two extra categories of over 1 ½ years but less than 2; and greater than 2 years. The addition of these categories reflected clinicians' consensus on symptom duration prior to diagnosis and the desire to broaden the criteria to ensure that no data were missed.

Date of first consultation

Participants were asked to give the date or best estimate i.e. month/year, of their first consultation. Participants were prompted that this first consultation may relate to a consultation with their family doctor, a doctor in an 'out of hours' service or the accident and emergency department. This date would be used in the calculation of the end of the patient interval, and the commencement of the primary care and diagnostic intervals.

How many consultations were made with GP, hospital consultant, consultant/specialist outside the NHS, or with a NHS physiotherapist/osteopath

Participants were asked to add a number representing the number of visits to different healthcare professionals. A further category was added to the ICBPM4 question to collect other healthcare professionals seen in primary care. This reflected 'patient story' reports from Myeloma UK, where consultations with allied healthcare professionals with musculoskeletal complaints were reported (personal communication Morgan (Myeloma UK)).

Length of time from referral from primary care to being seen in secondary care

Participants were asked to tick one box for the time category. This item was not modified from the ICBPM4 question.

Appointment in secondary care

Participants were asked to give the date they were first seen in secondary care or their best estimate of this time i.e. month/year. This date was used to measure the end of the primary care interval and the commencement of the secondary care interval. The name of the treating consultant in secondary care was also collected to allow completion of the secondary care questionnaire.

Date the diagnosis of myeloma was given to participant

In the absence of the secondary care data, this date was collected to end the diagnostic interval and the time to diagnosis interval.

Analgesia taken prior to diagnosis

Participants were asked to tick a box (yes/no) as to whether they had required pain killers prior to the diagnosis of myeloma. When the answer was yes participants were asked to tick a further box of 'category of pain killers'. The categories were described in detail with examples given. More than one box could be ticked. These categories were designated according to clinician consensus and the World Health Organisation (WHO) pain ladder for chronic pain (WHO, 1996). The primary reason for the inclusion of this item was to explore any relationship between the levels of pain and help-seeking activity that might be predictive of more serious symptoms. It reflected literature reporting an association with pain levels and dysfunction in newly diagnosed myeloma (Coleman et al., 2011).

Treatment

This item was modelled on the ICPBM4 questionnaire but modified to include categories of treatment for myeloma in the BSH diagnosis and treatment guidelines (Bird et al., 2011). Dates were collected for each treatment received which would facilitate the measurement of the treatment interval and the end of the secondary care interval in the absence of secondary care data.

Health status

Participants were asked to complete a scaled response, ticking only one box, to depict the level of 'health' they perceived themselves to have in the two years preceding their diagnosis of myeloma. This was the same question used in the ICBPM4 questionnaire. The rationale for keeping this question within the questionnaire was the lack of information on help-seeking in myeloma patients reported from the systematic review.

Multi-morbidities

Participants were asked to complete a box to report the presence of a series of more common multi-morbidities, as reflected in the ICPBM4 questionnaires. Participants were encouraged to tick as many multi-morbidities as they experienced and were given an additional box to add any that were not specified in the table. The inclusion of this category reflected the reporting of multi-morbidities associations with longer journeys to diagnosis in myeloma (Kariyawasan et al., 2007).

Ethnicity

Participants were asked to tick a box which best described their ethnic background. Ethnicity categories were derived from the Welsh Office of National Statistics ethnicity groups (https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11) so were appropriate to the Welsh population. The rationale for the collection of ethnicity was to assess relationships between longer intervals to diagnosis in ethnic

minority groups reported widely in early cancer research (Waller et al., 2015) but less frequently with myeloma (Friese et al., 2009).

Language preference

Participants in the ICBPM4 Welsh questionnaire were asked to report their main language used at home. This was added to the original myeloma specific questionnaire, but when reviewed by the PPI groups it was strongly objected to, and as it did not feature in the systematic review as an influence it was removed.

Assessment of deprivation

In the ICBPM4 questionnaires, educational attainment was used as a proxy for deprivation. This was considered in the original myeloma questionnaire but received a very negative response from the PPI group. Comments included the assessment of education across a wide age range, using assessment criteria reflecting the education systems currently in use, was not representative or equitable. Due to the strength in the response from the PPI group, and the opportunity to assess deprivation using the postcode given by participants, this question was removed. Deprivation assessment through the use of the postcode and the Welsh Index of Multiple Deprivation (WIMD, 2014). The WIMD score system is an assessment made on multiple categories associated with deprivation and equivalent deprivation models have been used in measurement of deprivation for other early diagnosis studies (Abel et al., 2015).

Smoking status

This question, which was a part of the ICPBM4 questionnaire, was removed from the myeloma questionnaire. The rationale for the removal of the question was that no link between smoking and myeloma had been identified in the literature within the review.

Free text box

A free text box remained at the end of the questionnaire replicating the ICBPM4 questionnaire. Due to the diversity in reporting in the Welsh ICBPM4 questionnaires (personal communication Neal/Law) participants were asked to add information relating to their diagnosis of myeloma specifically in order to focus the question.

Box 3-2: Modifications to the primary care questionnaire

Introduction

The introduction was made specific to the study and myeloma. The time anticipated to complete the questionnaire was added for GP information.

Duration of symptoms

GPs were asked to record how long they considered their patient to have had symptoms for. This item was the same as the ICBPM4 questionnaires but there were additional categories for longer symptom duration of 12-18 months, and over 24 months. This reflected the clinicians' consensus that symptoms may be present for longer in myeloma (Howell et al., 2013; personal communication supervisory committee).

Pathway of presentation

GPs were asked to report how their patient presented to them. The categories reflected those in the ICBPM4 questionnaire as these also reflected patterns of presentation seen in the systematic review. The category concerning presentation to primary care was sub-divided into two categories: presented in normal working hours,

or out of hours. The rationale for this was to determine how many patients present as an emergency in primary care versus routinely seeking help in primary care, with this having been identified as important in the systematic review.

The date of this presentation was collected alongside these data and was used as the end of the patient interval and the beginning of the primary care and diagnostic intervals.

Number of consultations in primary care

This was added to the primary care questionnaires to compliment data by Lyratzopoulos et al. (2012) regarding the number of pre-referral visits in myeloma participants. These data were additional to the patient data and used if missing patient data on the number of consultations in primary care occurred.

Number of different healthcare professionals seen in primary care:

An additional category was added collecting 'other consultations', people and number, involved in the diagnostic process, which reflected the number of non-GP consultations within primary care (Ridd et al., 2006; personal communication Morgan (Myeloma UK)).

Investigations performed in primary care in response to symptoms

Categories were modified from the ICBPM4 questionnaire to be myeloma-specific in line with the screening tests in the guidance from the BSH guidelines (Bird et al., 2011). Inclusion of this question aimed to collect data which could identify difficulty with the identification of myeloma in primary care (Ong et al., 1995), and the low levels of full diagnostic profiling reported in myeloma patients (Friese et al.,2009). Additional categories requesting the reporting of the tests recorded as 'abnormal' and 'repeated' were added. No guidance was added to the questionnaires to indicate what level of abnormality should be reported, which was left to the GPs interpretation.

Date myeloma suspected in primary care

This category was added to collect data about whether a consideration of myeloma was made in primary care and to calculate of the length of time spent in primary care before a suspicion was made. This reflected evidence about the referring of patients with myeloma into secondary care and whether the referral patterns related to a reduced level of suspicion (Kariyawasan et al., 2007).

Date referral to specialist care made

This category was added to the questionnaire to collect the interval between when myeloma was suspected and referral to specialist services.

Date the patient was first seen in secondary care

This date was collected to calculate the end of the primary care interval and commence the secondary care interval, in addition to data collected from secondary care questionnaires.

Was the diagnostic journey conducted mainly in the private or public sector?

This question was in the ICBPM4 primary care questionnaire, but was removed for the myeloma questionnaire. The rationale for the removal was that private healthcare use was not frequently reported in the systematic review, and any private system access could be assessed through the question capturing other healthcare professionals consulted.

Type of referral to secondary care

This question was maintained from the ICPBM4 Welsh questionnaire and reflected the type of referral possible from primary to secondary care services.

Team referred to from primary care

This item was added to specifically collect the team that the GP referred to in secondary care. This reflected reporting of multiple teams seeing myeloma patients in secondary care during the diagnostic workup (Kariyawasan et al., 2009).

Date of diagnosis

This question was removed from the primary care questionnaire as it would be collected from the diagnostic testing in secondary care questionnaires in line with the Aarhus statement (Weller et al., 2012).

Multi-morbidities

Collection of the presence of multi-morbidities was maintained in the myeloma questionnaire in the same format as that in the ICBPM4 questionnaire. This reflected data highlighting multi-morbidities influencing diagnostic journeys (Kariyawsan et al., 2007). Data was intended to complement that received from the patient questionnaire.

Access to primary care

In addition to collection of the number of consultations in primary care, GPs were asked to document when consultations occurred in primary care in the preceding 24 months to diagnosis. The rationale for adding this item was not only to determine whether there was an increased frequency in primary care contacts for myeloma patients (Lyratzopoulos et al., 2012), but also whether any increased access in primary care was clustered around certain time points.

Free text box

A free text box was maintained at the end of the questionnaire replicating the ICBPM4 questionnaire. Due to the diversity in reporting seen in the Welsh questionnaires (personal communication Neal/Law) GPs were asked to comment on anything which they considered could have made the diagnosis timelier, and then given an option to add any other comment.

Number of cases of myeloma seen

An additional item asking GPs to report the number of cases of myeloma they had been involved with care. The rationale for this was the lack of description in the systematic review as to whether experience helped consideration of symptoms and early identification

Number of years in practice

Alongside the item concerning the 'number of previous cases seen', to assess the experience of diagnosing GPs, GPs were asked to report the number of years in practice.

Box 3-3: Modification to the secondary Care questionnaire

Introduction

The introduction was made specific to the study and myeloma. In addition, the time taken to complete the questionnaire was added.

Date patient first attended hospital with symptoms related to myeloma

This question was maintained from the ICBPM4 questionnaire.

Team referred to in secondary care

This question was modified from the ICBPM4 questionnaire to collect data on multiple referrals made. This allowed the progression of the myeloma patient through secondary care teams to be determined (Kariyawasan et al., 2007).

Who made the referral to secondary care?

This was an additional item added to collect the person initiating the referral into secondary care. This would complement data reported in primary care questionnaires and provide data for any missing primary care reporting.

Date the patient was seen by haematology

This was an additional item to determine the interval from presentation/referral to secondary care and the transfer of care to haematology, and to measure the interval between presentation to haematology and diagnosis.

Referral in secondary care/haematology

These questions were modified from those within the ICBPM4 questionnaire to include more categories reflecting clinicians' consensus as to the presentation of myeloma patients in secondary care.

Date referral made to haematology

This item was added to the secondary care questionnaire to measure the time taken between inter-departmental referrals in secondary care. Rationale for the inclusion of this question was both anecdotal reporting from haematologists about complex referral patterns in secondary care, and reports of multiple teams being involved in the diagnosis of myeloma (Kariyawasan et al., 2007).

Diagnostic tests in secondary care

This question was modified from the ICBPM4 questionnaire to collect myeloma-specific diagnostic tests, as determined from the BSH guidelines (Bird et al., 2011). The date given for the bone marrow aspirate would be used to determine the end of the diagnostic and time to diagnosis intervals.

Classification of disease type

This question was modified to collect specifics of disease characteristics for myeloma taken from the BSH guidelines (Bird et al., 2011) to report monoclonal paraprotein and sub classification.

Date treatment commenced

This item was maintained from the ICBPM4 questionnaire and was used to calculate the end of the secondary care interval and the commencement of the treatment interval.

Treatment choice

This was an additional item added to collect data on the treatment pathway choice made for the myeloma patients and reflected the different intensity of treatment choices available, determined by the clinical condition and age of the patient at diagnosis (Bird et al., 2011).

Treatment choice – determining factors

An additional question was included to establish the reasons behind the choice of treatment intensity. This had the potential to be assessed against the intervals to diagnosis, highlighting any differences in treatment choice relating to intervals to diagnosis lengths. Categories of possible reasons for changing treatment choice were suggested to haematologists based on evidence in the BSH guidelines (Bird et al., 2011).

Clinical trial activity

Three items were added to the questionnaire which captured clinical trial activity, displaying the offer and uptake of clinical trial activity and also capturing the reasons for not entering a trial. The rationale for the addition of the questions was haematologists reported anecdotal experiences that patients who entered clinical studies had a better clinical status and did better in terms of survival.

Decision to treat – proxy for burden of disease

This question was added to the questionnaire as a proxy for the assessment of burden of disease at diagnosis and to ascertain whether more complications existed with longer intervals to diagnosis, as reported in one study in the systematic review (Kariyawasan et al., 2007). These categories were representative of the assessment of the disease at diagnosis made by haematologists and reported in the BSH guidelines (Bird et al., 2011).

International staging score

This item was modified from the ICBPM4 questionnaire collecting the stage of disease at diagnosis. In myeloma, a prognostic scoring system exists to assess stage of disease which is not directly representative of stage of disease in other cancer sites (Greipp et al., 2005), but rather offers a prognostic opinion.

Chromosomal abnormalities

This additional category was added to collect the activity of chromosomal assessment in Welsh patients at diagnosis, and add to the assessment of prognosis considered to be of increasing importance (Bergsagel et al., 2013). Categories for the assessment of cytogenetics were taken from those discussed in the BSH guidelines (Bird et al., 2011).

Histology

This was removed from the myeloma questionnaire as diagnostic tests were collected within secondary care diagnostic testing.

Response to treatment

This was an additional question added to collect the response to first line treatment. Categories were defined from the BSH guidelines (Bird et al., 2011).

Free text box

A free text box was maintained at the end of the questionnaire replicating the ICBPM4 questionnaire. Due to the diversity in reporting seen in the Welsh questionnaires (personal communication Neal/Law) GPs were asked to comment on anything which they considered could have made the diagnosis more timely and also then given the option to add any other comment they wished.

Questions within the questionnaire had a mixture of styles for retrieving answers, including multiple choice directed answers, free text and tick boxes. Some questions

were duplicated in two or more questionnaires, as it was assumed not all questionnaires would be returned from every participant group. The mix of questions replicated the styles of questions used in the ICBPM4 questionnaires. The style of questions used were also seen to be aligned with those recommended more generally for survey data collection (Boynton, 2004a; Boynton, 2004b; Goodman, 1997; Snyder, 2007). The diverse range of answers anticipated from the questions had the potential to make data handling difficult, therefore a data hierarchy system was developed for individual questions (Appendix 7). Data hierarchy allowed a consistent approach to analysing ambiguous reporting e.g. symptom onset date given as just a year or year and month only; number of consultations with GP reported as a range of numbers. This data hierarchy also demonstrated the transparency of the data handling process, adding quality to the outcomes reported (Mokkink et al., 2010; Weller et al., 2012). The data hierarchy development was informed by the process used in analysis of ICBPM4 data (Weller et al., 2016; personal communication Neal), and through clinicians' consensus within the supervisory committee.

3.9 Identifying the study population

When considering how best to identify newly diagnosed myeloma participants, systems used in the ICBPM4 study were first examined. In the ICBPM4 study patients with newly diagnosed breast, colorectal, lung and ovarian cancer in Wales were identified from the Welsh Cancer Intelligence Surveillance Unit (WCISU) and invitations sent to the potential participants' registered GP. GPs then forwarded potential participants' invitations to their home address, following checks that the invitation met with the inclusion criteria for the study (personal communication Law). However, evidence reviewed for the recruitment of newly diagnosed myeloma patients to studies reported recruitment mainly from the secondary care setting (Child et al., 2003; Morgan et al., 2012). In order to reduce recall bias, the questionnaires were required to be completed soon after diagnosis which made recruitment from the secondary care setting a favoured strategy.

3.9.1 Sample group clinical profile

Myeloma is a broad term for multiple disease types (Bird et al., 2011), as detailed in Chapter One section 1.2.4. How the heterogeneous disease type should be accommodated in the sample group was considered. Potentially all three groups of MGUS, asymptomatic myeloma and symptomatic myeloma could be included in

recruitment. Critical studies reviewed for the systematic review were found not to include MGUS and not to distinguish groups of asymptomatic and symptomatic myeloma when reporting intervals to diagnosis. MGUS was not associated with the progression rate of asymptomatic myeloma and did not require follow-up within the haematology speciality, therefore, it was not included in the inclusion criteria for the study.

Newly diagnosed asymptomatic and symptomatic myeloma were included in the inclusion criteria. The inclusion of asymptomatic myeloma reflected the known higher progression rate to symptomatic myeloma of the condition (Chapter One section 1.4) and the requirement of monitoring under the care of the haematologist (Bird et al., 2011). Follow up, is a significant intervention for the asymptomatic myeloma group and loss of the participant to follow an important consideration in the diagnostic journeys of participants. All cases of asymptomatic myeloma are discussed and registered in a MDT assessment, so no administrative barrier to recruiting could be seen. In asymptomatic myeloma cases, to collect the total interval of the journey 'surveillance under the haematologist' would be used as 'proxy' for 'treatment' start date. Efforts would be made to report the differences in the two groups, to give clarity where this did not occur in other studies, and exclusion or separate analysis (dependent on the number of asymptomatic myeloma participants recruited) would be made for time intervals to diagnosis analysis. The final inclusion and exclusion criteria for study recruitment was:

Inclusion criteria

- Patient over 18 years of age;
- Able and willing to give informed consent;
- Able and willing to complete the study interventions / complete questionnaire;
- Has been diagnosed with asymptomatic or symptomatic myeloma as defined by the MDT;
- Is fully aware of their diagnosis and nature of the disease as defined by the treating clinician; and
- Diagnosed within 6 months of study registration.

Exclusion criteria

- In the last few days or weeks of life and too unwell to complete questionnaire, as determined by clinician;
- Mentally incapacitated; and
- Not at liberty.

3.9.2 Sample size

An initial recruitment target was set through a power calculation based on the ICBPM4 recruitment target for Wales. Power calculations are based upon the number of cases (samples) necessary to reject a null hypothesis. Although this power calculation was used as part of the original recruitment plan in the approved protocol, it was anticipated that this would be modified following the systematic review and the development of the research hypothesis and questions. This was adopted as a practical application of methods that aligned with this myeloma study. This pragmatic approach was required because of a lack of literature relating to the recruitment potential in early diagnosis work for 'prospectively' recruited participants, and significance testing of variables for rarer cancer types. A consideration was made as to whether the ICBPM4 module recruitment was achievable for the Welsh myeloma population. This consideration consisted of reviewing the 'available' population figures (newly diagnosed cases of myeloma) to calculate the potential population, from Cancer Research UK and WCISU. To calculate the likely study population, the percentage of newly diagnosed myeloma participants recruited against those invited was assessed in reported studies. The percentage of patients recruited in studies, was then calculated against the number of potential participants. Assessment was made difficult due to the figures for the available population including all ICD 10 codes (International Disease Classification of Neoplasms) for the myeloma group. These, therefore, included all cases of multiple myeloma: plasma cell leukaemia; extramedullary plasmacytoma and solitary plasmacytoma (http://www.icd10data.com/ICD10CM/Codes/C00-D49/C81-C96/C90-). Many of these conditions were not eligible for the myeloma study, but the individual figures could not be determined from the available information. The likely study population figures were based on the experiences of the ICBPM4 programme in Wales (personal communication Neal) which were reported at 26% and the recruitment level reported by Howell et al. (2013) in a questionnaire based study of 65%. The

population group in this study was made from a group of participants who had already consented to be approached for research purposes and likely to have a higher response rates. A point between these two reported percentage figures was used in a pragmatic approach and set at 50%.

Adopted power calculation from ICBPM4:

Power calculation to predict recruitment target quantitative myeloma study: modified from the ICBPM4 Welsh study (Weller et al., 2016)

t tests - Correlation: Point biserial model

Analysis: A priori: Compute required sample size

Input: Tail(s) = Two

Effect size |ρ| = 0.2

α err prob = 0.05

Power (1-β err prob) = 0.80

Output: Non-centrality parameter δ = 2.8210518

Critical t = 1.9725951

Df = 189

Total sample size = 191

Amended recruitment target:

- Population size: Wales = 3,064 million

Incidence newly diagnosed myeloma in Wales 2013 = @ 250 year (Cancer Resarchorg/cancer-info/cancerstats/types/myeloma/incidence/uk-multiple-myeloma-incidence-statistics)

- Potential recruitment over 18-month recruitment period = 1.5 x 250 = 375 cases
- Estimated recruitment potential of 50% of the available population
- Recruitment potential - 50% of 375 participants = 187 participants.

The amended recruitment target was anticipated to be lower than the ICBPM4 target. As the research questions formed from the review were essentially explorative and explanatory this was not considered to be likely to affect the answering of the research questions. It was considered likely that failure to reach the amendment recruitment target was likely to affect generalisability of data outcomes.

The recruitment process was rigorously monitored and is clearly reported in later chapters (Chapter Four section 4.5.1/Five section 5.4.1/Six section 6.4.1). Comprehensive efforts were made to recruit all representative cases for analysis, with wide and open eligibility criteria and engagement of all hospital sites throughout Wales, and is discussed in detail in the quantitative study (Chapter Four section 4.5.1).

3.10 Data Management

Data collected from all three questionnaires was transcribed into bespoke datasets in ACCESS 2013 database. This database had demonstrated effectiveness and user friendliness with the collection and analysis of data for the Welsh ICBPM4 study (personal communication Law).

Data was managed by adoption of an established Data Management Standard Operating Procedure (SOP) for the North Wales Organisation for Randomised Trials in Health (NWORTH 6.WI.04 2013), providing guidance for confidentially, storage, audit and management of data. Modification to the database management instructions SOP were made to allow the use of the ACCESS database created specifically for the study.

3.11 Methods for reviewing and cleaning of data

3.11.1 Data hierarchy

A data hierarchy (discussed previously in section tool choice) was applied during analysis to clarify and reported consistently unwieldy or difficult to interpret data (Appendix 7). The data hierarchy applied followed the precedence used for the ICBPM4 study (personal communication ICBPM4 team), and where myeloma specifics were required, clinician consensus (from the supervisory committee) was additionally used.

3.11.2 Review/Audit

Quality checking of data was undertaken through audit and review to ensure robust outcomes, in line with the NWORTH SOP.

Checks for validity and accuracy of transcribed data on the research database against the source data were performed at two time points through the data collection period. This was a formal examination of data by an independent researcher, with checks to determine participant data was entered correctly: checking for missing values, transcription errors and any repeating themes. The auditor, in line with the SOP, was a researcher from the North Wales Centre for Primary Care Research, who had no researcher role or responsibility in the study. A less formal check by the student researcher was conducted at two monthly intervals through the study recruitment period and included a random check of ID, number of entries and out of range values. The audit consisted of manually cross-checking entries on the ACCESS database with the original questionnaires (source data) completed by the three participant groups. Checks and errors were recorded on an EXCEL spreadsheet. A selected sample of questionnaires were audited at the rate of 30%. This rate was higher than recommended in the SOP (recommended rate = 10%), and was chosen as an additional quality measure, recognising a single student researcher was solely handling data, who possibly was less experienced, and therefore an increased error rate was possible. When cases of incorrect entry were identified, amendments were made to the ACCESS database and an audit trail of any changes kept, with the reason for the changes logged. The audit findings were discussed between reviewer and researcher and logged changes were reviewed by a member of the supervisory committee. Audit findings are reported in Chapter Four (Section 4.5.2).

3.11.3 Data Extraction and locking

The dataset, in line with the NWORTH SOP, was considered locked following the cleaning process after the second formal audit, and these data used for analysis only.

3.11.4 Data analysis plan

Variables collected from the questionnaires were first analysed using descriptive statistics. This allowed the description of data collected through summarising these in clearly and concisely (Spriestersbach et al., 2009). Descriptive statistics are a favoured method of analysis when the intention of the research is to enhance understanding and knowledge of a less well described topic (Hussain, 2012), which made their use appropriate for this study. Descriptive statistics have been used in early diagnosis of cancer studies where the proportions of populations and factors

affecting intervals along with measurement of intervals to diagnosis are reported (e.g. Walter et al. 2015; Walter et al., 2016) giving a precedence for their use in this study.

The level of measurement of the variables recorded was assessed to determine the statistical method most appropriate for analysis and programming within the statistical database (Field, 2009).

Data were categorised as:

Categorical:

- Nominal – labels with no quantitative values e.g. decision to treat based on monoclonal paraprotein in serum or urine, lytic bone lesions, anaemia.
- Ordinal – where the order of the variable is important and significant but the differences between each variable is not known e.g. health status in the two years preceding diagnosis very good, good and fair.

Numerical:

- Interval – numerical scale where the exact differences between the values are not know e.g. age at diagnosis in completed years
- Ration – scales where the measurement is exact and scales are transparent

Variables were analysed and presented as:

- Independent – age, ethnicity, gender, socio-economic status, presence of multi-morbidity, presentation routes to primary and secondary care
- Dependent – Total interval to diagnosis with a further sub-division of the patient interval, the primary care interval, the secondary care interval, diagnostic interval, time to diagnosis and treatment interval.

Non-parametric data were recorded for the majority of variables. Continuous variables were reported with median, interquartile ranges, and 10^{th} and 90^{th} percentiles for intervals. The use of these statistical descriptions would make results comparable to many other studies reporting intervals to diagnosis in myeloma: Din et al., 2015; Howell et al., 2013; Keeble et al., 2014; Lyratzopoulos et al., 2015b. For categorical variables counts and percentages were used to display results, making

them comparable to other literature reporting categorical variables for myeloma diagnosis: Friese et al., 2009; Howell et al., 2013; Howell et al., 2015; Kariyawasan et al., 2007.

Following description of the individual variables, numerical independent variables were analysed using the Pearson's Product Moment Correlation Coefficient (Field, 2009), against the dependent variables of all seven intervals to diagnosis. Correlation was used to demonstrate how strongly pairs of variables were related by measuring the linear dependence between the two variables. Strengths of the associations were measured using the guide proposed by Evans et al. (1996).

- 0.00-0.19 'very weak'
- 0.20-0.36 'weak'
- 0.40- 0.59 'moderate'
- 0.60- 0.79 'strong'
- 0.80-1.0 'very strong'

Using the correlation coefficient had limitations for this study, as large numbers of variables measured and defined by descriptive statistics were categorical and correlation could only be used for single numerical variables.

Regression modelling was used to further understand the statistical significance of the multiple mixed categorical and numerical variables (Field, 2009). Regression analysis had the added ability to assess these multiple and different levels of measurements alongside each other, which was an important factor of consideration for the analysis of such an in-depth dataset.

There were over 250 variables collected which made analysis cumbersome. A backward (stepwise method) was chosen as the method of analysis, as it permitted the assessment of all the independent variables collected and, through the systematic rejection of the least significant variables in the model, highlighted the variables that were most significant in a change to the dependent variable.

Multiple regression models are standardly constructed from previously defined models, or by defining models from literature reviews (Field, 2009). No previous models for this topic field, which allowed for the breadth and depth of analysis required, were identified. Therefore, data synthesised into themes within the systematic review, were used to construct regression models. Limitations are

considered possible using the literature as a basis for model conception, as mixed theoretical quality and differences in methodological approaches can be unappreciated (Field, 2009). This would be a limitation in the analysis of this study but due to the lack of evidence available, this was an acceptable pragmatic approach.

The use of multiple numbers of constructed models in analysis was considered, possibly to lead to 'over fitting' models and identifying significance simply through over analysis. The use of a correction model to allow for this 'over fitting,' such as the Bonferroni correction model, can also be associated with a rejection of a genuine significant factor (Field, 2009). Consideration was made of these possible effects against the overall desire to highlight the most significant factors for each interval to diagnosis, through 'funnelling' down to the most significant factors. A choice was taken to apply the Bonferroni correction model in *'post hoc'* procedures, retaining the possibility of rejecting a significant factor, as the number of variables and models used was considered a greater factor to consider and adjust for.

All variables were included within a regression model, and assessed for the significance against all the individual intervals to diagnosis. Models were constructed from themed areas of influence from the systematic review, for example:

- Influences of demographics – age, gender, deprivation.
- Influences in primary care – route of presentation, number of GP consultations, number of different GPs seen, whether investigations were performed, type of investigation.

For this study, residuals and outliers were not formally considered as part of assumption testing, as would be standardly be performed to judge the ability to generalise analysed findings to the wider population, this was considered acceptable because this study's aims were essentially exploratory (Field, 2009). Outliers and residuals were identified through a coding process of data from the descriptive statistics reporting. In the coding process, categorical variables were assigned a numerical value before being entered into models. The assigned value was ordered to follow a hypothecated influence of the variable on the dependant variable, informed from the systematic review or descriptive statistical analysis e.g. if the variable was thought to make the interval longer, it received a higher numerical

value. This labelling ensured the linear relationship in associations was represented in regression analysis (Field, 2009). Independent variables which contained the description of non-event categories in descriptive statistical analysis e.g. 'no tests performed' or 'no consultations conducted in primary care', were not coded numerically, but removed from the regression analysis as they could distort the regression modelling linear relationship (Field, 2009).

3.12 Survival analysis

Survival analysis was considered of benefit to assess in this study. The systematic review reported limited evidence of a survival benefit for earlier diagnosis. This evidence was reported from studies using retrospective secondary care data, which could be considered less robust.

The literature assessing survival in myeloma (Attal et al., 2006; He et al., 2012; Kariyawasan et al., 2007) reports two components to survival analysis: overall survival, measured from the date of diagnosis to death; and disease-free progression or progression-free survival, measured from the diagnosis to first progression of the disease. Overall survival is an unambiguous measurement and data from local research sites was considered relatively easy to retrieve to measure this. The measurement of the length of progression free survival in myeloma is an important consideration also (from the first treatment for myeloma to relapse or progression of the disease), as this measurement is associated with longer journeys (Kariyawasan et al., 2007). To capture progression in myeloma, a measurement of a complex clinical criteria is required (Table 3-4). Although these are easily definable by a clinician and are commonly used in multi-centre myeloma clinical trials (Attal et al., 2006), they may be less readily assessed in centres that do not conduct randomised clinical trials of medicinal products (CTIMPS). The difficulties associated with collecting this variable (through assessment of this criteria, assessed by research nurses) led to consideration of a more 'real world' approach. Collecting of the date of the commencement of the next (second line) treatment for myeloma or death of the patient was considered to be a better approach. Clinician consensus within the supervisory team was that the collection of this fixed date would be a less interpretable variable for research nurses to report, but would still allow the demonstration of progression of disease. Additionally, the collection of this 'time to

next treatment' variable was in line with consensus statements that, 'time to next treatment' should be reported on in future clinical trials (Rajkumar et al. 2011).

Table 3-4: Criteria for assessing progression of disease (modified from Bird et al., 2011)

Myeloma Progressive Disease Definition - Any of.	
1	≥ 25% increase in the serum monoclonal paraprotein level which must also be an absolute increase of at least 5g/l and confirmed by at least one repeated investigation.
2	≥ 25% increase in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200mg/24 hours and confirmed by at least one repeated investigation.
3	For patients with light chain myeloma (the serum and urine M-protein are unmeasurable), ≥ 25% increase in the difference between involved and uninvolved serum FLC levels. The absolute increase must be > 100mg/l.
4	≥ 25% plasma cells in a bone marrow aspirate or trephine biopsy, which must also be an absolute increase of at least 10%.
5	Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas.
6	Development of new lytic bone lesions or soft tissue plasmacytomas. Development of a compression fracture does not exclude continued response.
7	Development of hypercalcaemia (corrected >2.8mmol/l) not attributable to any other cause.

Data for the survival analysis were collected via bespoke clinical research forms (CRFs). These were tested for face validity by a random sample of the research nurses and consultant haematologists participating in the study. Data were requested from research nurses supporting local recruiting sites, as this was considered more likely to facilitate timely returns. A decision was made to collect data on 'patients lost to follow-up', by requesting data from WCISU. Data available from WCISU were 'death of participant' only. However, it became apparent that data would not be available in a timely manner. Due to the anticipated low numbers of patients lost to follow-up, expressed by recruiting sites, survival data was only collected from participating sites.

Data were collected at six and twelve months following the closure of recruitment of the quantitative study. It is intended to continue to collect survival data beyond the completion of the PhD studentship to report complete survival analysis.

Survival analysis statistical techniques are based on representing the time until a single event. The event for this study being treatment failure determined by the commencement of further myeloma treatment or death. Survival analysis predicts the event of death or progression when the event has not yet occurred for all the study population, by using data collected from event time points along a given time period. This is called censored observation (Kirkwood, 1993). The use of 'Life Tables' demonstrates the proportion of surviving patients over time. Kaplan-Meier analysis uses death events to calculate and recalculate the survival rate rather than a fixed time point. As median survival in myeloma is five years (Bergsagel et al., 2013), it would be likely that survival events for half the study population would be available at the end of a five-year period. If a higher percentage of disease progression is recorded at an earlier time point, survival analysis would be calculated using Kaplan–Meier at this earlier point. Within the life tables, Kaplan Meier analysis will express survival based on groups which will be divided into prompt, average and longer diagnostic journey groups. It may also be possible to display survival based on groupings of age and gender or other significant factors identified from analysis of the quantitative data.

3.13 Qualitative study

The qualitative study was designed to contribute to the further answering of the research questions:

- What are the factors, interactions and experiences that influence the pathway to diagnosis?
- What factors may influence more timely diagnosis?

These research questions were also considered in the quantitative study, but in the review of the research questions it was apparent (Table 3-1) aspects of these questions would be informed through qualitative approaches. This part of the study, therefore, looked to explore the personal, social, contextual and behavioural aspects surrounding the individual journey to diagnosis of patient participants who had provided data in the first quantitative study.

As the systematic review reported long primary care intervals in myeloma, the interactions between patient participant and their GP in primary care were considered of interest and likely to expand the understanding of influences in the diagnostic journey. GPs of the interviewed patient participants were also, therefore, included in the qualitative study.

3.13.1 The methodological approach

Although there were a range of possible qualitative methods available, including focus groups, participant observation and structured or unstructured interviewing (Mason, 2002), semi–structured interviews were the method of choice. Consideration of all methods available to the researcher were made before decisions were made and the reasons these were not chosen individually reported.

Participant observation was considered inappropriate as it would not allow the development of a dialogue between researcher and participant. This would prevent guiding and exploration of specific topics to inform the research questions. The primary object of this approach is to observe the participant in their normal environment and record how they react and behave in different situations, which would require prospective assessment of the diagnostic process (Ritchie and Lewis 2003).

Focus groups were considered, as they draw participants together and allow questioning and soliciting of personal perceptions and perspectives desired for this study. The nature of the sharing is within a group situation and as there was a potential for the participants to experience distress through recalling their diagnostic journeys this was an overriding concern and made the focus group approach inappropriate (Ritchie and Lewis, 2003).

Telephone or face-to-face interviews were considered as an approach. Joubish et al. (2011) supports the use of face-to-face interviews as the most likely method of enquiry to solicit the perspectives/perceptions of participants. Conducting face-to-face interviews with patient participants in their chosen setting, i.e. home or treating hospital, allowed the environmental and contextual surroundings to be considered within the interview through completion of researcher field notes (Ritchie and Lewis, 2003). It also allowed the patient participants to maximise their feeling of equality and safety with the researcher within the interview and ensured the well-being of the patient by preventing the need to travel (Ritchie and Lewis, 2003). Face-to-face

interviews also complemented the discussions of sensitive subject matter within the interviews and allowed support within the interview if or when distress occurred for patient participant. This was considered appropriate and emphasised in the ethical application as necessary if anxiety or distress in the patient participants arose. Interviews in the ethical application would, therefore, signpost to refer back to clinical team if considered necessary (Appendix 8). For these reasons, face-to-face interviews were chosen as an approach for the patient participant interviews.

GP interviews were conducted via telephone for two reasons: arranging individual interview slots with GPs was likely to be time consuming and difficult to organise given GPs' busy schedules; completing interviews across Wales with GPs would be resource-heavy in terms of time and money and likely to be prohibitive to the research budget. Telephone interviews with the GPs would still afford privacy and allow the perceptions and perspectives of the GPs to come to the forefront, but equality between the interviewee and GPs was of less concern and the GPs' environmental and contextual surroundings of less significance to that of the patient participant. A disadvantage was seen that interviews would not be as revealing or dialogue would be more stilted with interviews by telephone for GPs. This was considered, but on balance did not change the approach chosen (Joubish et al., 2011; Ritchie and Lewis, 2003).

A semi-structured interview format was used for both participant groups. This allowed flexibility in the interviews to explore areas of interest emerging from participants or the identification of new themes and allowed participants to drive dialogue towards their own areas of interest and priority. The structure also retained the ability to use prompts for questions of interest on the topic when areas remained unexplored or the dialogue moved off topic (Ritchie and Lewis, 2003). Joubish et al. (2011) and Ritchie and Lewis, (2003) recommend this approach for reducing the possibility of a researcher-imposed hypothesis, formed from professional understanding, influencing the collection of data.

The cancer care and research career of the student researcher was strongly influenced by pre-existing knowledge and experience of the diagnostic processes in myeloma. This was considered to have a potential to bias the collection of data by exploring areas of interest from an imposed hypothesis. This was considered to be better managed through a semi-structured interview format (Creswell, 2014).

Management of the interview process was guided by the development of topic guides for both sets of interviews, which primarily protected the participant perceptions and helped managed or minimalize the imposing of the researchers own theories and preconceptions, and, additionally, provided structure for the student researcher to follow with prompts for the discussion around themes identified through the systematic review and quantitative data (Ritchie and Lewis, 2003).

3.13.2 Development of the interview topic guide

The interview topic guide was developed to allow the further exploration of the research questions to be answered through the collection of qualitative data (Table 3-1). Although this focused on areas of interest identified in the systematic review and quantitative data the guide was developed with flexibility in mind; areas for exploration were included to encourage participants to respond in their own terms. These included topics of: exploration of the patients' perceptions and interactions around self-referral; the primary and secondary care diagnostic experiences and; intervals. This then allowed the diagnostic journey components and intervals to be discussed in relation the participants' own particular social and cultural situation. The topic guide prompted dialogue around symptom appraisal, myeloma diagnosis and intervals through a discursive process, with discussions aiming to be free-flowing and avoiding rigidity (Ritchie and Lewis, 2003). Whilst the supervisory team acknowledged the student had refined communication skills and a clinical background which was likely to aid the interview process and discussion, the researcher had never undertaken qualitative research before and the guide was considered useful to act as an aide memoir if the researcher became distracted or felt too much loss of control in the dialogue. This is considered good practise by Ritchie and Lewis (2003) and Mason (2002).

The draft interview topic guide was peer reviewed by a research department active in cancer, primary care and qualitative research. The process generated feedback from senior and experienced researchers for validity in capturing data of interest and usability (Ritchie and Lewis, 2003). The feedback was used to amend the interview topic guide (Appendix 9) prior to the commencement of interviews. The amendments made are listed in Box 3-4.

Box 3-4: Amendments to interview topic guide following peer review

Before the interview

- Quality checks were added to check equipment before arriving for interview

The introduction

- Addition of reminder to 'turn on tape' at the beginning of the interview
- Expansion of the general introduction
- Clearer outlining of confidentiality checks
- Thanking the participants for their time and participation

Warm up

- A helpful debate about the usefulness of this section occurred through peer review. The building of trust with the participant through the use of exploratory questions focusing on the participant's life and situation were welcomed by about half the reviewers. These questions were modified to reduce the number of exploratory questions, but the theme itself and the 'settling in' of the participant into the interview was considered too important to remove the section completely

Symptoms

- There was general agreement that the symptoms questions were appropriate and worthy of their place in the guide.
- Questions were sub-divided into three sections: first symptoms and assessment; seeking advice and; reassurance and reflection. This modification was made simply for ease of use

Primary care interactions and experience

- No modifications were made following peer review

Secondary care interactions and experience

- No modifications were made following peer review

Reflection of experience

- No modifications were made following peer review

Reassurance

- This section was modified after peer review to include a reminder of confidentiality and thanks the participant

The process was repeated to form a topic guide for the GP interviews. The themes were developed from the areas of interest identified from the systematic review and quantitative data and focused around the identification of symptoms, response to symptoms, suspicion of myeloma in primary care referral to secondary care and patient factors related to difficulties with diagnosis. The questions within the guide permitted a similar pattern of discursive responses to question of themes from a GP perspective (Appendix 10).

3.13.3 Sample size

A sample size of 24-30 patient interviews and 10-15 GP interviews was chosen from consideration of similar studies that either explored behavioural and contextual factors in primary care, or the early diagnosis of cancer (Emery et al., 2013; Green et al., 2015; Ridd et al., 2006; Place et al., 2011; Walsh et al., 2012; Whitaker et al., 2015a).

As the GP interviews build on from the experience of participants around the patient-doctor interaction, interviews were linked to the patient participant interviews, and invites sent to GPs following the completion of the patient participant interview. This meant GP interviews were entirely dependent of the number of patient participant interviews conducted.

At the outset of the interviews a full cross section of patients/participants with experience of myeloma were sought from the recruitment categories in order to explore experiences across the full range of

Purposeful sampling and recruitment (see Box 5 below) of this scale is considered feasible for semi structured interviews, as opposed to in-depth interviews, which generate considerable volume of detailed conversation and narrative data (Suri, 2011).

However, once participants were asked about their experience or treatment and diagnosis journey, they talked at length and in rich detail. Therefore, theoretical saturation was achieved earlier than anticipated. Theoretical saturation is a term most associated with the Grounded Theory qualitative approach, and is the point when the researcher finds their analysis of data leads to no more information. In saturation, the researcher sees that data reveals similar instances over and over again, categories become unchanged or do not develop further. The researcher concludes the categories are 'saturated'. However, at this point the researcher must be able to determine that the descriptions of these categories are thick and a theory can emerge from existing data for true saturation to be achieved (Seale, 1999).

3.13.4 Sampling

Purposive sampling was undertaken in the patient participant population as this allowed the most information-rich diagnostic journeys to be identified for interviews (Suri, 2011). Samples were drawn from 'prompt' and 'longer' diagnostic journey groups to explore the extremes of the influences on the journeys and report the

negative and positive effects of behavioural and contextual factors on the timing of the diagnosis. A third group was sampled from those myeloma cases who were diagnosed in the absence of symptoms. These cases were reported in data identified from the systematic review, but there was no appreciation in the reported findings of how this influenced the journey to diagnosis (Howell et al., 2013; Howell et al., 2015; Ong et al., 1996). Asymptomatic/smouldering myeloma patients were also sampled to be represented in each sample subgroup, as little appreciation of their diagnostics journeys was seen in the review.

Box 3-5: Sample groups for qualitative interviews

Longer journeys to diagnosis group:

Sample of (n=8-10) patients reporting time to diagnosis within the upper quartile sample range. The sample will be purposive to include a representative sample number of asymptomatic myeloma patients.

Prompt diagnostic journey group:

Sample of (n=8-10) patients reporting time to diagnosis within the lower quartile range. The sample will be purposive to include a representative sample number of asymptomatic myeloma patients.

Asymptomatic group:

Asymptomatic presentation: Sample of (n=8-10) asymptomatic presentation of myeloma, the sample will be purposive to include a representative sample of asymptomatic/smouldering myeloma patients.

GP group:

Sample of 10-15 GPs sampled from the patient participants interviewed.

Sampling for the 'prompt' and 'longer' groups were determined from calculated participant time to diagnosis intervals from the analysis of the quantitative study and were measured against the upper and lower quartile ranges for the myeloma group within the Howell et al. (2013) study. This study demonstrated good quality assessment in the systematic review, was the most recent data reporting 'time to diagnosis' intervals for myeloma and reported intervals to diagnosis in line with the Aarhus statement (Weller et al., 2012).

Participants were invited to participate in the qualitative interview study when their time to diagnosis interval was less than 84 days for the 'prompt' sample group; and greater than 306 days for the 'longer' interval group.

Participants in the quantitative study had given consent to be approached to interview. However, because the calculation of the time to diagnosis interval was dependant on returns of the GP and haematologist questionnaires, there was a delay in the invitation. Safety procedures were added to the recruitment of participants to ensure participants were not approached in the event of clinical deterioration. The procedure involved the student researcher checking the potential participants' status with the recruiting site to ensure they were 'fit' to undertake an interview. There was a potential for 'gatekeeping' activity by adding this check as a safety measure, but the avoidance of any undue suffering caused by approaching participants who had clinically deteriorated or died was considered more important. When recruiting sites confirmed the participants' clinical conditions were satisfactory, patient information sheets and consent forms were sent to participants, and in line with the participants' information sheets, participants were given an 'opt out' slip to return if they no longer wished to participate in the interview study. Otherwise, they were contacted by telephone to request an interview two weeks later.

3.13.5 The interview

The interviews took place in an environment chosen by the patient participant or in the case of GPs over the telephone with GPs. Using familiar surroundings was intended to make a better interview experience for the patient participant, that would be more likely to reveal in-depth experiences and perceptions (Mason, 2002; Ritchie and Lewis, 2003). Offering to conduct the interview in the patient's own home was also felt likely to increase participation, acknowledging that there was a possibility that mobility issues, poor performance scores and clinical status (Augusten et al., 2005) could potentially reduce the available sample, if travel was required. No restrictions were given on whether the participant could have a family member or friend accompany them in the interview, in efforts to make the interview as conducive and inclusive to all participants. Where participants were accompanied the contribution and potential co-production of data by partners or carers was noted in the field notes. This was taken into consideration in the analysis.

The interviews were designed to last about 60 minutes for the patient participant group and about 30 minutes for the GP group. Duration was considered likely to be dependent of the flow and depth to the conversation which would be primarily led by

the interviewee, but monitored through the checking that all areas had been addressed in the topic guides (Ritchie and Lewis, 2003).

Following the interviews, field notes were made for both participant groups, describing the content, depth and relationship between interviewee and interviewer, the setting and context of the interview. Field notes were used in analysis, along with transcriptions, to provide reminders of the interview setting and dynamics that might be less obvious or missed in the transcribing of words only (Ritchie and Lewis, 2003).

All interviews were audio-recorded and transcribed verbatim by transcription services. Transcriptions were anonymised for identifiable names, locations, hospitals, general practices, and clinician names. A small number of transcripts were checked completely against the audio recordings (N= 4 patient participants; N= 2 GP participants) and the remainder had sections of transcripts and audio recordings checked. Transcripts were then checked by a supervisor to assess the communication between student researcher and participant groups. This process reviewed the development of dialogue, ensuring the interviews were participant-driven and, when necessary, guided by the researcher, rather than the researcher imposing and creating the agenda for discussion (Ritchie and Lewis, 2003).

3.13.6 Analysis of the qualitative data

The Framework Method of analysis (Ritchie and Spencer, 1994) was used to organise and structure the analysis process. Framework analysis was adopted for four main reasons:

- A *priori* assumptions, taken from the systematic review and quantitative data, formed a predefined analysis plan and made Framework Analysis a more appropriate method choice (Lacey et al., 2009) for the strongly post-positivist researcher.
- Framework analysis is a more commonly used and accepted method of analysis for qualitative healthcare policy research and complemented the aims of the study to inform policy and practice. An assumption was made that this method would facilitate dissemination better as well (Pope et al., 2000).
- The more systematic approach, clearly defined in Framework analysis, gave the student researcher guidance in conducting the analysis, through the unfamiliar process of qualitative analysis (Lacey et al., 2009).

- Framework Analysis allowed for the immediate commencement of analysis following the first interview allowing the development of the themes emerging from the interviews to be incorporated in successive interviews and complementing the exploratory nature of the approach (Lacey et al., 2009).
- Framework analysis facilitated through its defined steps, rigour and transparency which would be more likely to impact the biomedical and clinical field targeted for dissemination (Lacey et al., 2009).

Framework analysis was implemented following a systematic process described by Ritchie and Spencer, (1994) (Box 3-6)

Box 3-6: Implemented by the recognised systematic structure (Ritchie and Spencer, 1994)

Familiarisation: The student researcher became familiar with data through checking for validity, whole transcriptions were read and reread for all participant interviews by the student researcher.
Identification of a thematic framework: Using the priori issues identified from the systematic review, an initial coding exercise was performed across the dataset. New or unexpected/anticipated data were identified and coded with in the datasets.
Indexing: Thematic analysis was applied to data, using contextual codes which identified specific extracts within the dataset which were seen to correspond with divergent themes.
Charting: Headings from the thematic analysis were used to create charts (visually prompted mind maps and tables) allowing the summarisation of the dataset. Charts were initially developed as tables to represent individual cases and then mind maps used to depict themes across the dataset summarising themes within them
Mapping and interpretation: Through thematic analysis – detailed Box 3.7

Following the organisation and processing of the dataset using Framework Analysis, Thematic Analysis was applied to inform analysis and facilitate interpretation.

Phases of Thematic Analysis, described by Braun and Clarke (2006) and detailed in Box 3-7, provided guidance for analysis and interpretation that did not intentionally narrow or limit the process. This guidance provided an outline for analysis and

development of themes which helped the student researcher to structure the analysis process and describe, fully and openly, the processes followed.

Box 3-7: Phases of application of thematic analysis (Braun and Clarke, 2006)

Familiarizing with data:
Data was read and re-read, and initial ideas were noted down.
Generation of initial codes:
Interesting features within data were coded in a systematic fashion across the entire dataset. Relevant data to each code were collated.
Theme searching:
Coded data were collated into potential themes, with all data relevant to each potential theme gathered together.
Theme reviewing:
Checking of the themes identified back across the coded extracts to see if they are correct, firstly with individual coded extracts (Level 1) and then across the entire dataset (Level 2). A generated thematic 'map' of the analysis was then created.
Theme definition and naming:
Themes were given clear definitions and names through an ongoing analysis process. The specifics of each theme were refined, and the overall story of analysis produced.
Production of the report:
The final process involved selection of vivid, compelling extract examples, final analysis of selected extracts. These were related back to the original research question and literature, producing a scholarly report of the analysis.

A non-linear process was applied to reading transcripts in both participant groups; as more interviews were conducted transcripts from all interviews were re-read. Initial coding was undertaken using a deductive process (Braun and Clarke, 2006) strongly linking codes to the dataset, avoiding potential for the researcher to "fit" codes into a pre-existing coding frame and analytic preconceptions. Codes, therefore became data-driven and were not restricted to the predefined research questions, but allowed the exploration of data. Codes were identified based on 'prevalence' within the dataset as identified by Braun and Clarke (2006). Prevalence was determined by the number of words or space given within transcripts to the code, or the emphasis placed on the code by the individual or, prevalence in terms of the number of participants that made reference to the particular code.

In the patient participant analysis, codes were then used to identify semantic (word driven) themes. Using semantic themes allowed the identification of explicit or surface meanings within the words (Braun and Clarke, 2006), therefore, what the participants said, rather than interpreted or deduced meanings, became apparent. Semantic themes, therefore, ensured indexing remained data-driven and reduced the interpretation of 'latent themes' in the positivist driven student researcher.

In the GP participant interviews 'latent coding' was applied to theme development. Latent coding allowed more deducing of real meaning and interpretation of the words in the dialogue in interviews earlier in the coding process (Braun and Clarke, 2006). A benefit of understanding deeper meanings in the GP conversations through interpretation of meanings by the student researcher was considered beneficial for this analysis, and the use of the student researcher epistemological stance likely to be beneficial, in deriving deeper meanings in the GP data.

Themes were charted for individual participants, then charted across the dataset to form final themes. Tables were used to chart individual semantic text and themes and mind maps were used to summarise the themes and semantic or latent extracts across the dataset. The student researcher remained data-driven throughout the analytical process. Whilst, inevitably, the research questions informed the interpretation of the themes, themes were derived and deduced from data.

During the development of codes and themes, the student researcher and a member of the supervisory committee met to discuss the basis of coding and rationale for themes proposed. This was an additional quality check, with the supervisor assessing that codes created and themes developed, were reflective of data derived from the interviews and were not the student researcher's own views and perspectives.

Theorising then took place alongside the existing evidence supported in the literature to draw conclusions.

3.13.7 Interpretation phase

The final phase of the explanatory sequential programme of research was the interpretation of the quantitative and qualitative findings, to produce final results and make recommendations for policy and practice. This interpretation forms a discussion of the reported findings of the individually analysed phases of the

quantitative and qualitative research (Creswell, 2014). The aim of the interpretation process, for the explanatory sequential design, is to present a deeper understanding of the quantitative findings by explaining or expanding the understanding through the qualitative findings (Creswell, 2014). This model is reported to prevent the narrowing of the quantitative findings by the qualitative findings that convergent interpretation methods permit (Creswell, 2014).

As each phase of the study had been previously analysed and reported with conclusions and recommendations made, the last three phases of thematic analysis were applied across the datasets (Box 3-7). The themes were analysed across the datasets and organised into themes representing those reported in the quantitative study e.g. patient factors; symptoms development and evaluation in patient; assessment of symptoms in primary care; responses to symptoms; referral patterns from primary care; passage and investigations in secondary care. Each theme was assessed through reviewing the outcomes reported across the dataset and theorising with the known literature. These outcomes then formed a final report making recommendations for policy and practice.

3.14 Research design limitations

Throughout the design process, considerations for achieving validity and reliability were made (Mokkink et al., 2010; O'Cathain et al., 2008). Within the individual methods sections in this chapter, the additional checks to ensure validity and reliability have been discussed. However, some limitations are still present in the design of the study

The research design (explanatory sequential design), in itself, allowed the collection of data to ensure the research questions were answered or informed i.e. quantitative and qualitative data. However, the design requires a more complex analysis process which is highlighted by Creswell (2014), as being a more challenging research methodological approach. The complex analysis process was undertaken by a student researcher who would be considered a novice in apply research methodology as this is the purpose of the apprenticeship. Therefore, although expert supervisory guidance and checking was in place throughout the study, it is possible that the naivety of the researcher has affected the application of these chosen and more difficult methods.

The modified questionnaires as the 'tool choice' were modelled on questionnaires that had received positive reporting of validity and usability (Weller et al., 2016). Modifications to these questionnaires were justified using the evidence from the systematic review. Modified questionnaires received face validity testing by 'expert' groups and edited from observations made. However, no piloting was performed of the modified questionnaires prior to their use and, therefore, no validity or reliability testing could be performed.

The sample size for the study has been made rather pragmatically from the available information. The potential for recruitment of this population of patient participants was an unknown quantity, and has the potential to be less than calculated. This was considered as possibly affecting the generalisability of outcomes. Whilst it was acknowledged that the study's aims and objectives were exploratory and generalisability not the highest priority, it was also acknowledged that this may impact the ability of the outcomes to influence policy and practice.

3.15 Ethics

Ethical applications were made to the School of Healthcare Sciences at Bangor University and Wales Research Ethics Committee (MREC 5). NHS ethical approval was required as the identification and recruitment of patient participants was conducted at NHS hospital sites (Appendix 8). Full ethical approval was granted from both committees with only minor points for modification, which mainly focused around the wording of some patient information. General feedback from both School and NHS ethics committees were positive.

Research and Development (R&D) approvals were provided by the health board R&D departments of all hospital sites with haematology MDTs (Box 3-8). All applications made were favourably considered for the recruitment of the patient and GP participants, with only minimal amendments.

Box 3-8: Research and development approvals obtained

Betsi Cadwaladr University Health Board:

- Gwynedd Hospital
- Glan Clwyd Hospital
- Wrexham Maelor Hospital

Cardiff and Vale University Health Board:

- Heath Hospital (Also serving Llandough Hospital MDT)

Aneurin Bevan University Health Board:

- Royal Gwent Hospital
- Nevill Hall Hospital

Hywel Dda University Health Board:

- Withybush Hospital
- Glanwili General Hospital
- Prince Philip Hospital

Cwm Taf University Health Board:

- Royal Glamorgan Hospital
- Prince Charles Hospital

Abertawe Bro Morgannwg University Health Board:

- Singleton Hospital (Also serving MDTs for Morriston Hospital, Neath Port Talbot Hospital)

3.16 Affiliations

The study was adopted by the National Institute of Health and Social Care Research (NISCHR) portfolio (now rebranded as Health and Care Research Wales) and also added, through a reciprocal adoption process, to the portfolio list for the National Institute of Health Clinical Research Centre (NIHR CRC).

4 Chapter Four: Determining the diagnostic journey in myeloma: how long does it take to diagnose and what, where and to what significance do factors affect the length of the journey?

4.1 Summary

This chapter reports the findings from the survey data collected from patient participants, general practitioners and diagnosing haematologists close to the patient participant's diagnosis of myeloma. The evidence in the chapter closes the gaps in the knowledge identified from the systematic review (Chapter Two section 2.7). The intervals to diagnosis and treatment, and the factors or variables that influence the timeliness of a diagnosis of myeloma, are reported through statistical evaluation providing significance testing of these variables on the intervals to diagnosis and treatment. The results, therefore, provide evidence to demonstrate where, across the diagnostic journey, these factors are of influence, and to what degree they influence the timing of the journey. Recommendations are made from these findings for areas of priority for policy initiatives to provide a real opportunity for the timelier diagnosis of myeloma.

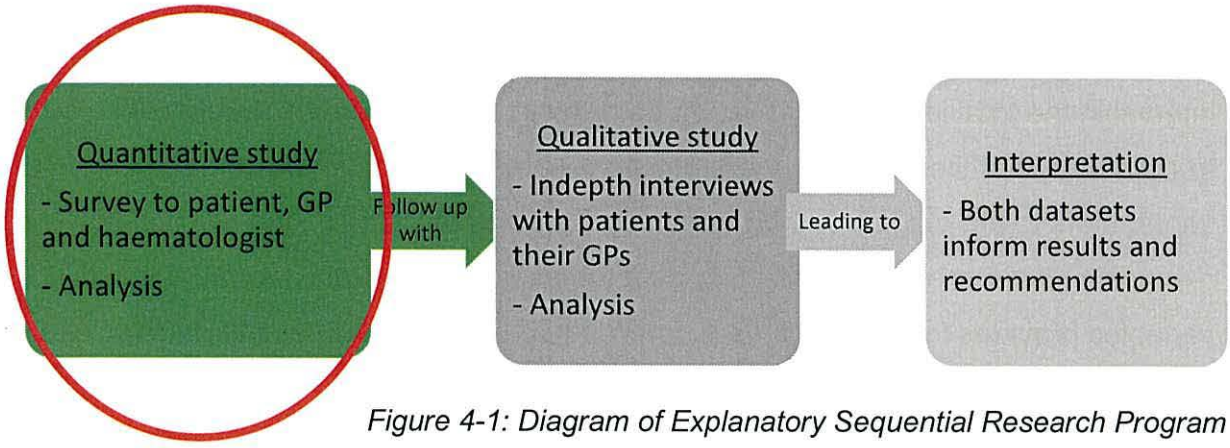

Figure 4-1: Diagram of Explanatory Sequential Research Program

(Adapted from Creswell, 2014)

4.2 Background

The systematic review, reported in Chapter Two section 2.9, concluded that there were only limited data to aid the understanding of the diagnosis of myeloma, which were insufficient to make recommendations for current practice or inform future policy. The review specifically highlighted gaps in the assessment of the journey to a diagnosis of myeloma, including no assessment of the secondary care interval, the treatment interval and the total interval to treatment, which results in an inability to assess the relative contributions of these intervals in the total journey. The review found that myeloma diagnosis was associated with: longer primary care and diagnostic intervals; increased numbers of GP consultations prior to onward referral; higher frequency of emergency presentation to secondary care and worse outcomes

for longer intervals. The review recommended that these factors and variables should be collected alongside the measurement of the intervals to diagnosis in a cohort of myeloma patients. In addition, the review reported differences in the length of intervals measured according to which data collection method was used, such as extraction of data from routinely collected records held on the digital primary care records database, or the collection of symptom data directly from patient participants. The review found that collecting participant self-reported symptom data reported longer patient intervals.

This quantitative study aimed to describe the journey to diagnosis for myeloma patients through measurement of each interval within the total interval to diagnosis and treatment, allowing the relative contribution of each interval to be determined along the whole journey. In addition to the measurement of these time intervals, the study aimed to collect the factors and variables which potentially influenced each interval in the total journey. This would be done through the depth of data collected, from factors identified within the systematic review and obtained from the three contributors to the diagnostic and treatment process: the patient, the GP and the diagnosing haematologist. Collecting data to assess all intervals and factors and variables provides for the first time a detailed picture of the journeys to diagnosis of newly diagnosed myeloma patients.

4.3 Methods

A detailed account of the methodology and rationale for the chosen method is provided in Chapter Three. Described here are the practical implication of the chosen methods.

4.3.1 Approvals

Ethical and R and D approvals are listed in the methods chapter (Chapter Three section 3.15 and 3.16). Twelve recruitment sites were approved to invite and recruit patient participants and collect data from GP practices and secondary care haematologists. The approval of the 12 sites across Wales allowed recruitment from all hospitals hosting haematology MDTs (Multi-Disciplinary Team Meetings), where consensus of diagnosis and registration of the myeloma occurs.

4.3.2 Identification and recruitment of participants

Potential participants were identified at the MDT meetings by research nurses, specialist nurses or haematologists, and were invited to participate if they met the eligibility criteria within the study Protocol for asymptomatic or symptomatic myeloma (Appendix 11). Written study information was given to potential participants. Participants were encouraged to take the documentation home and fully read and complete questionnaires if they wished to participate in the study. Participants were not excluded from participation if they could not complete the study questionnaire themselves. Instead, they were encouraged to ask a family member, friend or research nurse to help them complete the document. Participation was registered after return of a participant completed consent form and questionnaire. Following registration, participants were given a unique study number, which was used from the point of registration onwards for anonymised analysis of their data.

The number of participants screened and the number invited to participate were recorded on screening logs and collected from each site at monthly intervals. National MDT logs were collected from haematology MDT coordinators quarterly, allowing assessment of the numbers offered participation at each site and the number of new myeloma cases registered on national Welsh cancer databases. Non-responders were sent one reminder letter from the local site after a period of four weeks had elapsed from the initial invitation to participate, taken from the screening logs.

On return of the patient participant questionnaire, when consent was given to approach the participant medical team, questionnaires were sent to the GP and haematologist identified within the patient questionnaire. When questionnaires were not returned, reminder letters, generic to GPs and haematologists, were sent. Two GP reminder letters were sent in the event of non-returns, at intervals of no less than four weeks apart. As secondary care were supported by research network nurses, if questionnaires were not returned from haematologists following two reminder letters, research nurses were approached via e-mail to complete the questionnaires.

4.3.3 Data management

Data was processed and transcribed into a bespoke database (ACCESS 2013). This database and the source data (completed questionnaires) were audited. These processes are described in full in the methods chapter (Chapter Three section 3.11).

Data queries were not generated for missing data within questionnaires, only for incorrect completion of consent forms. These were followed up only when the participant provided contact details.

4.3.4 Data hierarchy

The combined questionnaires collected multiple variables for analysis (>200). Many of the returned questionnaires contained data provided in an unquantified or incomplete way e.g. date of first symptoms frequently given as a month and year, less frequently as a year. A data hierarchy was developed to allow for these anticipated variances and applied to all data to allow the quantification of data before transferring into the IBM SPSS (version 22) statistical programme for analysis (Appendix 7).

4.4 Statistical analysis

4.4.1 Descriptive statistics

All variables were analysed descriptively. Continuous variables were reported using median, interquartile ranges, and, for intervals, the 90th percentiles. Categorical variables were reported using counts and percentages. Analysis of data using descriptive statistics was in keeping with the study's exploratory design, allowing the depth and breadth of data collected to be reported in a descriptive but quantified way and was comparable to other studies reporting cohort data for early diagnosis of cancer research (Walter et al., 2015; Walter et al., 2016).

4.4.2 Correlation

Pearson's Product Moment Correlation Coefficient analysis on numerical variables against the measured intervals to diagnosis was conducted to look for associations between factors and intervals. This exploratory analysis showed the strength of relationships between many of the numerical variables previously unexplored.

4.4.3 Regression analysis

Prior to regression model construction, data were re-examined and modified to create a linear representation of categorical variables. This process was informed by the systematic review's recorded influences of factors and clinician consensus i.e. routes of referral to secondary care 1 = Two-week wait; 5 = Non-urgent referral.

Regression analyses were carried out, building models of factors associated with the measured intervals to diagnosis identified from the systematic review (Field, 2009) as described in Chapter Three section 3.11.4. Variables were grouped according to

categories of evidence i.e. multi-morbidities/symptoms, or the area the activity within the total interval to diagnosis had influence i.e. activity in primary or secondary care. Stepwise backward regression analysis was then applied. Thirteen regression models were constructed, reflecting the number of independent variables collected and available for examination. Regression models varied in number of independent variables examined from 2 to 29. Each regression model, for completeness and full exploration, was run against each interval to diagnosis, measured by descriptive statistical analysis. Dependant variables were: the patient interval, primary care interval, secondary care interval, diagnostic interval, time to diagnosis, treatment interval and total interval to diagnosis. These were calculated in line with recommendations from the Aarhus statement (Weller et al., 2012). Two additional dependant variables were calculated (labelled non–Aarhus) for the primary care and secondary care intervals within the study. These intervals were calculated to compensate for the low case numbers contributing to the calculation of the Aarhus compliant primary and secondary care intervals. Case numbers in these two intervals were reduced to the lower primary care questionnaire returns which prevented the calculation of the start or end dates of the intervals.

The first phase of regression analysis was completed by analysis of co-efficient tables and rejection of variables within each model with statistical significance $p>0.05$. Second phase analysis was conducted by building models using the statistically significant independent variables (with $p<0.05$) identified from the 13 first phase models. These models were then run with a backwards stepwise regression analysis against the appropriate dependant variable interval. Correction for the number of regression analyses were made using the Bonferroni correction (Field, 2009). The correction accounted for the 13 models using the equation 0.05 (level of significance) /13 (number of models) = p 0.003 correcting for over fitting. Variables with significance of $p>0.003$ where then rejected from the model leaving factors with significance of $p<0.003$ reported.

Assumptions for data were not formally examined because the study had an exploratory design and the desire to generalise to the wider population was not the main aim (discussed in Chapter Three section 3.11.4). However, assessment for outliers and residuals was conducted through the descriptive statistical analysis. The

possibility of distorting the analysis was considered to be significant with single variant cases and would be acknowledged when reporting the results.

4.5 Results

4.5.1 Recruitment

All of the 12 approved sites recruited to the study. There was variation in the number of recruited, screened and MDT registered cases across sites (Table 4-1). During the 18-month recruitment period, a total of 258 new cases of myeloma were registered at MDTs across Wales. One hundred sixty-five (63%) patients were screened, approached or offered participation, 84 (50%) participants were recruited. Overall 84 of the 258 new cases of myeloma diagnosed and registered at MDTs across Wales were recruited into the study (32%). Explanations for lower recruitment figures from sites cited difficulties with having dedicated research staff to conduct screening and recruitment as the biggest barrier. Overall a reduced number of newly diagnosed cases were recorded from the national MDT database during the recruitment period of this study compared with those reported as an annual incidence of myeloma for Wales in 2013 (Cancer Research UK, 2017a) and meant the available population was lower than originally anticipated.

Table 4-1: Final recruitment by NHS site

Site	Screened/ approached / offered	Recruited	No. cases registered at MDT	% approached vs recruited	% approached vs identified at MDT (available)	% recruited vs identified at MDT
BCUHB West	11	11	14	100	78	78
BCUHB Central	13	4	23	30	17	56
BCUHB Wrexham	19	13	22	68	59	86
Cardiff and Vale (Heath)	36	14	66	39	21	54
Aneurin Bevan Royal Gwent	25	11	29	44	37	86
Aneurin Bevan Nevill Hall	7	4	8	57	50	87
Hywel Dda Withybush	15	8	10	53	*	*
Hywel Dda Glanwili	9	6	11	66	54	81
Hywel Dda Prince Phillip	4	1	15	25	6	26
Cwm Taf Prince Charles	4	2	0	50	*	*
Cwm Taf Royal Glamorgan	1	1	17	100	5	5
ABMU Singleton	21	9	43	42	20	49
Total	165	84	258	50	63	32

**Missing data*

Of the 84 patient participants recruited into the cohort, 83 gave permission for the collection of diagnostic details from their GP and hospital haematologist. Eighty-three GPs and haematologists were sent myeloma-specific questionnaires, 54 (65%) GP and 83 (100%) haematology consultant responses were received.

The original target recruitment of 190 participants was found to be unachievable due to the reduced available population of newly diagnosed myeloma cases. A modified target of 90 participants was adopted, based on population figures for cases recorded in the MDT logs for the first two quarter periods of recruitment (Figure 4-1).

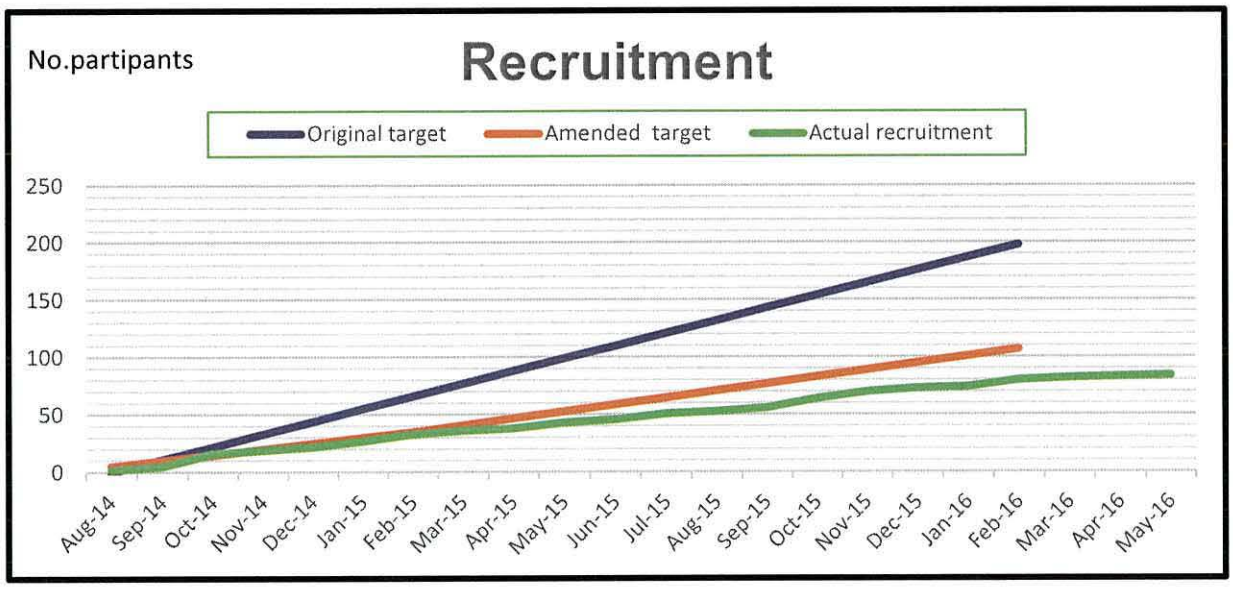

Figure 4-2: Recruitment graph DJiM study showing actual, target and modified target recruitment

Data from 84 patient questionnaires, 54 GP questionnaires and 83 haematologist questionnaires were transcribed into a bespoke ACCESS Microsoft database.

4.5.2 Data audit

Independent auditing (described in detail in Chapter Three section 3.11.2) revealed error rates in transcribed data of 2.1% for the first audit and 1.6% for the final audit. The combined categories of errors recorded were: 0.8% 'missing data' group and 0.4% 'incorrect data' group. The recording of ethnicity was the most frequent error category at 0.2%. Corrections were made to data following the audits and observations made for repeated errors to increase awareness for future handling of data by student researcher.

4.5.3 Descriptive statistics

Table 4-2: Characteristics of the study population

Age	**Years**
Median	67.00
25th percentile	60.00
75th percentile	74.75
90th percentile	82.50
Min	39
Max	90
Gender	**N (%)**
Male	42 (50)
Female	42 (50
Ethnicity (WIMD)	**N (%)**
White British	83 (98.8)
Mixed/Multi ethnic – white black African	1 (1.2)
Deprivation quintiles (WIMD)* †	**N (%)**
10% most deprived	5 (6.1)
10-20% most deprived	8 (9.9)
23-30% most deprived	9 (11.1)
30-50% most deprived	11 (13.7)
50% least deprived	48 (59.2)
Work status at diagnosis	**N (%)**
Retired	46 (54.8)
Employed for wages	20 (23.8)
Home-maker	4 (4.8)
Self- employed	8 (9.5)
Out of work	1 (1.2)
Unable to work	5 (6.0)

84 cases reported. 0 missing

**WIMD= Welsh Index of multiple deprivation*

† 81 cases reported 3 missing cases

4.5.3.1 Gender

Equal numbers of males and females were recruited to the study. Myeloma incidence, in the wider population, is two-times greater in men than in women, exclusive of ethnicity (Waxman et al., 2010), making the population unrepresentative for gender (Table 4-2).

4.5.3.2 Age

Median age at diagnosis of the 84 recruited participants was 67 years, compared with a median age of 70 in the UK as a whole (Bird et al., 2011) (Table 4-2).

4.5.3.3 Ethnicity

There was very little ethnic diversity with the study population with 98.8% reporting their ethnic group as 'White British', compared with 86% reported across England and Wales (ONS, 2011) (Table 4-2).

4.5.3.4 Deprivation measurement

Postcodes from three participants, whose registered homes were within English boundaries, were unable to be assessed in the context of the population and were recorded as missing data. The population was slightly underrepresented within the quintiles of 10% most deprived, 30-50% most deprived and slightly over represented in the quintile 50% least deprived. These were only small variations and the population was representative in terms of deprivation (Table 4-2).

4.5.3.5 Work status of participants

Over half of the population were retired (54.8%) which reflects the median age of diagnosis of 67 years; 33.3% were in employment, and 6% were able to work (Table 4-2).

Table 4-3: Disease characteristics of the population

Monoclonal paraprotein*	**N (%)**
Immunoglobulin G (IgG)	49 (59.0)
Immunoglobulin A (IgA)	24 (28.9)
Light chain disease	7 (8.4)
Non-secretary/no abnormal chains	2 (2.4)
Immunoglobulin M (IgM)	1 (1.2)
Sub-class of paraprotein †	**N (%)**
Kappa	52 (63.4)
Lambda	28 (34.1)
Non-secretary	2 (2.4)
Stage of disease (ISS) ††	**N (%)**
Stage I	23 (28.0)
Stage II	30 (36.6)
Stage III	23 (28.0)
No staging performed	6 (7.3)

**83 cases reported – missing data x 1*

†82 cases reported – missing data x2

†† ISS = International Staging System for Myeloma as reported by diagnosing haematologists

4.5.3.6 Disease specifications

The distribution of monoclonal paraproteins was similar to the wider myeloma population in the UK (Smith and Yong, 2013) (Table 4-3).

4.5.3.7 Stage of disease at diagnosis

Stage of disease was as follows:

- stage I, 28%
- stage II, 37%
- stage III, 28%
- no stage given 7%

This was similar to the distribution reported in a larger sample of participants (*N*= 818) in the Medical Research Council (MRC) Myeloma IX trial (Morgan et al., 2012) (Table 4-3).

Table 4-4: Characteristics of participants in the pre-diagnostic phase

Health status	**N (%)**
Very good	38 (45.2)
Good	25 (29.8)
Fair	13 (15.5)
Poor	8 (9.5)
Very poor	0 (0)
Analgesia taken prior to diagnosis	**N (%)**
Yes	54 (64.3)
No	30 (35.7)
Category of analgesia taken	**N (%)**
Simple analgesia	24 (28.6)
Weak opioids	21 (25.0)
Strong opioids	9 (10.7)
Adjuvant therapy	1 (1.2)
No analgesia	29 (34.5)

84 cases reported. 0 missing

4.5.3.8 Participant self-assessed health status

Health status in the two-years preceding the diagnosis was reported as very good or good in three-quarters of the population (75%). No participant recognised themselves as having a very poor health status (Table 4-4).

4.5.3.9 Requirement for analgesia prior to the diagnosis of myeloma

Over half the study population reported requiring pain medication prior to their diagnosis (64%) and 35% took weak or strong opioids (Figure 4-4).

4.5.3.10 Multi-morbidities prior to diagnosis of myeloma

A range of 27 separate multi-morbid features were recorded from the primary care questionnaires as the primary source and, if unavailable, from patient questionnaires. Diabetes was the most frequently reported co-morbid condition (23%), then cardiovascular disease (20%), hypertension (18%) and lung disease (12%). Other multi-morbidities occurred in less than 10% of the population (Figure 4-2).

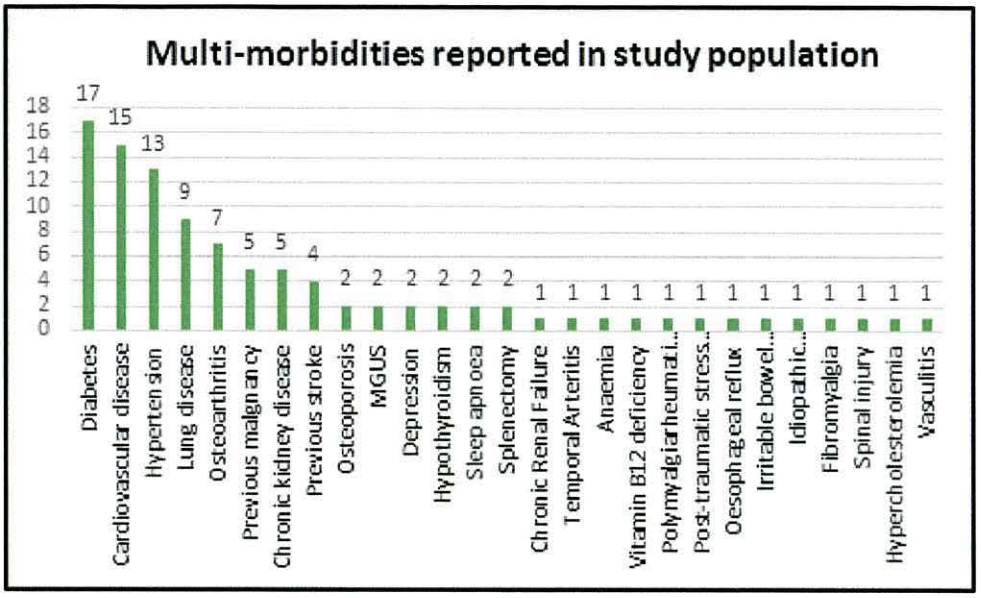

Figure 4-2: Multi-morbidities in the study population

**72 cases reported missing data x12. % >100% as participants may record more than one morbid feature*

Two-thirds of the population reported multi-morbid conditions (68%) prior to the diagnosis of myeloma (Table 4-5), which is similar to the 63% found in the general primary care population for the age range 65-74 years (Salisbury et al., 2011). The number and type of multi-morbid conditions were also similar. The multi-morbidities question was a less frequently completed item, with only 72 cases available for analysis.

Table 4-5: Number of multi-morbidities

Number multi-morbidities reported	N (%)
0	23 (31.9)
1	23 (31.9)
2	18 (25.0)
3	3 (4.2)
4	3 (4.2)
5	1 (1.4)
7	1 (1.4)

**72 cases reported missing data x12*

4.5.3.11 Self-reported participant symptoms prior to diagnosis of myeloma

All symptom data were reported from self-reported participant data. Thirty-nine different symptoms were reported by participants prior to the diagnosis of myeloma. The most frequently occurring symptom was musculoskeletal pain (pain in muscles and joints) and was reported by 58% of the population. The second most frequently reported symptom was new or unusual bone pain reported by 54% of participants and the third was fatigue reported by 50% of participants. The remainder of the seven symptom groups suggested to participants were reported in less than 30% of the population. Symptoms reported within free text boxes were recorded by less than 10% of the population. As symptoms were not quantified in free text boxes, only the seven symptoms offered to participants and occurring at higher levels were used for further analysis.

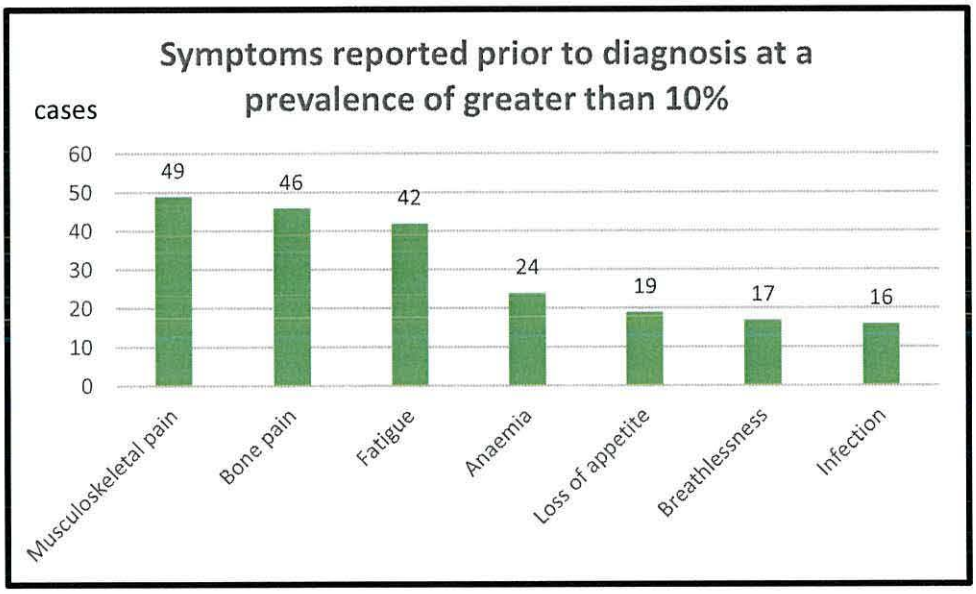

Figure 4-3: Symptoms reported as present prior to the diagnosis of myeloma

84 cases reported 0 missing data

Results = >100%

The median number of reported symptoms in participants was three, with a range of 0-7. Five participants (6%) reported no symptoms prior to the diagnosis of myeloma (Table 4-6).

Table 4-6: Number of Symptoms Experienced by Participant Prior to diagnosis

Number of symptoms	**N (%)**
0	5 (6.0)
1	14 (16.7)
2	13(15.5)
3	21 (25.0)
4	15 (17.9)
5	7 (8.3)
6	5 (6.0)
7	4 (4.8)
Number of symptoms analysis	**N (%)**
Mean	3.05
Median	3.00
Min	0
Max	7

84 cases reported 0 missing data

Results = >100%

Twenty-two participants reported experiencing all of the three most frequently occurring symptoms: bone pain, pain in muscles and joints, and fatigue (Figure 4-4). Two symptoms were reported by 21 participants and individual symptoms were reported by 29 participants (Figure 4-4).

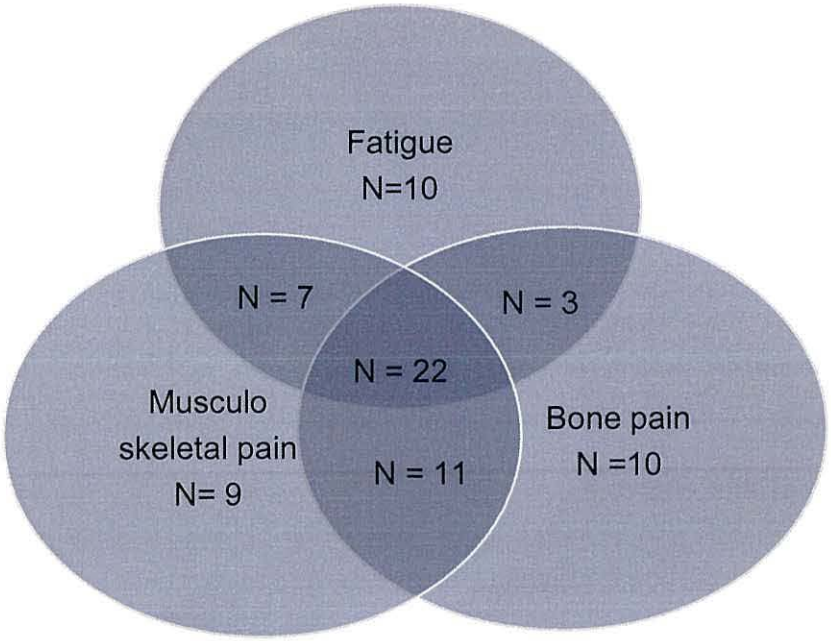

Figure 4-4: Venn diagram showing the presence and relationship of musculoskeletal pain, bone pain and fatigue

Analysis from 72 symptomatic participants

4.5.3.12 First symptoms reported by participant

Participants reported which of their reported symptom/s was the first experienced. Responses to this question fell from 84 to 57. There was a wide range and variation in the first symptom experienced as this was answered within a free text box. To better display the range of the first symptoms reported, symptoms were grouped into categories related to the type or location of pain. The pain group was the largest proportional group in pooled data (N- 38 (66%)). Back pain in this group was specifically reported by 13/38 (34%) participants. The second highest proportional group was fatigue which was significantly lower than the pain group being reported by 9 (15%) of participants.

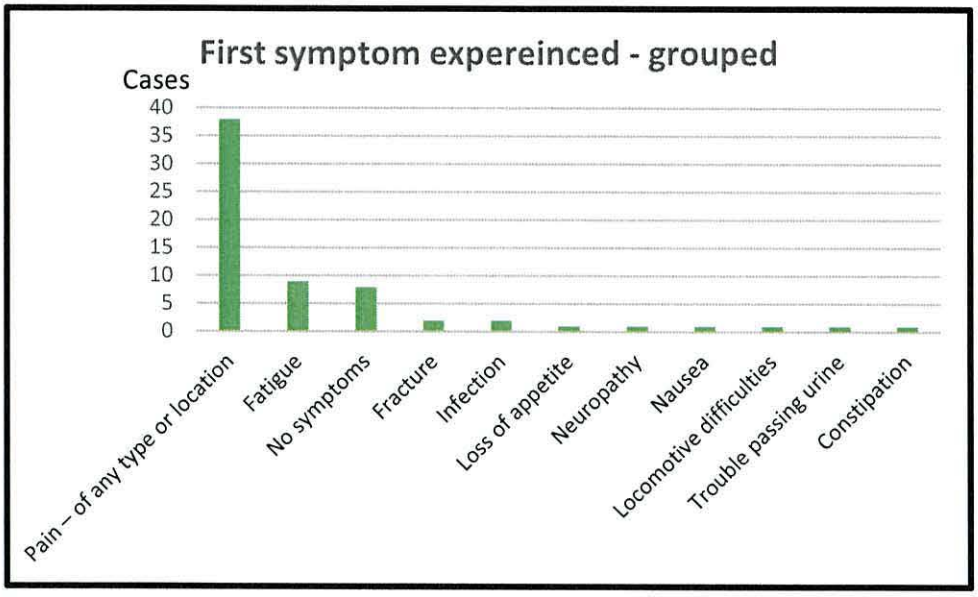

Figure 4-5: First symptoms reported in participants

**57 cases reported 27 missing data*

Results = >100%

Table 4-7: Consultation and presentation patterns of participants

Time to help-seeking	**N (%)**
No help-seeking	12 (14.6)
< 1 week	12 (14.6)
1-2 weeks	9 (11.0)
3-4 weeks	18 (22.0)
5-7 weeks	7 (8.5)
2-5 months	14 (17.1)
6-12 months	5 (6.1)
➢ 1 year but < 2	1 (1.2)
➢ 2 years	4 (4.9)
Time to get a GP appointment	**N (%)**
No waiting (surveillance/incidental finding)	6 (7.2)
Same day/next day	32 (38.6)
Within 1 week	32 (38.6)
1-2 weeks	6 (7.2)
No visit (no symptoms)	4 (4.8)
No waiting (emergency presentation)	3 (3.6)
Number of GP consultations in PC	**N (%)**
0	17 (20.5)
1	7 (8.4)
2	19 (22.9)
3	17 (20.5)
4	9 (10.8)
5	9 (10.8)
6	2 (2.4)
8	1 (1.2)
10	2 (2.4)
Analysis of number consultations in PC (whole population)	**N (%)**
Mean	2.61
Median	2.00
10th percentile	.00
25th percentile	1.00
75th percentile	4.00
90th percentile	5.00
Min	0
Max	10

Analysis of consultations in PC (presenting population)	N (%)
Mean	3.29
Median	3.00
10th percentile	1.00
25th percentile	2.00
75th percentile	4.00
90th percentile	5.00
Min	1
Max	10
Number of different GPs consulted with	**N (%)**
0	9 (18)
1	20 (40)
2	12 (24)
3	7 (14)
4	1 (2)
5	1 (2)
Number of health professionals consulted with (excluding GP)	**N (%)**
No visits to other health professionals	69 (83.1)
Osteopath/physiotherapist/chiropractor	11 (13.3)
Non- NHS consultant	3 (3.6)

83 cases reported. 1 missing data unless otherwise specified

4.5.3.13 Length of time to seek help from a doctor

One-quarter (N- 21 (25%)) of participants sought help within two-weeks of symptom onset, with nearly two-thirds (N – 49 (59%)) waiting longer than three-weeks, and 10 (12%) participants waiting more than six-months. Twelve (14%) had not sought help at all (Table 4-7).

4.5.3.14 Time to get an appointment with the doctor

The majority of participants had arranged appointments with their GP within one week of deciding to seek help (N -64 (77%)). A further six participants (7.2%) had arranged appointments within 1-2 weeks. Therefore, a total of 70 participants (84%) had arranged visits within two weeks of deciding to seek help. All other participants reported that they had not arranged appointments for various reasons such as: surveillance, incidental finding, no symptoms or they had had an emergency presentation to secondary care (N- 13 (15%)) (Table 4-7).

4.5.3.15 Number of GP consultations in primary care

The median number of consultations for the cohort was two, with a maximum number of 10 (N-2), and 'no consulting' reported by 17 (20%). In those that consulted in primary care, the median number of consultations was three (Table 4-7).

4.5.3.16 Number of different GPs consulted with in primary care

GP-reported data recorded a smaller number of participants having no consultations compared to patient-reported data. GPs reported that 20 (40%) patient participants saw one GP but an equal proportion (21 (42%)) saw 2 or more GPs (Table 4-7).

4.5.3.17 Number of different health professionals seen prior to diagnosis

The majority of participants reported no other consultations conducted outside the primary care practice (N-69 (83%)). A minority (N-14 (16%)) had consultations with other healthcare providers such as osteopaths, physiotherapists or chiropractors or non-NHS consultants (Table 4-7).

4.5.3.18 Events leading to presentation

Eighteen (25%) participants reported presenting to secondary care as an emergency in the patient data. Most of these reported having seen their GP with symptoms first (N- 18 (21%)). In the primary care data, the reported number of emergency presentations was reported to have occurred in 4 (6%) participants. Missing data was high in the primary care data, with 32 missing reports. In the combined patient data categories reporting events in primary care, 68 (80%) of participants reported that their initial presentation was made to primary care compared with GPs reporting in primary care data 38 (73%) presented to primary care initially. Twelve participants (14%) reported being diagnosed through a surveillance programme either in primary or secondary care in patient data and in primary care data surveillance this was reported in 7 (13%) of participants (Tables 4-8 and 4-9).

Table 4-8: Presentation to primary care presentation events

Presentation event	N (%)
I had symptoms/noticed a bodily change and went to see my doctor/GP	14 (16.7)
I had symptoms/noticed a bodily change and went/was taken to Accident and Emergency (A&E)	3 (3.6)
I had seen a doctor/GP with symptoms, but went/was taken to A&E when the condition worsened	18 (21.4)
I was being investigated by my doctor(s) for another problem during which time the myeloma was diagnosed	28 (33.3)
I was being monitored by my GP/hospital doctor having previously been diagnosed with 'high protein' (monoclonal gammonopathy of undetermined significance MGUS), and was then diagnosed with myeloma	10 (11.9)
I was having routine tests and I was referred for further investigations and diagnosed with myeloma	8 (9.5)
I was being monitored by my GP/hospital doctor having previously been diagnosed with a plasmacytoma (a cancer lesion within the bone or soft tissue) and was then diagnosed with myeloma	2 (2.4)
Other – Referred from allied health carer	1 (1.2)

**84 cases reported 0 missing data*

Table 4-9: GP-reported presentation events

Route of presentation described by GP	N (%)
Presented within normal working hours	36 (69.2)
Presented to A&E (with or without your involvement)	2 (3.8)
Your patient presented to PC then went on to present as an emergency (with or without your input)	2 (2.8)
Patient was within surveillance programme	7 (13.5)
Other – not specified	5 (9.6)

**52 cases reported 32 missing data*

4.5.3.19 Investigation and referral in primary care

Forty (75%) patient participants had investigations in primary care, and 13 (24%) had no investigations in primary care. Missing data occurred in 31 cases. The group potentially includes participants who presented to secondary care as an emergency, and participants in surveillance programmes in secondary care, rather than primary care.

The most frequent investigation performed was full blood count (FBC) (N 36 (68%)), followed by urea and electrolytes (U&Es) (N-31 (56%)). Protein electrophoresis of serum or urine (SEP or SFLC/BJP), a definitive test for referral to a haematologist

(Bird et al., 2011) when positive, was performed in half the diagnosed population (SPE – N 2 (50%) SFL/BJP N-26 (49%)). Erythrocyte sedimentation rate (ESR), now recommended in the NICE (2015) referral guidelines as a predictive clinical test in myeloma (Shephard et al., 2015), was carried out in 22 (41%) participants. Less than half the population was investigated with x-rays of symptomatic areas 23 (43%) and there was a lower level of physical examination completed 14(26%) (Table 4-10).

Table 4-10: Clinical Investigations performed in Primary Care

Test	Undertaken	Abnormal *#	Repeated #
	N (%)	N (% of done)	N (% of done)
FBC	36 (67.9)	18 (50)	12 (33.3)
ESR / PV	22 (41.5)	14 (63.6)	2 (9.0)
U&Es	30 (41.5)	13 (43.3)	7 (9.0)
X-ray of symptomatic area	23 (43.4)	11 (47.8)	1 (4.3)
SPE	27 (50.9)	25 (92.5)	2 (7.4)
SFLC / BJP	26 (49.1)	14 (53.0)	0 (0)
Physical examination	14 (26.4)	1 (7.1)	3 (21.0)
CRP	20 (37.7)	5 (25.0)	1 (5.0)
Other radiological assessment	4 (7.5)	2 (50.0)	0 (0)

53 cases reported 31 missing data unless specified

** 49 cases reported*

 # % abnormal results vs test performed

4.5.3.20 Abnormal clinical investigations in primary care

The clinical investigation most frequently reported to be abnormal was SPE 25 (92%), then ESR 14 (63%). SPE was performed at a higher frequency than ESR, at 50% and 41% respectively, and reported a higher percentage of abnormal results (Table 4-10).

4.5.3.21 Referral from primary care for onward investigation

Twenty-three patients (43%) were referred via the recommended pathway for suspected cancer, the two-week wait (TWW). Thirty patients (56%) were referred to secondary care with a 'possibility of cancer' when groups of TWW and "less urgent – cancer raised as a possibility" were combined. The 'no referral made' group included seven (13%) participants from the group of participants self-referring to secondary care as an emergency and those in surveillance for MGUS/plasmacytoma within secondary care (Table 4-11).

Table 4-11: Type of referral from primary care into secondary care

Referral made to secondary care	N (%)
No referral made by GP	7 (13.2)
Two-week wait – urgent referral for suspected cancer (TTW)	23 (43.4)
Urgent referral without cancer mentioned (non-cancer speciality team)	2 (3.8)
A less urgent referral in which cancer is raised as a possibility	7 (13.2)
More general referral for investigation and assessment without cancer mentioned	4 (7.5)
Emergency admission	9 (17.0)
Re-referral	1 (1.9)

**53 cases reported 31 missing data*

4.5.3.22 Team referred to in secondary care by primary care

Fifteen different teams and departments received referrals for the study population. Direct referral to haematology was seen in 27 (50%) cases. Seven (13%) participants were not referred (Table 4-12).

Table 4-12: Team referred to in secondary care by primary care

Team referred to in secondary care	N (%)
Haematology	27 (50.9)
Urology	1 (1.9)
Care of the Elderly	2 (3.8)
Ear Nose and Throat	4 (7.5)
General Medicine	5 (9.4)
Surgery	2 (3.8)
Respiratory	1 (1.9)
Oncology	1 (1.9)
Orthopaedics	3 (5.7)
Nephrology	1 (1.9)
Cardiology	1 (1.9)
Osteoporosis clinic	1 (1.9)
Surveillance	1 (1.9)
Musculoskeletal team	1 (1.9)
Emergency Medicine	1 (1.9)
No referral made	7 (13.2)

**53 cases reported 31 missing data*

Multiple referrals were reported for five (9%) participants.

4.5.4 GP experience

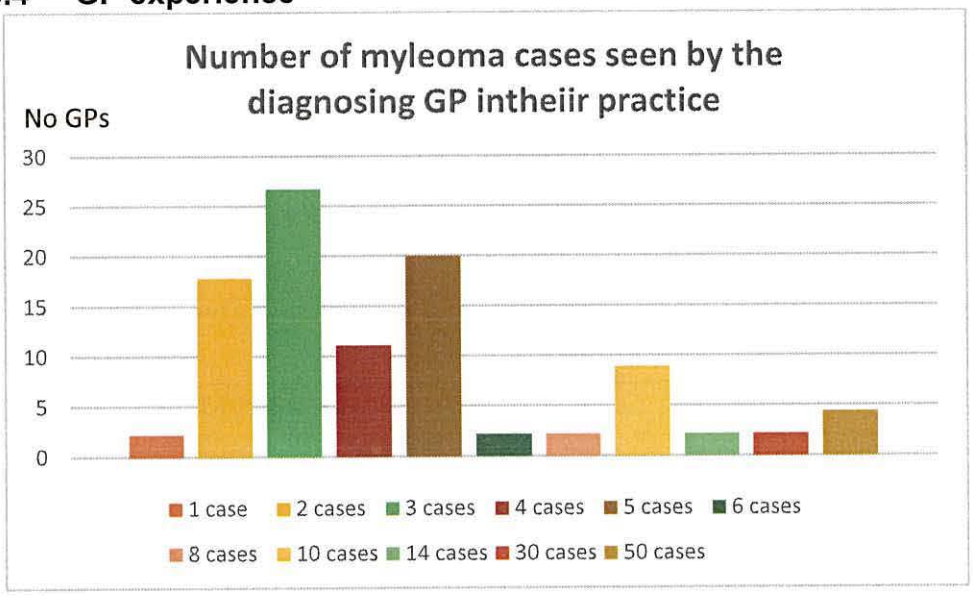

Figure 4-6: Number of previous myeloma cases seen

45 cases reported 39 missing data

Welsh GPs reported having experience of a median of four patients with myeloma, with a mode of three cases (Figure 4-6).

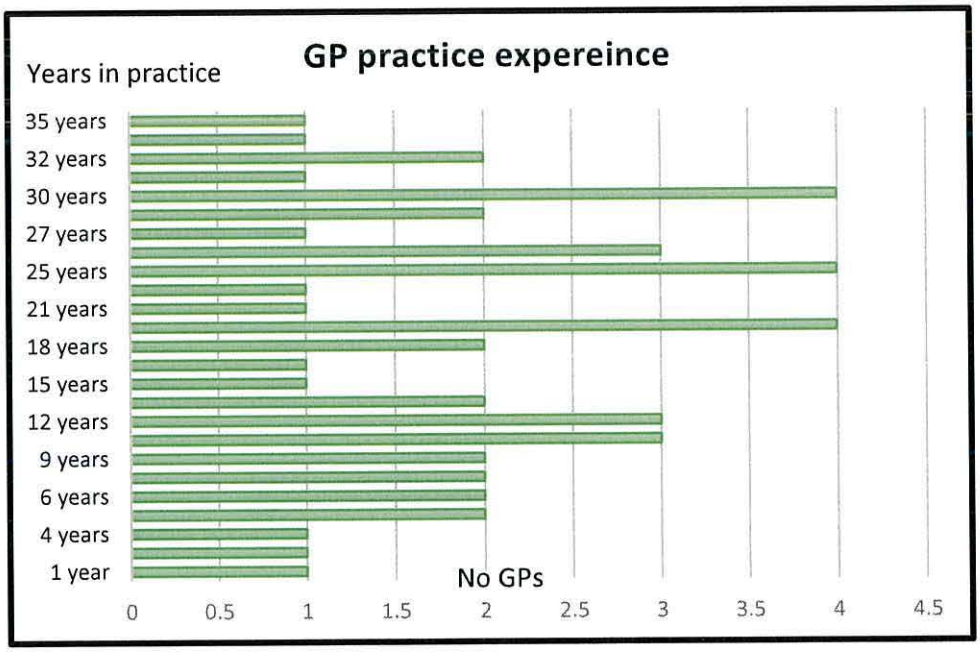

Figure 4-7: Number of Years in Practice of diagnosing GPs

48 cases reported 36 missing data

There was a range of practice experience from 1- 35 years with a median of 10 years (N=48) (Figure 4-7).

4.5.5 Secondary care pathways

Referral routes to secondary care calculated from secondary care questionnaires had a higher response rate than primary care data with an almost complete profile of data available.

Secondary care data recorded the majority (N - 60 (74%)) of participants were referred from GPs. This data was comparable with primary care data that presentation is made to primary care with symptoms and referral onto secondary care for further investigation occurred in 38 (73%) participants. Secondary care data reported participant self-referral to emergency departments occurred in 9 (10%) participants. In participant data, combining emergency presentation categories was recorded at 18 (25%) participants. Lower levels of surveillance cases were reported in the secondary care data 3 (4%) compared to the primary care 7(13%) and participant data 12 (18%), suggesting a minority of participants in surveillance are monitored in secondary care. Out-of-area or internal referrals were recorded at a combined rate of 9 (10%) participants.

4.5.6 Team referring to Haematology

Haematologists reported that 40 patients (48%) had been referred directly from their GPs to haematology. Sixteen (19%) were identified following abnormal laboratory tests. There was a diverse referral pattern from 18 different secondary care departments or general practice. Reported referrals amounted to more than 100% with a total of 110 department interactions identified from the secondary care data for 83 participant pathways (Table 4-13).

Table 4-13: Referrals received by haematology

Team referring	N (%)
General Practice	40 (48.2)
Laboratory	16 (19.3)
Renal	8 (9.6)
Surgical team	2 (2.4)
Radiology	2 (2.4)
Surveillance	5 (6.0)
Acute Medial admissions	11 (13.3)
Orthopaedics	7 (8.4)
Acute surgical admissions	2 (2.4)
External out of area referral (orthopaedics)	5 (6.0)
General medicine	3 (3.6)
Respiratory	3 (3.6)
Rheumatology	1 (1.2)
Anaesthetics	1 (1.2)
External out of area referral (oncology)	1 (1.2)
Pain team	1 (1.2)
External out of area (non- specified)	1 (1.2)
Ophthalmology	1 (1.2)
	>100%

**83 cases reported x1 missing data*

4.5.6.1 Number of teams contributing to the pathway to diagnosis in secondary care

Twenty-seven (33%) participants received a direct referral to haematology with no other departments involvement i.e. one team. Fifty-six (67%) passed through two or more teams on their way to a diagnosis. A higher percentage of participants was reported to have received a direct referral to haematology when compared to primary care reported data, but the secondary care data were more complete.

In 'selected case' analysis, participants who received a direct referral to haematology who had a SPE or SFLC/BJP completed in primary care were 22/27 (76%).

4.5.6.2 Departments consulted within secondary care

The departments consulted within the secondary care interval in individual pathways recorded the largest proportionate group as 'laboratory identification of a monoclonal paraprotein or other abnormal results' for 16 (19%) of the cohort. Orthopaedic consultation was the second highest group (N - 14 (16 %)), followed by emergency department (N - 10 (12%)). Emergency department use represents those participants presenting to the Accident and Emergency (Emergency Department) department and not patients referred 'in hours', but urgently to medical or surgical acute admissions. When categories were combined, they represented an 'unscheduled care' access group where the number of cases and percentage rose to 22 (26%) (Table 4-14).

Table 4-14: Departments consulted with in secondary care

Department accessed	N (%)
Emergency department	10 (12)
Acute medicine	9 (10.8)
Acute Surgical team	3 (3.6)
Orthopaedics	14 (16.9)
Laboratory	16 (19.3)
Surveillance	7 (8.4)
Gastroenterology	3 (3.6)
General medicine	6 (7.2)
Renal medicine	9 (10.8)
Oncology	2 (2.4)
Urology	1 (1.2)
Radiology	2 (2.4)
COTE	1 (1.2)
Musculoskeletal team	2 (2.4)
Cardiology	1 (1.2)
Respiratory	3 (3.6)
Metabolic clinic	1 (1.2)
Rheumatology	1 (1.2)
Minor injuries	1 (1.2)
	>100%

**83 cases reported x1 missing data*

4.5.6.3 Diagnostic investigation in secondary care

Diagnostic testing in secondary care was in line with British Society of Haematology (BSH) guidance (Bird et al., 2011) and was recorded at: bone marrow biopsy 81 (97%), serum free light chains/Bence Jones protein 83 (95%), skeletal survey 80 (96%). $Beta_2$ microglobulin assessment, necessary for staging assessment, was completed in only 71 (85%) of cases (Table 4-15).

Table 4-15: Diagnostic testing in secondary care

Diagnostic test	N (%)
Bone marrow aspirate	81 (97.6)
Bone marrow trephine	69 (83.1)
Protein electrophoresis of serum	83 (100)
Serum free light chains/Bence Jones protein	79 (95.2)
$Beta_2$ microglobulin	71 (85.5)
Skeletal survey	80 (96.4)
Bone biopsy	1 (1.2)
Other radiological tests	4 (4.8)
Full blood count	82 (98.8)
Erythrocyte sedimentation rate/Plasma viscosity	44 (53.0)
Urea and electrolytes	80 (96.4)
Calcium	81 (97.6)

**83 cases reported x1 missing data*

4.5.6.4 Assessment of cytogenetic risk

The assessment of the cytogenetic risk for myeloma was conducted in only 26 (32%) participants. There was a low level of sample failure (N - 2 (3%)) and a proportion of participants where assessment of cytogenetics were carried out within a clinical trial setting and treating haematologists were not privy to results (N – 8 (11%)). Fourteen (19%) participants, therefore, had cytogenetic profiling available to their haematologists. This question was less frequently answered by haematologist with 10 missing data entries (Table 4-16).

Table 4-16: Cytogenetic risk assessment

Category of cytogenetic risk	N (%)
High risk	5 (6.8)
Standard risk	1 (1.4)
Normal cytogenetics	8 (10.8)
Not done	48 (64.9)
Analysis performed within a clinical trial and not know the treating clinician	8 (10.8)
Unsure	2 (2.7)
Sample failed	2 (2.7)

**74 cases reported x10 missing data*

4.5.6.5 Criteria for treatment: proxy for burden of disease

Bone disease (lytic bone lesions or osteoporosis with compression fractures) was the most frequently reported complication at diagnosis (N - 55 (66%)), followed by anaemia (N – 42 (51%)), renal impairment (N - 19 (23%)) and then hypercalcaemia (N - 18 (22%)) (Table 4-17).

Table 4-17: Decision to treat criteria

Criteria present for ROTI	N (%)
Monoclonal plasma cells in the bone marrow >10% and/or biopsy-proven plasmacytoma	69 (83.1)
Monoclonal paraprotein present in serum and/or urine	71 (85.5)
Corrected serum calcium >10mg/L (0.25mmol/L) above the upper limit of normal or>110mhg/L (2.75 mol/L)	18 (21.7)
Renal insufficiency Creatinine >20mg/L (173 mmol/L)	19 (22.9)
Anaemia <20g/L below the lower limit of normal or haemoglobin <100g/L	42 (50.6)
Lytic bone lesions or osteoporosis with compression fractures	55 (66.3)
Other – symptomatic hyper viscosity, amyloidosis, recurrent bacterial infection |(>2 episodes in 12 months)	8 (9.6)
	>100%

**82 cases reported x 2 missing data*

1.1.1.1 Treatment choice

Three (4%) participants entered surveillance programs having been diagnosed with asymptomatic myeloma. Intensive treatment was initiated in 44 (53%) participants, with non-intensive treatment commenced in 36 (43%) making the population comparable to populations observed in larger studies (MRC Myeloma IX where 58% of participants received intensive treatment and 42% non-intensive (Morgan et al., 2012).

1.1.1.2 Influences in the choice of treatment initiated

The most influential factor in determining treatment pathway choice in the study population was age (N - 74 (90%)), followed by disease burden (N-39 (53%)), then multi-morbidities (N - 35 (41%)). There were a range of other influences recorded from data demonstrating that Welsh haematologists adhere to recommendations that treatment choice be assessed on an individual basis accounting for age, multi-morbidities and performance score (Bird et al., 2011) (Table 4-17).

Table 4-18: Treatment choice influences

Influence affecting treatment choice	N (%)
Age of participant	74 (89.2)
Pre-existing multi-morbidities	35 (41.0)
Burden of disease at presentation	39 (53.0)
Not fit for autologous stem cell transplant	28 (33.7)
Patient choice	17 (20.5)
Guidelines for treatment/surveillance	12 (14.5)
Other influences	1 (1.2)
	>100%

83 cases reported x 1 missing data

1.1.1.3 Clinical study activity

Fifty-three participants were considered eligible for clinical trial entry by their treating haematologist (64%) and 40 (48%) went on to enter a trial at their treating hospital, making the study cohort comparable to cancer clinical trial participation, where initial participation is reported at a rate of 76% but when treatment is randomised reduced to 44% (Fallowfield et al., 1998). The questions exploring the reasons for not participating in a clinical trial were was less frequently answered by the treating haematologists, with response rates reduced from 83 to 67 cases. No one group appeared to have an overwhelming influence on the decision to participate. Eleven

(16%) participants did not have a clinical trial open at their recruiting site; ten (15%) participants did not meet the clinical conditions of the study; seven (10%) chose not to enter a study and in one (2%) clinical deterioration made the study unsuitable (Table 4-19).

Table 4-19: Clinical trials activity

Participant eligible for clinical trial*	**N (%)**
Eligible for trial	53 (63.9)
Eligible and entered trial	40 (48.2)
Reason for not entering clinical trial #	**N (%)**
Entered a study	38 (56.7)
Patient choice	7 (10.4)
Clinical decision	10 (14.9)
No trial at site	11 (16.4)
Rapid deterioration of clinical condition	1 (1.5)

**83 cases reported x 1 missing data*

 # 67 cases reported x 17 missing data

4.5.6.6 Response to induction treatment

Very limited data was collected for 'response to treatment' with only 23 (27%) cases available for analysis. This was due to the data collection from haematologists occurring prior to the completion of induction therapy. Of the cases analysed the most frequently reported response to treatment group was the 'very good partial responses group' 10 (44%) (Table 4-20).

Table 4-20: Response to treatment

Category of response	**N (%)**
Complete response (CR)	5 (21.7)
Very good partial response (VGPR)	10 (43.5)
Partial response (PR)	5 (21.7)
Minor response (MR)	1 (4.3)
Progressive disease (PD)	2 (8.7)

**23 cases reported x61 missing data*

4.5.6.7 Access to primary care in the preceding 24 months of the myeloma diagnosis

GPs reported the answering of this question was time consuming as it required accessing electronic data over many months to complete; many GPs chose, therefore, not to complete this section of the questionnaire and responses fell from 53 to 41. Monthly visits were pooled and are displayed for the whole population of participants. A decrease in the number of 'no attendance' in primary care can be seen in the six months preceding diagnosis. There was a parallel increase in the groups attending one or more occasions but most noticeable for the group of participants consulting two or three times. Increased activity in primary care is seen, therefore, in the six months preceding the diagnosis of myeloma (Figure 4-8).

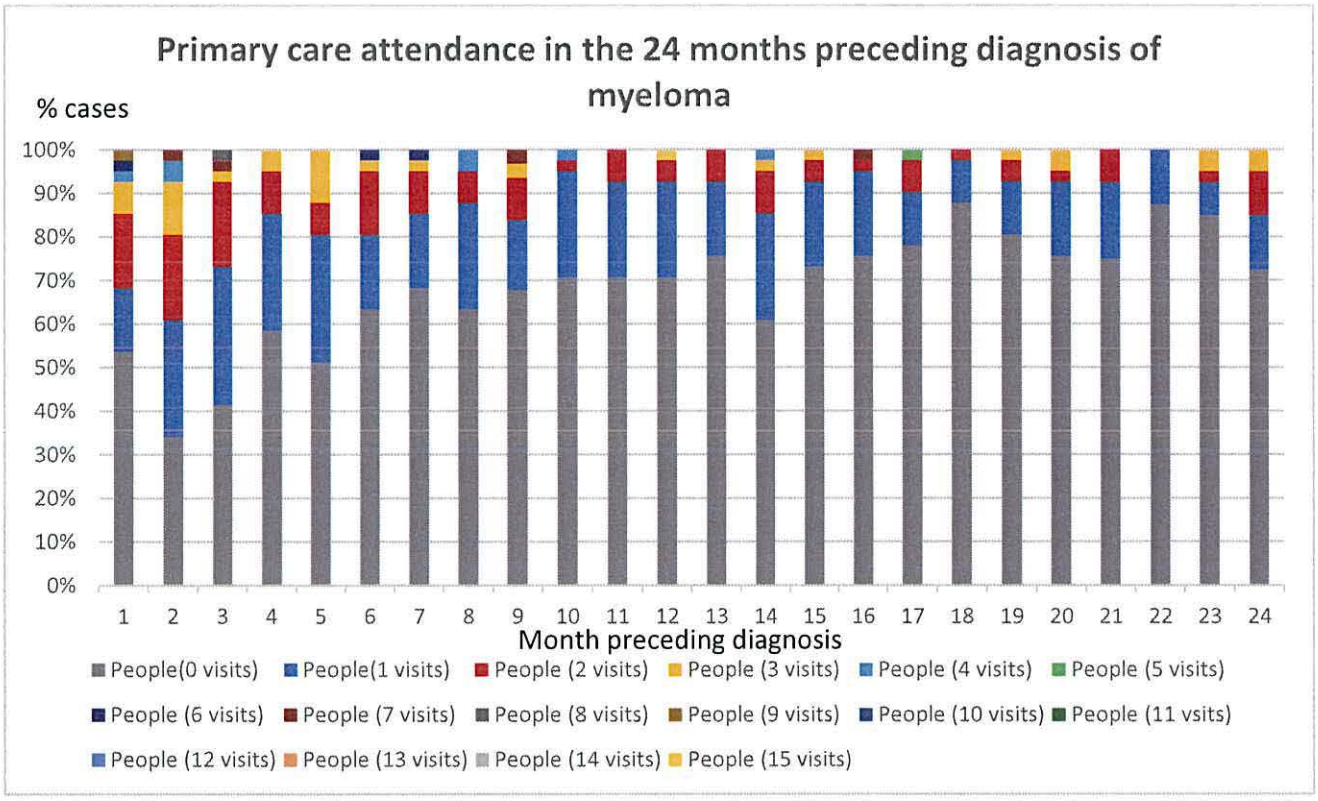

Figure 4-8: Attendance in primary care in the preceding 24 months of myeloma diagnosis

**41 cases reported for month 1-20 / 40 cases for month 21- 24*

4.5.6.8 Survival analysis

Partial reporting of survival analysis is displayed based on the number of cases reported six months following the closure to recruitment (September 2016). The number of cases is limited as this is a premature survival analysis and interpretation of results is limited. Median survival calculated from 19 cases who had received second-line treatment for relapsed myeloma was less than one year (309 days).

Overall median survival was calculated at 438 days. Continued collection of survival data is planned to complete a survival analysis (Table 4-21).

Table 4-21: Survival analysis

Disease free survival	**N (%)** (days)
Median	309.00
10th percentile	137.00
➢ 25th percentile	212.00
74th percentile	416.00
90th percentile	617.00
Case number	19
Overall survival	**N (%)**
Median	438.50
10th percentile	148.20
25th percentile	320.25
75th percentile	438.50
90th percentile	586.25
Case number	10

4.5.7 Measurement of the intervals to diagnosis in myeloma

4.5.7.1 The Patient Interval

Measured from the date of first symptom or body change to presentation to a health professional; 60 cases could be calculated from available data. The median time for participants to present to a healthcare professional following symptom onset or body changes was 35 days (IQR = 0.25- 94 days). The 90th percentile was 254 days (Table 4-22).

4.5.7.2 The Primary Care Interval

Measured from the first presentation to a healthcare professional to onward referral and transfer of care to specialist services. Measurement of this interval was reduced to 37 cases. The median primary care interval was 24 days (IQR 13- 98 days), the 90th percentile was 205 days (Table 4-22).

4.5.7.3 The Primary Care Interval (non-Aarhus compliant)

This additional interval, reported from patient and secondary care data, calculated a primary care interval measured from date of presentation to healthcare professional to date of first consultation in secondary care. The use of these data allowed an

additional analysis of 21 cases (total N = 58). The calculation of this interval does not incorporate the time between referral from primary care to the date the participant was first seen in secondary care. The median of this interval was 41 days (IQR 15-134 days), which was a higher median than measured for the primary care Aarhus compliant interval. The IQR was 15-134 days and the 90th percentile 561 days (Table 4-22).

4.5.7.4 Secondary Care Interval

Measured from the referral to secondary care to commencement of treatment and calculated in 41 cases. The median of this secondary care interval was 45 days (IQR 23 -74 days); 90th percentile 142 days (Table 4-22).

4.5.7.5 Secondary Care (Non-Aarhus compliant)

This additional interval, reported from secondary care data, calculated from the date the participant was first seen in secondary care to the commencement of treatment. The interval loses the calculation of referral from primary care. A total of 73 cases were available for analysis. In the median of this interval was 24 days (IQR 10-62 days). This duration was less than measured in the secondary care Aarhus compliant interval, calculated from 41 cases. The 90th percentile was 127 days (Table 4-22).

4.5.7.6 Diagnostic interval

Measured from the first presentation to a healthcare professional to the date of histological confirmation of the disease, and was measurable in 60 cases. The median from first symptom to diagnosis was 66 days (IQR 36-142 days). The 90th percentile was 240 days (Table 4-22).

4.5.7.7 Time to diagnosis

Measured from symptom onset to the date of histological confirmation of the diagnosis, this was measurable in 65 cases. The median was 138 days (IQR 55 -287 days) and the 90th percentile 592 days (Table 4-22).

4.5.7.8 Treatment interval

Measurement of the interval from date of diagnosis to the commencement of treatment was measured for 81 cases. The median was 9 days (IQR 1-25 days) and the 90th percentile 61 days (Table 4-22).

4.5.7.9 Total interval to diagnosis

Measured from symptom onset to commencement of treatment, incorporating all the intervals of patient, primary and secondary care, diagnostic, time to diagnosis and treatment. A total of 62 cases were measurable. The median was 140 days (IQR 77-267 days) and the 90th percentile 641 days (Table 4-22).

Table 4-22: Intervals to diagnosis in myeloma

Interval	Median	IQR	90th centile	Range
Patient (n=60)	35.5	0.2 - 94.2	254.7	0 - 891
Primary care (n=37)	24.0	13.5 - 98.0	205.2	0 - 297
Primary care * (n=58)	41.5	15.7 -134.5	218.9	0 - 561
Secondary care (n=41)	45.0	23.0 - 74.5	142.4	0 - 290
Secondary care* (n=73)	24.0	10.0 - 62.0	127.2	0 - 524
Diagnostic (n=60)	66.5	36.2 -142.0	240.0	5 - 579
Time to diagnosis (n=65)	138.0	55.5 - 287.0	592.4	10 - 946
Treatment (n=81)	9.0	1.0 - 25.0	61.2	0 - 518
Total interval (n=62)	140.0	77.7 - 267.2	641.2	10 - 1110

**non-Aarhus compliant measured interval*

Data to one decimal point

4.5.8 Correlation

Weak correlations were found for the primary care interval and the number of symptoms experienced by the participant; the primary care non-Aarhus interval and the number of GP consultations made in primary care; and the diagnostic interval and the number of GP consultations in primary care (Table 4-23).

Table 4-23: Correlation results

Interval of relevance *r =Pearson T* *p = significance* *n-= number cases*	Age of participant	No of multi-morbidities	No of symptoms experienced	No GP consultations	No different GPs seen	No different healthcare profs seen	No myeloma cases seen by diagnosing GP	No years in practice of diagnosing GP	No of teams seen in SC pathway
Patient	*r* = 0.021 p= 0.872 n = 60	-0.006 0.965 53	0.211 0.105 60	0.108 0.142 34	0.125 0.460 37	-0.107 0.801 8	0.186 0.271 37	-0.180 0.265 40	-0.232 0.077 59
Primary care	r = -0.059 p = 0.728 n = 37	110 0.523 36	0.388* 0.018 37	0.257 142 35	0.470 0.006 33	0.387 0.343 8	0.026 0.891 31	-0.181 0.314 33	-0.122 0.473 37
Primary care non Aarhus	r = 0.014 p = 0.917 n = 58	-0.096 0.496 53	0.057 0.669 58	0.316* 0.024 51	0.442 0.006 37	0.177 0.648 9	-0.067 0.695 37	0.026 0.875 40	-0.066 0.621 58
Secondary care	r = -0.032 p = 0.845 n = 41	-0.128 0.432 40	-0.224 0.160 41	0.162 0.338 37	-0.114 0.514 35	-0.112 0.792 8	0.025 0.885 35	-0.009 0.960 37	0.206 0.195 41
Secondary care non Aarhus	r = 0.130 p = 0.273 n = 73	-0.035 0.786 63	-0.180 0.127 73	-0.062 0.641 59	-0.257 0.119 38	-0.192 0.621 9	0.046 0.783 39	0.193 0.222 42	0.049 0.681 73
Diagnostic	r = 0.116 p = 0.378 n =60	-0.053 0.704 54	0.028 0.834 60	0.338* 0.013 53	0.427 0.007 38	0.196 0.612 9	-0.079 0.640 37	0.063 0.701 40	0.010 0.939 59
Time to diagnosis	r =0.008 p = 0.952 n = 65	0.019 0.890 57	0.149 0.236 65	0.187 0.168 56	0.227 0.165 39	-0.173 0.682 8	0.118 0.474 39	-0.175 0.268 42	-0.132 0.298 64
Treatment	r = 0.041 p = 0.715 n = 81	-0.151 0.216 69	-0.107 0.343 81	-0.089 0.490 63	-0.223 0.166 40	-0.195 0.590 10	0.178 0.252 43	0.052 0.730 46	0.003 0.977 80
Total interval	r = -0.025 p = 0.849 n = 62	-0.090 0.516 54	0.132 0.305 62	0.178 0.193 55	0.222 180 38	-0.213 0.590 10	0.164 0.333 37	-0.129 0.427 40	-0.151 0.245 61

*Correlation is significant at the 0.05 level (2-tailed)

4.5.9 Regression

Standardised coefficients with significance for the models and the relevant individual interval to diagnosis (dependant variable) are displayed in the tables below.

Table 4-24: Regression model Patient interval

Independent variable	Dependant variable = Patient Interval		
	Standardised coefficient-beta	t test	Significance
Participant assessed 'poor' health status in two years prior to diagnosis	0.47	06.7	<0.001
Analgesics taken prior to diagnosis	-0.27	-4.67	<0.001
Number of different GPs consulted in primary care by participant	0.30	5.24	<0.001
Referral from primary care to ENT	0.28	4.96	<0.001
Referral from primary care to nephrology	0.31	4.72	<0.001
Emergency department use in secondary care pathway	-0.26	-3.84	0.001
Rheumatology department use in secondary care pathway	-0.37	-4.53	<0.001
Pathway choice influenced by not fit for Autologous Stem Cell Transplant (ASCT)	-0.23	-3.58	0.002

Results for the patient interval recorded significance for multiple independent variables. Longer patient intervals were associated with:

- Participants who reported having a 'poor' health status in the two years preceding the diagnosis;
- Participants who did not take analgesics prior to a diagnosis of myeloma;
- Participants who saw more different GPs in primary care;
- Participants who were referred to secondary care by primary care to ENT or Nephrology;
- Participants who did not access emergency department or rheumatology; and
- Participants who were considered 'fit' for autologous stem cell transplants.

Table 4-25: Regression model primary care interval

Independent variable	Dependant variable = Primary Care Interval		
	Standardised coefficient-beta	t test	Significance
Other radiological examinations in primary care (other than x-ray symptomatic area)	0.64	5.87	<0.001
Acute surgical department use in secondary care pathway	0.36	3.30	0.003

Results for the primary care interval recorded significance for two independent variables. Longer primary care intervals were associated with:

- Participants who were investigated in primary care with radiological investigations, other than x-rays of symptomatic areas; and
- Participants who were admitted to secondary care via acute surgical admissions.

No independent variables of significance were measured for the primary care non-Aarhus interval.

Table 4-26: Regression model secondary care interval

Independent variable	Dependant variable = Secondary Care Interval		
	Standardised coefficient-beta	t test	Significance
Type of referral made from primary care to secondary care	0.30	4.54	<0.001
Referral from primary care to the musculoskeletal team	0.33	5.71	<0.001
Haematology referral received from general medicine	0.00	4.83	<0.001
Musculoskeletal department use in SC pathway	0.56	9.81	<0.001
Rheumatology department use in SC pathway	0.43	6.93	<0.001

Results for the secondary care interval recorded multiple significant independent variables. Longer secondary care intervals were associated with:

- Participants who were referred into secondary care via general, non-cancer referral routes or without referral from their GP;
- Participants who were referred from primary care to the musculoskeletal team or accessed this team during the secondary care pathway;
- Participants who were referred to haematology via general medicine; and
- Participants who accessed the rheumatology team.

Table 4-27: Regression model for secondary care non-Aarhus interval

Independent variable	**Dependant variable = Secondary Care (Non-Aarhus) Interval**		
	Standardised coefficient- beta	t test	Significance
Analgesics taken prior to diagnosis	-0.32	-4.58	<0.001
Referral from primary care to the musculoskeletal team	0.29	4.16	<0.001
Secondary care diagnostic tests - bone biopsy	0.72	10.40	<0.001

Longer secondary care non-Aarhus intervals were associated with:

- Participants who reported not taking analgesia prior to the diagnosis of myeloma;
- Participants who were referred to musculoskeletal team from primary care; and
- Participants who had bone biopsy as part of diagnostic testing.

No independent variables of significance were measured for the diagnostic interval.

Table 4-28: Regression model for time to diagnosis interval

Independent variable	**Dependant variable = Time to Diagnosis Interval (Non-Aarhus) Interval**		
	Standardised coefficient- beta	t test	Significance
Referral from Primary Care to Nephrology	0.40	3.70	0.001

Results for the time to diagnosis interval recorded one significant independent variable. A longer time to diagnosis interval was associated with:

- Participants who were referred to nephrology from primary care.

Table 4-29: Regression model treatment interval

Independent variable	Dependant variable = Treatment Interval		
	Standardised coefficient-beta	t test	Significance
Analgesics taken prior to the diagnosis	-0.30	-3.35	0.002
Referral from primary care to COTE	0.255	3.241	0.002
Referral from primary care to the musculoskeletal team	0.66	8.15	<0.001

Results for the treatment interval recorded three significant independent variables. Longer treatment intervals included:

- Participants who did not take analgesia prior to the diagnosis of myeloma; and
- Participants who were referred to secondary care via musculoskeletal or Care of the Elderly (COTE) teams.

Table 4-30: Regression model for the total interval to diagnosis

Independent variable	Dependant variable = Total Interval		
	Standardised coefficient-beta	t test	Significance
Time to get a GP appointment	0.28	4.42	<0.001
Participant assessed poor health status in two years prior to diagnosis	0.47	7.39	<0.001
Analgesics taken prior to diagnosis	-0.26	-4.09	0.001
Number of different GPs consulted in primary care by participant	0.36	6.19	<0.001
Other radiological examinations (other than x-ray of symptomatic area)	0.27	4.07	0.001
Type of referral made from primary care to secondary care	0.28	3.86	0.001
Referral from primary care to ENT	0.27	4.55	<0.001
Referral from primary care to the osteoporosis/bone health clinic	-0.41	-5.63	<0.001
Haematology referral received from acute medical admissions	-0.44	-3.35	0.003
Acute medicine department use SC pathway	0.48	3.67	0.002

Results for the total interval recorded multiple significant independent variables. Longer total intervals were associated with:

- Participants who took longer to secure an appointment with their GP;
- Participants who reported having 'poor' health status;
- Participants who reported not taking analgesia prior to a diagnosis of myeloma;
- Participants who saw a greater number of different GPs in primary care;
- Participants who had radiological investigation in primary care, other than x-ray of a symptomatic area;
- Participants whose referrals from primary care were through 'non-cancer' specific routes or did not have referral by a GP;
- Participants who were referred from primary care to ENT;
- Participants who were not referred through the bone health clinic (osteoporosis clinic);
- Participants who were not referred via acute medical admissions to the haematologist; and
- Participants who accessed acute medical department in secondary care.

4.6 Discussion

4.6.1 Summary of findings

The study population was representative of the wider myeloma population for deprivation, disease characteristics, stage of disease at diagnosis and treatment pathways initiated. Additionally, the population was representative of the general practice population for the presence of multi-morbidities. These factors were without significance in correlation or regression analysis.

The measurement of all the intervals to diagnosis, for the first time, allows the reporting of the complete diagnostic journey for myeloma in a single population of patients. The quantification of three new intervals additionally allows better understanding of the breakdown of the overall journey. The measurement of the secondary care interval is an important new contribution, and although measured from small number of cases in the Aarhus compliant interval, the interval calculation shows a relatively long contribution, equal or longer to the primary care interval. Possibly, then, there are influences that affect progression through secondary care as well as in primary care that require an equal focus and assessment. The

measurement of the median, interquartile ranges allows comparability with other studies, with the 90th percentile adding the range and variance in the length of the intervals to diagnosis. It is of interest that the more significant influences were recorded by regression modelling for the patient and total intervals, suggesting focus in these areas to be important.

Unsurprisingly, given the median age of the population, over half the participants reported being retired. More surprisingly, only 6% of the remaining participants reported being unable to work. This possibly demonstrates a higher performance status and function in younger patients than anticipated, but this was not significant in statistical testing and 'performance score' was not formally assessed. It may also be possible that the collection of data so close to the diagnosis of myeloma does not allow the appreciation of 'fitness to work' assessments which are likely to take place sometime after diagnosis.

The help-seeking period in this myeloma population is long, with three-quarters of participants taking three weeks or more to present their symptoms. Whilst poor health status and not recognising pain or initiating analgesia, may contribute to this, data from this phase of the study has a limited ability to contribute to the understanding of why longer help-seeking occurs and is unable to ascertain why some participants experience extremely long help-seeking intervals of more than one year.

The patient and total interval in myeloma appear not to be influenced by difficulties accessing primary care in Wales, with access timely for the majority of patients once help-seeking was considered necessary.

GPs in Wales were generally experienced with many years of practice, but their experience of myeloma, specifically, was limited to a small number of cases.

A median number of consultations in primary care for this myeloma population, when considered for the whole population of patients, was two. However, with further analysis of the frequency of consultation for the group of participants who attended primary care, the median consultation rate rose to three. This is an important distinction as there is the potential to distort the representation of consultation rates in primary care with the inclusion of the group of participants that do not present.

The majority of myeloma participants present their symptoms to primary care. Participants who did not present symptoms were diagnosed either through

surveillance programs in primary or secondary care, as an incidental finding or presented directly to secondary care through emergency routes. Surprisingly, these routes showed no associations with shorter intervals or longer intervals to diagnosis in correlation or regression analysis.

GPs responded to symptom presentation in the majority of myeloma patients by the completion of clinical tests. However, variations are seen in the type of investigations performed, to make a differential diagnosis. Although the most frequently performed clinical test was FBC, this was undertaken in less than 70% of the population and other testing rates fell to 50% or less. Tests of SPE or SFLC/BJP, X-ray of symptomatic or ESR/PV (which potentially help a GP form a differential diagnosis of myeloma, and are within the guidelines for investigation and determining myeloma (Bird et al., 2011) were completed in only half the population of patients in primary care. Of note, ESR/PV was performed in only 41% of the population, when this now forms part of an investigative plan for assessing myeloma in NICE guidance (NICE, 2015). Also of surprise was the low-level testing by x-ray of symptomatic areas (43%) and physical examination (26%) performed in response to the high levels of pain in muscles and joints and bone reported by the population.

4.6.2 Comparison to other literature

4.6.2.1 Intervals to diagnosis

Table 4-31: Comparison of the intervals to diagnosis recorded with other literature

Interval	DJiM Myeloma	Comparative myeloma	Author and year comparative study	Comparative other cancer Median (IQR)	Author and year comparative study
	Median (IQR)(90th percentile) (days)	Median (IQR) (90th percentile)			
Patient	35	14 (0-40) (95)	*Keeble et al. (2014)*	7 (1-27) breast	*Keeble et al. (2014)*
	(0.25-94) (254)	14 (0-31) (93)	*Lyratzopoulos et al. (2015a)*	30 (7-62) oropharyngeal	
	NR	31 (1-122)	*Howell et al. (2103)*	NR	
Primary care	24	21 (5-55)	*Lyratzopoulos et al. (2013)*	0 (0-1) breast	*Lyratzopoulos et al. (2015a)*
	(13-98) (205)	NR	NR	200 (4-39) gallbladder	
	NR	20 (5-62) (134)	*Lyratzopoulos et al. (2015a)*	NR	
Primary care non - Aarhus	41	NR	NR	NR	
	(16-134) (218)	NR	NR	NR	
Diagnostic	66	149 (54-263)	*Din et al. (2015)*	27 (15-62) (210) breast	*Din et al. (2015)*
	(36-142) (240)	83 (34-167) (334)	*Howell et al. (2013)*	113 (45-249) (326) lung	
Time to diagnosis	65	99 (27-526)	*Friese et al. (2009)*	41 (17-85) AML	*Howell et al. (2013)*
	(55-287) (592)	163 (84- 306)	*Howell et al. (2103)*	421 (139-709) myelo-proliferative neoplasm	
Total	140 (77-267)	NR	NR	60 (39-106) breast	*Hansen et al. (2011)*
	NR	NR	NR	134 (93-181) bladder	

NR = not measured

4.6.2.2 The patient interval

The median measured for this population is the longest recorded measurement for myeloma, but is more closely aligned to the median recorded by Howell et al. (2013). The median is considerably longer than reported for oropharyngeal cancer but is less than recorded in breast cancer. The study reported in this chapter and Howell et al. (2013) both calculated the patient interval from self-reported participant information and the variations in the median intervals for myeloma possibly results from the different methodological approaches taken and demonstrates the interval is longer when measured with these methods. Interquartile ranges for the study population were more aligned with Howell et al. (2013), although the upper-quartile range was higher for this study population. Only two previous measurements of the 90th percentile have been measured and when compared to this study the 90th percentile a considerably longer. Comparing medians, IQR and 90th percentiles for other cancer site intervals, this study population had considerably longer intervals than breast cancer, which is considered to have shorter patient intervals, and longer than the longest interval recorded by Keeble et al. (2014) for oropharyngeal cancer (Table 4-33).

4.6.2.3 The primary care interval

The median measured for this study is longer than any median previously measured for myeloma. Comparing IQRs and 90th percentiles also demonstrates that longer intervals were recorded in this study population. Comparison of the interval measurements to other cancer types reveals considerably higher medians and wider IQRs than recorded for breast or gallbladder.

Measurements from the primary care non-Aarhus interval show similar findings, with the statistical measurements recording a higher median, IQR and 90th percentile (Table 4-33).

4.6.2.4 The secondary care interval

This interval has not previously been measured for myeloma and therefore comparison to other literature not possible.

4.6.2.5 The diagnostic interval

The median for this study population was lower than previously reported diagnostic intervals for myeloma (Din et al., 2015; Howell et al., 2013), although the length of the median and 75th percentile were more comparable to data reported by Howell et al. (2013). Comparison of the 90th percentile revealed shorter extremes of the

longest intervals, but the absence of the reporting of the 90th percentile by Howell et al. (2013) does not allow comparison to figures more aligned with this study's reported outcomes. Compared with other cancer types, the median for myeloma is within the middle of the range of reported outcomes. Similar comparison for the IQRs and 90th percentiles can be seen for breast and lung (Din et al., 2015) (Table 4-33).

4.6.2.6 Time to diagnosis interval

The median for the study population was lower than previously reported medians for myeloma (Table 4-36). Comparison of IQRs with other myeloma studies saw the study IQRs fall in between the previously reported outcomes. No comparison of 90th percentiles could be made. Comparison to other cancer type's intervals saw the medians and IQRs for this study fall midway between the shorter and longer intervals reported for Acute Myeloid Leukaemia (AML) and myeloproliferative neoplasms (Table 4-33).

4.6.2.7 The total interval

This study reports the first measurement of the total interval for myeloma. In comparison to other cancer types the myeloma total intervals is longer with higher medians and wider IQRs. The 90th percentile has not been measured for other cancer types and therefore no comparison was available.

In comparison to previously reported literature, the intervals of patient, primary care and total are longer than any previously recorded myeloma intervals, and the longest reported for other cancer types. This may be a result of the collection of targeted data direct from the main parties involved in the diagnostic process, with accurate measurement of the primary care and secondary care intervals from GPs and haematologists and the collection of symptom onset date to commence the intervals of patient, time to diagnosis and total. It is possibly important to acknowledge the contribution of the methods in changing the recorded measurement of these intervals. The addition of the secondary care interval and treatment intervals, whilst not comparable, add to the relative appreciate of the total journey to diagnosis (Table 4-33).

4.6.3 Health status

Table 4-32: ICBP Module 4 health status results compared to Myeloma

Caner type	Very good N. (%)	Good N. (%)	Fair N. (%)	Poor N. (%)	Very poor N. (%)	Total number cases
Myeloma	38 (45.2)	25 (29.8)	13 (15.5)	8 (9.5)	0 (0)	84
Colorectal	121 (40.0)	123 (40.7)	40 (13.2	10 (3.3)	4 (1.3)	302
Breast	119 (44.4)	101 (37.7)	38 (14.2)	9 (3.3)	0 (0)	268
Lung	61 (27.2)	83 (37.0)	59 (26.3)	17 (7.5)	6 (2.6)	224
Ovarian	43 (47.8)	31 (34.4)	15 (16.7)	1 (1.1)	0 (0)	90

** Kind permission of the ICBP module 4 central team – unpublished data.*

*** These crude figures may vary from published work due to inclusion/exclusion rules applied for analysis*

**** Notes for lung cancer detail the double entries x 3 1x VG+G, 2x |P + VP Total % >100*

*****Values for breast, ovarian and colorectal <100% in total*

Comparison of health status for myeloma could be made with breast, colorectal, lung and ovarian cancer types scoring for Welsh participants recruited to the ICBP Module 4 study (personal communication ICBP module 4 central team). Similar patterns of distribution were seen for myeloma as ovarian, colorectal and breast cancers (Table 4-34). Slightly higher proportions of the groups 'very good' and 'good' were recorded for ovarian cancer (82%), breast cancer (82%) and colorectal cancer (80%), in combined data, than for myeloma (74%). These were not significantly dissimilar. Perceived health status scores for 'very good or 'good' categories for lung cancer participants were lower (64%) than recorded for myeloma patients and the other cancer types of breast, ovarian and colorectal. Although there was not of a large difference for reporting in the myeloma groups, there was more difference seen for lung and myeloma than that of breast, ovarian and colorectal. It is possible that lung and myeloma patients have a reduced sense of wellbeing and this affects their health expectation and response to symptoms in similar ways.

Previous studies have reported variations in the number of participants who experience 'no symptoms' prior to a diagnosis of myeloma, reporting frequencies of 21% (Howell et al., 2013); 31% (Howell et al., 2015) and 12% (Ong et al., 1995). This study population recorded a much lower level of an absence of symptoms prior to the diagnosis of myeloma at 6%. The methods of collecting symptom data close to diagnosis (through quantifying well recognised symptoms and adding free text boxes

for further clarification by the participant) is likely to be responsible for the variation recorded. This method appeared to provide additional guidance that helped participants identify and report their symptoms.

The collection of such a diverse range of symptoms in this study, that essentially may exist in a large proportion of the primary care population, supports previous reports that myeloma is hard to diagnose because symptoms are vague and non-specific (Lyratzopoulos, et al, 2015). The study reports a range of symptoms similarly reported by Howell, et al (2013), and confirms musculoskeletal pain is the most frequently reported individual symptom. Howell et al. (2013) reported the presence of 'tiredness' within myeloma participants at just over 20%. This is seen to be greater in this study population, but was specifically labelled as 'fatigue' and gave a definition to clarify symptom. It is possible that participants recognised this term as a 'clinical' symptom more than general tiredness and this affected the frequency of reporting the symptom.

Back pain, which is often associated with myeloma (Lytratzopoulos et al., 2014), was not as widely reported as anticipated. In this study only 31% of the group reporting pain as a 'first symptom experienced' (66% of the total population) reported back pain specifically. This possibly adds to the further understanding as to why there are difficulties identifying symptoms of myeloma in primary care.

The positive predictive value (PPV) of single or paired symptoms in myeloma has previously been reported as low (Shephard et al., 2015), but the PPV is reported to increase when symptoms are paired with abnormal clinical investigations such as ESR. This study has highlighted that the majority of clinical investigations are performed at a low level which reduces the opportunity to pair symptoms and abnormal clinical investigations. Importantly, though, of the clinical investigations performed, the tests most likely to report an abnormal finding was the SPE with more than 90% reporting abnormal tests results. The breakdown of the three most frequently reported symptoms in myeloma in this study demonstrates that paired or triple symptoms are reported only slightly less than single symptoms and strengthens the reporting of single symptoms not being predictive of myeloma possibly.

The literature relating to the diagnosis of myeloma frequently reports myeloma having no 'symptom signature'. A lack of a single symptom associated with the disease that is absent in the healthy population makes connecting symptoms and the disease difficult (Howell et al., 2013; Lyratzopoulos et al., 2015a; Rubin et al., 2012). This is a somewhat ambiguous term, as there is no actual quantification of what prevalence of a symptom is required to determine it as a 'symptom signature'. However, this study has been able to demonstrate that >80% of the myeloma patients experience one of three symptoms and that 25% experience all three of the symptoms of pain in muscles and joints, bone pain and fatigue. This study contributes, therefore, to an understanding of the symptom profile of myeloma in pre-diagnostic period.

The number of symptoms experienced, unsurprisingly, was associated with an increased primary care interval (weak correlation reported). Whether the number of symptoms results in longer intervals, or longer intervals results in higher numbers of symptoms should be considered. It is most likely that the patient experiences more symptoms as the primary care interval lengthens, because the disease progresses and greater disease burden results in complications and therefore more symptoms.

The number of primary care consultations made by this study population was comparable to that reported by Lyratzopoulos et al. (2012) with both studies reporting 50% of participants had three or more consultations before secondary care referral was made. However, this study added to the significance of these multiple consultations by demonstrating associations between longer intervals and more consultations and longer intervals and consulting with greater numbers of different GPs.

There were fewer emergency presentations (25%) for this study population than reported by Elliss-Brookes et al. (2012) for their myeloma population (37%). Possibly there have been improvements in the access to secondary care via acute presentation, or methods were more successful at recording these events from clinician and patient participant-generated data compared to using database or registry data.

The low level of SPE ordered in this study population (50%) supports findings from Friese et al. (2009) of high levels of incomplete diagnostic workup in myeloma. This

study additionally demonstrates that the low level of testing of SPE, SFLC/BJP/ESR/X-raying of symptomatic areas occurs within the primary care setting. The low level of testing of ESR/PV was seen to be in contrast to recommendations in the revised urgent suspected cancer NICE referral guidance (NICE, 2015). However, this may reflect guidance publication after the first half of the study population and before its impact on practice was made.

Bone disease and anaemia were the two most commonly reported complications of myeloma at diagnosis which supports findings reported by Kariyawasan et al. (2007). However, this study additionally could report that those participants considered fit for transplant had longer intervals to diagnosis and possibly this relates to haematologists reporting that burden of disease at diagnosis influenced treatment choices in over 50% of cases.

The slightly lower age of participants in this study may be a reflection of the disparity reported in cancer trials engagement of the older population (Hori et al., 2007), and not a study population difference specifically.

It is of interest that, although the patient interval recorded for this population of participants was the longest ever reported for myeloma, and was considerably longer than other cancer types such as breast, no patient or demographic factors were measured as significant in correlation or regression analysis. This may indicate there are greater influences in appraising and interpreting symptoms of ill health that delay help-seeking, other than social or contextual factors in the diagnosis of myeloma.

4.7 Strengths and limitations

The major strength of this study is the depth of data collected which has allowed the measurement of all the intervals to diagnosis in myeloma alongside the assessment of factors affecting the length of these individual intervals. The use of statistical testing adds relevance in the understanding of the associations between factors and intervals, allowing targeted strategies for timelier diagnosis to be recommended. Despite the depth and complexity of data collected, transcribed and audited revealed a low error rate.

The collection of data directly from patient participants benefits the analysis of symptoms, reflected by the depth of information recorded. Additionally, the collection of data so close to the diagnostic date (patient recruited within six months of

diagnosis) lessens the possibility of recall bias. However, a large number of missing data for primary care limited the case numbers for analysis. Potentially recruiting from primary care or securing research nurse support for completion of the questionnaires in primary care may have improved the case numbers for analysis. Additionally, no data queries were raised to clarify responses given in the questionnaires, as the 'tools' (questionnaires) were being assessed as to their ability to collect the information of interest. This meant that some data was ambiguous and could not be managed within the data hierarchy process or was missing. These data were, therefore, excluded from analysis and further limited cases for analysis.

The spread and diversity of recruitment of participants across the Welsh nation allows the representation of the diagnostic processes and practices across a single nation. This possibly makes the study particularly useful for policy practice in Wales.

The major limitation of the study is the number of cases available for evaluation, particularly those in the primary care analysis (discussed above). Lower numbers limit both statistical analysis and generalisation. Whilst the main aim of the study was explorative, it is acknowledged that lower case numbers may limit the interpretation for policy practice recommendations and, therefore, require additional research in larger numbers to underpin any national policy change.

It is specifically acknowledged that assumptions to allow generalisation of data rely on a sample size which facilitates statistical significance. Field (2009) reports for every variable entered into a regression model, 15 cases are required to allow generalisation. Therefore, a population of 195 cases would be required for this study which was not achieved.

The study population was not representative of the wider population for gender, ethnicity, or age, and is therefore limited in representing these influences in the wider myeloma population.

The study has limited assessment of the behavioural influences on the intervals to diagnosis. Therefore, it is limited in contributing to the better understanding of 'why' longer intervals to diagnosis occur. This is particularly important given the longer measurement recorded for the patient interval in myeloma. Qualitative assessment may provide further understanding.

Although questions allowed the capture of data for the tests completed in primary care which were recommended as 'screening' tests within the diagnostic guidelines by the BSH (Bird et al., 2011). The questions did not capture additional testing outside of these guidelines, such as Liver Function Test (LFTs). It is possible, therefore, that GPs are investigating symptoms at a higher rate, but if this is the case, these tests are not facilitating the suspicion of myeloma.

Discrepancies were seen between datasets for patient and primary care in the reporting of emergency presentation. A pragmatic approach of using the most complete dataset was believed to provide the best possible depiction of emergency route presentation, but the discrepancies are acknowledged as a possible limitation.

The study methods prioritised capturing data close to the date of diagnosis to facilitate symptoms analysis from data unaffected by recall bias. However, these methods did not facilitate the assessment of the response to treatment as data collection in the majority of cases occurred before first line treatment had been completed. The way in which intervals to diagnosis influence the response to treatment therapies initiated is missing from these results. Similarly, methods did not permit a survival analysis. It is acknowledged that survival analysis is an important contribution to further understand the effect of longer journeys to diagnosis in myeloma (Chapter Two section 2.7). The intention for this study population is to continue to assess survival annually until the five-year median survival period is reached. Whilst it is acknowledged that these two factors cannot be adequately assessed by the methods implemented, it is an endorsement that participants were recruited promptly after diagnosis and collection of data was very timely.

4.8 Implications for policy and practice

People with myeloma may be expected to take longer than other cancer groups to appreciate symptoms and present to their GP. It is important for GPs to appreciate this and act promptly to reduce the primary care period, but there is also a need to increase awareness of the disease and its symptoms in the general public. There is some evidence that health expectation may play a part in assessing symptoms in myeloma. This is possibly a wider public health issue. Awareness campaigns are challenging to devise and expensive to implement. However, if targeted efforts are to have influence in the patient interval then observations made here may help third sector groups better establish targeted awareness campaigns.

Participants who are experiencing pain prior to the diagnosis of myeloma may not take analgesia and this, therefore, in myeloma, may not be a proxy for recognising symptom development or dysfunction as serious at GP consultation. GPs should therefore further-investigate the complaints of pain even when analgesia has not been self-administered or requested.

There is a wide and diverse range of symptoms experienced by patients prior to the diagnosis of myeloma supporting that symptoms in the pre-diagnostic stage of myeloma are non-specific. Whilst the identification of the wide range of 39 different symptoms does nothing to aid patients or GPs with their suspicion of myeloma, it provides some explanation as to why the patient and primary care intervals are long. The three single symptoms appearing in greater than 80% of the population and the three grouped symptoms appearing in 25% (bone pain, fatigue and pain in muscles and joints) does contribute to the understanding of the likely symptoms that occur pre-diagnostically in myeloma and the symptoms that are most likely to be presented to primary care. This knowledge can now help GPs to suspect myeloma or serious illness earlier and become an impetus to investigate widely.

The pain symptom profiling described here should also alert GPs to the wider and varied pain symptoms experienced by myeloma patients pre-diagnostically to help GPs form a more timely differential diagnosis. GPs should be aware that the reporting of pain prior to a diagnosis of myeloma may be reported as originating from bones, joints or muscles, and that this is varied in terms of location in the body and not limited to the back specifically. A wider profile of pain in myeloma age range should therefore be used by GPs likely to initiate earlier investigation, with targeted investigations to identify monoclonal paraproteins. Additionally, the systemic feature of fatigue, whilst not easily quantifiable for a GP, occurs at a higher frequency than possibly previously appreciated, and should be an impetus for earlier investigation when reported in an association with pain.

The study has identified that the first symptom of myeloma in the majority of patients is pain and GPs should be aware of this when assessing symptom/s in consultations. It is possibly reassuring to GPs that this study reports the majority of myeloma cases will have symptoms (94%) which provide a prompt to seek help when recognised by patients because this does give the GP an opportunity to suspect myeloma and investigate.

The majority of myeloma patients with symptoms will present to primary care through normal 'in hours' services. Therefore, the GP may expect to see these patients first through a routine presentation. Once presentation to primary care is made, diversity can be seen in the individual pathway through the variations in consultation rates. GPs should be aware that multiple consultations in primary care are associated with longer intervals to diagnosis and act to reduce these through earlier recognition and investigation of the symptoms identified here and prompt referral to secondary care. The finding that consultations with different doctors is also associated with longer intervals requires consideration within primary care practices in order to facilitate continuity in follow-up for patients in order to reduce the intervals to diagnosis. Despite participants, in the majority, presenting to primary care, a quarter of myeloma presentations went on to present to secondary care as an emergency. The ability to demonstrate that the majority of these patients had first presented to their GPs can highlight to GPs a need and opportunity to suspect myeloma in primary care earlier and prevent disease burden increasing and emergency presentation occurring.

The tendency to under-investigate or delay investigation of non-specific pain and fatigue should now change in primary care with the identification of the more commonly occurring symptoms in the pre-diagnosis stage of myeloma. The response from primary care must be to investigate earlier and more broadly with a wider range of clinical investigations based on the evidence of investigative procedures reported here. The use of physical examination and x-ray of symptomatic areas can provide better assessment of these symptoms and should be included in a general assessment in the response to symptoms in patients within the age range for myeloma. Additionally, protein electrophoresis of urine and serum should be conducted more widely at a lower threshold in vague and non-specific symptom presentation, where pain in the absence of trauma occurs and is more heavily indicated if fatigue is present. Protein electrophoresis of serum or urine is a widely available, relatively inexpensive test, easily performed with no additional inconvenience to the patient and gives a greater opportunity to suspect myeloma for the GP demonstrated by the high frequency of positive testing reported by the study (>90%). GPs and hospital laboratories may have concerns with increasing the frequency of SPE testing, but in relation to the expense and ability to identify and target referral to haematology this is likely to mean shorter intervals to diagnosis.

Additionally, when a less wide profile of investigations is performed at initial symptom presentation, GPs should invoke a low threshold for repeating investigations and widening the profile of testing on repeat presentation of the patient.

It is likely that a GP will see a change in access for their patient to primary care services in the six months preceding a diagnosis of myeloma. It is possible that the numbers of consultations made in primary care increase in this period and GPs can be alerted to changing patterns of access in these patients, which may additionally prompt investigation.

Finally, the secondary care interval is possibly longer than previously thought. The recording of this interval allows the relative contribution of it to the overall total interval and allows comparison to the primary care interval and reveals an interval as long as that the primary care interval. This possibly highlights a need to assess the possibilities of improvement of the passage through this interval to allow earlier diagnosis of myeloma.

Referral into secondary care is clearly problematic for the myeloma patient with multiple teams receiving referrals (>50%) and these in around 50% not having an urgent suspected cancer tag, with even less using the TWW referral route (43%). Unsurprisingly the TWW was seen to be associated with shorter intervals in regression analysis and is, therefore, the most efficient and prompt referral pattern for the myeloma patient. Many of the non-haematology teams who were referred to had associations with longer intervals in regression analysis. The study also saw that in referral to secondary care categories, patients who were not referred via a GP referral had associations of shorter intervals to diagnosis for secondary care and total intervals. This possibly relates to the patients in surveillance programmes and would be a positive reinforcement of continuing continuation of monitoring through haematology services of at-risk groups. These factors need appreciating from both the primary care and secondary care clinician perspective. Identifying areas of streamlining referral to haematology requires a focus and the lack of urgent suspected cancer and non-haematology referrals suggests that myeloma is not suspected, or a cancer more generally is not suspected, before the myeloma patient receives a referral or presents to secondary care.

It is possible that new initiatives being piloted or early secondary care access for symptoms that are vague but worrying via the ACE programmes (Cancer Research

UK, 2017 b) may provide some opportunity to hasten investigation and widen access to specific tests, avoiding random referral to non-haematology teams. However, the large proportion of myeloma patients who have referrals that do not have a 'suspected cancer' tag are unlikely to benefit from these rapid access routes. The focus must remain, therefore, on improving the suspicion of myeloma in primary care and this can be done through the better understanding of symptoms and lowering thresholds for early investigation for lower level symptoms.

Once referral is with the haematologist, there appears to be a more direct pathway to a diagnosis, although there was surprisingly no association in regression modelling of direct referral to haematology and shorter intervals to diagnosis. Possibly, identifying those patients who enter secondary care through non-haematology routes could promote timelier diagnosis. It was of interest to see the frequency of laboratory identification of abnormal tests being reported as a contributing factor in the identification of myeloma in secondary care in almost 20% of cases. It is possible that this may help identify paraproteins or other abnormal tests that allow guidance for further testing to be initiated from haematologist from samples either from primary or secondary care. Haematologists were seen in the majority, to follow guidance for the diagnosis of myeloma when patients reached their care, although cytogenetic risk assessments were performed at a very low level of 32% but this is related to prognostic evaluation of confirmed myeloma and not the diagnostic workup. Therefore, it is unlikely to affect the timeliness of a diagnosis. In the diagnostic workup to myeloma by haematologist, participants who required examination with bone biopsy for diagnosis were seen to have associations of longer secondary care intervals. This most probably relates to atypical presentations of the disease or difficulties identifying the disease through other diagnostic testing, and is likely to remain a challenge to haematologists and possibly be impacted by the NICE guidance for 2016 for the assessment and identification of myeloma in secondary care (NICE, 2016a) and the call for earlier MRI and SFLC use. The newly recorded treatment interval measured the longest intervals recorded for the 90th percentile were three months or more. Haematologists should be aware of delays in commencing treatment and look for explanations as to why this occurs. It is possible that treatment does not commence until stabilisation of disease complications has

been achieved, but the aim to commence timely treatment should be promoted to haematologists to reduce overall total intervals.

Missing assessment of staging of disease in 7% of participants is contentious, and suggests Welsh haematologists do not adhere completely to the British Society of Haematology diagnostic practice guide (Bird et al., 2011), although this was not significant in regression analysis for longer intervals and appeared unrelated to the diagnostic timeliness. Additionally, a proportion of the staging group would have assessment of stage of disease in the absence of $Beta_2$ microglobulin assessment, as this was missing in 14% of the study population. There is, however, no evidence that this was associated with longer intervals to diagnosis.

Other activity in secondary care, choice of treatment or clinical trial activity, was not seen to be associated with the length of intervals to diagnosis, so it may be assumed once a diagnosis is made by the haematologist the length of intervals to diagnosis are less influenced.

4.9 Recommendations for further research

There is now a need to better understand the observations made from the questionnaire study through qualitative methods to provide the 'why' behind the findings reported. Particularly, the behavioural aspects that contribute to the lengthened patient interval require assessment to better understand why myeloma patients respond to symptoms and help-seeking in different ways and take a long time to present their symptoms in primary care. Better understanding of these factors has the potential to aid the development of strategies to reduce the patient interval in myeloma. The further exploration of perceived poor health status prior to the diagnosis of myeloma and longer patient and total intervals additionally requires qualitative assessment to understand how this impacts the patient interval. There is a possibility that having an existing poor health status lowers the 'health expectation' in some people and, therefore, appraisal of symptoms and the disease itself have an insidious onset with lower levels of physical dysfunction initially occurring with discreet changes in health taking time to be acknowledged by the patient. These factors require assessment in research that allows interpretation of perceptions, experiences and understanding of myeloma patients.

Qualitative exploration of GP perceptions and experience diagnosing myeloma are also required to break down and assess the difficulties GPs experience in identifying

and investigating myeloma that contribute to the lengthened primary care interval and total interval.

It is possible that GPs see very few cases of myeloma in their practice and this contributes to the poor assessment of symptoms because of reduced knowledge. However, this study was unable to assess these factors due to the low level of primary care data returns. It is possible that a qualitative assessment of the attitudes, perceptions and knowledge of GPs can contribute to the better understanding of the processes involved in suspecting and diagnosing myeloma in primary care.

4.10 Conclusions

This study reports some of the missing evidence in the poorly understood process of diagnosing myeloma. Additionally, it contributes to informing policy makers on how a diagnosis of myeloma may be made timelier. The results confirm there are no easy solutions to these difficulties demonstrated by the depth and complexity of the diagnostic processes. However, there are improvements that may be made that could potentially affect all the intervals to diagnosis and treatment. It may well be that in myeloma, small changes across the different intervals are the way forward in reducing the total interval.

Through greater appreciation of symptoms in both the patient and primary care group, there is an opportunity for alerting both groups to suspecting myeloma or serious illness more promptly. Alerting the patient groups relies on increasing awareness of the symptoms of myeloma and appropriate campaigns for this to help appraisal and help-seeking. GPs require knowledge transfer of the newly identified symptoms in the pre-diagnostic stage of myeloma to prompt suspicion and therefore targeted investigation. Opportunity then exists to identify abnormalities in myeloma patients earlier in primary care by GPs responding to pain with physical examination and x-ray of symptomatic areas and adopting a policy of wider screening tests. Using ESR/PV or SPE/SFLC/BJP for assessment of early symptoms of pain, skeletal or muscular and systemic changes of fatigue provides a better opportunity for GPs to suspect myeloma and target a referral to haematology. A targeted referral that is based on a suspicion of cancer is likely to then promote a timelier passage through secondary care and onto a diagnosis by bypassing the obvious delayed routes seen in multiple non-haematology teams.

In conclusion, there are possibilities to reduce the intervals to diagnosis in myeloma, whether this improves outcomes in survival remains unexplored but will need to be analysed in ongoing analysis of this population of participants.

5 Chapter Five: Exploring the behavioural and contextual factors in the individual journeys to a diagnosis of myeloma: patient perspectives

5.1 Summary

This chapter reports the exploration of patients' experiences, perceptions and the context of their journeys to a diagnosis of myeloma. The findings explore and answer some of the reasons why the patient and primary care intervals are longer in myeloma journeys. The findings here allow the explanation of the results reported in the quantitative study (Chapter Four section 4.5) by providing a deeper understanding of the factors reported by reporting how these factors influence the intervals to diagnosis.

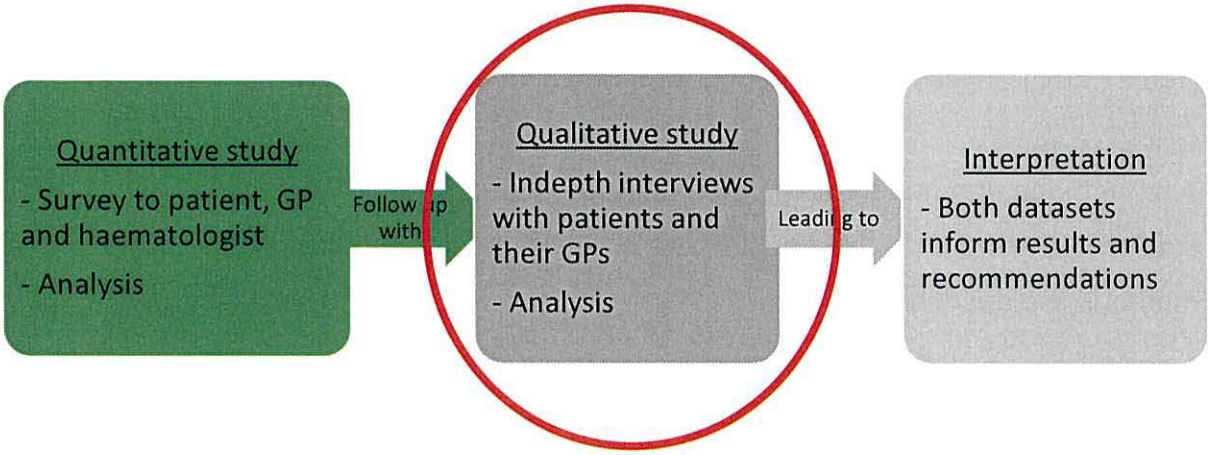

Figure 5-1: Diagram of Explanatory Sequential Research Program

(Adapted from Creswell, 2014)

5.2 Background

The findings from the systematic review (Chapter Two section 2.4) and the quantitative study (Chapter Four section 4.5) reported the intervals of patient, primary care and diagnostic were longer in myeloma patients. The quantitative study also reported that the secondary care interval in myeloma was relatively long when compared to the primary care interval, but found no literature to compare this with other cancer types' secondary care intervals. Whilst these intervals were all acknowledged as long, the systematic review reported there was little evidence to allow policy recommendations for reducing these. The quantitative study was able to make some recommendations for practice, but it was acknowledged that there was little understanding of the behavioural or contextual factors which may contribute to these longer intervals. However, the reporting of the complete quantified journey to diagnosis does allude to the possibility that the patient interval is affected by contextual, behavioural and social influences and understandings, through the reporting of longer help-seeking and appraisal period for symptoms. Additionally, the

passage through primary care is longer for myeloma patients and may be influenced by interactions and understandings of ill health, symptom communication and appraisal in the interactions within GP consultation. Qualitative methods are required to explore and assess the possible behavioural and contextual factors in these complex journeys, to build a deeper understanding of 'why' and 'how' diagnostic journeys for myeloma are altered (Creswell, 2014). This then allows findings that can aid clinicians and policy makers in their decisions on how myeloma may be more timely diagnosed and inform government policy for the United Kingdom to better cancer outcomes and survival by diagnosing cancer more timely (Department of Health, 2011; Welsh Government, 2016; Scottish Government, 2016).

5.3 Methods

The methods and underpinning methodology are reported in detail in Chapter Three section 3.1 and 3.8. In this chapter, the practical implementation of the chosen methods are described.

5.3.1 Sample selection

A sample size of 24-30 patient participants (three groups of 8-10) was set as a target recruitment, but sampling was linked to theoretical saturation and would cease when theoretical saturation was assessed (Seale, 1999). Sampling was purposive, to select participants from groups that were most likely to yield information rich experiences (Suri, 2011).

Participants with time to diagnosis intervals above or below the interquartile ranges of the Howell et al. (2013) study or had asymptomatic presentations (no reported symptoms in the pre-diagnostic stage in the patient questionnaires) were eligible for the study (Chapter Three section 3.9). When patients had given consent to receive further information about the interview study and secondary care recruiting sites had confirmed the participant was well enough to receive information, patient information sheets were sent by post to the participant's home address.

Participants were telephoned two weeks after being sent information to discuss whether they were willing to participate in an interview. When participants agreed, interview dates were arranged over the telephone.

5.3.2 The interview: data collection method

Participants were interviewed in the venue of their choice, either their own home or the hospital where they received treatment. Face to face interviews were conducted

with participants to solicit their perspectives/perceptions of the journey to diagnosis (Joubish et al., 2011). The interview followed a semi structured approach in its dialogue. Interview topic guides were utilised throughout the interview providing structure to the interview for the researcher to work from (Ritchie and Lewis, 2003), but equally flexibility for the development of the emerging topics discursively within the interviews as they arose (Chapter Three section 3.13.5).

The interviews were around 60 minutes in duration. All interviews were audio recorded, with participant permission, transcribed verbatim and transcripts were checked by the student researcher for accuracy, and a smaller number co-checked by a supervisor.

5.3.3 Analysis

The Framework Method of analysis (Ritchie and Spencer, 1994) was used to organise and structure the analysis process. (Analysis is fully discussed in Chapter Three section 3.13.6). Following the organisation and processing of the dataset using Framework Analysis', Thematic Analysis was applied for final analysis and interpretation. Thematic analysis also followed a structured approach and ran alongside Framework Analysis complementing and building on the Frameworks structure (Braun and Clarke 2006).

Audio tapes were transcribed as interviews were conducted and reviewed immediately, allowing for immediate analysis. A non-linear process was applied to the reading and rereading of transcripts. Initial coding was undertaken using a deductive process allowing data to emerge and not restricting codes to predefined research questions (Braun and Clarke, 2006). Prevalence was assessed in codes by the amount or words or space given to the code in transcripts or by the number of participants that discussed the code. Codes were then used to identify semantic themes emerging from data in an indexing process using what participants said rather than interpreting or deducing meanings within the words (Braun and Clarke, 2006).

Themes were charted firstly for individual participants, and then across the dataset to form final themes. Tables were used to chart individual semantic text and themes with mind maps used to summarise themes and semantic extracts across the dataset.

The process of interpretation was a progressive analytical process involving summarisation of the themes individually described alongside semantic evidence. Theorising was made alongside existing evidence supported in the literature and findings from the quantitative study.

Journey experiences were, additionally, mapped in reporting in line with a recognised theoretical model "Pathways to treatment" (Walter et al., 2012) (Chapter One section 1.6).

5.4 Findings

5.4.1 Participant recruitment

From the cohort of 84 participants registered in the questionnaire study, three participants declined approach for interview in the first phase consent process. The diagnostic journeys of the first 51 participates were examined sequentially to identify possible participants for the interview study. The journeys of 21 participants (21/51) fell within the three identified categories for purposive sampling.

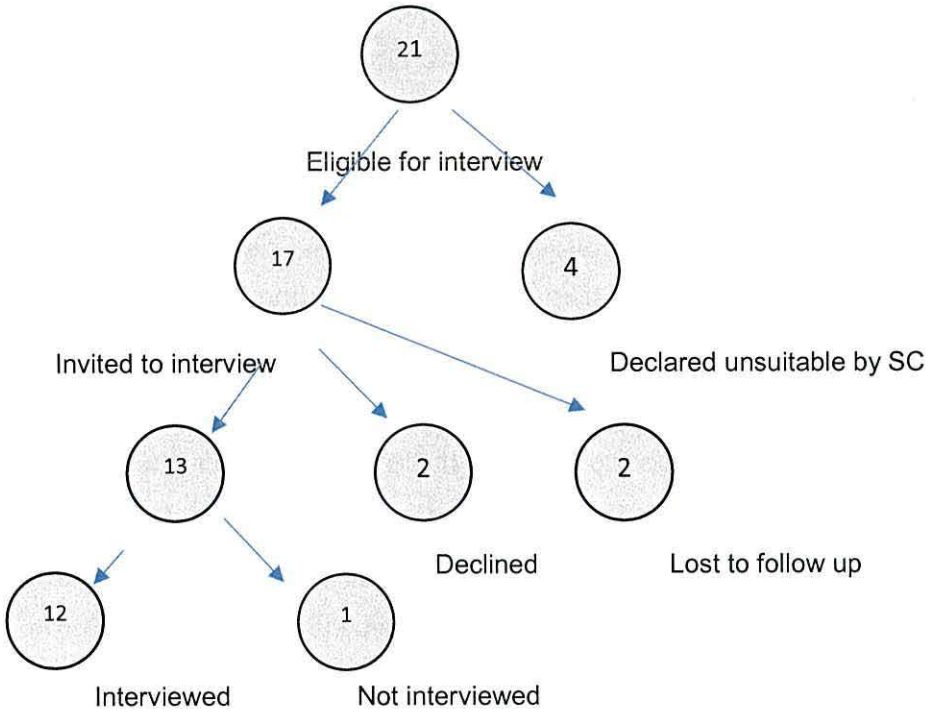

Figure 5-2: Participants invited to interview

Secondary care sites reported four participates were not clinically suitable for an approach to interview. Interview invitations were, therefore, sent to 17 participants. Thirteen participants agreed to be interviewed. Two participants were lost to follow

up due to a change in contact details and two patients declined the interview. Of the 13 participants who agreed to be interviewed, 12 interviews were conducted. One participant was unable to attend the scheduled interview due to acute illness and hospitalisation. The intention was to examine the remaining 33 participant journeys and recruit more participants to the interview study until saturation was met. Early saturation was seen at 12 interviews so the examination of further 33 journeys was not required.

5.4.2 Sample group

Table 5-1: Participant characteristics and time from diagnosis to interview

Name (pseudo)	Sample group	Time interviewed following diagnosis (Days)	Age	Deprivation quintile: 1,2,3,4,5 (Welsh Index of Multiple Deprivation)
Sam	Longer	299	46	5
Carys	Prompt	161	62	5
Arthur	Longer	171	82	5
Audrey	Prompt	189	61	5
Daphne	Prompt	322	84	3
Tom	Longer	245	65	5
John	Prompt	167	59	3
Charlie	Longer	247	70	5
Shan	Asymptomatic	231	56	4
Harriet	Longer	233	64	5
Trefor	Longer	126	73	3
Jan	Prompt	298	77	5

The interview sample group had equal numbers of males and females as seen for the larger cohort in the quantitative study (Chapter Four section 4.5.3). The age range was wide (range 46-84) as also seen in the larger cohort, but deprivation status in the sample group for the interviews had a higher proportion of affluent participants (quintile 5) (Appendix 12). No ethnic diversity was seen with all participants being White British and was reflective of the wider cohort in the

quantitative study (Chapter Four section 4.5.3) (Appendix 12). Participants registered in the quantitative study, unexpectedly, did not include many asymptomatic presentations of myeloma (3/83), resulting in the asymptomatic sample group population being reduced (1/12) (Table 5-1).

5.4.3 The interview

5.4.3.1 Setting

Out of the 12 interviews conducted, 11 took place in the participants' homes. One interview was conducted in the hospital setting due to the participant being hospitalised (having initially requested a home interview) on the day the interview was scheduled.

As no conditions were placed on the interviews as to whether participants should be alone or accompanied in the interview, diversity was seen in the choice of having a third-party present. Half the participants were interviewed alone, but about half of these had a family member within the house whilst interviews were being conducted. The remainder of the group had a family member present throughout the interview. All third-parties were family members. The choice as to whether to have a family member present during the interview did not appear to be linked to age or deprivation, but during the dialogue within interviews the researcher assessed this was more related to the contribution made by the family member to the diagnostic journey. The presence or absence of a third person appeared to have no bearing on the interview process or the discursive nature of the conversations. Where third parties contributed to the interview dialogue, field notes were made following the interview. The researcher used reflexivity to capture the context and contribution of the carer's narratives. The observations of these individuals gave an unplanned but important contribution which added richness to the analysis and findings. As no formal consent was received, these contributions were reported using descriptive text from the field notes.

5.4.4 General summary of the interviews: content, style and process

The interviews were very inductive and less structured than was originally planned in the methods (Chapter Three section 3.13.5). The interview opened with an exploratory open-ended question (Ritchie and Lewis 2003), to encourage a dialogue and develop trust between the researcher and participant (Appendix 9). The initial question "Tell me about how you were diagnosed with myeloma?" was used and led,

in the majority of interviews, to an outflow of a verbal narrative that required very little guidance from the researcher. Participants were found to be open and engaged and keen to tell their 'stories' of diagnoses. The interview guide provided pointers for clarification and exploration rather than a prompt for discussion but, in application, appeared to be well situated and ably implemented. Although some areas of the discussions were sensitive and appeared to invoke frustration or anger in participants, the interviews generally were appraised by the researcher to be therapeutic rather than distressing. The interview dynamics between researcher and participant were comfortable and appeared equitable to the researcher. The flow and depth of conversations within the interview seemed to support this. Interviews, in the majority of cases, lasted one hour or more. This was the result of the depth of the 'story telling' from the participants and the level of engagement in the interview. For the vast majority of the interviews the participant was the main speaker, again reflecting the willingness of the participants to tell their 'stories'.

Although the original recruitment target for the sample was 24-30 participants (3 groups of 8-10 participants) (Chapter Three section 3.13.3), saturation was seen at 12 interviews and recruitment discontinued. Saturation was assessed throughout the analysis process and was found to have occurred when no further themes were seen or emergent and only recurring or repeating themes in sequential interviewing and analysis were found (Seale, 1999; Mason 2002; Ritchie and Lewis, 2003). Whilst reaching saturation after 12 interviews was unanticipated, it is possible that identifying the participants likely to have rich stories to tell, at the extremes of the diagnostic journey durations, through purposive sampling, led to this rapid development of themes arising from the deep, revealing and illuminating personal experiences given in these highly discursive interviews.

5.4.5 Themes

Four main overarching meta themes were developed spanning the entire diagnostic journey (Figure 5-2). Whilst some themes developed that related to priori formed from the systematic review and the quantitative study findings, such as symptom appraisal difficulties, new themes were emergent from data such as lay influence in appraising symptoms, help-seeking and presentation of participants to primary care. Theme categories were seen to have different degrees of influence and complexity within the diagnostic journey. Some themes were clearly highly influential and

complex, such as appraising symptoms, whilst others appeared to have less prominence and complexity. The more complex themes were typified by multiple subthemes, reflecting their complexity within the journeys portrayed by participants in the interviews. The overarching themes had a revolving non-linear process, which saw participants moving forward and backwards between the meta themes (Figure 5-2). Themes appeared to have an influence independently or in conjunction with each other, and equally had an influence that peaked and ebbed, depending on influences from other themes.

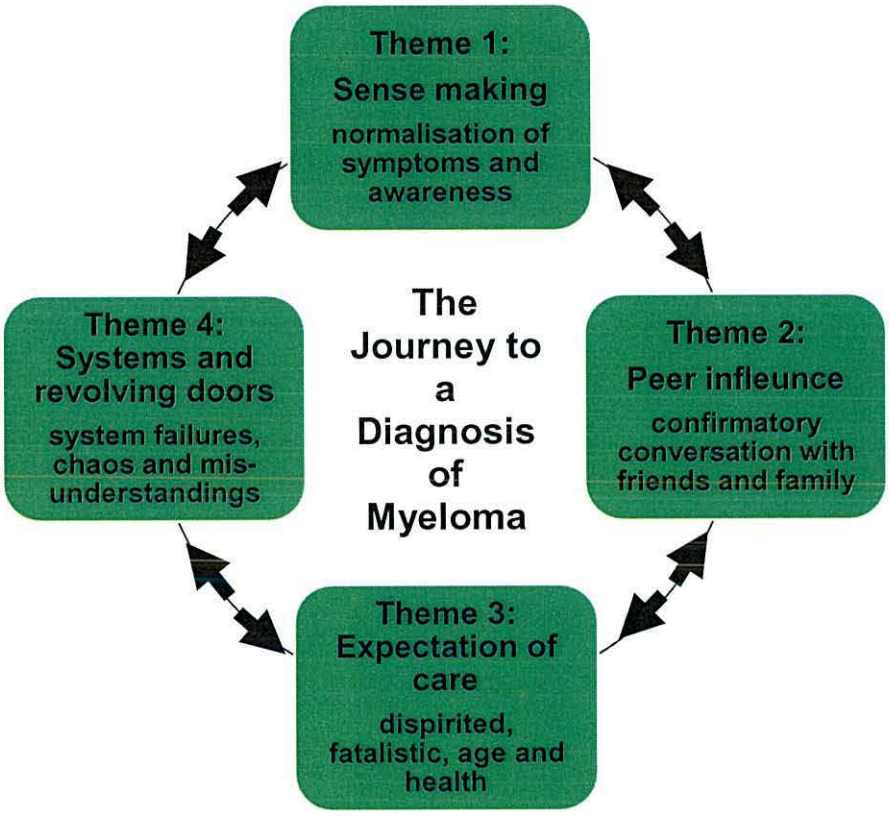

Figure 5-3: Meta themes within the diagnostic journey of myeloma patient

Quotes are offered as supporting evidence within the themes and have been edited for punctuation to improve readability. This has included the removal of pauses where the interviewee has paused for breath or thought and the pause is displayed by the punctuation of a comma. The quote in its essence and meaning remains unchanged.

5.4.5.1 Theme one: Sense making

A complex and multifactorial theme emerged from the data which described a process, where participants made sense of the symptoms they experienced. This was a theme that dominated the conversations in the interviews. Multiple sub-

themes emerged within this one larger theme, which focused around the complexity of recognising, appraising, responding to and decision-making processes taken in the presence of symptoms. Subthemes were seen to sometimes contribute to a progressive process, where factors built on phenomena within other subthemes, adding to the complexity and difficulty of 'sense making'.

5.4.5.1.1 Awareness/knowledge

Participants described a complete lack of awareness of myeloma prior to their diagnosis. This included, in all but one participant, never even having heard the name 'myeloma' before. This lack of awareness of the disease, appeared to have no bearing on the duration of the journey.

"One cancer I'd never heard of." – Carys, female, prompt journey.

Relatives of the participants equally displayed a lack of awareness of the disease and some remarked on how they were aware of campaigns for other cancers but not myeloma.

The lack of awareness of the disease made connecting symptoms experienced by participants and their carers impossible to relate to the disease. In retrospect though, some carers recognised that they had seen symptoms but doubted their judgement because of poor awareness and feeling they were not an 'appropriate' person to 'diagnose'.

Failure to recognise symptoms of myeloma was seen to be present even after the diagnosis of myeloma, when treatment had been commenced or finished. Some participants and carers during the interviews sought clarification of what the symptoms of myeloma were. Some patients acknowledged they still did not know what the symptoms were whilst carers sought clarification as to whether certain symptoms, such as pain, were associated with myeloma.

"I don't know what the symptoms are." – Harriet, female, longer journey.

5.4.5.1.2 Appraisal of symptoms

How symptoms were appraised and assessed was a frequent topic of conversation within the interviews, and was overwhelmingly reported as difficult and problematic.

Symptoms were considered not to follow a pattern that would raise immediate concern in participants, hence linkage between the recognition of a symptom with a serious illness was not made.

> *"[Wife] said she noticed the dragging of the hip about mid last year, but I knew that anyway because I was lifting my leg up to get into the, quite a low-slung car, I was just thinking I've got pain in the hip. The only way I can sort of describe it was I was mincing round [location] with a pain in, in my chest, sort of holding my chest and sort of mince my way about, you know trying to get from A to B as it were. There was nothing, there was nothing that seemed to that was glaringly obvious to anybody."* – John, male, prompt journey.

Participants appeared focused on the fact that if they had cancer then they would have a definitive symptom, much like an 'alert' symptom described for lung or breast cancer. Participants reported that they assumed these alert symptoms would give clues to an underlying serious disease and were seen to have a degree of irritation that myeloma did not appear to have this. A 'false sense of security' was felt by participants because of not experiencing any 'alert' symptoms.

> *"You haven't got a marker, as such."* – Jan, female, prompt journey.

> *"I mean I was aware of all the other major cancers, you know that, the lungs the ones that have an effect on people that stand out".* – John, male, prompt journey.

Participants discussed that their symptoms were of a lower level of intensity initially and therefore only had a minor impact on their everyday lives; they were able to live and function relatively normally. In interviews, these early symptoms were referred to as 'insidious' in nature, being misleading. These symptoms were also reported to be further 'confusing' in recognition as 'serious' by an absence of something tangible to aid the recognition of the symptom as serious such as a lump or visible swelling.

> *"This is a very odd cancer to me, because I thought cancer was extremely painful; terribly obvious. It's like a silent thing to me. Because it is silent I find it very hard to recognise any symptoms".* – Audrey, female, prompt journey.

As well as discussing the initial slow development of symptoms, participants uniformly reported feeling well alongside symptoms. This was discussed as 'confusing' the recognition of symptoms' seriousness. Participants reported this

regardless of whether their time to diagnosis was prompt or longer, and the ability to recognise symptoms as serious in the face of feeling well relied on continued appraisal and final recognition, by themselves or the GP, that these symptoms required investigation or referral.

"And I felt as fit as a fiddle." – Carys, female, prompt journey.

"I wasn't ill. I wasn't feeling ill." – Arthur, male, longer journey.

5.4.5.1.3 Normalisation

The consequence of poor awareness of the disease and symptom appraisal was the overwhelming phenomena of normalising symptoms to the natural ageing process. Here, all participants described the use of, what they portrayed as, a logical sense-making process, rooted in their level of knowledge and understanding of the symptoms they were experiencing. Whilst this normalising of symptoms was reported in every interview, the strength of the normalisation was key to the length of time spent appraising symptoms as 'not serious', and the level of tolerance of these symptoms that followed. Although this normalisation reported, related to an understanding and expectation of how pain and discomfort was expected in 'old' age, there was no difference seen in normalising these symptoms across the age range interviewed, with all participants demonstrating normalisation of symptoms to ageing. Therefore, there was a resignation witnessed, in the entire interview group, that being 'elderly' meant symptoms of pain and fatigue were inevitable and 'blame' or attribution to ageing was logical.

"Oh you're just getting old, shut up. Stop moaning about it and just get on with it." – Sam, male, longer journey.

"I started feeling a bit tired and the big thing was I just put it down to my age." – Audrey, female, prompt journey.

"I'm just slowing down. You know, yeah." – Harriet, female, longer journey.

"Thought it was something to do with age." – Arthur, male, longer journey.

5.4.5.1.4 Reflection and symptom onset

During the retelling of the diagnostic journey, reflecting on symptom development and responses to symptoms, some participants realised and expressed that their symptoms had been present for longer than they had realised. For some

participants, this made the journey considerably longer and would have changed the participant status as prompt or longer journey group member. The length of some of the reporting of symptom duration was extreme, with symptoms duration periods of two years being reported. This realisation was seen to conflict with their assessment of symptom onset in the quantitative study (Chapter Four section 4.5.7) and would impact on the patient, time to diagnosis and the total intervals to diagnosis and treatment if measuring of the journey had occurred following the interview study.

> *[In reference to symptom onset] "Good God, if I was really honest, I would say two years. I would say leading up, looking back, leading up to things… and various things that was going on, I would say possibly up to two years."* – John, male, prompt journey.
>
> *"Looking back now I said I was tired. For the last year and a half I was tired."* – Audrey, female, prompt journey.
>
> "*It only really got started in May, although if I look back on it in the October before I kept thinking I'd pulled a muscle in my bum."* – Carys, female, prompt journey.

5.4.5.1.5 'Acceleration' and change in assessment of symptoms

Many participants described what they considered as an 'acceleration' of their symptoms where initial lower level symptoms were described as progressing and intensifying in nature. This was said to have then prompted a change in the appraisal of their symptoms, with help-seeking or repeated presentation then occurring and on occasions resulted in an emergency presentation. This was discussed by many participants from the longer 'time to diagnosis' group.

> *"More of a grumbling problem, the symptoms changed. This is not right, it's changed, more severe, the pain was quite intense. To the point, you grab your side."* – Sam, male, longer journey.
>
> *"That three weeks my pain in my neck was still getting worse. You're going to have to take me in hospital 'cause I'm in too much pain. Can't take it anymore."* – Charlie, male, longer journey.

Although some participants reported this 'acceleration' being a prompt for appreciating that symptoms were more serious, this progression of symptoms was

associated with becoming acutely unwell, and some participants discussed actually being too unwell to seek help or indeed to care about their health.

> *"I was too, I was too ill to really argue a case."* – John, male, prompt journey
>
> *"The actual physical effort of trying to get to the GP – too much when you're so unwell."* – Harriet, female, longer journey.

5.4.5.1.6 Influence of work and appraisal of symptoms

Participants discussed the context of their work having had an influence on their response to the symptoms they experienced. Participants who worked in physically demanding jobs reported their level of tolerance to symptoms of pain and fatigue was higher, as they justified their symptom tolerance by the physical nature of their work.

> *"It's a very physical job, you get used to aches and pains."* – Carys, female, prompt journey
>
> "[At work*] you think just because I'm lifting stuff all the time you know, that's just, a bit of a joke in work "Glass back" kind of thing, and haha very funny – you just have to get on."* – Sam, male, prompt journey.

Equally, participants discussed factors such as having a strong work ethic, pressure in performance or financial commitments having an effect on the appraisal of their symptoms that related to either the attribution of symptoms to the physical effort of the work undertaken or the pressure of work commitments forcing the individual to 'ignore' the symptoms being experienced. This was also confirmed by attending carers.

> *"I was taking myself back to work and I couldn't walk. I literally couldn't walk. I couldn't get off the bed and I said to her "I've got to go back to work" because after so many weeks you go up a stage in your 'absence monitoring' in work and all this thing. I don't want that on me."* – Sam, male, longer journey.
>
> *"I don't think I was thinking because I think what happened was, the survival thing in your brain, things that I was doing like the day I went to work,"* – John, male, prompt journey.

5.4.5.1.7 Risk awareness and influence on appraising symptoms

Participants across the board showed little risk awareness/consciousness where symptoms and disease attribution to myeloma were concerned. The majority did discuss having a 'risk knowledge' or 'candidacy' for diseases more generally, but this related to more commonly occurring cancers such as breast, lung and colorectal, as well as non-cancer diseases such as cardiovascular disease. Participants, therefore, demonstrated an ability to assess their personal risk for higher profile diseases, but not for myeloma. Some participants went on to reveal that their risk assessment knowledge had acted as a 'red herring' in symptom appraisal as they suspected their symptoms related to another cancer or health concern.

> *"You know, you automatically go, 'it's bowel cancer.' My Granddad died of bowel cancer."* – Sam, male, longer journey.
>
> *"But my Mum and Dad both died of heart trouble, but I don't smoke, you see, so I never had trouble that way either. I would have expected heart trouble. I would know the symptoms."* – *Carys,* female, prompt journey.
>
> *"If somebody said what's going to get you in the end, I'd have said like, must be a bit of excess booze, my Mum had lung cancer, smoking. My brother had lung cancer, smoking previously."* – Charlie, male, longer journey.
>
> *"I'm very surprised to have been diagnosed with that because I haven't led the life that should lead to that. I've gone completely the opposite. If you get lung cancer and you smoked a packet a day, would you not expect to get lung cancer?"* – *Harriet,* female, longer journey.

5.4.5.1.8 Miscommunication

Participants described a process where the communication of their symptoms to GPs, when help-seeking, was difficult as they recalled a lack of ability to adequately describe their health changes or concerns effectively. A number of participants and carers appeared to blame themselves for not being able to describe their difficulties well enough for the GP to attribute these to myeloma or any other serious illness.

> *"At no point did I say, 'I can't walk!'"* – John, male, prompt journey.

Conversely, those participants who were able to describe their symptoms more meaningfully, through an ability to quantify changes in their physical function or daily

life activities, described responses from their GPs being more prompt and led to investigation and referral.

> *"I just told him that I'm more tired than I usually am, and that I don't seem to have the energy levels that I used to have. 'Cause I was saying to him how I'm up at the allotment and I find it's getting, not too much for me, but I'm finding it more noticeable that I'm getting worn out and I have to stop for a while. And it's not like me because I used to work from dawn to dusk without a break."* – Jan, female, prompt journey.

A number of participants discussed that when their symptoms progressed or 'accelerated' they became unable to discuss their symptoms meaningfully with their GP or hospital doctors because of acute health changes.

> *[In hospital] "All I remember is a sea of faces. I don't really remember much about it."* – Audrey, female, prompt journey.

These participant observations were confirmed by accompanying carers who reflected just how serious and debilitated their loved one's condition was when symptoms progressed and acute illness occurred.

5.4.5.2 **Theme two: Peer influence**

A meta theme emerged related to the process by which participants sought lay opinions and had lay consultations related to seeking or confirming the assessment of their symptoms was correct and justified. Lay consultations were rarely discussed as being influential in prompting help-seeking in the early development of symptoms by participants. Participants reported that lay consultations in the majority did not lead them to contradict their own assessment of their symptoms or change their sense-making processes (discussed in the previous theme). Instead these lay consultations contributed to delayed help-seeking as they confirmed the participant's own sense making processes as correct. Even when a lay person did not confirm the participant's sense making processes were correct the strength of the participant's normalisation overrode any opinion that did not complement their own in early symptom development. This was a deductive latent theme emerging from data, with participants not reporting this directly as a factor delaying the appraisal of symptoms as 'serious' or help-seeking, but something that almost fell out of conversations as a justification of their own assessment of the situation.

Participants discussed having conversations with various 'lay people', partners, close relatives and in some cases work colleagues or private therapists such as an osteopath and personal trainers. These focused around symptoms or physical changes experienced. These conversations were reported as informal in nature, with the primary motive not being to seek reassurance regarding symptoms but more part of a typical conversational dialogue. Even when the lay consultations were more formal, as in an osteopathy appointment, these were not the primary reason for consultation. Discussions strongly suggested that these lay consultations did not influence the help-seeking behaviour in many participants in early symptom development, although there was reporting that these lay consultations had greater influence in more advanced and later symptoms. Multiple underlying reasons were reported influencing these lay discussions and conversations.

5.4.5.2.1 Confirmatory conversations

Many relatives/friends/colleagues were reported to display cohesive impressions about the participants' health changes, appraising changes as 'non-serious' and due to ageing and thereby being confirmatory with the participants' assessment and opinions that help-seeking was not necessary.

> *"I remember just the week before saying to Jamie, my personal trainer, 'Ah, my back is starting to play up,' and everything. He said, 'Oh I've got a marvelous chiropractor, go to her and I went to her and I actually said to her, 'Do you think I ought to have an x-ray?' and 'Oh there's no need! I know what's wrong with you. Your pelvis is out of sync or the pelvic bone's out of sync.'* – Audrey, female, prompt journeys.

5.4.5.2.2 Normalising overrides lay prompt

In some cases, lay influence that was not concurrent with the thinking of the participant was obvious from participant accounts of conversations with friends/relatives or others. When advice was offered in these conversations regarding a need to seek help by the lay person, this 'lay prompt', when it occurred in the early development of symptoms appeared to be ignored by participants, whose strong desire to normalise the vague misleading symptoms overrode advice offered (discussed in Theme 1).

> *"For about a week she [colleague] kept saying, 'Why are you holding your back?' I said, 'Oh I know, I've just got a bit of a twinge.' She said, 'Oh you*

should go and see about that.' I said "Yeah yeah yeah yeah. When I've got the time.'" – Audrey, female, prompt journey.

Some carers present in the interviews confirmed that in the early development of symptoms, even when they felt something could possibly be wrong, their relative overrode their concerns and prompts to seek help. Some carers even discussed their advice being ridiculed and dismissed by their relative demonstrating a strength in the resistance to seeking help in their loved one.

5.4.5.2.3 Lay person awareness and normalisation

Normalising the symptoms that the participant was experiencing to ageing, by lay carers, was also reported and followed a similar process to that seen in the participant normalisation to aging process. Lay people demonstrated a similar lack of awareness and understanding of the disease myeloma either through direct conversations in interviews or through reporting of conversations with them by the participant in interviews.

5.4.5.2.4 Lay prompt influence in late appraisal

Lay conversations were discussed as having more influence in the later stages of symptom development, when an 'acceleration/progression' and clinical deterioration (discussed in Theme 1) in the layperson's relative/friend had occurred. Progression through the pathway was then seen to be heavily influenced and almost 'managed' on occasions by the lay person. Both the patient and carer acknowledged this phenomenon.

"It was far too painful. He [partner] was beside himself, he rang the doctor and said, 'Look, it's not about painkillers, I want her x-rayed.'" – Audrey, female, prompt journey.

Carers displayed frustration with the way GPs responded to the symptoms their relatives had presented to them and inferred the GP had a lack of desire to investigate. Other carers discussed feeling that the investigation of symptoms was driven by their own identification of symptoms as serious or related to a disease they had identified through google searching or picking up 'bits and pieces' from conversations with secretaries. There was reference to a need to 'pester' the GP to get things recognised as serious or investigated.

5.4.5.3 Theme three: Expectation of care

Participants discussed openly their view of the world of medicine and expectation of the service they receive, with elements of their personality providing insights into their behaviour in the journey to diagnosis. This meta theme had a relatively complex set of subthemes that also had elements building on individual phenomena.

5.4.5.3.1 Deference and reverence – no questioning

More elderly participants spoke in a more deferential way about interactions with health professionals, demonstrating a deference to the older wiser medic that led to them not questioning decisions made.

> *"It was cracked. In fact it's still a lump there where the bone cracked. I got next door which is a very good neighbour, [Name], she took me to the doctor at the hospital on the Sunday which 4th of May. It got worse by Tuesday so I asked her to run me to A&E which she did. First of all I was told I was getting painkillers. Give me 60 painkillers. 'Oh you'll have to go to your own GP for that.' So I said, 'Well I have an appointment,' which was the 14th of May I think. 'Oh well keep that appointment then.' So I did."* – Daphne, female, prompt journey.

Participants who appeared to revere medical professions, a position of power in the relationship was apparent within the conversations. There was then, described in conversations, more of a reluctance to repeat their consultation or again question the assessment of their symptoms or decisions made. An easy concurrence was discussed where the participants easily accepted the GP assessments made.

> *"I accepted it. That's what they'd said and they are the ones that know, not me."* – Harriet, female, longer journey.

> *"My head's in the sand and I want to be told."* – Trefor, male, longer journey.

5.4.5.3.2 Equity in relationship with GP

Where individuals reported being more astute and reported having a less submissive relationship with health professionals, repeat presenting appeared to occur more timely.

> *"I just wanted them to sort it out. I didn't want painkillers."* – Audrey, female, prompt journey.

5.4.5.3.3 Negative expectations

Some participants reported such a negative opinion of healthcare services that their expectations of how they would be managed within the system affected their desire to seek help. Many participants revealed in interviews that help-seeking or repeat presentation was delayed by themselves, as they felt there would be little achieved by going for a consultation, anticipating a poor response to their symptoms from their GPs or other health carer. Participants additionally reported anticipating their GP would be uninterested in their symptoms or would treat with medication first, in preference to investigating and, therefore, they had a low impetus to present initially or repeat a consultation.

> *"Well I thought it's a waste of time going to see him actually."* – Arthur, male, longer journey.
>
> *"All the GP would just give me was a prescription for painkillers."* – *Harriet,* female, longer journey.
>
> *"Well. They only do, they give you six weeks. So that usually in that six weeks, your back is either better or you're, its worse, so, they try to sort you out that way. So I never, we never went."* – Harriet, female, longer journey.

This feeling was also expressed by carers in interviews.

Participants discussed these expectations and purposeful delaying, and linked them to the reported vague and insidious symptoms, feeling they required significant symptoms in order to warrant a consultation. Participants' expectations were that healthcare professionals were only interested in 'significant' symptoms.

> "*But I wasn't that bad if you know what I mean. I wasn't serious enough, do you know what I'm saying?"* – Trefor, male, longer journey.

These factors were clearly reported by participants to impact on the interval between symptoms and first consultation or first consultation and repeat consultation. Although the effect on help-seeking was clear, it was not easy to decipher which came first, the impression of how the doctor would respond due to previous experiences, or whether these were deep rooted opinions and expectations in the wider general population which included these participants.

Carers equally discussed how they felt that visiting the GP with an unknown diagnosis would be futile. Some expressed the feeling one needed to present to the doctor with a clear picture of what was wrong to avoid delays. Additionally, this was reported to be rooted in previous experiences and interactions between their relatives and the GPs.

5.4.5.3.4 Fear of wasting time

The majority of participants alluded to having a fear of being labelled a malingerer. In many cases, participants were eager to point out that they were infrequent presenters to primary care, almost apologetic of their need and use of services. There was little evidence that participants demonstrated assertive behaviour with regards to help-seeking or repeated consultations in primary care. There was a sense that resource was sacred and should be protected and therefore any unnecessary access was wasteful.

> *"If you're not considered to be a hypochondriac then they think that you are more genuine. And I don't take much notice of aches and pains as a rule, you know. So, I don't see him very often."* – Jan, female, prompt journey.

> *"Yeah, I-I and they're gonna get malingerers too, going to see them. Probably an awful lot of them, you know."* – Charlie, male, longer journey.

Lay carers had some sympathy for how difficult it must be for GPs to decipher true illness when people go to the GP with mild symptoms all the time.

5.4.5.3.5 Influence of media negativity

In the interviews, it became apparent that many of the participants were tuned into the media interest in the NHS as a service, and this was seen to instil negativity and the expectation of poor service. Many participants or partners/relatives of participants raised current NHS political concerns unprompted in interviews. Issues raised focused around reported inefficiencies within primary care mainly, but some secondary care issues also appeared. These reports appeared to have a heavy burden on participants' perception of services, with a weighted interest in the negative aspects reported in media coverage affecting trust and resulting in scepticism in the service provision. There were no obvious distinctions by participants in the services provided across the wider NHS in the UK as the NHS was being discussed as a whole rather than having devolved responsibilities. In

some carers there was a strong display of disgust in the level of care their relative received. Carers additionally reflected their experiences were not isolated cases and referenced other media reporting of 'poor care'.

Scepticism of NHS services was, for some relatives, a hot topic causing outbursts of frustration and anger in the interviews that were essentially rooted in poor expectations, lack of trust and increasing intolerance of health issues and system difficulties with a lack of respect obvious. Insults to health care professionals were forthcoming from some carers which focused around insinuating staff were of a substandard intelligence.

5.4.5.4 Theme four: Systems and revolving doors

In the interviews, many participants talked about their diagnostic journeys being associated with confusion, misunderstandings, miscommunication and loss of continuity. Journeys were portrayed as chaotic and disjointed with a strong sense emerging that the process was not seamless.

5.4.5.4.1 Revolving doors

Participants reported a feeling of going 'round and round' and 'revolving' backwards and forwards in the primary and secondary care systems with obvious multiple consultations associated with their diagnostic journeys. This was reported by the majority of participants and was prevalent in conversations and was associated with frustration in the participant accounts.

> *"I just felt like I was a bloody nuisance to be honest with you. That's-that's how I genuinely felt, I mean I'm going back and back. It's like going back through [Wife's] diary and I going back to the doctors an awful lot there and that wasn't like me. You know there's obviously something wrong if I'm saying I've got to go back to the surgery… you know, time and time again. Not picking it up, not picking anything up, I don't, I don't, I don't know."* – John, male, prompt journey.

5.4.5.4.2 Lost in the process

Participants reported feeling lost in the process of their investigative journeys, which involved multiple people, visits and sometimes places, resulting in feeling confused about responsibilities, processes and the onward journey to a diagnosis.

"Well I'd seen so many doctors for different things. That had got very confusing knowing which hospital to go to and which doctor to see there." – Arthur, male, longer journey.

Carers in interviews reflected much the same thoughts, commenting on the complexity of multiple visits and the subsequent 'barrage' of communication from different health professionals that followed.

5.4.5.4.3 Transfer of care and false expectations

Participants discussed how they deduced the transfer of their care to a hospital specialist would lead to investigation and a diagnosis and, therefore, a 'false sense of security' prevailed in them which meant repeat consultation to primary care with new symptoms or problems was unnecessary.

"I just thought that was my only hope because I kept sort of breaking the rib and things like that and I kept thinking, 'Now when I get the medication hopefully it will make my bones stronger.' No well they're [GPs] cautious if that's what their patient's been diagnosed with that's what they have to go along with, isn't it?" – Harriet, female, longer journey.

There were also reports from carers that when their relatives did repeat their presentation to primary care, with increased or unresolved symptoms, they were told by their GP that their care had been transferred to the hospital setting and their management was, therefore, under the care of the specialist.

5.4.5.4.4 Chaos

There was strong evidence from the participants' and their carers that referrals into secondary care were 'chaotic' and often 'perplexing'. Participants reported that multiple appointments led to a confused state. Carers reported that when many teams were involved in the process of investigation in secondary care this added to chaos, misunderstanding and led to torturous processes.

"Poor calendar's full of my hospital appointments." – Arthur, male, longer journey.

"I can't remember her name. She's still there. [Doctor]. She phoned, the surgery phoned. I went in on the Monday for blood at [Hospital]. I'd forgotten about the colonoscopy thing because when they'd done that they just said, 'Oh we can't find anything.' So I was like, 'Oh great, must be IBS!' [Laughs]

And err, he'd sent me to [Hospital] to have blood tests and I got a phone call. He said, 'You need to come in.'" – Sam, male, longer journey.

5.4.5.4.5 System failures

The interviews appeared cathartic for many participants or their partners/relatives and was particularly so in longer or more convoluted journeys. The interviews gave an opportunity to unload some of the frustration and disharmony that surrounded the patients' or relatives' interpretation of the processes followed. These interviews were especially rich and emotive and revealed much negativity about systems failures. Participants and/or partners/carers were vocal and animated during the interview, demonstrating an underlying anger with the pathway. Experience focused around:

- Being unable to get GPs to do home visits when participants were too unwell to attend the surgery;
- Having to navigate past the receptionist and this adding to the burden of pain and discomfort being experienced;
- Loss of follow-up from secondary care;
- Poor communication between secondary and primary care;
- No 24-hour cover in the hospital setting;
- General ineptitude of the medics trained today; and
- Poor continuity of care within primary care.

"The doctor wouldn't come out to see me." – John, male, prompt journey.

"I felt like throwing the phone across the floor and bursting into tears [getting an appointment with the GP]. *I was so bad. Then I thought, 'Well that's no good because then I've got a broken phone and I still haven't got anywhere.' That was just the receptionist."* – Harriet, female, longer journey.

Some carers were very vocal in the interviews about the dismissive approach of their doctor in consultations. Carers complained GPs were more focused on 'in putting' data onto a computer than engaging with the patient in front of them. There were additional comments which were quite insulting and questioned the integrity of the GPs and their education. These comments were, however, in a minority and when offered were observed as emanating from relatives of participants who were involved in very difficult diagnostic journeys.

5.4.5.4.6 Loss of continuity

Many participants reflected when their consultations involved multiple different doctors in primary care. This added confusion to the journey. The loss of continuity was discussed in terms of the clinical picture of the participants' symptoms and situation being lost in the transfer of care between different doctors.

> *"And I was seeing various doctors as opposed to my own doctor. I don't really know, until I became, until it became, you know, until it was, he told me what it was as it were and then there's. Well they didn't know. I mean the fact of the matter is that the last contact I had with them was that [Name] was still on holiday and that I'd seen his protégé. You know they look after somebody within the surgery ranks, one of the young doctors. Kids yeah. And she said to me, 'I think if things go on, [Name] will have to probably do a blood test.' And then, then from then I became quite ill. I started to lose my legs and what have you. So, and was offered a handful of drugs to get me through the weekend when [GP] was back from holiday. She wouldn't come out to see me."* – John, male, prompt journey.

> Participants and carers in interview dialogues discussed their difficulties with the lack of continuity with the doctors they consulted with. They added that these 'transient' doctors often moved practices before a patient's onward referral, which added a further dimension to the diagnostic process.

5.4.5.4.7 Interactions with the GP and safety netting

Interaction within GP consultations and participants' understanding of the process of assessment, investigation and referrals were discussed frequently in the interviews.

A difference was seen in the participants retelling of how symptoms were acted on to by GPs. Participants with prompt journeys recounted consultations where GPs immediately acted on the symptoms reported, responding with assessment investigation of the condition even when the participant presented these symptoms in an ambiguous manner.

> *"I went and she said, 'What can I do for you?' and I said, 'Well I think I've got a prolapsed bladder and I'm having this pain in my bum, you know, and this pain in my groin here.' 'That's probably your hip,' she said. Anyway, examined me, moved my leg. 'Oh yes!' she said, 'That's your hip, I'll send you*

for an x-ray,' you know. And within two days the x-rays came back, lesions on both hips and somewhere in my back." – Carys, female, prompt journey.

Additionally, GPs of participants who asked them to return if symptoms remained unresolved, and these instructions were followed up by participants, reported their symptoms were investigated with more vigour on a repeated consultation.

"Well first of all he gave me the gel. He took my blood pressure, all various things. He said, 'If it doesn't work, come back and see me.' So of course, a week went past and they got better. But a couple of weeks later I had them again, and I thought, 'This is a bit odd, getting them so soon.' And so I made an appointment and went and saw them. So I said, 'I've got the ulcers back again.' And of course, he said, 'Oh well, right, we'll have to look into it further.'" – Jan, female, prompt journey.

5.5 Discussion

The findings from this interview study provide a better understanding of the behavioural and contextual issues that contribute to the individual journey to a diagnosis of myeloma. These findings offer an explanation of some of the reported associations and longer intervals to diagnosis reported from the quantitative study. Overall, the study findings show the processes of assessing and responding to symptoms in myeloma are complex and multifaceted and these processes lead to misattribution of symptoms to ageing. Additionally, navigating the health service to achieve a diagnosis is shown to be a fragile and tortuous process that is easily disrupted by multiple factors involving participants' preconceptions, expectations and interactions.

Myeloma patients appraise their symptoms with a purpose of 'making sense' of them and misinterpretation of these symptoms can alter the intervals of patient, primary care, time to diagnosis and the total interval to diagnosis and treatment. Poor awareness of the disease and its accompanying symptoms is prominent and is associated with delays in help-seeking, misunderstanding and miscommunication of symptom seriousness. This is additionally confounded by low levels of candidacy or poor risk knowledge. The myeloma patient is focused on the need for an 'alert symptom' to conclude that the symptoms, of an initially lower level of intensity, could be related to cancer or anything 'serious'. The consequence of this complex set of factors is the normalisation of symptoms to the natural ageing process in order to

'make sense' of them. This occurs regardless of age of the patient. The conclusion that symptoms are related to ageing results in the portrayal of symptoms as less sinister to the GP, and patients experience difficulty quantifying these subtle changes meaningfully to health professionals. The normalising reported by some myeloma patients is so strong that the process extends well into serious and relatively debilitating symptoms, before a change in symptom appraisal is made. The strong normalising of symptoms with accompanying delayed consultation or delayed investigation of symptoms is then associated with increasing disease burden. This is witnessed in the reporting of symptom progression and increased emergency presentation.

Unexpectedly, participants, through reflection, came to realise their symptoms had been present for far longer than they originally thought or indeed reported in the quantitative questionnaire study (Chapter Four section 4.5.7). This means that the patient interval in myeloma is possibly longer than reported in the quantitative study. This is concerning, as it means that myeloma patient and total intervals are possibly even longer when compared to other cancer types reported in the quantitative study.

Interestingly, a near identical picture of assessment of early symptoms occurred in lay people and participants when assessing relative's or friend's symptoms and ill health. This was characterised by both groups normalising symptoms to ageing. A 'lay prompt' in the early symptom development in myeloma does not occur, which potentially contributes to longer help-seeking intervals. The parallel with patient participant's experiences continues with lay persons becoming an influence as symptoms 'accelerate' or intensify and they become more debilitating. The lay prompt in myeloma is then highly influential with lay persons becoming very active in the pathway progression and particularly important when participants become acutely unwell and the lay person adopts a 'history telling' role.

Contextual understandings and beliefs do influence the diagnosis of myeloma through interactions with clinicians and passage through the heath service. This appears to be associated with multiple intervals across the journey, affecting the patient, primary and secondary care intervals. Reverence for health professionals and service use was prominent with concerns about overusing services and not 'questioning' decisions made by clinicians. This particularly affects the timing of the initial and repeat consultations in the face of new or increasing symptom

development. There is a fatalistic nature to the way some myeloma patients interact with primary or secondary care services that comes from an 'expectation' that the healthcare they will receive will be poor or managed sub-standardly. This is an intricate process and is possibly less specific to myeloma and more rooted in underlying changes in perspectives and attitudes towards the NHS more generally, with the theme including many other healthcare issues and experiences of family members or friends.

Myeloma patients report an extremely non-linear process through the intervals following presentation to primary care. This provides an explanation as to why the journeys to diagnosis and treatment, reported from the quantitative study, are longer when compared to other cancer types (Chapter Four section 4.5.7). The sheer prominence, depth and complexity of this theme was overwhelming in interviews, and really does lead to the conclusion that myeloma is possibly one of the hardest cancers to diagnose promptly.

Structural problems can disrupt the intervals to diagnosis in myeloma with the description of very chaotic and confusing pathways and poor continuity which is not limited to primary care but extends into secondary care services as well. The extent of the disruption of the journey is eloquently described by participants along with their frustration in the retelling of events. The limited reporting of uncomplicated pathways in myeloma is concerning and possibly reflects of the complexities reported. The description of the difficulties in secondary care in this study is new, and provides an explanation as to the reporting of the relatively long contribution of the secondary care interval in the total interval in myeloma (Chapter Four section 4.5.7). However, this extended secondary care interval possibly highlights the impact of the referral type and the team referred to by primary care in the quantitative study (Chapter Four section 4.5.5), with these findings supporting that the 'revolving door' pathway and loss of continuity of treating teams is prominent for myeloma patients and leads to a loss of engagement and control for the patient.

5.5.1 Comparison to the literature

This study has reported the behavioural and contextual experiences in myeloma adding a unique contribution to understanding myeloma as previous reporting of these factors is limited to the reporting of behavioural aspects of help-seeking (Howell et al., 2015). The depth and richness of the reporting here has allowed the quantitative measurement of the diagnostic journey in myeloma to be further

explained and possibly adds to the debate and call for the use and wider publication of qualitative methods in healthcare research (Greenlagh et al., 2016).

This study supports the findings of Bloodwise research which reports very low levels of awareness of myeloma in the general public (Leukaemia and Lymphoma Research, 2015). Additionally, the study is able to demonstrate an association of a lack of awareness resulting in a 'disconnect' in symptom appraisal as 'serious' which increases the help-seeking period.

This study also supports the previous reporting of the normalising of symptoms to ageing and its association with deterring help-seeking (Whitaker et al., 2015a). Additionally, the study reports the contribution to normalising symptoms made by poor risk awareness or candidacy in delaying the recognition of symptoms as serious. This study, therefore, also supports other work that reports poor candidacy in cancer can interfere with the recognition of symptoms as serious (MacDonald et al., 2013).

An interesting phenomenon of miscommunicating symptoms to GPs by patients is reported in the diagnosis of myeloma. This is rooted in lower level symptoms which are poorly recognised and the normalisation of these to ageing symptoms resulting in patients' findings the reporting of these symptoms difficult. This miscommunication can potentially disturb diagnostic reasoning in the GP, which has been previously reported as contributing to misdiagnosis and delays in achieving prompt diagnoses in primary care (Institute of Medicine, 2015).

Possibly surprisingly, myeloma patients do not appear to delay help-seeking based on a fear of an impending cancer or serious illness diagnosis. This is in contrast to other cancer types (Whitaker et al., 2015a) and possibly relates to participants stating they remain 'well' initially, blaming their symptoms on ageing, which is then enough for patients to not suspect any serious underlying illness. This lower level of reporting of 'fear' as an underlying cause for not help-seeking in myeloma was also reported by Howell et al. (2015).

This study supports the 'lay person' group act differently in myeloma as the 'lay effect' prompting help-seeking for myeloma occurs only in late symptom development, which is in contrast to the earlier 'lay prompt' reported for other illnesses (Cornford and Cornford, 1999).

The fatalism demonstrated in myeloma patients impacts the inclination to consult or repeat a consultation and supports previous work reporting that poor expectations influence this process (Williams et al., 1992). Additionally, negative media reporting of the NHS alters expectations and perceptions (Judge et al., 1992). What this study has also been able to demonstrate is the impact of these two factors contributing to a delay in help-seeking or repeated consultation in myeloma specifically.

This study has reported a complex and non-linear process in the diagnosis of myeloma through patient accounts of their diagnostic journeys. However, the extent of these non-linear processes was surprising. Although these findings are comparable to previous reporting of non-linear cancer diagnosis journeys (Walter et al., 2012), possibly the extent of the non-linear journeys for myeloma offers explanation as to why the total interval is longer for myeloma than other cancer types (Chapter Four section 4.5.7).Whilst this is supportive of the Walter et al. (2012) reporting of non-linear cancer journeys, it demonstrates that the myeloma journey is possibly more extreme in its non-linear pathway than other cancer types.

It is not a new concept that structural changes in primary care have caused system strain and loss of continuity for patients, resulting in the loss of timeliness in the cancer journey (Ridd et al., 2006; Round et al., 2013; Green et al., 2015). This study adds to the evidence for this. What possibly was more of a surprise and lacking in the reported literature was the structural difficulties observed in secondary care, with loss of continuity and the revolving door phenomena occurring with great prominence. Possibly this is not helped by the reported loss of input from primary care when secondary care is seen to have 'taken over' care. Kariyawasan et al. (2007) alluded to longer time to diagnosis intervals for participants referred to other than haematology in secondary care, which this work would support. These findings add the behavioural context of a loss of control experienced by the patient rooted in a failure to understand the system and the processes they are entered into or the seriousness of their illness. The modern NHS is working towards better patient engagement and a cohesive approach to health and wellbeing (Bevan Commission, 2013), but this is in contrast to what is witnessed in the journeys to diagnosis of myeloma patients.

5.5.2 Strengths and limitations

The major strength of this study lies in the depth and unique contribution the findings offer. The method approach was complementary to the explorative study aims, generating detailed in-depth and illuminating evidence from the interviews. Methods were acceptable to the patient group and were seen to be cathartic rather than distressing. Analysis produced unique themes allowing greater understanding of the behavioural and contextual contributions to journeys and providing explanation of many of the quantified variables and associations reported in the quantitative study (Chapter Four section 4.5).

Analysis of the dataset was undertaken using a structured approach allowing transparency in reporting. Thematic analysis was applied to coding and theme development to compensate for the strong epistemological background of the researcher, with semantic coding used to keep themes data driven and to reduce interpretation of the narrative by the student researcher. Reflective examination by the student researcher acknowledged this was a challenge. This possible difficulty in bracketing preconceptions may have influenced theme development. However, the checks applied across thematic development (Chapter Three section 3.13.6) should have compensated for the strong post-positivist stance of the student.

Purposive sampling allowed the identification of participants with rich stories to tell and led to the depth of the data collected. This process possibly was responsible for the early saturation seen. The measurement of saturation was rigidly assessed, applying observations from published guidance (Seale, 1999) and the checking of transcripts and theme development by the student researcher and a supervisor. The strength and depth of the themes identified were so strong within data analysis and so consistently discussed across the participant groups that this became the overriding factor in the assessment of saturation. However, the number of participants interviewed was small and the study might not have identified all the behavioural or contextual factors related to the diagnostic journey in myeloma. It is possibly important to acknowledge that this could affect the impact of these findings.

As no exclusion was made as to whether participants had a family/friend in attendance in the interview, it is possible that the participants who had company had their personal experience less readily retrieved with many accompanying third persons being highly vocal in the interviews. However, the interviews were found to

be equally discursive with or without the attendance of a third person, and the priority was given to maximise comfort and relaxation of the participant by giving a choice of a third person's attendance.

The development of the peer 'influence theme' was unexpected and was possibly more prominent because lay carers were present for some interviews. However, because these lay carers were not formally invited to participate in the study they may not be truly representative of the 'lay group' as there were differences in engagement across interviews with lay carers and this is acknowledged.

Unexpectedly, only one participant with an 'asymptomatic' presentation of myeloma was identified for interview. This was representative of the wider cohort recruited into the quantitative study (Chapter Four section 4.5.1), but limited the asymptomatic sample group. It is therefore not possible from this study to offer findings for the asymptomatic presentation group.

The addition of a gatekeeper check in secondary care successfully added a safety net to prevent the approach of any participant who had clinically declined. However, it did allow a potential 'block' of recruitment of participants who had difficult journeys generally or through secondary care that resulted in early clinical deterioration. Secondary care sites declined the approach of four participants. This could potentially mean that participants who were in some of the longest journey groups and deteriorated early were not included in the sampling for the interview study.

The exploration of symptom onset during the interviews led to many participants reporting, with reflection, that their symptoms had been present for considerably longer than reported in the quantitative study. This led to the appreciation that some participants in the prompt journey sample group on recalculation of their time to diagnosis journeys would no longer be a 'prompt journey' sample participant. This potentially means that the longer journey group was over represented and the prompt journey group under represented and may have contributed to many of the findings not demonstrating a difference between prompt and longer diagnostic journey groups in themed findings.

Interviews were completed as close to recruitment as possible following the returns of the quantitate study questionnaires (Chapter Three section 3.13.4). This was observed in the interviews as being successful with participants being able to recall

the complexities of their journeys to diagnosis. However, the completion of interviews at this phase of the participant's treatment meant that the vast majority of participants (10/12) were interviewed when their induction treatment was completed and they were experiencing first remission. This is possibly a period when the patient feels 'well' and is positive in their outlook and therefore has the potential to influence their view of their journey to diagnosis. Only one interview was conducted with a participant who was in a 'palliative' stage of their treatment receiving no further treatment (Appendix 12).

5.5.3 Recommendations for policy and practice

The main recommendations from this qualitative patient interview study are related to the assessment of symptoms of myeloma that affect both the patient and GP groups.

Low awareness of the disease myeloma, absent known risk factors and normalising symptoms to ageing combine as a phenomenon to make the diagnosis of myeloma difficult and longer. As a result of these findings, there is a clear need to increase the awareness of the disease myeloma and its symptoms to allow a connection between the disease and symptoms in the general population. The symptoms reported from the quantitative study (Chapter Four section 4.4.1) should be uplifted into public health and awareness campaigns for myeloma as this has the potential to increase the knowledge of both the undiagnosed patient and their lay person and promote more prompt help-seeking.

Public health policymakers need to be aware of the messages the population receive about 'health expectation' in older age and the effect this has on the tolerance of symptoms and loss of function. An increasing ageing population who continue to tolerate or expect debility, dysfunction and pain in older age are likely to increase the levels of delay in help-seeking in myeloma and possibly other cancers associated with poor awareness or vague symptoms.

GPs should, following the findings of this study, be made aware that symptoms of myeloma may be present for longer than they perhaps currently perceive possible. This will mean GPs have the potential to suspect symptoms as serious and diagnose early through investigating these symptoms at first presentation. GPs should now also be more cautious of symptoms that have been experienced for some time as there is a longer symptom duration before help-seeking occurs in myeloma. Longer

standing symptoms should equally be investigated as potentially serious by GPs and given a full diagnostic workup. GPs, additionally, should be aware that symptoms may be presented by patients who do not explain their symptoms well because they do not recognise feeling 'unwell'. GPs need to be less concurrent with the patient assessment of their symptoms and be prepared to investigate these more timely and widely to define the disease. This is recognised as very challenging for GPs, as it promotes the early investigation of possibly many more patients who themselves feel they are not unwell. However, if the longer intervals to diagnosis in myeloma are to be influenced, a more proactive response from GP to early symptoms is likely to result in a more timely diagnosis.

GPs also need to appreciate that the consequence of not identifying symptoms early in primary care is the increase in complication of the disease and presentation of the patient with myeloma as an emergency. GPs should aim to avoid this through the recognition of the above behavioural and contextual factors to avoid emergency presentation of these patients.

GPs need to be aware and refine their systems to stop a revolving door process in myeloma patients. Systems of communication need to be refined to promote proficient transfer of information between doctors within the primary care practice and secondary care, to ensure the history and investigation of the patient is understood. It may be unrealistic to ask the GP practice that their patients see the same doctor on repeat consultations, but the consequence of loss of continuity may be better managed with more proficient documentation of symptoms, investigations and differential diagnoses ruled out or hypothesised. This, then, may make the timing of the primary care interval less and promote a more optimal pathway into secondary care possible.

GPs also need to maintain a responsibility in primary care of the patient under investigation and be prepared to continue management in primary care with follow-up of new or deteriorating symptoms in order to progress the journey to diagnosis for the myeloma patient.

Public health policy makers need to be aware of the effect of the media representation of the NHS and the impact this has on patients' initial or repeated consultation in primary care and secondary care investigation. Disengagement of the

patient through the process rooted in fatalism of their assessment and investigation is detrimental to the diagnostic timeliness.

5.5.4 Recommendations for further research

Participants report a concurrence with GPs that early symptoms are not sinister, which possibly contributes to the longer primary care interval seen in myeloma (Chapter Four section 4.5.7; Lyratzopoulos et al., 2013; Lyratzopoulos et al., 2015a). GPs, possibly, require patients to present their symptoms in a more bio medically framed manner, where physical dysfunction can be reported and quantified against normal activity. The effect of this miscommunication and the impact on the primary care interval and GPs' perceptions of the effect require further exploration and will be assessed in the GP interview study (Chapter Six).

There is the need to further assess the revolving door phenomena seen both in primary and secondary care. The interpretation of the findings from the quantitative study (Chapter Four 4.6) and the qualitative interview studies for both patient and GPs should be used to examine this phenomena in greater detail to provide recommendations for the more timely diagnosis of myeloma.

Whilst the studies identified in the systematic review focused on the primary care interval (Chapter Two section 2.4.1), there is little knowledge of the processes undertaken when the patient arrives in secondary care. The extent to which this disruption in secondary care is reported in this study requires further assessment, and it is possible in synthesis of all three phases of this research study that some explanation can be offered.

5.6 Conclusion

The findings from this qualitative interview study overwhelmingly support that the timely diagnosis of myeloma is extremely difficult and that possibly this cancer will never be as straightforward or timely to diagnose as other cancer types such as breast or colorectal.

The findings do, however, contribute to the understanding of the behavioural and contextual influences that explain why some of the documented objective measurements reported for myeloma diagnostic journeys occur, which have only previously been hypothesised. The study provides understanding of the process of delayed help-seeking in myeloma patients and the consequences of this. It also,

worryingly provides evidence of a non-linear tortuous pathway to diagnosis in both primary and secondary care that is associated with a lack of ability to connect the symptoms experienced by patients to their underlying disease. Importantly, though, there are areas for improvement that could potentially allow for better timing of the diagnosis of myeloma.

6 Chapter Six: Exploring General Practitioners' perception and experiences of diagnosing myeloma: A qualitative interview study

6.1 Summary

This chapter reports the findings of the qualitative assessment of the perception and experiences of GPs recently involved in a diagnosis of myeloma. It adds novel information and contributes to the understanding of why primary care intervals are longer for myeloma when compared to other cancer types. The chapter provides unique insights into the difficulties of practising GPs identifying, investigating and referring patients with myeloma. The results further contribute to the understanding of how the diagnosis of myeloma may be made more timely, that the thesis ultimately aims to answer, by adding to the assessment of the quantified journeys to diagnosis and the personal, behavioural and contextual experiences and perception of patient participants.

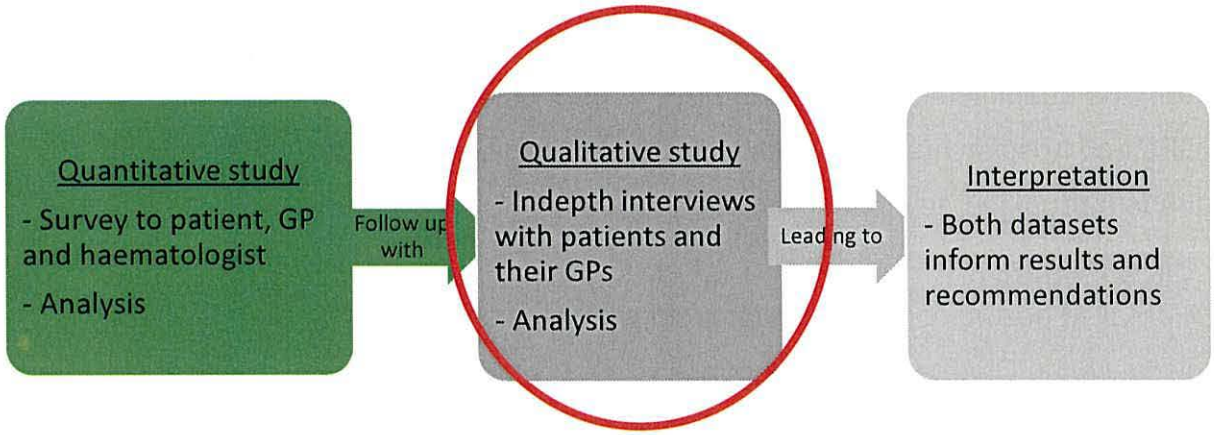

Figure 6-1: Diagram of Explanatory Sequential Research Program

(Adapted from Creswell, 2014)

6.2 Background

Myeloma is associated with the longest reported primary care intervals of any cancer type as reported within the systematic review (Chapter Two section 2.5.1: Lyratzopoulos et al., 2013; Lyratzopoulos et al., 2015b), and further evidenced through its measurement in the quantitative study (Chapter Four section 4.5.7). Whilst there is some evidence as to why the primary care intervals are longer in myeloma e.g. multiple consultations in primary care (Lyratzopoulos et al., 2012) and higher frequency of emergency presentation (Elliss-Brookes et al., 2012), the full understanding for these influences could only be hypothesised in the systematic review. The quantitative study (Chapter Four section 4.4.1) reported the majority of myeloma patients will have symptoms and that these symptoms are presented to primary care for assessment. Additionally, the study reported low investigation of

these symptoms and non-specific myeloma investigations are conducted for the majority of patients in primary care, which were possibly related to low suspicion of the disease. Additionally, the study identified lower levels of cancer-specific referral and non-targeted referral processes which were associated with longer overall total intervals (Chapter Four section 4.4.3). The qualitative interview study reported difficulties conveying symptoms to GPs and tortuous processes involved in the lead up to a diagnosis (Chapter Five section 5.4). It is reasonable to assume that discussing how the diagnosis of myeloma is made, with GPs recently involved with a diagnosis, is likely to provide useful insights into understanding what makes the identification of myeloma in primary care so difficult and results in these longer primary care intervals. This, in turn, will help to form recommendations for policy and practice for timelier diagnosis of myeloma. These findings then build on the evidence from the quantified diagnostic journeys of newly diagnosed myeloma patients, their GPs and hospital haematologists, and the exploration of the patient experience of the individual journey to diagnosis.

6.3 Methods

A detailed description of the methodology underpinning this GP interview study is discussed in Chapter Three section 3.13. Described here are the practical implementations of the chosen approach.

6.3.1 Sample selection

GPs of patients who consented, registered in the quantitative study and then were interviewed in the qualitative study were eligible to participate in the GP interview study. GPs were identified by the participant as the GP most involved with their diagnosis within their returned patient questionnaires. Details of the potential invites to interviews were given to GPs within detailed information sheets sent with primary care questionnaires for the quantitative study. Additionally, e-mail details were sent, via the all Wales GP information service, to all GP surgeries in Wales. Information sent out detailed telephone interviews would be conducted and last about 30 minutes and would involve discussing the GP's views about diagnosing myeloma in primary care. Two monthly newsletters where also sent out as mail shots to all GP surgeries in Wales. These mailshots aimed to inform and highlight the study and, additionally, promote engagement and interest in the GP group. No monetary reward was available to act as a GP incentive. GPs who did not complete the primary care questionnaire were not excluded from participation in the interview study.

GPs were approached directly by telephone or via practice managers or receptionists. Practices that requested additional information were sent supplementary information as requested via e-mail and then followed up by telephone. Due to the method of approach of some GPs via practice managers or receptionists, it was not possible to track approach to GPs or ascertain exactly how many GPs received a request to interview. It was presumed all GPs received invites to interviews when messages were left with surgeries. Details for the GP to contact the student researcher were given to the GP or the practice managers/receptionist. When GPs did not respond to a verbal invitation, a follow-up call to the surgery was made by the student researcher a week later. This occurred only with the GPs whose invitations were made via third person as invitations made directly by the researcher permitted either a verbal consent or an immediate decline.

6.3.2 The interview: data collection

All interviews were conducted by telephone. An interview topic guide (Appendix 10) was implemented. This was not developed to be restrictive, but was used more as a guide when interviewing, providing structure for the student researcher to work from (Ritchie and Lewis, 2003). GPs were encouraged to develop themes of priority for themselves through open ended questions that were explorative and encouraged dialogue (Ritchie and Lewis, 2003).

Interviews were recorded and transcribed verbatim. A selection (N=2) of full transcripts were checked by the researcher and a member of the supervisory committee for authentication against audiotapes. Sections from the remaining transcripts were additionally checked by the student researcher. Fieldnotes were written post interview, collecting the context and interaction of the interview (Ritchie and Lewis, 2003) and used to inform analysis.

6.3.3 Analysis

A full description of analysis is given in Chapter Three section 3.13.6.

Audio tapes were transcribed as interviews were conducted and analysis commenced immediately. A non-linear process was applied to the reading and rereading of transcripts; as more interviews were transcribed all transcripts were re-reviewed. Initial coding was undertaken using a deductive process (Braun and Clarke, 2006) which allowed codes to be strongly linked to data. Codes were not restricted to the predefined research questions, and so allowed the identification of

new codes and themes emergent from data. Codes were identified based on prevalence of words or space given to the code, within the individual transcript or secondly, prevalence, in the number of participants that made reference to the particular code. Whilst in the patient participant interviews, the student researcher looked for what was said by participants rather than making an effort to interpret or deduce meanings within words, within the GP interviews the researcher used interpretation earlier in the process of theme development, allowing the strong epistemological background of the researcher to identify codes to produce both semantic and latent themes (Braun and Clarke, 2006).

Themes were charted firstly for individual GP interviews and then across the dataset to form final themes. Tables were used to chart individual narrative text and themes, with mind maps used to summarise themes and extracts across the dataset. The analytical process remained data driven, revisiting and checking both semantic and latently developed codes across and within the dataset.

The process of interpretation was a progressive analytical process which involved the summarisation of the themes drawn from charting, which were individually described and narrative evidence given alongside each theme. Theorising then took place which was made alongside existing evidence supported in the literature, the quantitative study and the patient participant interview findings, to draw conclusions.

6.4 Findings

6.4.1 GP Recruitment

Twelve GPs were eligible to be interviewed. Eligible GP numbers were limited by the early saturation seen in the patient participant interviews. Of the 12 GPs eligible, one GP was excluded from participation due to their academic role within the study. A discussion within the supervisory committee led to the decision to exclude this GP based on their supervisory role of the student researcher and study, and the potential for this GP to be influenced in their responses by an increased understanding of the study aims and objectives.

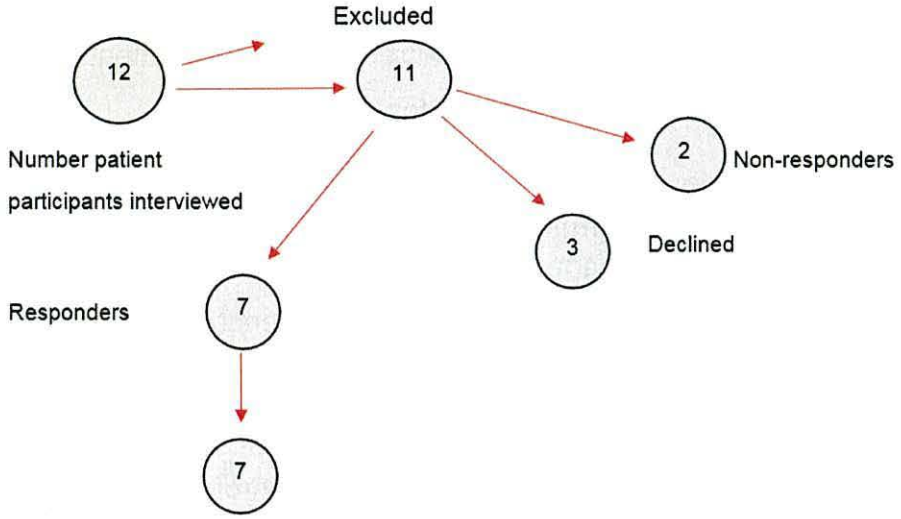

Figure 6-2: GP recruitment

Table 6-1: GP sample group characteristics

DIAGNOSTIC JOURNEY GROUP OF PATIENT PARTICIPANT	GP STUDY NUMBER / PATIENT PSEUDO NAME	DAYS FROM REFERRAL OR PRESENTATION TO SECONDARY CARE TO INTERVIEW	LOCATION OF GP PRACTICE
PROMPT	01/John	212	Hywel Dda
PROMPT	02/Jan	336	Cardiff and Vale
PROMPT	03/Audrey	340	Cardiff and Vale
PROMPT	04/Daphne	455	Hywel Dda
LONGER	05/Harriet	136	Hywel Dda
LONGER	06/Tom	339	Aneurin Bevan
LONGER	07/Arthur	578	North Wales

No difference was observed in the uptake of interviews by GPs based on their patient participant's diagnostic journey length. Two GPs were interviewed that did not complete a primary care questionnaire in the quantitative questionnaire study. The interval from referral by the GP (or, when not available for measurement, the presentation to secondary care) to the interview date was measured (Table 6-1). There was an extensive interval observed which resulted from the delay in calculation of the time to diagnosis intervals in returned questionnaires and the completion of the patient participant interviews. GPs were asked, therefore, to recall

events surrounding the diagnosis of their patients from a range of 136–578 days. GPs were encouraged to refer to the medical records of their patients to inform their responses during interviews to compensate for this.

6.4.2 The interview

6.4.2.1 General summary style and process

GPs were generally easy to engage with and their dialogue forthcoming, although varying degrees of enthusiasm for the interviews were encountered across the group. GPs who were more reticent were hesitant and slightly cautious at the outset of the interview, with measured responses. However, this dissipated over the interview. A small minority of GPs remained defensive throughout the interview. GPs contributed the vast majority of the dialogue in the interviews.

> *"I think you know obviously when you have got a patient and he's coming to you with certain issues you will have a look at what's been done and check the recent letters in discussion with the patient as well, but I have to say we do get obviously loads of correspondence every day, so unless there's anything mentioned on the letter we need to look into the details, we quite often find them, unless obviously they want us to do something, we can't really look in to every individual note, you know, every time we get a letter."* – GP 07, longer journey.

Most GPs appeared to find the process of the interview to be a positive way of reflecting on the journeys of their patients, even in cases where diagnosis had not been straightforward or easily achieved. The reflection led to a deeper understanding of the experiences surrounding the diagnosis and some honest reflections of their own contribution to the process.

> *"She couldn't have asked for it to have been diagnosed any quicker. It's only because I ordered that x-ray, looking back. If I hadn't have ordered it, it would have dragged on for another few weeks."* – GP 03 Prompt journey.

> *"In the last 12 months I've picked up two. So you know there are some unusual things so again one of them was clear cut the other one was less clear cut. Um so, you know, I don't think I'm bad at taking histories and examining it's just in this case, sometimes you look at somebody you think, you put, what you want the diagnosis to be, it's, sometimes you lose that sort*

of objectivity and I've just wondered if that's what sort of happened there. Staring in the face but you don't believe it". – GP 01, prompt journey.

GPs were generally concise in their responses and the interview duration was shorter (<38 minutes) when compared to the patient interviews (>1 hour) (Chapter Five section 5.4.3). No difference was observed for the length of the interview based on the patient's diagnostic journey sample group, but the length was more outwardly influenced by the work pressure of the GP. GPs who gave their time 'out of work hours', either in the evening or on a scheduled day off, appeared less hurried during the interview and were more inclined to expand on their answers to questions. Where GPs attempted to complete an interview whilst in 'surgery', a more hurried interview was observed and GPs appeared 'distracted' at times. A minority of GPs displayed a strong agenda of their own which appeared to be focused around a 'defence' of their own management of the participant or the surgery's management. On occasions when this had a strong influence in the interview, the researcher directed the conversation back to the interview guide.

Data were rich, and even when interviews were short, the concise nature of the GP dialogue revealed illuminating narratives and is evidenced by one GP extract below. This extract sets the context of the GP experience in primary care, detailing the complexity, breadth and exhaustive process GPs refer to as diagnostic 'workup'. This extract introduces many of the subthemes further explored in the findings but is not included here as part of analysis but as an illustration of a typical narrative in the interviews.

6.4.2.1.1 An illustrative case

"It's (myeloma) a bit tricky and it presents in ways which don't necessarily make someone think of that straightaway. I think one patient had had some rib pain for a while. I, it all seemed to be musculoskeletal, all his bloods on investigation were essentially normal to start with. You know ESR, CRP, bone profile, calcium, everything you know. Then when I did a chest x-ray on him it started the ball rolling of requiring a CT scan which then as I remember it showed lytic lesions. I think he got a cough and was admitted to hospital because they thought there was a cervical axial instability – but even then he had to go to a tertiary centre to get the actual diagnosis. The study patient she had seen an excellent young doctor with some shoulder pain which was

nonspecific to start with, and then he organised an x-ray which showed a pathological fracture. So the lady had a bone scan done and I had to go out and see her, and I'd never met this lady actually, because the bone scan reported an impacted fracture of her hip. So she really needed to go to orthopaedics. But when I went round to see her, I rang her just a couple of times, there was no reply, and when I went round I found her coming back into the house from one of the county [community] cars walking with a stick. We went into the house basically together. We sat down and talked for some considerable time about the results and arranged for her to go into hospital. I think she came out of hospital and the diagnosis was not myeloma, she was waiting for a bone biopsy at that stage. So there was some time after I admitted her that we got to the bottom of her having myeloma. I sent her to hospital and it'll be a month later that we ended up with a diagnosis. When we talk to students and we're a training practice, we have registrars here, we talk about how looking for myeloma and considering it, but of course sometimes you come up with these other globulins which are not multiple myeloma. I guess the answer is that it can be a difficult one to pin down and presents in sometimes a barn door way but other times it's like more difficult to pin down". – GP 04, prompt journey.

GPs narratives described individual perception and experiences diagnosing myeloma patients and their view of the perception and experiences of their colleagues. Additionally, the narratives referenced the GPs' experiences of the patient cases registered in the study. Emergent themes were finalised into three broad categories. Analysis was guided by the original research questions for the wider study and results from the quantitative study analysis. This deductive analysis incorporating both the convergent themes, where consensus with the literature was seen, and divergent themes which were seen to contradict what was understood or reported in the literature, saw subthemes develop within the three broad themes identified.

6.4.3 Identified themes categories

- Theme 1: Suspecting myeloma
- Theme 2: Investigating and referring myeloma cases
- Theme 3: How to improve myeloma diagnosis

These three themes were broad and encompassing, with multiple factors contributing to the wider headings. In places, these themes overlapped, making clearly dividing boundaries more difficult to establish.

Quotes are offered as supporting evidence within the themes and have been edited for punctuation to improve readability. This has included the removal of pauses where the interviewee has paused for breath or thought and the pause is displayed by the punctuation of a comma. The quote in its essence and meaning remains unchanged.

6.4.3.1 Theme 1: Suspecting myeloma

This theme developed out of multiple subthemes demonstrating a complex process by which GPs come to suspect myeloma or not.

6.4.3.1.1 Spotting symptoms

GPs, generally, reported they felt they had a good grasp of the symptoms of myeloma, but also reported symptoms as varied in their presenting patients which were often ill-defined. Although GPs felt they had a good grasp of symptoms, when they specifically discussed what they might expect to see in myeloma patients presenting in primary care, accounts were varied and vague. Nearly all GPs reported they considered back pain or musculoskeletal aches and pains as a possible sign of myeloma, and felt that these were signs they would be concentrating on identifying, in order to help with a suspicion of myeloma.

> *"I think it's quite a difficult condition to diagnose. The symptoms are quite vague quite often. They may have back pain. They may just generally feel tired, not very well."* – GP 05 Longer journey.

> *"I mean the 'osteos' are like with a lot of general symptoms that patients present with frequently such as essentially aches and pains and, you know muscle, bone pains, muscle pains. Those sorts of symptoms which you know are a very common general practice presentation."* – GP 06, longer journey.

GPs did not report considering systemic changes in patients as frequently as considering 'aches and pains' to help suspect symptoms were sinister. When systemic symptoms were considered, this was reported to specifically help with the suspicion of something more sinister.

"If people are getting night sweats, weight loss, diffuse pain. Those types of things, particularly in an older person you sort of start thinking more neoplastic things are going on here. Particularly you nearly always see sort of persistent back pain, things like that, which can be more common with myeloma. So I can't think the last time I actually had a myeloma picked up as someone presenting with back pain. It tends to be more of nonspecific malaise rather than focal one persistent specific symptom that they can come in with. I presume it's probably why myeloma is one of the ones that gets picked up a bit later." – GP 01, prompt journey.

GPs reported when patients had vague symptoms, these symptoms were not very well conveyed to them, which made suspicion of something more serious difficult.

"I mean generally you know most patients are reasonably good at a story, you get a fairly reasonable sort of story, but with something like myeloma the symptoms are quite vague." – GP 05, longer journey.

Generally, GPs across the group reported not suspecting symptoms they identified as sinister in their patients, and therefore myeloma was simply not considered as an initial differential diagnosis.

"It wasn't going through my head myeloma with this lady so it's just severe back pain." – GP 03, prompt journey.

There was little reporting of a wider appreciation or assessment of 'wellbeing' or contextual or behavioural differences by GPs when assessing symptoms in the individual patient. The majority of GPs reported they were focused solely on assessing symptoms to aid the suspicion of something sinister in their patient.

"Yeah it was just about the symptoms." – GP 03, prompt journey.

GPs reported patients remained relatively well and function was high in the early stages of their illness and symptom development. These subtle changes, GPs considered, made it more difficult to determine the seriousness of the symptoms experienced in their patients and therefore whether there was a need to further investigate.

"I'd never met this lady actually because the bone-scan reported an impacted fracture of her hip. So she really needed to go in to orthopaedics. But when I

went round to see her, I rang her just a couple of times, there was no reply, and when I went round I found her coming back into the house from one of the county [community] cars walking with her stick." – GP 04, prompt journey.

6.4.3.1.2 Ruling out the other possibilities

GPs recounted their suspicion of serious illness or myeloma came to the forefront only when more commonly occurring conditions had been "whittled" down from a set of differential diagnoses. Myeloma was rarely discussed as being considered in an initial differential diagnosis.

"It tends to be sort of more, "Oh it might be this, it might be that." And you do blood tests and things to whittle it down. I think in this case it wasn't even particularly a common sort of myeloma symptom." – GP 02, prompt journey.

6.4.3.1.3 Consulting technique

The assessment of symptoms was reported to prompt suspicion when history taking was thorough, rigorous and questioning in nature. GPs reported the influence of spending time in the consultation listening to the patient as positively contributing to a thorough assessment which heightened their suspicion of serious or sinister disease.

"*You just have to make sure you take a good history from the patient because if you listen to the patient long enough they will give you the information to hopefully be able to make the diagnosis and tell you what's going on.*" – GP 04, prompt journey.

6.4.3.1.4 Character traits

Personality traits within the patient, such as stoicism, were acknowledged to be confounding to the identification of symptom seriousness, with GPs reporting responding more passively when symptoms were 'played down' by the patient. GPs reported stoic patients were inclined to tolerate symptoms for longer or not report the full intensity of their symptoms, making a good assessment of symptom seriousness difficult. Stoicism was reported occasionally to have caused alarm and raised suspicion of symptom seriousness and promote a swift GP response. However, when this was reported, it was more frequently discussed as a response to symptom tolerance over a period of time and progressive and more debilitating symptoms and repeat consultation. These personality traits were reported retrospectively as an

assessment of why symptoms had not been considered serious and appeared not to have been appreciated within initial consultations.

> *"I guess he's one of those people who is stoic, possibly put up with a degree of back pain for longer than he admitted until it became quite acute with him. But then I had a phone, a call to go and visit him at home because he'd now gone off his legs. That in itself was unusual because they never ask for a visit, so I went to visit him and he had a paralysis of his left leg".* – GP 01, prompt journey.

6.4.3.1.5 Age as a risk factor

GPs demonstrated an awareness of increased risk of myeloma in the older patient, with age consistently discussed as a risk factor. This was discussed as an aid to the assessment of symptoms, therefore beneficial to early suspicion. However, the focus on age was seen to have a negative effect on the suspicion of myeloma in younger patients, with this being considered 'off the radar' by GPs in younger patients.

> *"I've only really thinking about it [myeloma] in a patient over the age of 50 or 55. I wouldn't really think about it in any younger patient."* – GP 06, longer journey.

> *"People of sixty and above it would be higher on my list than someone who was forty or fifty. Younger people get this but if you, if you're asking me who I would have a higher-index of suspicion in then it would be in that sort of age-group."* – GP 04, prompt journey.

Age was also indicated to be a 'red herring' for the suspicion of symptom seriousness and myeloma by GPs, with GPs to a degree 'normalising' the type of symptoms experienced by their patients to ageing.

> *"So they come with sort of often what appears to be like a musculoskeletal, you know sort of thing, where they've got back ache or they got arm ache or something and you know it isn't necessarily your first thing, you think more likely that they may have a bit of a you know osteoarthritis somewhere, that's your sort of because the cohort of people do tend to generally be older."* – GP 05, longer journey

6.4.3.1.6 Continuity and familiarity

Familiarity with the patient was most frequently reported as a positive factor in helping a GP to assess and suspect that symptoms were serious. Some GPs reported identifying a change in their patient's condition more easily when the patient was more familiar to them, this familiarity being gained from long-term, consistent primary care responsibility. When familiarity was discussed as a negative impact, this was said to potentially lead to complacency in suspecting something serious developing over time in the patient.

> *"I've been in the job for 28 years. I've got people who are middle-aged who have now become elderly and they had children, well one or two who are grandparents, you get to know people, you get to know who's unwell. You know you've seen them well and suddenly you see them looking drawn and you can spot a change there. It helps potential earlier diagnosis. I mean the drawback with that is you might know them too well and miss something that's glaringly obvious to somebody who doesn't know them. That tends to happen less often I think."* – GP 01, prompt journey.

> *"I think the answer to that is knowing your patient."* – GP 04, prompt journey.

Loss of continuity and repeated presentations to multiple healthcare professionals in primary care was also discussed, but this was not acknowledged by the GPs in the interviews as unusual or detrimental to the process of suspicion but more of the 'norm'.

> *"Presented initially to the nurse practitioner with back pain, particularly at night, anti-inflammatories were helping things. She obviously asked questions about bowel and bladder which you always wonder whether a back problem - is there a disc or something causing the problem. A couple of weeks later she had back pain and was seen by the 'out of hours' people who felt it was some sort of sciatica at that stage. She was then because of increasing pain and not coping with pain relief in any shape or form, was seeing one of my partners who assessed her at the time and though she was quite tender on her upper lumbar spines but everything else was normal. He wondered about whether she had osteoporotic collapse at that stage but he admitted her for further investigations."* – GP 05, longer journey.

6.4.3.1.7 Multiple morbidity

GPs reported they found symptoms more challenging to identify as serious in myeloma patients because of the presence of multiple morbidities. Some GPs concluded multi-morbidities made the identification of new symptoms difficult simply because of the amount observed in this particular patient group. Others related this to the number of people involved in the care of an individual and others related it to being due to discrete changes in the patient's clinical profile of investigations which were considered acceptable because of the pre-existing multi-morbidities.

> *"He's had prostate cancer before and sort of you know bit of anaemia in December 2013. And then he's been referred to the care of the elderly team in December by my colleague. Well it's, it's something difficult, if too many cooks are involved it's obviously it um distorts the picture."* – GP 07, longer journey.

> *"But the patients are ever more complex with ever more multiple pathologies and we have older people running around with less than normal haemoglobins anyway. You know borderline anaemias through chronic disease and of course that can compound the problem."* – GP 04, prompt journey.

6.4.3.1.8 Time

Some GPs described a process where they used 'time' as a tool to assess the seriousness of patient symptoms. This process of 'watch and wait' was described as a widely used and necessary tool in the management of patients with non-specific symptoms. GPs intimated that patients with these symptoms would need to present on multiple occasions, before symptoms would be recognised as serious or sinister.

> *"Looking at change which may take a few visits to the GP over a period of several weeks or months or so I suppose."* – GP 04, prompt journey.

> *"That's the whole thing about general practice we see a lot of vague illness, some of which turns out to be organic and some of which is functional. And sometimes you just have to try and follow the progress and see what happens. So you use time as part of your armoury of tools and that needs a bit of confidence."* – GP 01, prompt journey.

The use of time relied on the patient's repeat consultation and there was little evidence in the GP interviews of formal safety netting procedures to facilitate future consultation. When safety netting was used it was rather more individually applied. There appeared to be a more general assumption that patients would know they needed to return if problems persisted, rather than a formal system to ensure the patient would return in the event of symptoms becoming worse or persisting.

> *"Maybe if she'd have kept coming back to us more regularly and bothering us, you know, that sounds awful but you know coming in to our view then because I mean sometimes, you know there's a lot of firefighting in our job and you know out of sight is out of mind sometimes, so if people don't keep coming to see us we assume they're alright. Um and you know obviously when she did come we did act. But she'd gone six months really without coming to see us."* – GP 05, longer journey.

6.4.3.1.9 Doing a good job

Generally, GPs reported that myeloma had a low profile and, therefore, their suspicion of it was lowered. GPs considered themselves to be doing a good job 'under the circumstances'. Myeloma was accepted as something that was difficult to diagnose and, therefore, almost inevitable that patients would have a protracted journey to diagnosis. GPs discussed challenges such as being a 'jack of all trades' and the reality that myeloma was just one of many conditions, let alone one cancer, that they are responsible for trying to diagnose promptly.

> *"I think it's a relatively low-profile condition, it's not something that we as doctors know a lot about."* – GP 01, prompt journey.

> *"It's quite a rare sort of diagnosis that we don't come across a lot."* – GP 03, prompt journey.

> *"I think we know that it's sort of a diagnosis you can easily miss? And um you just have to think about it, you know, um really."* – GP 07, longer journey.

Table 6-2: Theme 1 'suspecting myeloma' summary of subthemes

Spotting symptoms - varied in patients; GPs consider back pain and musculoskeletal aches but not systemic changes; symptoms assessed as not sinister; behavioural and contextual assessment missing; miscommunication of symptoms occurs; symptom normalisation to ageing; loss of continuity
Consulting technique - rigorous and thorough reveals greater appreciation of symptom seriousness
Multiple morbidities - myeloma group complex with multiple disease and complications
Character traits - stoicism in patients contributes to assessment symptoms not serious
Ruling out the other possibilities - suspicions of myeloma occurs only after whittling down other diagnoses
Time - watch and wait practice adopted as symptoms assessed as non-sinister
Doing a good job – GPs feel they are doing OK with the current level of understanding of diagnosing myeloma

6.4.3.2 Theme two: Investigating and referring myeloma cases

A theme emerged surrounding the perception and experiences of GPs investigating myeloma. This was multi-faceted and presented the intricacies that occur in GPs' decision-making processes around when and how to investigate symptoms and how and when to refer their patients to specialist care.

6.4.3.2.1 Need to suspect first

GPs discussed the impetus to investigate symptoms came from either suspecting the symptoms presented were the result of an underlying illness or myeloma itself. Generally, this was discussed as not happening frequently in these myeloma cases, and there was a picture that emerged of a preference for using time and watch and wait, rather than investigating early.

> *"Well in retrospect I would have done a spinal x-ray probably and the myeloma screen. But the picture, I think, sometimes with back pain you see a lot of confusing back pains where you don't really know what's going on. We see lots of people with back spasm where people are in a lot of pain, you've sometimes got to wait for that spasm to ease off before you can reassess the situation and work on from there."* – GP 01, prompt journey.

6.4.3.2.2 Access to investigations and threshold for conducting them

GPs reported no difficulties accessing tests that could potentially identify myeloma. There were discussions about justifying costs for investigation in primary care and comments that definitive testing for myeloma could not be performed in primary care as it required specialist diagnostic tests and their interpretation. These comments occurred in a minority of GPs.

> *"Some of the other investigations are not actually available for us in primary care because there is rationing, you know, the available resources or tests in primary care to sort of a cost saving exercise so we haven't got carte blanche for everything under the, if you, under the sun."* – GP 05, longer journey.

GPs who reported having lower thresholds for the initiation of clinical investigations, and commented that myeloma screens were conducted a lot in their practices, did appear to reach earlier referral of patients and generally reported investigating earlier in the interviews.

> *"I think she just came in with sort of recurrent mouth ulcers, did full blood counts and that which showed slight anaemia that, I think globulins were up and so did the further tests and things from there and then it turns to myeloma diagnosis."* – GP 02, prompt journey.

GPs were divided equally in the degrees of having a greater inclination to investigate widely in the initial 'upfront' investigation of symptoms, or a more reserved approach to their investigation. Those GPs who had a reserved approach discussed using tests that they considered more of a 'screening' assessment, which they considered appropriate for the vague symptom profile they had been presented with. A laddered approach to investigation was described, where 'screening' investigations were built on to rule out differential diagnoses but could also, when negative, stop further investigation. GPs, who reported their investigation activity as more proactive in the upfront assessment of patients' symptoms, appeared to use a wider profile of tests upfront and progress more rapidly through the diagnostic investigations.

> *"I think we all tend to have some sort of baseline set of bloods we tend to run in certain groups of patients, of which the sort of ones for myeloma like a full blood count and then if you've got abnormalities and certainly if the globulins are raised then you'll tend to do a protein electrophoresis and we wouldn't*

normally do that as a first line if there are non-specific symptoms." – GP 02, prompt journey.

"I mean when you've got somebody who sort of describes sort of multiple symptoms of not anything as specific you do tend to do screening blood tests which would include inflammatory markers like the ESR and then I suppose if that was negative or low or normal then that would sort of reassure me not to go significantly further down that road because that tends to be one of the sort of trigger bloods to make you think more of, "Why is the ESR rate, have they got myeloma? Have they got polymyalgia?" You know and then make you do the sort of the Bence-Jones proteins so I suppose the ESR particularly if it's persistently raised would be a trigger." – GP 05, longer journey.

There were comments from some GPs, cautioning too many tests can be confusing. Again, this was in the minority.

"I mean some of these resources, although you as a GP can request them you've got to be able to interpret the results as well and act on the results." – GP 05, longer journey.

A number of GPs discussed how clinical testing led to a false sense of security when test results were reported within normal ranges, this being seen as an inclination to stop investigating rather than investigating further.

"Sometimes you even do the blood tests and they're not always very definitive and even doing protein and myeloma screens and things don't always seem to give you the right answer on the first occasion and er on my experiences of it with quite a few people who've been diagnosed with myeloma they may've had basic bloods done er and screened and they've all been fine." – GP 05, longer journey.

"It all seemed to be musculoskeletal. All his bloods on investigation were essentially normal to start with you know the ESR, CRP, bone profile, calcium, everything but then when I did a chest x-ray on him it started the ball rolling of requiring a CT scan which as I remember it showed lytic lesions." – GP 04, prompt journey.

One of the emerging factors influencing early investigation of symptoms was the acceptance by GPs that back pain did not warrant immediate clinical investigations unless it was new or un-resolving.

"Well people with new aches and pains which seem to be sort of strange you know a strange onset but don't appear to be an inflammatory arthritis would raise my suspicions rapidly." – GP 04, prompt journey.

"We do quite a lot of you know myeloma screenings you know for people who have got sort of you know ongoing back pain which is not settling." – GP 07, longer journey.

"He came in with a history of back pain which I thought at first was straightforward muscular-skeletal thing. I think at that stage he'd had the pain, I can't remember, but had it for one or two weeks. Maybe two weeks, I don't know. Um but he was in pain which in itself was unusual for him. And then I can't remember the sequence now. But he saw my trainee, I think he must have seen my trainee first and then saw me and I said, "Well we'll see you again in a couple of weeks' time if things are no better." – GP 01, prompt journey.

6.4.3.2.3 Prompts for referring and the barriers and frustrations experienced

GPs who discussed the referral of myeloma cases into specialist care identified good pathways in haematology referrals, and they discussed feeling reassured of a fast and appropriate response to their referral.

"Yes, I mean it's sort of a clearer pathway really with that, you'd know you're going straight through to the haematologist who's gonna look and make diagnosis and manage things that, it's a bit more straightforward, the instigation of the referral process for them." – GP 02, prompt journey.

However, contrasting experiences were given by GPs who referred outside of the haematology pathway, where frustration was seen in the retelling of the patients' progression to a diagnosis. These frustrations stemmed from what appeared to be a loss of the GP's involvement and understanding of the progression and care of their patient through interdepartmental referrals within secondary care. In interviews, GPs did not identify the referral from primary care impacting on the patient pathway in

secondary care or the effect this could have on the length of the journey to diagnosis.

> *"I mean I haven't been able to look through all the hospital notes but I think sort of you know, you know and as I say because in 2014 really our GPs they've hardly any involved, you know, and it seems to be done coming from the care of the elderly."* – GP 07, longer journey.

> *"I mean she was seen by the orthopods but she was also seen by the medics and to be honest the team that she saw you know they were, they're quite competent doctors, so you know I don't think they would normally have missed something."* – GP 05, longer journey.

In the GPs' narratives referral into secondary care were discussed as being based on the identification of abnormal clinical tests and this dictated who the referral was made to. There was frequent reporting of blood test results being 'normal' or only mildly deranged and this was discussed as adding confusion to the process of when and who to refer to.

> *"You know her haemoglobin was 11.4 at the time which is, which only point-one below the normal range so. It did go down to 10.3 but um when she was actually seen the first time it was only 11.4 which is hardly going to ring lots of bells."* – GP 04, prompt journey.

> *"If they obviously come back normal you know everything is normal then obviously you know I probably would be you know, it's likely to repeat them soon again really you know. But obviously if there's anything abnormal other than the myeloma screening then we would follow up on that."* – GP 07, longer journey.

> *"Recurrent infections start to make me think. "Well why is this person having recurrent infection? And doing blood counts and things like that, but if their blood count is essentially normal then you might not go any further anyway."* - GP 04, prompt journey.

A few GPs reported very varied and almost frenzied patterns of diagnostic investigations that were driven by the investigation by differential diagnoses other than myeloma. These primary care intervals appeared protracted as the GPs attempted to identify any abnormal clinical investigation that would prompt a referral

to a specialist team in secondary care. This led to referrals being made to teams other than haematology.

> *"It was noted that her calcium was quite low, er, was high at that stage while she was in hospital. Her parathyroid hormone was low, but we arranged then because of the you know possible osteoporotic fracture for her to have a DEXA scan to check bone densitometry."* – GP 05, longer journey.

6.4.3.2.4 Confidence in role

A group of GPs were highlighted who were generally more confident in their role as investigators and gatekeepers in primary care. These GPs viewed their role as integral to the wider health service structure, and conveyed clearer boundaries, expectations and confidence in investigating and referring their patients. These GPs reported a timely, active process of investigation and referral of their patients, and within surveillance they appeared to remain actively aware of processes and responsibilities. GPs who referred to themselves as generalists, and of having less 'expertise' than secondary care doctors, appeared to have less clear views about investigating and their role in the overall management of their patients in surveillance and referral.

GPs across the group reported welcoming prompts from secondary care indicating further follow-up or blood tests.

> *"I know what it [myeloma] is but I don't know how we'll manage it or how we investigate it further so there is a limit, not because GPs are not competent but the problem with it is we're trying to multi-task in so many different directions and I think that if we take these roles on in primary care it actually starts to belittle the role of secondary care."* – GP 05, longer journey.
>
> *"It can make you less [surveillance/referral in secondary care], as a doctor, slightly less involved. Less responsibility. Because they're under someone else's care."* – GP 06, longer journey.
>
> *"We as GPs don't deal with a lot of myeloma. I can only think of two people with it out of my list of two-and-a-half thousand. When you put that into the context of people who have other diseases like other malignancies or haematological malignancies, there's not so many. So you're never going to spend lots of time teaching people about it, when they won't see it for five*

years. But it's really just trying to get the basics right, the early diagnostics right. Because everybody knows about myeloma but we don't need to know the in-depth management of it." – GP 01, prompt journey.

6.4.3.2.5 Safety netting

There were differences across the GP group in 'safety netting' practises that were discussed in Theme 1 and suspicion of myeloma, but also influenced the investigation of myeloma. Where GPs encouraged active participation from their patients whether this be returning for consultation or phoning for results of investigations, this was seen to actively promote a timely process of initiating or further investigating screening investigations.

"Well if you safety-net with the patient by saying, "Well if things aren't getting better then I want you to come back and see me." Then the patients usually will come back and see you. If you give a clear explanation of what you are expecting and a treatment regime and plan. The other, the other important thing is to have clear documentation and notes and even an aide-memoire in the notes so that if it's not you that sees them, the other person will understand what perhaps you are thinking." – GP 04, prompt journey.

"Well the results will come through - we tell the patient to ring back about results. Because I've known patients in the past who haven't rung to check tests. It's just something that I really think you know if it was slightly up cholesterol or a borderline test you might not necessarily chase them but I think this case I'd actually rung them up and, "Oh we need to, you need to come in, we need to have a look at things again". So if there's one where I'm thinking actually there's looking like it's something more significant here then I will tend to ring them up and prompt them to come back in." – GP 02, prompt journey.

6.4.3.2.6 Use of guidance

Across the GP group, there was little evidence of the use of formal guidance informing decision making for the investigation of myeloma. Even when GPs were specifically asked about how guidance may inform their practice, GPs did not offer any specific guidance criteria as influencing their decisions for how and when to investigate and refer. When asked more specifically about their use of guidance, only one GP recognised the existence of guidelines and offered these as helpful for

assessing appropriate referral pathways. There was evidence of GPs considering their own personally generated guidance based on knowledge and experience to inform their decision making.

> *"It's [guidance] useful having a structure knowing what for investigation. Still knowing what tests to do and sort of referring on and things like that, it can sometimes, you sometimes get into situation, not just myeloma, but similar conditions where you think, who is the best person to actually take this forward in secondary care?"* – GP 02, prompt journey.

Referral guidelines were discussed as not being used by some GPs and, therefore, not influential to their practice, because they could not keep abreast of the volume or updates of guidance being published.

> *"Well the problem with guidance is there's guidance on absolutely everything these days and it gets updated and sometimes the guidance which comes out may or may not be applicable to primary care and actually reading the guidance on everything is almost an impossible aspiration."* – GP 04, prompt journey.

> *"In general, my suspicions are normally quite high for it [myeloma] and you know I've got my own guidelines that go on in my head as to how, at what point I would investigate somebody as being a potential myeloma sufferer."* – GP 01, prompt journey.

Table 6-3: Theme 2 'Investigating and referring myeloma' cases summary of subthemes

Need to suspect – initiation of investigations made only after assessment that symptoms are serious and have an underlying illness
Investigation access and threshold – high threshold for initiation of investigation; screening tests used initially and fail to identify abnormalities as they do not include myeloma specific investigations
Prompts for referring and the barriers and frustrations experienced – referral to haematology optimal pathway; referral outside haematology appear protracted and often initiated because of the investigation profile used by the GP; GP reliant on abnormal investigations to refer patients into secondary care
Confidence in role – confidence and knowledge in their gatekeeper role results in GPs who have an active and timely role in investigation, surveillance and referral
Safety netting – poor practice of safety netting procedures in practices, when applied this is applied on an a more individual basis

Guidance – no obvious use of guidance to inform practice in the investigation of myeloma

6.4.3.3 Theme 3: How to improve the diagnosis of myeloma

In the interviews, GPs discussed factors that might help the easier suspicion or achieve better investigation of myeloma and gave their perceptions on how this may contribute to diagnosing myeloma more timely. These perceptions were made from direct questioning on improving the diagnosis of myeloma in primary care. Without the directed questioning, GPs did not offer their thoughts.

6.4.3.3.1 Training

GPs generally reported that they had received little formal training in diagnosing myeloma, although there was mixed reporting about training received and clinical development programs accessed for other disease specific areas. Some GPs discussed having a more formal training programme in place to 'update' themselves, whilst others reported this to be self-motivated and directed.

Those GPs who had training roles discussed the training of future GPs with regards to myeloma as being very informal. There was discussion on the use of reflection in clinical practice in the review of difficult cases, but this was reported as informal or self-driven. Many of the GPs who reported problems accessing training were fatalistic, generally, about training and access to it.

Although only reported by one GP, there was a recognition that overseas students completing GP training in Wales, had a wider exposure to haematology within their junior doctor training. This was discussed as influencing positively their ability to recognise symptoms and suspect myeloma.

> *"Not designated time I suppose we have um once a month or, every other month we'll have an afternoon off on a Wednesday educational thing but it's sort of varied, what tends to get done in those. Most professional development tends to be fitted in your own time, I think."* – GP 02, prompt journey.

> *"Yeah, for example significant events. If they're sort of, you know, obviously with our appraisals we have to reflect. I usually reflect on difficult cases or what something you know hasn't gone right or you know or you know I tend to reflect on the cancer diagnosis of the last year I've made as well you know*

just to see, is anything which could've been done better, you know." – GP 07, longer journey.

"When we talk to students and we're a training practice, we have registrars here, you know, we talk about you know looking for myeloma." – GP 04, prompt journey.

"We do supervision from you know case review with them. I think they, I feel that they are quite, quite well trained you know and that is usually in their mind as well so you know I think they, they are OK." – GP 07, longer journey.

"Knowledge means updating in the realms of myeloma which I do not do. We've had some overseas doctors who've done a lot of general medical work before settling down to general practice, at a physician type level they're very competent. Their level of knowledge I assume would be better. The home-grown graduates they'll be coming through to us having done two years hospital based work. I guess it depends on what sort of jobs they've done." – GP 01, prompt journey.

6.4.3.3.2 What would help?

When GPs were asked what might help them suspect and diagnose myeloma earlier there were some extreme responses, highlighting an almost hopelessness felt by GPs diagnosing this condition.

"Anything that you could do? I suppose the two best instruments for that would be a crystal ball and a retrospectroscope." – GP 04, prompt journey.

There were, however, a number of more measured responses to the question. Online access to, for example, BMA training was suggested, as there were comments that the rural position of some GPs in Wales restricts access to training and makes it difficult to keep updated. There were calls for short aide memoires in the form of flyers or posters, giving prompts for symptoms and investigations. Other suggestions included the inclusion of myeloma in GP hot topic days, and access to advisory groups for GPs. In general, there was an appetite demonstrated for myeloma education within the GPs interviewed.

"Well you have to [keep updated] whether you like it or not. I mean it is achievable, yes. The problem is that you know you can't always focus in one direction so you know one year you may focus in one direction, the next year

maybe in another direction. There are now courses that are GP hot topic courses which is where you have a day where you're all sort of flooded with information that's been sort of sifted and reviewed by GPs. You know sort of all the journal and guidelines are read and digested and they come up as a sort of active guide of how to move on with these things". – GP 05, longer journey.

"Unless there is a small leaflet which would have a list of unusual symptoms which might suggest myeloma; if there was a common theme coming out of your research, "Lots of these people had this symptom"". – GP 04, prompt journey.

Table 6-4: Theme 3 How to improve the diagnosis of myeloma summary of subthemes

How to diagnose earlier
Training – not specifically for myeloma; no dedicated time given, often accessed in GPs' own time; access for rural GPs difficult; reflection on practice not a formal process; training of other GPs not formalised and often case study focused
What would help – equity in access for Welsh GPs with online training; BMJ online courses; aide memories in surgery; hot topic myeloma days; access to myeloma advisory groups

6.5 Discussion

6.5.1 Summary of the main findings

This is the first study to explore and report the in-depth views and experiences of GPs diagnosing myeloma. Overall, GPs in the interviews focused on two main areas: the difficulty assessing symptoms and making a link to myeloma or serious disease; and the prompts and difficulties investigating and referring myeloma patients. There were overlapping subthemes, and boundaries between the two main meta themes were not always clear. Themes were multi-faceted and contributed to the initial conclusion by GPs that symptoms were not sinister in presenting patients or not related to myeloma. This resulted in a delay in investigation of the symptoms or the completion of screening style investigations in attempts to identify or rule out differential diagnoses. This failure to identify myeloma in primary care impacted the primary care interval with referrals into secondary care though non-optimal routes.

A combination of factors affect the way GPs assess and make sense of symptoms in their myeloma patients. These frequently lead GPs to conclude the symptoms presented to them are not sinister and suspicion of myeloma or other serious pathology. However, GPs feel they are knowledgeable about the symptoms experienced by myeloma patients. GPs focus on back pain and general musculoskeletal pains as 'alert' symptoms and they have less appreciation of systemic symptoms in myeloma. There is a 'disconnect' between the knowledge the GP thinks he has and the early symptoms of myeloma which is probably rooted in the poor understanding of symptoms in the early stages of myeloma (Chapter Two section 2.5.2).

GPs misattribute symptoms of myeloma to other morbid conditions that are said to be high in this older patient group. This leads GPs to conclude the symptoms the patient complains of are not sinister and possibly lengthens the primary care interval. GPs also normalise the vague symptoms to ageing in their patients. This informs symptom assessment as 'normal' in much the same way as reported by patients in the interview study (Chapter Five section 5.4.5). This possibly results in concurrence between GP and patient that symptoms are not sinister and lengthens the appraisal of symptoms in primary care.

Interestingly, there appears to be little appreciation of behavioural or contextual factors by GPs when assessing symptoms in consultations with patients. GPs, instead, are focused on the physical changes the patient communicates in order to identify symptoms as serious or sinister. This possibly contributes to less timely identification of 'symptoms seriousness' and stops early prompts for investigation. Possibly, the GPs' misunderstanding of the symptoms is hampered by the vague terms and unquantifiable parameters that patients use to describe their symptoms of myeloma, as reported in the patient interviews (Chapter Five section 5.4.5), and is in contrast to the way GPs look to assess the seriousness of symptoms in their everyday practice. However, GPs whose assessments involve an in-depth symptom history taking and appraisal are better able to identify symptom seriousness. This relies on time in consultation to explore symptoms, which is possibly confounded by short consultation times.

There is an acceptance and even an expectation in GPs that symptoms related to myeloma will take multiple consultations before GPs suspect symptoms are sinister.

The use of time as a 'tool' in assessing the symptoms and low safety netting practices are possible explanations for these multiple consultations and longer primary care intervals. Additionally, increased risk of loss of continuity in myeloma patients occurs as the number of consultations increase which potentially adds to the poor identification of symptom seriousness.

There are differences in GPs' thresholds for commencing clinical investigations in response to symptoms in myeloma. Lower thresholds see earlier investigation of symptoms with GPs investigating lower level or less well-defined symptoms and this possibly reduces the need for repeat consultation and shortens the primary care interval. Additionally, this lower threshold can include an initial wider spectrum of testing that has an explorative intention, and possibly results in the identification of the underlying disease earlier rather than relying on identifying the complications of the disease and allows earlier referral to specialist care. GPs who were reassured by the reporting of normal or near normal investigations have a raised threshold for repeat investigations in the face of persisting or new symptoms. Higher thresholds exist for investigation of back pain by GPs, although this possibly reflects NICE guidance for the investigation of low back pain in place at the time symptoms in this study were assessed. Guidance advises GPs to wait and assess low back pain before investigating (NICE, 2009) at the time, whereas updated guidance (NICE, 2016b) now directs GPs to exclude malignancy in the initial assessment of symptoms. Although no direction is given on how malignancy should be excluded, it is likely to include clinical investigation of symptoms and this possibly could lead to the identification of myeloma earlier.

The return of investigations that are reported as within normal, or only slightly abnormal, reassures GPs symptoms experienced are not sinister and possibly adds to the lengthening of the primary care interval. Patients then return to the GP when symptoms progress or worsen and results in a frenzied investigation process commencing as the clinical condition of the patient deteriorates or becomes of more concern to the GP.

The poor use of safety netting by GPs is likely to contribute to an increase in the primary care interval as these vague symptoms, which are not suspected as serious, are not considered necessary to ensure the patient returns for a further consult in persistent or worsening conditions.

Surprisingly, guidance for the investigation and referral of cancer is not commonly used in the assessment of symptoms in myeloma despite NICE guidance being in place and available to GPs during the recruitment of participants to this study (NICE, 2011). It is possible that this relates to GPs not considering symptoms as sinister and there being no reason to, therefore, look for guidance related to a cancer diagnosis or referral. It is possible that the newer guidance, updated in 2015 (NICE, 2015) may be more impactful but this requires assessment after a period of implementation.

The referrals made into secondary care by GPs are problematic when routes other than haematology are used. The route of entry to secondary care for myeloma patients appears to be reliant on the identification of abnormal investigations by the GP, with the referral then following the path of the abnormality identified i.e. fracture=orthopaedics; raised creatinine=renal medicine. GPs are dependent on identifying abnormalities because suspicion of sinister pathology is low in myeloma. The passage through secondary care becomes more difficult in these non-haematology routes because GPs become distanced from the process of gaining a diagnosis as they wait for the appointments for patients. This possibly contributes to the higher levels of emergency presentation of myeloma patients as acute illness develops whilst the patient is investigated as an outpatient.

GPs have an appetite for education and training to improve the recognition of myeloma in primary care and earlier diagnosis, but they require this to be equitable in access and time. Electronic training and short courses require consideration in rolling out information programmes for myeloma to GPs. It was noticeable, and possibly of concern, that a large proportion of GPs carried out their training and updating in their own time, which inevitably adds strain and personal cost. GPs require shorter, succinct reference tools to aid their assessment and investigation in the workplace and appeared to not have an appetite for more complex decision tools, manual or electronic or risk assessment tools. Instead, aide memoire leaflets that are easy to access and reference in clinical practice, in the surgery, to refresh 'signs and symptoms' were requested.

GPs are fatalistic about the anticipated length of time a journey to diagnosis in myeloma may take. This probably reflects the level of reporting of the difficulties in diagnosis and the absence of the ability to make recommendations for changes reflected by the systematic review (Chapter Two section 2.7). GPs had little to

contribute to the dialogue about improving the identification of myeloma in primary care. GPs require more education about the topic or practical 'in surgery' tools rather than technological advancements. Therefore, it is likely that, therefore, being able to offer some recommendations for practice will change the GPs' fatalistic approach and perspective to identifying myeloma earlier in primary care.

6.5.2 Comparison to the literature

It is not a new reporting that symptoms are wide and varied in myeloma (Howell et al., 2013), and GPs confirmed this in these interviews. GPs recognised musculoskeletal symptoms being attributable to myeloma as reported by Howell et al. (2013), Howell et al. (2015) and Kariyawasan, et al (2007). The reporting that GPs do not suspect myeloma and find it difficult to connect symptoms to the disease is supportive of work reporting that poor symptom appraisal by GPs can lengthen the primary care interval (Lyratzopoulos et al., 2013; Lyratzopolous et al., 2015a), but this work additionally identifies that this relates to GPs concluding that the symptoms presented to them are not sinister.

GPs reported that they find the presence of multi-morbidities can lead to loss of clarity in assessing symptoms. This is supportive of the Friese et al. (2009) and Ong et al. (1995) work reporting longer time to diagnosis intervals for participants with multi-morbidities. However, in the quantitative study, no association was demonstrated for the presence of multi-morbidities and longer intervals to diagnosis for this myeloma patient group (Chapter Four section 4.4.3), so possibly GPs reflect these as difficult but in practice they are more aware than they feel they are.

Surprisingly, there was no evidence of GPs considering behavioural or contextual issues in the assessment of symptoms in this myeloma patient group. Given the reporting of these factors as influences in the intervals to diagnosis for other cancers (Hiom et al., 2015) and the reporting of these factors within the patient interview study (Chapter Five section 5.4.5), this possibly provides some explanation as to why the primary care intervals are longer for the myeloma journey compared to other cancer types (Chapter Four section 4.6.2).

It is reassuring that GPs report no difficulty accessing tests for investigation of myeloma and reflects the wide access recommended to SPE, SFLC/BJP and symptomatic x –ray in the BSH guidelines (Bird et al., 2011). This is possibly advantageous to the diagnostic intervals for myeloma and is different to other cancer

types, where reported access difficulties impact negative diagnostic journeys (Rubin et al., 2015; Cancer Research UK, 2016; Vedsted and Olsen, 2011).

GPs reported that continuity helped with assessing symptom seriousness which supports work by Ridd et al. (2006). The high level of repeated consultation for myeloma patients reported by Lyratzopoulos et al. (2012) and in the quantitative study (Chapter Four section 4.5.3) is supported here in the accounts of primary care interactions by the GPs. This study, additionally, adds that these are confounded by the use of 'watch and wait' strategies to assess symptoms and poor safety netting. Safety netting has been targeted for potentially improving detection of cancer in patients with vague symptoms (Nicholson et al., 2016) which this study would support.

6.5.3 Strengths and limitations

The major strength of this GP interview study is the uniqueness of the findings that report the experiences and perception of primary care practitioners diagnosing myeloma.

Rigorous and transparent qualitative methods have been applied and reported to ensure authenticity of data.

The method of enquiry was successful in eliciting the GPs' perceptions of diagnosing myeloma and provided rich narratives for analysis. Some GPs did appear defensive in the interview and it is possible that this defensiveness lessened those GPs' narratives. However, GPs' defensiveness was not unsurprising given that myeloma is frequently associated with problematic and longer primary care intervals (Kariyawasan et al., 2007; Li et al., 2012; Lyratzopoulous et al., 2012; Lyratzopoulos et al., 2013; Lyratzopoulous et al., 2014). Although some GPs were defensive at the outset of the interviews, the student researcher was successful in maintaining a good dialogue which resulted in the inclination for defensiveness to lessen as the interview progressed. Focus groups may have provided a greater and more explorative narrative from GPs through the sharing of their experiences that this method approach allows (Ritchie and Lewis, 2003). However, logistics and budget restrictions made conducting focus groups across Wales prohibitive. These findings may have benefitted by the use of 'dyads' of GPs and patients in the narrative data collection and analysis. It is possible that this could have enriched the findings through the examination of the similarities and differences between two perspectives

or grouped perspectives. Using dyads, therefore, from prompt and longer journeys may have added to the understanding of how interactions and processes, undertaken in primary care, are different for different interval groups. Theoretically, this may have allowed the identification of factors to reduce delays in primary care intervals. The use of dyads in qualitative data collection and analysis is a developing field (Eisikovits and Koren, 2012). Dyadic analysis has been more commonly used when there is a known relationship between the participants within the dyads. This relationship is reported by researchers to enhance the inquiry (Eisikovits and Koren, 2012; Morgan, et al., 2016). Many dyadic interviews involve interviewing participants at the same time, with debates about the impact of this on developing dialogue within the interview (Eisikovits and Koren, 2012; Morgan, et al., 2016). Ethical issues may occur due to the sharing of information or the disclosing of information between partners within the interview. Additionally, there may be difficulties in the balance of the dialogue if one participant is more dominant than the other, although this can conversely enhance the dialogue in much the same way as focus groups are reported to. These limitations may be overcome by interviewing dyad participants separately and then using dyads within analysis and interpretation. However, where separate interviews are conducted it is recommended that larger cohorts of dyads are recruited and analysed, as this allows triangulation of the results (Eisikovits and Koren, 2012). As the population within this GP interview study was limited by the numbers of participants recruited into the patient interview study, a suitable GP sample was possibly not available to allow dyadic analysis. Additionally, the patient interviews revealed many patients, with reflection on their symptom development in their interviews, reported longer patient and total intervals. This resulted in these journeys, if measured from qualitative data, changing from prompt to median or longer journeys. If dyadic analysis had been performed based on the sampling of interval duration this may have distorted the interpretation. Eisikovits and Koren, (2012) stipulate that dyadic analysis should be implemented in sampling, analysis and interpretation and requires preliminary planning before the inquiry commences.

The GP interviews were linked to the patient interview recruitment (N= 12) (Chapter Five section 5.3.1). This link limited the number of GP interviews to seven due to the early saturation in the patient interview study. It was not possible to ascertain whether theoretical saturation had occurred in the GP interviews as themes after

seven interviews were not repeated, despite the data collected being deep and rich (Seale et al., 1999). Principally, this method of recruitment was devised to allow comparison of the experiences of the patient and their diagnosing GP adding a further dimension to the explanatory sequential research design (Creswell, 2014). However, there is the possibility that more themes could have been identified if further interviews with GPs had been conducted.

The invitation to interviews made to GPs could not be 'tracked' under the methods applied; therefore, it was not possible to access the acceptability or engagement of the overall GP group to the interview study. It is possible 'tracking' could have been achieved had the research network workforce for Wales been engaged in primary care recruitment of GPs, but this was not requested or established at the outset of the study. The recruitment of GPs may have also been improved with the use of a monetary incentive for the GP time in the interview. This was however, not possible within the realms of the scholarship budget. However, the recruitment of seven out of the 11 GPs invited to complete interviews was considered a good response.

As the GP sample groups were linked to the patient sample groups, the GP groups were equally affected by the change in the reporting of the symptom onset date in the patient interviews and the subsequent change in 'journey group' i.e. prompt or longer journey (Chapter Five section 5.4.5). This means that as for the patient participant sample groups, GPs interviewed as 'prompt journey' group participants were possibly not within this group. It may have, therefore, been better to have identified and sampled GPs through measurement of the primary care interval. It is possible that different themes would have emerged from this different sampling method.

The sample group recruited GPs who had previous experiences of diagnosing myeloma and did not capture the experiences of GPs who were yet to experience a diagnosis of myeloma. These GPs may be different in their perception and views but this study is unable to contribute to their understandings. The GPs interviewed were encouraged to talk about their experiences with other patients and also colleagues' experiences of diagnosing myeloma and not restrict their accounts to the patients registered within the study. This possibly added to the richness of data and its authenticity, but it still must be acknowledged that the sample is not representative of all GPs.

The length of recall required by the GPs during interviews was long, ranging from 19–81 weeks. Recall of experiences and interactions from such a long period of time may be challenging and could affect the quality of data collected. Although GPs were encouraged to use medical notes to inform their answers in the interview dialogue, there is the possibility that recall limits the validity of data collected.

6.5.4 Implications for practice

There are recommendations arising from this interview study to help with the suspicion and investigation of myeloma in primary care.

GPs require a better understanding of the symptoms myeloma patients initially present with in primary care to increase the assessment of initial symptoms as sinister or serious. Knowledge transfer of the symptoms reported in the quantitative study (Chapter Four section 4.5.3) can facilitate this. This knowledge transfer will allow GPs to better understand the significance of vague multiple symptoms in early myeloma and, additionally, appreciate the significance of the systemic nature of symptoms. Providing GPs with aide memories on symptoms can specifically help this dissemination and GPs are likely to be receptive to this. Additionally, myeloma should feature in educational programmes for primary care clinicians to facilitate knowledge transfer of the symptoms associated with early disease. These are likely to be best deployed through online training or short hot topic days

Importantly, raising the knowledge of the symptoms of myeloma in GPs is likely to increase the earlier investigation of these in primary care and the identification of the abnormalities that require further investigation or referral to specialist care. GPs need to lower the threshold for initial investigations of the symptoms recognised in the quantitative study (Chapter Four section 4.5.3) and be prepared to broaden their investigations to include myeloma screens and X–rays of symptomatic areas early in the assessment of symptoms. This is of particular relevance in worsening or persistent symptoms and could possibly reduce emergency presentation rates for this patient group (Elliss-Brookes et al., 2012; Chapter Four section 4.5.3). GPs should improve the assessment and investigation of myeloma by following the updated NICE guidance (2016b). It is additionally possible that the overall findings from this study may contribute to further understanding of the pathway of investigations required in response to symptoms for myeloma and inform future NICE guidance. GPs, who receive negative results from the early investigations of

patients who have persistent symptoms, should broaden their diagnostic investigation rather than be reassured by the negative results. The referral to haematology is the optimal referral pathway for patients with myeloma and these changes in practice of threshold lowering and broadening of the clinical investigations are likely to increase referrals via this route.

A formal policy of safety netting by GPs should be included in consultations where vague symptoms are present to encourage the prompt return of the patient and reduce the primary care interval. There are recognised algorithms which may be adopted to facilitate this (Nicholson et al., 2016).

Continuity of care in primary care needs improving through effective record keeping in order to allow greater communication between GPs in the event of repeated consultation. This is imperative for this patient group who have higher consultation rates than other cancers (Lyratzopoulos et al., 2012) and will possibly reduce the number of consultations through notification of persistent symptoms to promote earlier and wider investigation.

Transfer of care to a specialist team able to diagnose myeloma should be the priority for primary care clinicians. The use of the NICE (2016b) referral guidance may also facilitate optimal referral pathways into secondary care to haematology. However, the targeting of referrals to a haematologist relies on abnormalities identified through clinical investigations that GPs can identify as related to myeloma or anaemia or other changes in the blood count. This may be improved by the greater understanding of the early symptoms of myeloma and a lowering of the threshold for investigating these more vague symptoms more broadly, as well as improving communication between primary and secondary care and the maintenance of the GP involvement in the diagnostic process, whilst the patient remains in primary care.

6.5.5 Implications for further research

The impact of the recommendations made from this study require assessment alongside findings within the quantitative and qualitative patient interview studies to allow overall recommendations for the timely diagnosis of myeloma.

The unique and insightful data captured here makes the efforts of collecting data of this nature valuable despite the methodological challenges. The earlier interviewing of GPs following their involvement in a diagnosis of myeloma, as well as GPs who

have no previous experiences, would add further depth to the understanding of the challenges and good practices of GPs in primary care.

6.5.6 Conclusion

This first reporting of the perception and experiences of GPs diagnosing myeloma has led to unique insights into the challenges and difficulties identifying this particular cancer in primary care. The difficulties reported here demonstrate that the process is not straightforward and possibly the longer primary care intervals recorded for myeloma patients in primary care relate to the failure to recognise symptoms of myeloma as sinister and the less timely and vigorous investigation of these symptoms. Essentially, GPs require a better understanding of the early symptoms of myeloma in order to reduced their concurrent thinking with patients that symptoms are not serious and can be 'watched' to see what happens. This requires knowledge dissemination of early symptoms to GPs through educational programmes. GPs should then employ a policy of lowering their thresholds for investigation of these symptoms to aim to identify the underlying disease rather than later disease complications. Identifying the potential underlying disease will allow the prompt and targeted referral to haematology and avoid interdepartmental transfers of myeloma patients and possible longer secondary care and total intervals.

7 Chapter Seven: Diagnostic journeys in myeloma: Synthesis of the quantitative and qualitative findings to provide overall recommendations for the more timely diagnosis of myeloma.

7.1 Summary of the chapter

This final chapter describes the process by which the overall findings from the quantitative and qualitative studies are reviewed and synthesised to provide a consolidated final report of the influences and timing of the diagnostic journeys in myeloma. The chapter first reports the synthesis which is conducted through the review of the quantitate study findings, and consolidation of these with findings from the quantitative studies. This chapter then presents the interpretation gained through the synthesis of all the findings and reports how this informs and answers the research questions. Finally, the chapter reports the recommendations made, from the overall interpretation of the evidence, for healthcare research and policy and practice for the more timely diagnosis of myeloma.

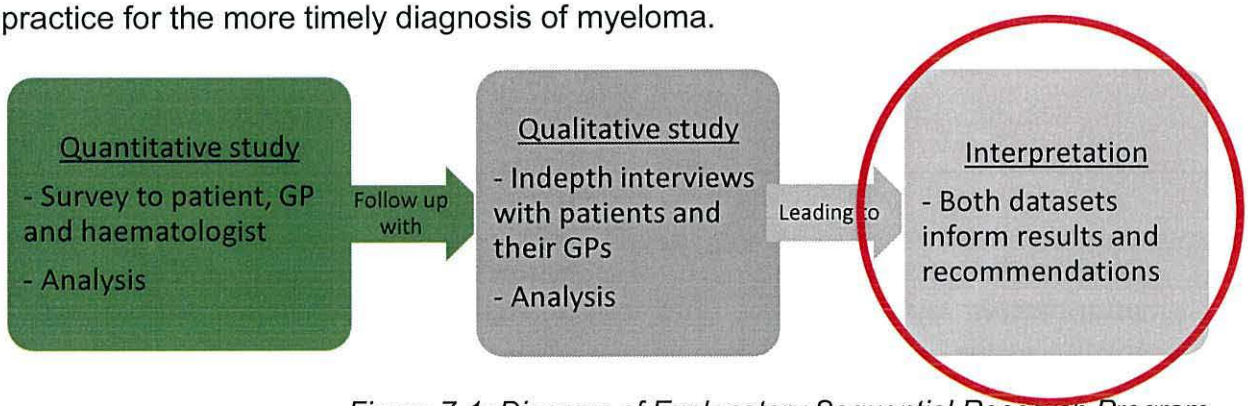

Figure 7-1: Diagram of Explanatory Sequential Research Program

(Adapted from Creswell, 2014)

7.2 Synthesis and interpretation methods

The methods for the synthesis of evidence and production of findings are reported in full in Chapter Three section 3.13.7. Described here is the practical implementation of the methods.

The synthesis reported is a culmination of all the work conducted in this thesis and provides of unique contribution of evidence to the literature on this topic.

In line with the methodological approach, the 'explanatory sequential programme of research' (Creswell, 2014), the synthesis was organised with the intention of integrating the quantitative and qualitative findings to form an overall interpretation of how, where, when and why the journeys to diagnosis in myeloma were altered. This was achieved by following the research designs approach (Creswell, 2014) of reviewing the categorised evidence from the quantitative study (Chapter Four section 4.5) and then exploring the findings from each category by integrating and

consolidating these with the findings from the qualitative studies (Chapters Five section 5.4 and Six section 6.4). The synthesised findings are formed through a thematic analysis of the categorised data, which allows a deep and rich evidence base to be revealed through repeated theme reviewing and analysis across these categories of evidence (Chapter Three section 3.13.7). The themes to emerge from the synthesis, which may confirm or refute the quantitative findings, allow a theory of where, when and why these phenomena affect the journey and allow insights into the consequences of some phenomena to emerge.

Importantly the final stages of thematic analysis produce a synthesis drawn alongside existing knowledge that allows interpretation that can then inform recommendations for healthcare research and policy and practice.

7.3 Results

Synthesis of themed evidence from the quantitative and qualitative studies and interpretation of the effect on the diagnostic journey.

7.3.1 Characteristics of the study population

There were no associations between age and the intervals to diagnosis or treatment recorded in the quantitative study. However, in the interview studies, a phenomenon of 'normalising' the symptoms experienced to ageing was described by both the patient and GP groups. Normalising symptoms to ageing affected the way patients 'made sense' of their symptoms and allowed them to conclude that symptoms were not of concern, and delayed their presentation to a health professional. GPs were also seen to 'normalise' presenting symptoms in their patients to 'ageing'. Therefore, although increasing age was not directly associated with longer intervals to diagnosis, age was used by patients and GPs to rationalise the symptoms present. This explains the long patient and primary care intervals recorded in this study and provides some explanation as to why the patient and primary care intervals in myeloma are longer than other cancer types.

The assessment of the patient perspective within a qualitative approach is novel in myeloma and provides greater understanding and a possible explanation for why the patient interval in this study was longer than any previously measured myeloma patient interval.

No associations were reported in the quantitative or qualitative studies between gender and the intervals to diagnosis or treatment. Gender, therefore, did not appear to affect the journey to diagnosis in myeloma.

No associations between different ethnic groups were reported in the quantitative or observed in the qualitative studies. However, the diversity in ethnic grouping for both the quantitative and qualitative study populations was extremely limited and did not represent the wider myeloma population (ONS, 2011). This study, therefore, was unable to provide evidence of the impact of ethnic grouping on the diagnostic journeys of myeloma patients.

No associations between different deprivation groups and longer intervals to diagnosis and treatment were reported in the quantitative or qualitative studies. Deprivation, therefore, appeared not to affect the length of the journey to diagnosis in myeloma.

No associations were reported between different 'work status' groups and the intervals to diagnosis in myeloma in either the quantitative or qualitative studies. This may mean that work status is unaffected by the length of the intervals to diagnosis. However, the assessment of this factor in the quantitative study was undertaken close to the diagnosis date and may be considered a premature assessment of this factor as the true impact of treatment and the disease may not be apparent until a later stage in the treatment pathway.

7.3.2 Disease characteristics

There were no associations between the intervals of diagnosis and treatment and myeloma disease type or subtype in the quantitative study. Additionally, there was no evidence of differences observed in the qualitative interviews with either patients or GPs. Disease type and subtype appeared not to have associations with the timing of the journey to diagnosis and treatment in myeloma.

There were no associations in the quantitative study between the stage of disease at the diagnosis of myeloma and the length of any interval to diagnosis or treatment. However, a 'progressive' disease state in patients whose journeys to diagnoses were protracted was reported in the qualitative interviews by both patients and GPs. This progressive disease state was associated with increasing symptom numbers and severity and the development of an 'acute' illness. This acute illness led to

unscheduled presentation to secondary care for many patients. This would suggest that longer journeys were associated with increased symptoms, possibly increased disease burden, complications and higher frequency of emergency presentation to secondary care. This provides some explanation for the high levels of emergency presentation in myeloma patients and the long patient, primary care and total intervals seen in this study. However, the evidence did not allow the determination of which part of the total interval length was most affected i.e. the patient or primary care interval.

7.3.3 Pre-diagnostic characteristics of the patient participants

Half of myeloma patients perceived that they had a 'very good' health status in the two years preceding their diagnosis, as reported in the quantitative study. However, a 'poor' health status prior to the diagnosis of myeloma was associated with longer patient and total intervals in regression analysis. This possibly relates to patients not connecting new symptoms with 'ill health' or that the recognition of ill health was masked by pre-existing conditions i.e. multi-morbidities. These findings were generally supported by the patient interviews where patients reported that they remained well prior to their diagnosis, had high levels of functioning and achieved their activities of daily living. The interviews revealed that this feeling of wellbeing led patients to consider that their symptoms were not serious, which contributed to the 'normalising' of these symptoms to normal ageing and a delay in seeking help. The GP interviews similarly reported that patients appeared 'well' during initial consultations, which led to difficulties attributing their symptoms to sinister pathology. This meant that for some patients, with a slow onset of symptoms, this feeling of wellbeing delayed presentation and extended the patient interval. Interestingly, the perception of 'wellness' in patients by their consulting GP had a similar effect, which possibly contributed to the long primary care intervals seen for myeloma. It is possible that this is a particular nuance in the help-seeking of myeloma patients and contributes to the difference seen in myeloma primary care intervals when compared to other cancer types.

Half of myeloma patients reported taking analgesia in a response to their symptoms prior to their diagnosis in the quantitative study. It was not possible to determine whether this analgesia was self-administered or prescribed by their GPs. However, over a third of patients took moderate or strong opioids that are prescription only

medications. In the interviews, patients reported that they felt 'well' before their diagnosis even though pain was frequently reported which required intervention. GPs similarly reported in interviews that pain was a frequent presenting symptom in primary care and analgesia was frequently prescribed to relieve pain prior to a diagnosis being made. Additionally, the interviews revealed that the prescription of analgesia by their GPs occurred prior to the investigation of these symptoms. This may have masked patients' symptoms and delayed the investigation of the myeloma. This would support that the assessment of pain by both patients and GPs contribute to lengthening the patient and primary care intervals and adds understanding as to why there are longer intervals for myeloma, demonstrated in this study when compared to other cancer types.

7.3.4 Multi-morbidities

The quantitative study demonstrated a wide range of multi-morbidities in the myeloma patients. Only one-third of the myeloma patients had no multi-morbidities and over half the patients had one or two multi-morbidities before the diagnosis was made. In the correlation and regression analyses, no associations were recorded between the number, presence or type of multi-morbidities and the longer intervals to diagnosis or treatment. However, in the qualitative interviews, GPs confirmed the range and prevalence of multi-morbidities in their patients, and that their presence hindered their ability to attribute the presenting symptoms to a serious cause such as myeloma. Possibly, GPs blame the presence of multi-morbidities on failing to recognise symptoms as serious when they reflect on the diagnostic process, but these do not actually interfere with the recognition of symptom seriousness and, therefore, are not responsible for the lengthened primary care intervals but rather the long intervals in myeloma are a result of other factors.

7.3.5 Symptoms

As reported in the quantitative study, multiple and varied symptoms were present in myeloma patients prior to their diagnosis. Only a small percentage of participants were diagnosed in the absence of symptoms, therefore, the majority of patients with myeloma experience symptoms prior to a diagnosis. Between one and seven individual symptoms were present in patients prior to their diagnosis and, in correlation, analysis associations were recorded between the number of symptoms experienced and longer primary care intervals. Although a wide range of symptoms were reported, 10% of the patients reported experiencing seven of these 39 different

symptoms and 50% reported experiencing three of these. The most frequently presented symptoms prior to the diagnosis of myeloma were pain in muscles and joints, fatigue and bone pain. Although the majority of patients had one of these three symptoms, they were more likely to report two or three of these than single symptoms. This was also confirmed in patient and GP interviews with both groups recounting multiple and varied symptoms occurring at high levels. The synthesised findings clearly demonstrate how varied the pre-diagnostic symptoms are in myeloma but the qualitative findings add to the understanding of how these variations in symptoms contributed to the difficulty of attributing these symptoms as serious. Ultimately, this can delay help-seeking and lengthen the patient interval, but may also contribute to longer primary care intervals.

From the quantitative data, the most frequently reported presenting symptom in myeloma was a pain, but the pain varied in type and location. In patients who reported pain as a first symptom, only a third reported having back pain specifically. The interviews with patients and GPs confirmed that pain was frequently present prior to the diagnosis, but did not provide insights as to whether pain was the first symptom experienced.

GPs reported that they focused their attention on back pain as the identifying 'alert' symptom in myeloma, but that they had less appreciation of fatigue as a presenting symptom. Interestingly, the GPs interviewed reported that they felt that they had a good knowledge of myeloma symptoms. Possibly, the difficulty GPs had assessing symptoms and recognising them as sinister could partially be explained by this knowledge gap. This provides further insights into why the identification of symptoms is difficult and an understanding of how this contributes to longer primary care intervals seen in myeloma.

The patient interviews supported the quantitative reporting that patients had frequent symptoms of pain and fatigue prior to a diagnosis but added that patients failed to recognise that these symptoms were serious or related to myeloma. This was partly explained by the very low level of awareness of myeloma and an inability to recognise that the symptoms experienced were related to the disease. This low level of awareness of the symptoms was exemplified by patients seeking clarification of the symptoms of myeloma during the qualitative interviews. The lack of awareness and inability to link symptoms with myeloma contributed to patients' attribution of

symptoms to the normal ageing process. The interviews also demonstrated that normalisation was contributed to by a lack of 'candidacy' or 'risk awareness' for myeloma, which was again rooted in the low awareness of the disease. All of these factors provide explanation for the increased patient and total intervals measured in myeloma. The low awareness seen particularly in this disease may also provide an explanation as to why patient intervals in myeloma were longer when compared with other cancer types.

The interviews with patients also revealed that patients had had symptoms for longer than expected. The process of reflection on their symptoms during interviews may have enhanced patients' abilities to recognise their pre-diagnostic symptoms and symptom onset date. This meant that the intervals to diagnosis were possibly longer than reported in the quantitative study but supports that there is an opportunity for earlier recognition of the disease and, therefore, earlier diagnosis. Additionally, this possibly supports the positive impact that greater awareness of myeloma could have on the better recognition of symptoms in patients which could potentially improve the patient interval.

GP and patient interviews provided an understanding of the consequences of the vague symptoms experienced in myeloma. Patients reported that they had difficulty presenting their symptoms in a meaningful way because they found these symptoms difficult to quantify or explain as they perceived these as not serious in nature. This then failed to prompt a response of 'concern' from the GP and led to a more conservative response which delayed the investigation of the symptoms and a 'watch and wait' approach. This 'watch and wait' policy provides an explanation for the extended primary care intervals and larger number of GP consultations associated with the diagnosis of myeloma.

The interviews reported that patients initially had 'low level' symptoms in myeloma and this confounded the early assessment of symptoms as serious. Patients, and to a lesser degree GPs, disclosed that these early lower level symptoms progressed when the identification of sinister pathology or myeloma was not made. What was then described by the patients, in interviews, was an 'accelerated' progression of symptoms. Symptoms became more severe and debility more obvious and this affected the patients' functional abilities. This 'accelerated' state of disease was linked by patients to the development of an acute disease state and resulted in help-

seeking via an 'urgent' unscheduled route. This increase in symptoms and acute illness with unscheduled access is possibly a consequence of the longer patient intervals where assessment of symptoms is prolonged, help-seeking delayed which allowed symptoms to progress over time. A similar symptom assessment occurred in primary care by GPs who reported assessing lower level symptoms as 'not serious'. This provides explanation for the higher levels of unscheduled access to secondary care, the higher frequency of GP consultation prior to unscheduled emergency presentation and the longer primary care intervals witnessed in this and other studies.

The interview studies reported that lay carers concurred with patients' assessments of symptoms as not serious. This extended the patient interval as lay carers reported that they encouraged tolerance of the symptoms in patients by not providing 'prompts' to seek help.

7.3.6 Consultation in primary care

Between 15% and 20% of myeloma patients did not seek help prior to their diagnosis, as reported in the quantitative study. Although there was a difference in the range of presentation reported in the patient and GP data, it was not too dissimilar. In patients who did seek help, one-quarter did so promptly within two weeks of their decision to present their symptoms. Nearly two-thirds waited longer than three weeks to seek help and a smaller number, 12%, waited for six months or longer. Patients in the interview sample group in the majority reported they did 'help-seek' and therefore were supportive of the high levels of help-seeking reported in the quantitative study. Regression analysis demonstrated that two factors were associated with delayed help-seeking behaviour and longer patient intervals: having a poor health status in the two years preceding a diagnosis; and not taking analgesia prior to the diagnosis. These factors in regression analysis possibly indicate that having a pre-existing health condition or multi-morbidities masked symptoms and delayed the presentation of the patient. In the interviews, the appraisal of symptoms was explored further and revealed that help-seeking was hampered by normalising symptoms to the ageing process which was rooted in a failure to identify the symptoms as serious. Patients had no awareness of myeloma symptoms and there was a 'disconnect' between the disease and their symptoms. Patients had real difficulties identifying that their early symptoms were serious and required

presentation to a health professional. This then provides an explanation for the extended patient and total interval.

The quantitative study reported that Welsh GPs provided timely appointments following a request for consultation, with three-quarters of patients having had appointments within a week of deciding to seek help. However, patients' interview narratives reported difficulty accessing primary care, especially when requesting home visits and arranging appointments. The evidence from the quantitative and qualitative evidence is contradictory, and it is uncertain whether access to primary care contributed to longer primary care intervals measured from the quantitative study and the higher frequency of GP consultations for the myeloma patient.

The quantitative data demonstrated that myeloma patients, who presented to their GP, had a median of three consultations prior to a referral or emergency presentation to secondary care. Additionally, higher numbers of consultations were associated with longer primary care intervals in the correlation analysis. In the regression models, the number of consultations was not a statistically significant variable for longer intervals, but the number of different GPs seen within these consultations was. This suggests that the loss of continuity of care was important within these multiple consultations. The interview studies with both patient and GP groups confirmed that multiple consultations occurred with many different GPs. Patients stated that this caused confusion and led to the need for repeated presentations to primary care. However, the GP interviews revealed an 'expectation' and 'acceptance' that patients who experienced these vague symptoms required repeat and multiple consultations before investigation or referral, and this inevitably led to many GPs assessing symptoms. The GP interviews also reported different perceptions of the effect of a 'loss in the continuity of care' in GP consultations. Some GPs reported that 'familiarity' with patients was useful for recognising a changing symptom profile, whist others saw 'familiarity' as a barrier to the assessment of symptom seriousness. The overall evidence suggested that multiple consultations extended the primary care interval, as did the greater the number of different GPs seen within these consultations. Therefore, continuity in consultations is likely to contribute to the increased intervals to diagnosis and treatment in myeloma and this possibly provides some explanation for the difference in myeloma than other cancer types' intervals.

The quantitative study reported that although the majority of myeloma patients presented to primary care (83%), a small proportion (13%) made visits to allied health professionals, such as osteopaths or chiropractors. This was supported by the patient interview narratives. GPs were the health professional most likely to see the patient in the early stage of their disease and, therefore, they were the health professional most likely be able to identify the disease early. Even when patients went on to present to secondary care as an emergency the quantitative data demonstrated that the vast majority had first presented their symptoms to primary care, which was also confirmed by the patient narratives in the qualitative interviews. This meant that there were missed opportunities in primary care to identify myeloma earlier.

The quantitative study demonstrated that there was increased use of primary care in the six months preceding a diagnosis of myeloma. The patient interviews were also supportive of this increase in access before the diagnosis but added understanding that this related to symptom progression nearer to the date of the diagnosis. Therefore, it was likely that myeloma patients had clusters of consultations which started to increase in the six months prior to a diagnosis. This means that there is an opportunity for GPs to increase suspicion when there are clustered consultations in primary care.

Poor safety netting practices contributed to longer primary care pathways as reported in both the patient and GP interviews. This was not assessed within the quantitative study but was a theme which emerged from the qualitative work. Patients reported that they failed to return to their GP because they felt either reassured by the GP assessment of their symptoms as not sinister, they were not prompted to return via a formal safety netting process or they failed to understand the requirement of a repeat a consultation. This failure to repeat the consultation occurred even when the progression of symptoms was accelerating, or new symptoms developed. The GP interviews confirmed that formal safety netting procedures in primary care for this group of patients were generally absent, and the decision to return for a further consultation was left to the individual patient.

7.3.7 Investigation in primary care

Around three-quarters of patients had an investigation in primary care in response to their symptoms. The quantitative data demonstrated that the type of test performed

varied, but that GPs most frequently performed a FBC (68%). The GP interviews confirmed there were variations in investigations with GPs stating this occurred because they have no specific 'workup' model to prompt their decision making. GPs confirmed the FBC was a 'screening' activity that was primarily undertaken to determine if an abnormality was present that might lead to a diagnosis. Therefore, a differential diagnosis of myeloma was unlikely to occur when these initial investigations did not include myeloma specific tests. Myeloma specific tests of SPE, SFLC/BJP were performed in only half the patients in primary care, and x-rays of symptomatic areas in just under half with a physical examination of patients being carried out in only a quarter. The GP interviews offered explanations for these lower levels of myeloma specific investigations, revealing this was related to a low level of suspicion of myeloma. GPs in interviews provided no explanation as to why physical examinations were performed at such low levels. GPs also stated that they had high thresholds for commencing investigations in this group of patients, as was confirmed by the quantitative data, and said that this was related to the vagueness of the symptoms presented to them and the interpretation that vague symptoms were not serious. The non-specific nature of these symptoms lowered the suspicion of sinister pathology by GPs and encouraged the adoption of polices such as 'watch and wait' before investigations were commenced. Overall, the combined findings found a relatively low level of investigation of myeloma patients in primary care, which was related to the use of 'watch and wait' strategies employed when symptoms did not arouse suspicion in GP assessments. Additionally, when tests were initiated they were not specific for myeloma, but instead looked to identify the complications of the disease. This meant that patients had to have a high burden of disease, causing substantial related organ and tissue damage (ROTI) before myeloma was suspected and investigated. All of these factors can be seen to increase the primary care interval and provide an explanation for the longer intervals measured in this study. Additionally, these factors possibly demonstrate a difference between the investigations of myeloma in primary care compared to other cancer types and, therefore, provides reasons for the differences between intervals measured for myeloma and other cancer types.

The quantitative study reported there were variances in the level of abnormalities recorded from the individual investigations performed in primary care. When SPE

was performed, a higher abnormality rate was observed with over 90% of tests positive for a paraprotein. When the tests ESR, FBC and SFLC/BJP were performed, about half the tests were reported as abnormal. Therefore, the identification or suspicion of myeloma is more likely to occur through the testing of SPE in primary care. However, the GP narratives revealed that negative tests had consequences for the diagnostic journey. GPs stated that they were reassured by the negative test results and assumed that no sinister pathology was present and that this delayed or stopped further or wider investigation. This explained the low levels of repeat investigations reported in the quantitative study, with only a third of myeloma patients having repeat investigations. Additionally, the GPs reported that they considered it necessary to have abnormal investigations to prompt and target the referral into specialist care. So, referral into secondary care was prompted by an abnormal investigation in myeloma patients, but the level of repeat testing was low.

7.3.8 GP experience

Overall, the quantitative study reported that the Welsh GPs involved in this study were experienced, with a median of ten years in practice. Despite this, these GPs had seen relatively few cases of myeloma in their practice, with a median of four cases. Neither years in practice nor the number of cases previously seen were associated with longer intervals to diagnosis in the correlation analysis. Regression analysis of these variables was not possible as the number of variables collected were too few to create a model. However, the interviews with GPs supported the quantitative findings that myeloma was infrequently seen by individual GPs in primary care. The GPs perceived that their experience and expertise was important when assessing symptoms and managing or monitoring these in myeloma. There was little evidence for the use of guidance in the clinical practice of GPs, with some GPs acknowledging that their practice was directed by their own clinical experience. However, GPs felt that they were doing a good job identifying pathology and referring their patients to specialist care. GPs demonstrated in these interviews little comprehension of how they could make improvements in their management of myeloma patients. Although the number of years' experience of the GP did not contribute to the regression models, there was evidence from the qualitative study that experience did contribute to decision making and management practices. It was also obvious that the use of guidance did not influence the GP in their decision

making in myeloma, quite possibly because in order to use guidance the GP must first suspect myeloma.

7.3.9 Referral to secondary care

The quantitative study demonstrated that there were varied patterns of referrals made by GPs into secondary care for myeloma patients. Regression analysis confirmed that referrals made to many of the different teams were associated with longer intervals. Perhaps surprisingly, regression analysis did not demonstrate that a haematology referral was associated with prompt diagnostic intervals. Possibly this relates to a few variant cases with atypical presentations that required additional tests, such as bone biopsy, resulting in lengthened diagnostic intervals. The type of referral into secondary care made by GPs varied. 'Urgent suspected cancer' referral was the most frequent referral type, but this was used for less than half the patients. 'Emergency admission' was the next most frequent referral route and used in nearly 20% of patients, a 'less urgent' referral, where cancer was raised as a possibility and 'no referral' was seen in 13% of patients. The combined data in the quantitative study demonstrated that secondary care referral with a cancer 'tag' was made in just over half the study population and was associated with more prompt intervals to diagnosis in regression analysis. The GP interviews provided some explanation for the variances recorded in the referral practices reported with GPs reporting referrals were influenced by a failure to suspect myeloma or sinister pathology which resulted in the initiation of less urgent pathways into secondary care. Longer secondary care and diagnostic intervals are likely to be the result of the urgent suspected cancer pathways not being activated in myeloma.

The quantitative data demonstrated myeloma patients were referred to a variety of different teams. Just over half the myeloma patients were referred directly to haematology, but apart from this 14 different teams received referrals for 25 participants. Additionally, nine percent of myeloma patients received referrals to more than one team. The interviews with patients confirmed this varied referral pattern and additionally reported these referrals led to a perceived 'chaotic' and 'confusing' pathway. The GP interviews explained that the referrals to a variety of different teams were the result of a low level of suspicion of myeloma in primary care. The interviews with GPs also revealed that referrals were targeted to speciality teams based on the clinical abnormalities identified by the GP in their investigations

of symptoms. The low use of investigations likely to identify myeloma, therefore, resulted in the referral being targeted to teams other than haematology. This provided further explanation for the lengthened secondary care, diagnostic and total intervals.

The interviews with patients and GPs further added an appreciation that both groups become distanced in the process of diagnosis once the referral has been made to secondary care. Patients perceived that GPs 'passed over' their care and failed to follow up or contribute to their future primary care management whilst they were waiting for the diagnostic journey to progress. This possibly extended the primary care interval as developing symptoms or a worsening clinical condition of the patients was not 'picked up' and no changes were made to the status of referrals into secondary care.

In both the GP and patient interviews a loss of communication between hospital and primary care was reported and perceived as lengthening the journey duration.

7.3.10 Secondary care pathways

The quantitative study's secondary care data allowed a more complete reporting of the secondary care pathway due to higher returns of the haematologists' questionnaires. In regression analysis, associations between the referrals from either GPs or haematologists and longer intervals to diagnosis were found for multiple different intervals across the pathway. The quantitative data additionally demonstrated that three-quarters of myeloma patients were referred into secondary care from a GP which agreed with the findings from the primary care data. There was a discrepancy between the datasets of patient and secondary care reporting of the frequency of emergency presentation. Patient data reported emergency presentation in a quarter of myeloma patients, whilst secondary care data reported a lower level of 10%. This discrepancy may relate to the way the information was collected from haematologists about the referrals made to them. The question formatting did not allow the collection of data to demonstrate a referral process which involved a referral initially to another speciality team then onto a second team and then finally to haematology i.e. first referral to emergency department followed by an onward referral to orthopaedics followed by a referral to haematology. It is likely, therefore, that the patient data demonstrates a better appreciation of the frequency of emergency presentation to secondary care of myeloma patients.

This emergency presentation to secondary care in both the patient and GP interviews was discussed alongside protracted journeys where a suspicion of myeloma or serious disease was not made. A consequence of progressive symptoms and the development of acute illness in patients was evident. The qualitative data, therefore, provided an explanation for the occurrence and frequency of emergency presentation rooted in the failure of both the GP and the patient to identify symptoms as serious and the development of acute illness.

The quantitative data demonstrated multiple interactions between teams in the secondary care interval in myeloma journeys. Eighteen different departments had interactions for 83 patients. In regression analysis, multiple teams had interactions in the diagnostic journey that were associated with longer intervals to diagnosis across the total journey. GPs referred just under half the patients directly to haematology and, therefore, only one interaction occurred for half the myeloma patients. The further analysis of the quantitative data identified the teams or departments, other than haematology, most frequently involved in the diagnosis of myeloma, which were unscheduled care (including the emergency department and acute services presentation) (26%); the laboratory (19%); orthopaedics (17%) and; renal medicine (11%). A large number of interactions, therefore, occurred for this patient group in secondary care with a total of 110 recorded interactions for 83 participants. These multiple non-specific referral patterns in patient interviews were linked with chaotic and frustrating pathways into and through secondary care. The more teams and interactions involved in the process the more chaotic and confusing the process was reported to be. GPs who referred directly to haematology reported clearer pathways, had confidence in a prompt diagnosis and reported no difficulties with system failures, with referrals being promptly actioned. GPs who referred via other teams discussed having more convoluted pathways to diagnosis. These haphazard referral pathways for half the patients with myeloma contributed to the lengthened secondary care and total intervals demonstrated in this study.

The quantitative data demonstrated that the majority of participants who received a direct referral to haematology were investigated with SPE in primary care (76%), and in the interviews, GPs reported that this referral to haematology was promoted by a suspicion of myeloma or another haematological abnormality. The use of SPE of

serum or urine in primary care is then likely to identify the disease myeloma and encourage the optimal referral of the myeloma patient to haematology.

7.3.11 Diagnostic testing in secondary care

Testing for a definitive diagnosis of myeloma in secondary care in the majority of cases was completed by haematologists in line with criteria for diagnosis in national and local guidelines (Bird et al., 2011; Sati et al., 2011). However, there were a few exceptions to this, with lower levels of bone marrow trephine biopsies (96%); SFLC/BJP (95%); $Beta_2$ microglobulin (85%) and cytogenetic risk assessment (32%). It is possible that the slightly lower levels of bone marrow trephines and SFLC/BJP recorded were due to patients who were under surveillance with previously defined paraproteins and during the progression of the disease to symptomatic myeloma these tests were not considered clinically relevant and were not repeated. The lower level of $Beta_2$ microglobulin assessment was possibly more significant as it meant that the stage of disease at diagnosis was not measured and was incomplete for 15% of patients. The very low levels of cytogenetic analysis demonstrated that this analysis was poorly assessed in Welsh patients and would not have contributed to the assessment of prognosis and risk in these patients at diagnosis. In the GP interviews, some GPs reflected that the tests for making a diagnosis of myeloma are in the domain of haematology and they were not equipped to contribute to this process. The patient interviews revealed that patients had little understanding of the processes involved in diagnostic testing or staging of their disease, possibly this was linked to the low awareness more generally of myeloma as a disease. However, there were no associations in the regression analyses between the absence of diagnostic tests and increased intervals of secondary care, diagnostic, time to diagnosis, treatment or total interval. Overall, the testing to make a definitive diagnosis of myeloma, performed in secondary care, did not affect the intervals to diagnosis and treatment for myeloma patients. There were some considerations to be made for missing tests and the failure to adhere to guidance more generally, but these did not seem to contribute to the diagnostic journey length and so are less relevant to this study. It was also interesting that GPs saw the diagnostic testing for myeloma as a secondary care responsibility and this may, in part, explain the low levels of testing in primary care with tests that specifically look to identify myeloma i.e. SPE or SFLC/JP or X-rays of symptomatic areas.

7.4 Criteria for treatment: proxy for burden of disease

The complications most frequently reported in the newly diagnosed myeloma patient were demonstrated in the quantitative data and used as a proxy for disease burden. Lytic bone lesions or compression fractures were the most frequently occurring complications and were present in three-quarters of patients; anaemia occurred in just over half the patients; renal impairment and hypercalcaemia in just under a quarter. These factors were, possibly surprisingly, not associated in regression analysis with longer intervals to diagnosis. However, in GP interviews these factors were the focus of GPs' clinical investigations in order to identify or rule out myeloma through investigations such as FBC, U&Es and X-rays. These tests, as previously discussed, were performed at low levels in primary care. Given that these investigations were performed at low levels and the complications they aimed to identify were varied and occurred at different frequencies, it would appear that the chances of identifying myeloma through a single clinical investigation in primary care were low. In the patient interviews, the occurrence of bone fractures and hypercalcaemia were discussed as late presenting symptoms and associated with the 'accelerated' phase or progression of symptoms and acute illness. It is likely, therefore, that GPs were identifying more advanced stage myeloma when using these non-specific investigations and this would mean they could possibly identify earlier stage disease by using SPE and SFLC/BJP. This provides a possible explanation for the longer primary care intervals and higher frequency of emergency presentations seen for myeloma patients.

7.5 Treatment

Haematologists base their decision to treat on multiple parameters in the individual patient, as demonstrated by the quantitative data. Decisions on the choice of treatment initiated in myeloma patients were most frequently influenced by age (90%), disease burden (53%) and the presence of multi-morbidities (41%). These factors showed no association with longer intervals to diagnosis in the regression analyses. In the patient interviews, discussions about the choice of treatment initiated by the treating haematologist did not enter the dialogue. No additional information was gained regarding influences for treatment choice from the GP interviews. The findings did not support decisions on the intensity of treatment pathway initiated was influenced by the length of the journey. However, it is likely that longer intervals were associated with a greater number of complications at

diagnosis and a higher disease burden. These factors were indeed considered influential in the choice of treatment initiated and it is possible that longer journeys affect treatment choice via this indirect route.

7.5.1 Clinical trial activity

Two-thirds of Welsh myeloma patients were considered for participation in clinical treatment trials in secondary care, as demonstrated in the quantitative data. Just under half of these patients entered clinical treatment trials, which overall demonstrated a good level of research activity for myeloma patients in Wales. There were no associations between participation in a clinical trial and the intervals to diagnosis or treatment in regression analysis. Participation in clinical trials did not enter into the dialogue with patients in the interviews in relation to their diagnostic journey. From the quantitative study, there was no evidence to support entering or not entering a clinical study was associated with prompt or longer diagnostic journeys.

7.5.2 Response to treatment

The assessment of the 'response to treatment' in patients following induction therapy from the quantitative study was limited by the early assessment of the diagnostic journeys from the haematologists' questionnaires. However, from the recorded data available, the largest proportion of response groups was 'very good partial response' (43%); followed by 'complete response' (22%); 'partial response' (22%); 'progressive disease' (9%) and; 'minor response' (4.3%). These categories show no associations in the regression analysis for longer intervals to diagnosis or treatment. At this early stage of analysis, this possibly supports that the response to first line treatment is not affected by the length of the diagnostic journey. Neither GPs nor patients discussed this 'response to treatment' in relation to the diagnostic journey experienced. In the patient interviews, only one participant had progressive disease and was in a palliative stage of their treatment. The patient interviews, therefore, in the majority, were conducted with patients whose perception and experiences were gained when treatment was either ongoing or they were in a 'first-remission' and possibly their views and experiences were quite positive.

7.5.3 Survival analysis

It is too premature to assess how the length of the diagnostic journeys and the interim intervals affect the survival of myeloma patients. Data on survival at the time of writing this thesis was limited. I intend to continue to collect survival data on study

participants until the point of predicted median overall survival, which is five years following diagnosis.

7.6 Discussion

7.6.1 Summary of the main findings

The findings from this programme of research have allowed an in-depth description of the entire diagnostic journey of newly diagnosed myeloma patients in Wales. For the first time, combining research findings from both the quantitative and qualitative studies has provided possible explanations for why the observed measurements in the quantified journey occur. This has greatly added to the depth of knowledge regarding diagnosing myeloma and how to contribute to more timely diagnostic journeys.

The results from this study demonstrate that a journey to a diagnosis of myeloma is highly complex and easily affected by behavioural factors, interactions within the journey and the pathways initiated. Additionally, for the first time, the study has demonstrated that these influences may affect all of the intervals within the total journey to diagnosis and treatment. No single factor or interval is responsible for the longer journey observed in myeloma.

The patient interval in myeloma was longer because patients considered that their early symptoms were not serious and therefore delayed presenting these symptoms to their GP. Multiple factors were responsible for this appraisal. A low level of awareness of myeloma in the general public meant symptoms were unknown to patients and their 'carers' and these symptoms of myeloma could not be associated with a need to seek help. Poor cancer candidacy contributed to patients being unable to associate their symptoms with a potential cancer diagnosis. Delayed help-seeking occurred when patients had poor health, which possibly included the presence of multi-morbidities being blamed for symptoms. Symptoms were also possibly masked by taking analgesia. Patients 'made sense' of their symptoms and concluded that they related to a natural ageing process which occurred irrespective of their age. Initial access into primary care does not appear to extend the patient interval as this appears timely and it is more likely, therefore, behavioural and contextual issues are responsible for long patient intervals in myeloma rather than service issues.

The primary care interval in myeloma was also affected by multiple factors. Patients with symptoms of myeloma did present to primary care once they judged their symptoms required assessment. However, the continued assessment of symptoms as 'non-serious' by GPs in consultations extended this interval. This was contributed to by patients being unable to present their vague symptoms in a meaningful way and GPs thinking they had a good knowledge of the symptoms of myeloma but were focused on back pain as the 'alert' symptom to prompt suspicion and therefore intervention. Multi-morbidities possibly also contributed to the appraisal of symptoms as not serious, as GPs attributed symptoms to other diseases.

The continued assessment of symptoms as 'not sinister' in primary care had a number of consequences on the diagnostic journey and the primary care interval. Firstly, GPs used time as a diagnostic tool to monitor symptoms which increased the time the patient spent in the primary care domain but failed to implement good safety netting practices and timely repeat presentation of the patient did not occur. This allowed progression of symptoms and possibly increased disease burden. Repeated consultations were then required before a referral to secondary care was made. Higher threshold for commencing diagnostic testing occurred in response to symptoms being assessed as not sinister and GPs' ordered non-specific investigations, which failed to identify the underlying myeloma, but rather relied on identifying organ and tissue damage associated with increased disease burden.

The secondary care interval was disrupted in a number of ways, and it was clear that there was an optimal and sub-optimal route of access to secondary care for the myeloma patient. A significant amount of myeloma patients entered secondary care through an emergency presentation and this appeared to be related to extended patient and primary care intervals, increasing symptoms and the development of acute illness. Presentation of the patient as an emergency invariably occurred after a previous presentation and consultation with their GP in primary care, which represented a potential missed opportunity.

When referrals were not made directly to haematology, multiple teams became involved in patients' care with associated longer intervals and chaotic diagnostic journeys. These routes of referrals were sanctioned following a failure to suspect and identify the underlying disease through symptoms not being recognised as serious.

7.6.2 Findings in the context of the literature

The findings in chapters Four (section 4.5), Five (section 5.4) and Six (section 6.4) have already been compared with the previous literature in the discussion sections of each chapter. The discussion in this section is limited to comparing the synthesised findings presented in this chapter with previous literature.

A small number of studies were identified that have used mixed methods to report diagnostic journeys in other cancer types. None of these had used the explanatory sequential research approach.

The complex system of symptom appraisal observed for myeloma patients was similar to that found by Emery et al. (2013), where the vagueness of symptoms, poor risk awareness and alternative explanations were associated with longer help-seeking intervals in breast, lung, prostate and colorectal cancer. This was also supported by a study in testicular cancer (Chapple, et al., 2004). Men diagnosed with testicular cancer who experienced vague symptoms or a 'fear' factor, had longer help-seeking intervals. However, in myeloma there was less influence from personality traits, such as stoicism, fewer competing demands of work and no 'fear' factor relating to a cancer diagnosis. This is possibly because myeloma patients fail to identify the myeloma symptoms as serious. In testicular cancer, observations of tangible symptoms, such as lumps or swelling, were associated with men presenting quickly. On the other hand, men who experienced 'patient delay' discussed 'feeling well' and 'not being in pain', delayed seeking help (Chapple, et al., 2004). In myeloma, longer intervals were associated with an absence of tangible symptoms, such as a lump or swelling, or generally feeling well during the pre-diagnostic period.

In testicular cancer (Chapple, et al., 2004) men interviewed discussed media publicity and public health information, relating to testicular cancer, influencing the promptness of their presentation. This was in sharp contrast with the myeloma patient group. In myeloma, this study demonstrated that knowledge and awareness of the symptoms and the disease were so low that this clearly influenced the perceived need to present to a health professional.

The benefits of lay prompts have been reported in studies assessing help-seeking in men with prostate and testicular cancer (Place et al., 2011; Chapple, et al., 2004). In these cancers, men reported seeking help following prompts from family or friends. In myeloma, help-seeking prompts from carers were rare in the early development of

symptoms, as carers appraised symptoms in a similar 'non-serious' manner to patients. The consequence of this was further delays in presenting the symptoms experienced in patients to a health professional. In an international comparative interview study across three countries (England, Denmark and Sweden), which recruited patients with lung or bowel cancer, delays were reported due to missing lay prompts. This study reported that carers delayed prompts until they recognised changes in the daily activities of their relatives. This, in turn, delayed help-seeking (MacArtney, et al., 2017). The observations of carer prompts in these cancers support the findings in myeloma. However, in the myeloma population the changes in daily activities were seen to be quite late, occurring when a more advanced disease stage was present. This is different from other cancer types and may be responsible for the higher acute presentation rate of myeloma patients.

In testicular cancer, prompt help-seeking was associated with a greater knowledge and greater cancer candidacy (Chapple, et al., 2004). This was also supported by the international comparative study of lung and bowel cancer (MacArtney, et al. 2017). In myeloma, very low levels of awareness led to a reduced cancer candidacy or risk assessment which in turn led to delayed help-seeking.

MacArtney, et al. (2017) reported that in lung and bowel cancer the journey through primary care may be altered by service difficulties. Patients in England and Denmark, but generally not in Sweden, discussed difficulties accessing their GP 'putting them off' presenting. In myeloma, the patient interview study supported these perceived difficulties with access. However, the quantitative data reported the access to primary care was good with reasonable response times. Additionally, McCartney, et al. (2017) reported that unclear safety netting and planning affected the progression through primary care in lung and bowel cancers. This was seen to be similar to the myeloma findings. Another parallel between the lung and bowel study to the myeloma study was the reassurance given by primary health care providers which resulted in patients putting up with their symptoms for longer. In myeloma, this concurrence between patients and GPs led both parties to assess symptoms as not serious which delayed the commencement of investigations. MacArtney, et al. (2017) reported in all three countries studied that lung and bowel cancer patients had repeated consultations with their primary health care provider before onward referral was made. This was confirmed by this myeloma study through observations in both

the quantitative and qualitative data. The quantitative data, however, further clarified a higher level of repeated consultations for myeloma patients which confirmed findings reported by Lyratzopoulos, et al. (2012).

The behavioural and contextual influences described in this study draw some parallels and stark contrasts with the processes described by psychological theories of health behaviour (Scott, et al., 2013). There was a clear demonstration in the myeloma qualitative findings of an initial assessment of symptoms by patients as described by Leventhal's Common Sense Theory (CST) (Scott, et al., 2013). Here, when bodily symptoms are expected or do not change the activity of the individual's life, symptoms are dismissed as not serious and are normalised to other factors. This was frequently seen in the myeloma patients, as normalisation to ageing was reported across the group. Other heuristic influences in the CST that affect the interpretation of the symptoms experienced are the severity, location, duration, novelty, rate of change and pattern of symptoms. In myeloma, the evidence from this study suggests that these factors are different. In myeloma, the interpretation of symptoms as serious is influenced by a lack of awareness of the symptoms of the disease. There is a disconnect between the symptoms that the patient feels and the symptoms that they associate with a pathological illness. Coping is discussed in the CST as a mechanism that affects help-seeking and this may be influenced by the knowledge of the individual. In myeloma, a lack of knowledge reduced the impetus to seek help, as did the experience of symptoms that were 'not of concern'. Importantly, in myeloma, fear did not affect the desire to seek help. In contrast to the CST, a lack of awareness of the disease and its symptoms appeared to guard against fear developing. In the CST, the role of a prompt from a lay person or carer is influential in the decision to seek help. A lay prompt is missing in myeloma and, therefore, self-regulation as part of social context that regulates help seeking behaviour within the CST, is different in myeloma.

Scott, et al. (2013) offers insights from Bandura's Social Cognitive Theory (SCT) into behaviour influencing the appraisal of symptoms and help-seeking. These sometimes resonate with the observations made in this myeloma study but also highlight distinct differences. The SCT discusses self-efficacy in symptom appraisal and help seeking. When patients perceive that they have an inability to explain their symptoms, they delay seeking help. In myeloma, patients had an inability to quantify

or describe their symptoms which influenced help-seeking behaviour. This behaviour was related to symptom vagueness or a low level of disturbance of daily living activities. Additionally, in the SCT, when patients perceive the act of help-seeking as insurmountable the result is a feeling that the service is 'unavailable'. Myeloma patients reported that they found it difficult to portray their symptoms in a meaningful way because they could not make sense of them. This led to them surmising that they should not request a consultation. In the SCT, self-efficacy is disrupted by social–structural constraints, this includes the level of trust between the health professional and the patient, or the previous experiences of the patient, either first hand or via friends and colleagues. In myeloma, there were parallels with these phenomena. Trust and respect in health care professionals were commonly reported as barriers to prompt myeloma diagnostic processes and previous poor experiences resonated with reluctance to engage with health care. In the SCT, negative physical outcome expectations, such as painful procedures or suffering, reduce patients' incentive to seek help. In myeloma there were no expectations of suffering painful tests or a fear of dying. Additionally, patients did not consider the consequences of a cancer diagnosis affecting their 'life schedule'. In the SCT, negative social outcome expectations, such as being perceived as a time waster, also reduces incentives to seek help which was seen in the myeloma group. Symptoms considered to be minor or related to a non-serious illness resulted in not seeking help in both myeloma patients and within the SCT. The SCT discussed lay prompts that direct individuals to avoid seeking help and offer reassurance that symptoms are serious. In myeloma, patients and carers labelled myeloma symptoms as being due to ageing. Negative outcome expectancies such as lack of self-worth, threat to pride or independence reduces help-seeking. In myeloma, there was no evidence of this.

Overall, findings from this study supported the many publications which reported that the diagnosis of myeloma was difficult and related to symptoms being non-specific and vague (Lyratzopoulos et al., 2015a; Rubin et al., 2015). However, this study greatly added to the understanding of why these diagnoses are difficult with longer intervals than other cancer types. This study did support previous findings of a lack of a single symptom signature in myeloma (Howell et al., 2013; Lyratzopoulos et al., 2015a, Shepherd et al., 2015), but demonstrated that patients with myeloma were more likely to present with two or more symptoms as a complex.

7.7 Strengths, limitations and critical appraisal of the study design

The strengths and limitations of the individual quantitative and qualitative studies are discussed in the relevant chapters (Chapters Four (section 4.7), Five (section 5.5.2) and Six (section 6.5.3)). The strengths and limitations of the explanatory sequential research design (Creswell, 2014) are critically appraised and reflected on in this section.

The systematic review (Chapter Two section 5.5) found very limited evidence on the diagnostic journey for myeloma. The review recommended an in-depth description of the journey to diagnosis in myeloma by the quantification of all intervals within the total interval to diagnosis and treatment. It also recommended the assessment of the behavioural and contextual influences on this journey, particularly the interactions with health professionals. The research design was chosen because the research questions required both quantitative and qualitative evidence (Chapter Three section 3.6). A strength of this research design was the ability to describe the observed and measured diagnostic journeys in detail and to provide explanations of why the observed measurements occurred. This has greatly increased the knowledge and understanding of the diagnostic and treatment journeys in myeloma and has provided insights into how these could be made more timely. The 'explanatory sequential research design' (Creswell, 2014) allowed the measurement of the diagnostic journey to be explained by the qualitative findings through the merging of findings from all datasets by a synthesis. This provides a unique display of the diagnostic journey in myeloma. The research design gives equal precedence to quantitative and qualitative data (Creswell, 2014). This is a strength in that it gives equal weighting to both the quantitative and qualitative results. However, when the qualitative evidence contradicts the quantitative findings, the overall outcomes and priority may become unclear. This then makes it difficult to interpret data to make recommendations.

This design may have provided an in-depth description and explanation of the observed diagnostic and treatment pathways, but it did not allow the quantitative findings to be generalized to the wider myeloma population. We attempted to address this criticism by performing a power calculation using parameters from the previous ICBPM4 study (Weller et al., 2016). However, this recruitment target was seen to be unrealistic because the available study population from MDT registrations

was smaller than anticipated. The failure to recruit the original sample size could influence the interpretation of the quantitative findings when considered alongside guidance such as the COSMIN checklist (Mokkink et al., 2010). However, Creswell, (2014) does not discuss this model of design as being driven by an intent to generalise findings to a wider population. Instead Creswell, (2014) identifies the aims as informing a less well understood topic. To this end, the study design was able to answer the research questions and achieve the aims of the research by demonstrating the complexity and heterogeneity of diagnostic processes for the myeloma patients. However, the small numbers of cases might reduce the generalisability of these findings in a disease with such varied and heterogeneous presentations. This was not considered prior to the development of this study and should possibly be considered for future work on the early diagnosis of myeloma.

It was possible that the recruitment numbers in the quantitative study could have been increased by extending the recruitment field into England early in the study. This was considered but rejected because the study would be less relevant to NHS Wales and further delays in the regulatory approval process would have made the study unfeasible. The consideration of recruitment in relation to the choice of methods and recruitment strategy, at study set up, could have been advantageous in predicting recruitment difficulties. This may have led to an earlier consideration for recruiting in neighbouring or Welsh-bordering English health boards. This may have then included the population of patients who reside in Wales but are treated by NHS England and well as allowing generalisability of the findings.

A strength of the study design is that it facilitated the consideration of a wide range of factors. In order to describe the range of journeys to diagnosis in such an in-depth way, a large number of variables were collected. This could have led to difficulties managing these data and prompted data handling errors. It was necessary to manage these data in a hierarchy protocol with a standard operating procedure (SOP) to guide data management and auditing. This was believed to have strengthened the reporting of the quantitative data. The range of data available from analysis was very broad and may have proved difficult to manage and interpret. However, the use of qualitative methods in a sequential pattern allowed the organising and prioritising of the quantitative findings. This not only enriched the quantitative observational findings but gave structure to the synthesis process.

In order to collect data to describe the complexity of the diagnostic journeys studied, the questionnaires were time consuming to complete for patients, GPs and haematologists. This possibly affected recruitment in the patient group and questionnaire returns in the GP group. We attempted to minimise this through PPI and peer review. More tailored questionnaires could have improved recruitment or questionnaire returns, but at the expense of poorer quality data. Some of these rich data could have been collected during the qualitative interviews using the topic guide to help with capture. Potentially this could have reduced the burden of 'time' and 'effort' for patients completing the study questionnaires at the difficult time around their diagnosis. This may also have improved recruitment into the study.

The strengths and limitations of the questionnaires became apparent during their implementation. Strengths included the use of targeted questions for symptoms identified from a systematic review, with additional free text boxes, which allowed the collection of a breadth of pre-diagnostic symptoms in myeloma. A major strength of the questionnaire was that the data collected informed the design of the interview topic guide, which led to rich and illuminating topics within the interviews with patients and GPs and was a positive contribution from the explanatory sequential design (Creswell, 2014). For example, the identification of a range and variety of symptoms within the patient questionnaire and their incorporation into the qualitative interviews allowed for a rich exploration of the quantified findings. The questionnaire items regarding investigations in primary care were modelled on the BSH guidance for 'screening tests' in myeloma. This guidance did not include the completion of Liver Function Test (LFTs) and calcium and so these were not included in the questionnaire. On peer review of the questionnaire by haematologists and GPs, this was not raised as a concern. On reflection, it is quite possible that GPs found abnormal results from raised proteins or calcium reported in these tests, but this was not assessed because these data were not collected in the questionnaire.

Recruitment for the study took place within secondary care MDTs, which possibly reduced engagement with the referring GPs group. Every effort was made to engage with the GP group and maintain a high profile of the study through the use of regular bulletins, newsletters and dissemination of the early findings. However, a third of GPs did not return the primary care questionnaires and many declined to participate in the interview study, which may have introduced bias.

Inevitably, the design of the study required participants to register after their diagnosis and required them to be fit enough to complete the questionnaire and to attend an interview. It is known that a relative high number (10%) of myeloma patients die within 60 days of commencing treatment (Augusten et al., 2005). It is likely that some of these patients were not recruited or represented in this study and whether this group of early mortality patients are fully represented in this study is not known. Similarly, this study aimed to recruit asymptomatic myeloma patients to demonstrate how this population of patients came to their diagnosis. This group of patients were poorly recruited to the quantitate study and were absent from the patient interview study. Description and recommendations cannot therefore be made from this study for their diagnostic journeys.

This was the first regression analysis of the diagnostic and treatment intervals in myeloma in the world literature. Multiple variables were collected which required multiple regression models to be constructed. The use of so many models and the restricted sample size may have led to the rejection of an important factor, which might have influenced the overall synthesis with the qualitative findings. Additionally, as the study's statistical analysis was conducted at the end of the recruitment period, the regression analysis did not inform the interview topic guide. Therefore, significant regression findings could not be explored in the topic guide and interviews. Possibly, the sequential design would have been better implemented following a delay to the commencement of interviews until the regression analysis was complete. This was not possible due to time constraints, but it may be useful to consider this option in further implementation of the methodological design.

The student researcher was able to apply the design and methods chosen for the study despite the program of research being considered challenging (Creswell, 2014). A conscious effort was made by supervisors to balance the epistemological stance and understanding of the student researcher through checks applied across the different stages of the study, but specifically to the qualitative data collection and analysis. Through reflexivity, the student researcher acknowledged an inability to totally 'bracket' perceptions and understandings gained from previous experience and exposure to myeloma patient stories. This possibly has affected the way data were collected in the qualitative study and in the analysis of all datasets, including the synthesis. Whether the research findings would be reproduced by another

researcher with a different worldview is not possible to predict and possibly leaves the findings open to criticism. However, all reasonable efforts were taken by supervisors and the student researcher to account for these possible biases. The student researcher has, however, displayed a commitment and 'human' approach to this research. This led to an unexpected level of engagement in the interview dialogues, which in turn led highly revealing and emotive discussions. The student researcher acknowledges their background and training led to a secure and trusting relationship to build in the interviews between the participant and researcher. This, the student perceives, was highly significant in revealing the illuminating data and contributed to the early saturation.

7.8 Recommendations for policy and practice

This study has demonstrated how the patient interval is affected by low levels of symptom awareness in the undiagnosed patient group. One way to address this could be a general public awareness campaign. This could increase the knowledge of the disease and its symptoms in both the 'undiagnosed' myeloma patient and their lay carers and might result in an earlier presentation of their symptoms to primary care. However, health awareness campaigns are expensive, and debate continues about their long-term effectiveness for changing behaviour (Ironmonger et al., 2014; Montague et al., 2001). It is possible that such a campaign could be achieved through the collaboration with third sector parties such as Myeloma UK, Bloodwise, Cancer Research UK and Tenovus.

GPs should be made aware that the most likely symptoms presented to primary care by myeloma patients are pain in muscles and joints, pain in bones and fatigue. Improved understanding of the importance of these symptoms may raise the possibility of the diagnosis and encourage earlier investigation. When investigating suspicious symptoms, GPs should be encouraged to order specific investigations such as SPE and SFLC/BJP and x-ray of any symptomatic pain area. These findings, alongside other evidence about symptoms, should inform future guidance for myeloma diagnosis in primary care, along with the production of decision making tools.

Haematology referral appears to be the optimal referral method into secondary care and should be promoted as the route of entry for suspected myeloma cases. This may seem obvious, but it appears from this study, this is only possible when

myeloma is suspected by the GP. It is likely, therefore, that increasing the diagnostic investigations in the undiagnosed myeloma patient in primary care with myeloma-specific investigations could help target the referral to the optimal speciality group. The consequence of longer intervals via routes other than haematology could then be addressed. The pathway to haematology is clearly affected by the referral into secondary care services, but this may also be affected by the referral patterns within secondary care i.e. interdepartmental referrals, and this requires addressing. It is possible that the relatively large numbers of patients identified through the laboratory identification of a paraprotein or abnormal test, could possibly be utilised more effectively to provide feedback and alerts to primary care and non-haematology secondary care teams. This could possibly facilitate faster pathways to haematology.

7.9 Recommendations for further research

The use of the explanatory sequential design, and mixed methods more generally, provides an opportunity to gain a greater understanding of diagnostic journeys in rare or difficult to diagnose cancers and its implementation in further research into these particular cancer types has the potential to provide a deeper understanding of the difficulties with diagnosing these cancer types and making recommendations for their more timely diagnosis. Particularly the structure of the questions surrounding the identification of pre-diagnostic symptoms within questionnaires were found to be easily implemented and elicited the varied and in-depth response required. This structure to question, to elicit the required response i.e. a range of 'tick box' options of symptoms identified through systematic reviewing with additional 'free text' option boxes, is likely to be useful and transferable to research studies identifying cancer symptoms in other cancer types with vague symptoms. However, although the questionnaires were successful in the production of in-depth data, the limitation acknowledged would need to be addressed and modifications made based on the cancer type being investigated for future successful application.

The findings in this study of very low-level use of physical examination by GPs in the presence of a high frequency of reporting of pain requires further investigation as this may contribute to the poor assessment of symptoms as serious and the less timely investigation of symptoms.

The important factors identified in this study should now be studied in the wider myeloma population. Of particular importance is the measurement of the patient,

primary care and total intervals; frequency, continuity and presentation routes in primary care; investigations performed in primary care; type of referral made and team referred to in secondary team and; the pathway of progression through primary care. There is an opportunity to do this by including these measurements within larger scale multi-centre treatment studies. This has the potential to produce generalizable data which can better inform policy and practice due to larger recruitment numbers.

The recommendations made for policy and practice from this research, if implemented, now require formal assessment to test their effectiveness and efficiency for improving the timeliness of the diagnosis of myeloma. Cancer awareness campaigns are likely to require assessment of changes in behaviour over a short and longer period of time, as well as assessment of survival benefits. This, therefore, requires longitudinal study as observed in the 'slip, slop, slap and sun smart' campaign in Australia (Montague et al., 2001). Cost effectiveness of their implementation is also required to assess economic evaluation in the context of benefit to public health and returns to government (Sinclair and Foley, 2009). Transfer of knowledge to GPs of symptoms in myeloma to impact a change in clinical practice to promote earlier specific investigation for myeloma patients and faster routes of access into haematology, would require the assessment of behavioural change and impact on practice change This would require the designing of a 'complex intervention' and is a specialised area of implementation research (Campbell et al., 2007). There are recommendations for this to be undertaken through greater collaboration between research groups and implementation specialists to facilitate appropriate modelling of implementation and evaluation to effect a change in healthcare practice (Foy et al., 2001). Any changes in the symptom profiles (for myeloma patients in primary care, to guidance for earlier testing with SPE, SFLC/BJP i.e. future revisions of the NICE referral for suspected cancer guidelines) are likely to be monitored as part of an overall assessment of changes to diagnostic intervals in multiple cancer types as assessed and reported in the Neal et al. (2014).

There is an important need to continue the assessment of survival in these myeloma patients recruited to this study and assess the associations with the intervals to

diagnosis and treatment. This will allow the unique prospective assessment of the association of survival and length of the diagnostic journeys.

7.10 Conclusion

This programme of research has successfully provided evidence to fill some of the gaps in knowledge identified from the thesis's systematic review. Importantly this study has successfully described the behavioural and contextual influences on the journey to diagnosis for the myeloma patient identified as missing from the systematic review. Additionally, the entire journey to diagnosis and treatment has now been quantified, permitting comparison of all the interim intervals within the total journey. The study has also identified the multiple factors that affect the total journey which have confirmed many of the findings of the systematic review and identified new factors of influence. The synthesis has allowed explanation of why the factors affect the different intervals across the journey. Therefore, the study has provided a detailed account of the diagnostic journeys in myeloma and the influences, both behavioural and contextual, that change the course of the journey.

The findings from this study have demonstrated that patients take a long time to present their symptoms and this may be altered by better awareness in the general public. Myeloma is a difficult disease to identify in primary care, not because it requires a complex set of tests which GPs have difficulty accessing, but because it is hard for the GP to connect the symptoms that patients present with to a serious disease. This is rooted in low awareness, vague symptoms and poor understanding of early symptoms. However, this study has identified a set of symptoms that myeloma patients are likely to present with in primary care that should allow GPs to have a higher index of suspicion. In turn, this higher suspicion may prompt the GP to perform testing that will allow the identification of the underlying myeloma disease and not just the complications of the disease, shortening the primary care interval and possibly preventing progression of the disease. The identification of the underlying paraprotein abnormality would facilitate referral to haematology, reducing the secondary care interval.

It is clear that there is not one single factor that is responsible for the long total intervals to diagnosis and treatment associated with myeloma. This study has shown that there are multiple factors which all contribute to the longer intervals and these factors are seen to affect the entire journey. However, following the

recommendations made from this programme of research, there is the possibility of shortening the diagnostic journey for patients with myeloma. It is also likely that the recommendations made here are applicable to other cancers with low awareness and vague symptoms where longer intervals are recorded. Realistically, myeloma intervals to diagnosis may never equal that of cancers such as breast, but this study has suggested possible ways to improve the diagnostic journey for this group of patients.

7.11 The contribution of the thesis

This thesis has made a substantial contribution to the literature. Generally, the evidence from the thesis contributes to closing the gaps in the knowledge and understanding of difficulties in the diagnosis of this particular cancer type. This, therefore, builds a knowledge base which has been low compared to other cancer types, and increases the opportunity to improve the timeliness of diagnosing myeloma.

The thesis further contributes to evidence in many specific areas.

The thesis has quantified all the intervals to diagnosis and treatment in myeloma enabling the reporting of the relative contribution of each individual interval in the total journey. This, the student researcher believes, is the first reporting of the total journey and interim intervals for a cancer type. The reporting of these intervals and the total journey in myeloma, which were modelled on the ICBPM4 questionnaire study, will now allow comparison against breast, colorectal, lung and ovarian cancers on the publication of the ICBPM4 study findings. The measurement of the secondary care, the treatment and the total interval are reported for the first time in myeloma. In reporting the secondary care interval the relative contribution of this interval in the total journey was made apparent. The thesis, therefore, highlighted the important contribution of this interval in lengthening the overall journey in myeloma. This has led to a conclusion that there is a need to better understand the processes in the journey to diagnosis and treatment for the myeloma patient in secondary care. This is a new contribution and has not been reported in previous literature.

The thesis further contributed to the literature by assessing the influences affecting the secondary care interval. The thesis concluded that this interval was primarily

affected by the referral into secondary care from primary care and resulted in a high number of teams, outside of haematology, receiving referrals for myeloma patients. This provides a unique contribution of appreciating the lengthened journeys in this population of cancer patients. These findings as contributions, support the evidence of primary care influences in the processes of diagnostic delays (Rubin, et al., 2015b; Lyratzopoulos, et al., 2014), but gives a new perspective for myeloma by measuring the influence of decision making in primary care affecting the progression through secondary care.

The thesis provides evidence for a greater understanding of the response in primary care to the symptoms myeloma patients present with. This is a new contribution to the literature. The thesis was able to report, generally, a low level of investigation in response to symptoms and very low levels of myeloma specific investigations. The interviews revealed this was rooted in GPs failing to connect the symptoms experienced by their patients to myeloma. This complements the work of Howell, et al. (2013) who reported the wide variation in symptoms makes suspecting the disease difficult, but adds clarity on how myeloma patients are currently investigated in primary care. The thesis also reports a low level use of the urgent suspected cancer referral route which complements work published by Elliss -Brookes, et al. (2012) for myeloma. The thesis extends the understanding of the effect of these referral policies by quantifying the referral teams and processes through secondary care. Additionally, the thesis reported associations in regression analysis of longer intervals with non-haematology team referrals, providing new evidence and understanding which builds on the retrospective analysis completed by Kariyawasan, et al., (2007). The qualitative study was also able to provide understanding of these referral routes by reporting the influence of a failure by GPs to suspect myeloma.

The qualitative study has provided the first evidence of the behavioural and contextual factors surrounding the diagnostic journey in myeloma. This helps fill the recognised gaps in the understanding of the patient influences in myeloma that have been considered for other cancer types (Whitaker, et al., 2015a; Place, et al., 2011, Wardle, et al., 2001; Corner, et al., 1999). This new contribution greatly improves the limited findings in myeloma seen at the outset of this studentship (Howell, et al., 2015). This new evidence has provided parallels between factors of normalisation of

symptom to ageing, awareness and knowledge of the disease and cancer candidacy with other cancer types.

This thesis was not able to provide a contribution in its findings for the effect of ethnic diversity and deprivation on the journey to diagnosis in myeloma. The evidence remains limited for myeloma in these fields and lags behind evidence for other cancer types (Walter, et al., 2015; Rutherford, et al. 2015; Abel, et al., 2016).

The thesis provides new evidence in understanding the interactions between the patient and the primary care provider. This, to the student researcher's knowledge, is a new contribution. However, the contribution is limited in this domain due to the small sample size in the GP interview study.

It is believed that the methodological design implemented within this thesis has been adopted for the first time in research on the early diagnosis of cancer. It possibly provides a precedence as a method that may detail the diagnostic processes of a designated population, whilst additionally contributing to an understanding of why the phenomena observed exists.

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9 Appendices

9.1 Appendix 1: Protocol for applying CART criteria

DJiM

Phase one of the review was broad and inclusive; the aim was to identify, map and describe the full range of literature relating to pathways to diagnosis in myeloma. In phase 2 we narrowed the review with the aim of focusing in on data that best addresses the research questions and, therefore, we concentrated the available time and resource to the most relevant and fruitful areas. To ensure the appropriate CART criteria were drawn a group of experts were drawn together to review a study specific adapted CART criteria (Tennison B 2006), as a method for systematising the selection of studies for the in-depth review. This method has been used in a previous systematic reviews to effect and, therefore, was deemed appropriate for adaptation to the DJiM review (Whitaker et al., 2013).

To be included in the review studies would meet all four criteria:

C COMPLETENESS

We will not include in the in-depth review any reports that are incomplete, i.e.

- After exhaustive searches only a partial record such as an abstract or short report can be obtained
- A report of an intervention where the components of the intervention are not fully described
- A report of an evaluation that does not fully describe the methods used
- A report that does not contain data that addresses the review question

A ACCURACY

Accuracy is generally assessed using quality appraisal criteria. Studies will not be excluded from the in-depth review on the grounds of poor quality as long as they pass the screening questions of the MMAT (Mixed Methods Appraisal Tool) since further appraisal may not be feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions:

- Are there clear qualitative and/or quantitative research questions (or objectives), or a clear mixed methods question (or objective)?
- Do the collected data allow the research question (or objective) to be addressed? E.g., consider whether the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components).

Studies that pass the screening questions and meet the criteria for completeness, relevance and timeliness will be included for in-depth review, undergo full quality appraisal, and quality of studies will be addressed in the discussion.

R RELEVANCE

The expert panel agreed that worldwide literature was relevant to this study, therefore, no exclusion based on country or origin was applied. Studies retrieved in a foreign language would be translated via "google translate"; articles that are of a quality translation which inhibited analysis and data extraction will be rejected. Translation by more formal routes is not permissible in the confines of the PhD budget. Articles considered to be relevant but not sufficiently translatable will be acknowledged as such in the text of the report and discussed in the limitation section.

- The relevance question will be applied more vigorously on review of retrieved 'full articles'; we will include articles whose main outcome measures will answer the research questions and inform the knowledge of pathways to diagnosis in myeloma in the domains of patient, primary care and secondary care.

T TIMELINESS

The panel agreed that although advances in diagnosis and treatment of myeloma have occurred over the past few decades, the scarcity of evidence identified in a scoping exercise makes the inclusion of all available literature that meets the other CART criteria on review, important. No exclusion on dates will be applied.

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Adapted from:

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9.2 Appendix 2: Example data extraction: a bespoke tool permitting data extraction from quantitative and qualitative studies

Table 9-1: Example data extraction: a bespoke tool permitting data extraction from quantitative and qualitative studies

Reference details, study design and aims	Setting and participants	Data collection analyses
Author, year: Howell et al., 2015 **Country of origin:** United Kingdom, England **Study design:** cohort observational questionnaire study **Purpose of study:** To describe detailed findings related to haematological malignancies relating to risk factors and barriers to help-seeking in an earlier study then present data on a wider range of subtypes focusing on symptoms that are known to be common in these diseases and examining barriers that may be specific to these cancers **Theoretical perspective identified by author (s):**	**Setting (and method of selection or setting rationale):** A subset of participants who participated in the National Cancer Patient experience Survey (NCPES) who agreed to further contact **Sample size and sample type** 5925 participants with haematological malignancies **Sample rationale:** Large cohort from 158 trusts in England **Method used to recruit:** Patients consent for further contact within the NCPES **Response rate:** Response to survey in myeloma patients Alive at Nov 2011 = 1695 (78.8%) invited 200 –responded 150 (76.1%)	**Data collection method:** Participants registered within the NCPES study who agreed to further contact were sent a survey by mail which examined time to presentation and risk factors for waiting >3 months before first presentation to a doctor **Method of recording data:** Questionnaire survey **Date of data collection:** Original registration in NCPES study 2010, questionnaire distributed between November 2011 and January 2012 **Researchers perspective:** Not reported **Data analyses method:** Measurement of time to diagnosis, specified interval, Area based Index of Deprivation (IMD) used to categorise individuals into quintiles (1-

None reported Aarhus statement used to define appraisal interval measurement		5). Relative risks (with 95% CI) were calculated for time to presentation of >3 months by subtype, presenting symptoms and any reason for putting off going to the doctor. Age, sex and deprivation category were controlled for (owing to the possibility that these might influence time to diagnosis). **Quality control method:** None reported

Results: relating to the DJiM systematic review aims and objectives only:

- Myeloma (ICD C90 category) patients alive Nov 2011 1695 (78.8) – responded to survey (N = 200 per subtype) N 150 (76.1)
- Age and IMD and ethnicity not broken down or reported for individual cancers
- Presence or absence of symptoms varied per cancer type – myeloma symptoms reported in 78.7% of the population
- Similarities and differences were identified in disease subtypes across all diagnoses (including myeloma) extreme fatigue/tiredness, unusual sweating at night, unexpected weight loss and pallor. Beyond this disease symptoms were seen to be more disease specific. Myeloma symptoms reported highest for bone pain/discomfort (77.1%).
- Symptoms reported by Myeloma patients 150 (100) with at least one symptom. Total patients 150 (100) total number with symptoms 118 (78.7) **Systemic symptoms** 62 (52.5),(extreme fatigue or tiredness 51 (43.2%), unusually pale 10 (805); unusual sweating at night 12 (10.2); unexpected weight loss 20 (16.9); nausea 2 (1.7); faint or dizzy 0(0.0); loss of appetite 0(0.0) **Pain symptoms 91 (77.1)-** pain or discomfort in bones 87 (73.7); pain or discomfort in tummy 8 (6.8); other 0 (0.0) **Chest symptoms** – 26 (22.0) shortness of breath 22 (18.6); lots of coughs and cold 6 (5.1); sore throat 0 (0.0) **Lump** 5 (4.2) - lump in neck or groin or armpit 0 (0.0); lump swelling in tummy 2 (1.7); other lump 3 (2.5). **Bleeding symptoms** 15 (12.7) – unusual bruising, rash/red spots 9 (7.6); unusual bleeding 8 (6.8); black stool 0 (0.0). **Other symptoms** fever 1 (0.8); skin unusually itchy 4 (3.4); unusually thirsty 6 (5.1), skin went yellow 2 (1.7); headache 1 (0.8); swollen leg 1 (0.8); bowel symptoms 2 (1.7)
- There was a marked variation in the reporting of reasons why people did not go to the doctor "what put them off" for different subtypes – Myeloma total patients 150 (100) total with symptoms 118 (78.7) total with symptoms reporting reasons for putting off going to the doctor 51 (43.2) **Barrier** – did not realise symptom was serious 30 (25.4); worried about wasting doctor's time 4 (3.4); too many other things to worry about 6 (5.1); too busy to go to the doctor 3 (2.5); worried what the doctor might find 4 (3.4); difficult to make an appointment 1 (0.8); doctor difficult to talk to 2 (1.7); other 1 (0.8)
  Risk factor and time to presentation: patients waiting > 3months before presentation with those who did not separated by cancer subtype therefore myeloma not accessible individually

Comments: relating to the DJiM systematic review aims and objectives only:

Author's conclusions:

- Waiting for >3 months before symptomatic presentation to a doctor common across all haematological malignancies included in the survey. This varied by subtype considerably.
- Some symptoms frequent across all sub-types such as fatigue. Others more specific such as, including pallor and bruising/bleeding in acute leukaemia and bone pain in myeloma.
- Risk of waiting >3 months before help-seeking varied by disease and symptoms (I'm not sure this was evidenced by "disease" – yes for symptom) with many patients reporting that this occurred because they did not realise their symptoms were serious.
- Few studies have evidence pre-diagnosis symptoms in haematological malignancies – most that have use blood parameters and clinical signs and complications or pre-determining symptom choices. Studies examining time intervals preceding diagnosis are associated with similar inconsistencies e.g. in definition of time periods examined, the methods used and the way in which results are presented
- Symptoms reported in this study comparable to literature for myeloma. Findings comparable for positive predictive markers for myeloma.
- Symptoms associated with increased risk of >3 months presentation were night sweats, pallor, abdominal pain and extreme fatigue – these were not separated out per cancer subtype making interpretation difficult for myeloma
- **Interpretation and implications for practice.** "Not realising symptoms were serious" was a clear risk factor for waiting >3 months before presentation; this has been previously reported. May be a factor of many symptoms being common in the general population and often benign and self-limiting. Patients may justify such symptoms: fatigue considered natural consequence of aging; bone pain wear and tear. This process of normalising symptoms has been reported in other studies (this is generalised to all haem cancer types).
- Further factor to thinking symptoms not serious is the patient's expectation of what cancer might be like i.e. expectation of pain, constant and associated with a feeling of ill health and gradually becoming worse.
- Despite some symptoms being indicative of certain subtypes these may be varied and a clear symptom signature does not exist
- Lack of awareness about these disease and the range of symptom combination that may accompany them among the general public – campaigns such as "Be clear on cancer" may be more challenging in haematological malignancies but would be a useful step in raising awareness of these cancers- any such innovations must be balanced against finite resource
- Array of laboratory and clinical tests used to diagnose haematological malignancies but there is no screening test available
- The differences noted by subtype in proportion of people waiting >3 months before presentation are unsurprising and relate predominantly to the acute aggressive presentation or more indolent subtypes
- The importance of avoiding prolonged time to diagnosis of haematological malignancies to ensue earlier stage of disease at diagnosis and accrue survival advantages is not as clear. It is likely that tumour subtypes and biology have greater impact on outcomes for some subtypes than time to presentation.
- Future research – presentation to the doctor is just one aspect of the time taken to diagnose haematological malignancies. The doctor must recognise that the presenting symptom could indicate a haem malignancy and make timely and appropriate referrals to secondary care. Further research is needed, alongside primary care practitioners to identify mechanisms by which patients can be identified as early as possible, and routes a to haematology and diagnosis can be seamless as possible

Other comments:

- Strength and weakness identified – has theoretical model underpinning Aarhus, symptom categories haematology specific and pre-determined by clinical experts thereby limiting options with those symptoms that could be commonly associated with target diseases. Whilst this minimised reporting of symptoms related to other diseases it may have discouraged reports of rarer symptoms. The categorisation of prolonged presentation was identified for all cancers combined in the original study. Use of this time point may not be wholly appropriate for haematological malignancies
- Limitations- impact on generalisability participants are younger and more affluent than average for these diseases, sample of participants derived from NCPES and the number of ethnic minority respondents to this survey was reported to be substantially less than the population as a whole. Findings may not be applicable to non-White ethnic origin. The NCPES was directed to patients with in patient/outpatient episodes rather than solely outpatient; these patients' experience/characteristics may be different. NCPES patients were diagnosed at various time intervals prior to completing the survey, therefore using self-reported symptoms as data collection may have recall bias for symptoms recall. This study targeted patients who participated in NCPES and therefore had survived in order to be invited into this study – survivor bias may be introduced. Importantly the early deaths may comprise a greater proportion of patients with later stage disease at diagnosis, possibly as a result of longer time to presentation/diagnosis, as well as those with more aggressive disease.

9.3 Appendix 3: Mixed Methods Analysis Tool

Table 9-2: Mixed Methods Analysis Tool

Quantitative non-randomised trials		Abel et al., 2015	Din et al., 2015	Elliss-Brookes et al., 2012	Friese et al., 2009	Howell et al., 2013	Howell et al., 2015	Kariyawasan et al., 2007	Keeble et al., 2014	Li et al., 2012	Lyratzopoulos et al., 2012	Lyratzopoulos et al., 2013	Lyratzopoulos et al., 2015b	Neal et al., 2014	Ong et al., 1995	Shephard et al., 2015
Screening questions																
1.1 Are there clear quantitative or qualitative research questions (or outcomes) or a clear methods question or objective?	*Yes -clear*	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	No- unclear															
	unsure															
1.2 Do collected data allow address of the research question/ objective? (e.g. consider follow up period)	*Yes -appropriate*			√		√		√		√					√	√
	No -inappropriate															
	mixed	√	√		√		√		√		√	√	√	√		
Sampling strategy																
2.1 Is the source relevant to the population studied?	*appropriate*				√			√		√					√	√
	inappropriate															
	Mixed relevance	√	√	√		√	√		√		√	√	√	√		
2.2 When appropriate, is a standard procedure for sampling, and the sample size justified (e.g. power calculation given)	*clear*		√			√			√		√	√	√	√	√	√
	unclear							√		√						
	mixed	√		√	√		√									
Sample representative																
3.1Are inclusion and exclusion criteria explained	*appropriate*		√	√	√	√	√		√		√	√	√	√		√
	inappropriate							√		√					√	
	unsure															
3.1Are the reasons detailed for eligible patients not participating explained?	*appropriate*															
	inappropriate															
	unsure / unclear	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Measures																
4.1 Are the variables clearly defined and accurately measured?	*clear*	√	√	√		√		√	√		√	√	√	√		√
	unclear				√		√			√					√	
	not described															
4.2 Are measures justified and appropriated for answering the research questions?	*clear*	√	√	√	√	√										
	unclear															
	unsure															
4.3 Do the measurements reflect what they are supposed to measure?	*appropriate*		√	√	√	√	√	√	√	√	√	√	√	√	√	√
	inappropriate															
	unsure															
Response rate																
5.1 Is the response rate pertinent for case series and case reports (e.g. no expectation that a case series would include all patients in a similar situation)	*appropriate*					√										
	inappropriate															
	unsure / unreported															
	NA	√	√	√	√		√	√	√	√	√	√	√	√	√	√
Ethics																
6.1 Clear & coherent reporting of ethical considerations?	*clear*		√		√	√	√		√		√					√
	unclear															
	unsure /unreported	√		√				√		√		√	√	√	√	
Overall quality: G=Good; M=Moderate P=Poor		M	G	M	M	G	M	M	M	M	M	M	M	M	M	G

9.4 Appendix 4: Extracted data: themed tables for systematic review

Table 9-3: Theme 1 intervals to diagnosis

Author and year	Interval reported	Outcome	Theoretical underpinning or defined measurement
Din et al., 2015	Diagnostic interval As affected by age and gender	N = 1158 No with symptoms and analysed – N = 500 Mean 161.8 SD 114.0 Median 149 IQR 54 – 263 90th centile 334	Yes – well defined (no theoretical model identified) but capped at data one year prior to the first diagnostic code for cancer in the PC records(data cap for symptoms cut off 1 year)
Friese et al., 2009	Time to diagnosis - Claim via Medicare from sign or symptom to diagnosis of myeloma	N = 3831 Sample claim for S and S up to one year prior to diagnosis – mean 137 days SD 120 range 1- 365 median 99 days IQR 27- 525	No – measurement not defined (study capped at one year prior to diagnosis and six months after diagnosis). Delayed group measured by portion of patients who had a claim prior to diagnosis and diagnosed after median diagnostic interval of study sample
Howells et al., 2013	Patient, diagnostic, time to diagnosis	N = 152 Patient = 31 (1-122 IQR) Diagnostic = median 83 (34-167 IQR) Total = median 163 (84-306 IQR)	Yes - measurements defined and underpinned by the Aarhus statement but not referenced – Walter Anderson Model referenced
Kariyawasan et al., 2007	Time to diagnosis – grouped in to referral and presentation routes	N = 103 patients 30% diagnosed with 3 months of first symptom. 70% took >3 months to diagnose Overall a delay of >6months between first symptom and definitive diagnosis was seen in 43 patients	Interval defined – not with full transparency – no theoretical underpinning

Keeble et al., 2014	Patient interval Ordered into binary categories Prompt (0 – 14 days) Non- prompt (15+ days) as affected by promptness of presentation	N = 127 25th centile 0 median 14 75th centile 40 90th centile 95 95th 193	Yes – interval well defined (no theoretical model identified) and rationalised
Li et al., 2012	Time to diagnosis – first symptom to diagnosis – not further defined – grouped into 2 groups 1 = presented to nephrologist Group II presented to haematologist	N = 109 patients Group I 2 – 24 months (median time was 6 months : 6.0 + - 4.2 months Group II 0.2 – 2 months (median 0.5 month 0.5+ - 0.31 months (p<0.001)	Interval defined but not underpinned by theoretical model
Lyratzopoulos, et al 2013	Primary care interval as affected by pre-referral consultations	N = 176 % of patients with 3+ cons 46 Median primary care interval 21 IQR 5-55 Median PC interval by no cons 1= 1 IQR 0-12 2 14 IQR 5-33 3 = 38IQR 21 -65 4 45 IQR 22-82 5 += 82 IQR 34-129	Yes – Aarhus

		N 176 spearman's r 0.73 ROC are under the curve 0.88 ROC area 95% lower CI .83 PRC area 95% upper CI 0.93	
Lyratzopoulos, et al 2015	Measurement of patient and primary care interval – pre-referral interval Ratio of mean and median patient and primary care interval	N = 124 Patient interval = (days) mean 44 25th centile 13.5 75th centile 31, 90th centile 93 median 13.5 PC interval= (days) mean 56 25th centile 5, 50th centile 20.5 , 75th centile 62 90th centile 134 median 20.5 (95% CI) Pre-referral = (days) mean 100 25th centile 22, 50th centile 46 75th 11.5 90th centile 213 Mean patient interval/primary care interval 0.8 (0.4 -1.3) median patient interval/median primary care interval 0.7 (0.3 – 0.1.0) Ratio of mean and median patient interval over mean and median primary care interval 0.7 (0.3- 1.0)	Yes - Aarhus underpinning decision making

Table 9-4: Themes 2 Symptoms

Author/year	Context of the analysis of symptoms	Association reported
Din et al., 2015	N= 1158 500 (43.2%) had recorded symptoms; 497 (99.4%) with NICE symptoms Regression analysis of diagnostic intervals by NICE status NICE n 497 median 149 IQR 54-263 90th centile 334 N= Non NICE 3 median 28 IQR 8-244 90th centile 244 =mean difference (95% CI) crude -68.8 Adjusted -65.8 (-195.8- 64.2) P value 0.32 Cut off for symptom collection 1 year prior to diagnosis	-ve association (not significant) of diagnostic journey length increased by presentation with non- NICE symptoms
Friese et al., 2009	Number of insurance claims for symptoms prior to diagnosis Anaemia or Packed Red Blood Cell (PRBC) transfusion 50%; back pain 39% and for both anaemia and transfusion 19%	No association reported with diagnostic interval group Descriptive statistics for some symptoms
Howell et al., 2013	N 493 Number with no symptoms 152 (10.3%) Number with symptoms 341 (69.2) 10% of participants reported symptoms that could not be matched to NICE guidelines Most common symptom reported pain – not quantified fully >40% Second most common symptom reported tiredness >20% Other symptoms listed included shortness of breath and cough; infections, stomach & bowel problems.	Descriptive information 69% patients with myeloma experience symptoms prior to diagnosis Most commonly reported symptoms in this study tiredness and pain 10% of symptoms reported not NICE detailed First time data from self-reported symptoms
Howell et al., 2015	Myeloma patients recorded an incidence of symptoms in 78.7% Highest proportion of symptom reported bone pain/discomfort 77.1% Symptoms reported:	Descriptive information available for myeloma. Symptoms occur in 78.7% of myeloma patients pre- diagnosis

	Systemic symptoms n= 62 (52.2%) Fatigue/tiredness 51 (43.2%) Unusually pale 10 (8.5%) Unusual sweating at night 12 (10.2%) Unexpected weight loss 1 (1.7%) **Pain symptom n 91 (77.1%)** Pain or discomfort in bones 87(73.7%) Pain or discomfort in tummy 8 (6.8%) **Chest symptoms n 26 (22.0%)** Shortness of breath 22 (18.6%) Lots of coughs and colds 6 (5.1%) **Lumps n = 5 (4.2%)** Lump/swelling in tummy 2 (1.7%) Other lump 3 (2.5%) **Bleeding symptoms n = 15 (12.7)** Unusual bruising, rash/red spots9 (7.6%) Unusual bleeding 8 (6.8%) **Other symptoms:** Fever 1 (0.8%) Skin unusually itchy 4 (3.4%) Unusually thirsty 6 (5.1%) Skin went yellow 2 (1.7%) Headache 1 (0.8%) Swollen leg 1 (0.8%)	Most commonly occurring symptom bone pain/discomfort No reporting of risk for >3 months to present for myeloma only group

	Bowel symptoms 2 (1.7%) Study design to predict the symptoms and barriers to prevent prompt presentation in patients. Analysis, however, based on all haematological cancers analysed and not referenced for myeloma separately	
Kariyawasan et al., 2007	N=92 Major presenting symptoms in secondary care Bone pain 67% Asthenia 14% Fatigue 9% Dyspnoea 5% Weight loss 5%	Descriptive information. Presenting symptoms to secondary care – most common symptom bone pain
Ong et al., 1995	Symptoms of bone pain and fractures present and attributable to myeloma in 11 out of 127 patients where diagnosis was not made and misdiagnosis occurred. 5 initially diagnosed with osteoporosis or lower back pain without further diagnosis 2 radicular compression 1 osteomyelitis 3 suspected of bone metastasises of cancer diagnosed earlier	Descriptive information – typical symptoms of myeloma may occur but be misattributed to other disorders – no measurement of impact on time to diagnosis available
Shephard et al., 2015	Assessment of symptoms in myeloma and control group examined to facilitate positive predictor values for symptom that may lead to a diagnosis of myeloma. 62 symptoms were considered 11 symptoms were significant: Back pain Chest pain Chest infection Shortness of breath	-ve association for single symptom and risk of myeloma +ve association reported of combined paired symptoms giving predictive value for a diagnosis of myeloma

	Nausea Fracture Joint pain Combined bone pain Weight loss Rib pain Nosebleeds Single symptoms had low predictive value for myeloma. And few combined symptoms have PPV > 1.0 The use of a symptom PPV > 1.0 could prompt GP to order blood tests PPVs for myeloma symptoms in patients >60 years for single and paired features PPVs with significance + Back pain and Nosebleeds 1.5 Rib pain and back pain 1.1 (features with <5 cases not calculated, features <10 PPV given but CI omitted) When symptoms are paired with clinical tests there is higher PPV. PPVs for myeloma blood tests with symptoms in patients ≥60 years: risk estimate for single investigations and paired with symptoms. (PPVs not calculated if < 5 cases had the feature, where < 10 cases or controls had combined features CIs of 1.0-1.9%; orange test + 2.9-4.9% and red of ≥ 5% **Leucopenia and back pain second episode = 2.0** **Leucopenia and nosebleeds >10** **Leucopenia and fracture >10** **Leucopenia and combined back pain >5**	+ve association of symptoms when combined with clinical tests predicting the diagnosis of myeloma +ve association of myeloma risk in the presence of hypercalcaemia +ve association of joint pain and rib pain in conjunction with leukopenia or hypercalcaemia

	Low platelets and nosebleed 1.2 Raised inflammatory markers and back pain second visit 1.1 (0.7 – 1.6) Raised creatinine and nosebleeds 0.2 (0.1 – 0.4) Raised MCV and rib pain 1.1 **Hypercalcaemia and back pain first episode 4.0** **Hypercalcaemia and back pain second episode >10** Hypercalcaemia and SOB 1.5 Hypercalcaemia and chest pain 1.9 **Hypercalcaemia and chest infection 2.0** **Hypercalcaemia and fracture >10** Hypercalcaemia and nausea 1.0 Hypercalcaemia and combined back pain 1.4 **Hypercalcaemia and joint pain >10** **Hypercalcaemia and rib pain >10** 11 symptoms and 5 investigations were associated with the disease Individual symptoms have low PPV for myeloma – these are higher with multiple symptoms Risk estimates for individual and most combinations of symptoms were low, back pain and nosebleeds or rib pain had a PPV of over 1% If hypercalcaemia is present the risks were considerable higher, the highest being 10% for hypercalcaemia accompanying fracture or various skeletal pain variables Several features of bone marrow suppression were associated with myeloma, the strongest associations were noted with leukopenia. This has a risk factor of over 10% when reported with fractures or nosebleeds	

Feature	Cases n (%) n- 2703	Controls n (%) n= 12157	Likelihood ratio (95%CI)	Odds ratio in multivariable analysis (95% CI)
Symptom:				
Back pain:1-6	766 (28)	753 (16)	4.6 (4.2 to 5.0)	2.2 (2.0 to 2.4)
Chest pain: 1-3	397 (15)	531 (4)	3.4 (3.0 to 3.8)	1.6 (1.4 to 1.8)
Chest infection: 1-2	319 (12)	770 (6)	1.9 (1.7 to 2.1)	1.4 (1.2 to 1.6)
Shortness of breath: 1-2	277 (10)	661 (5)	1.9 (1.7 to 2.2)	1.3 (1.1 to 1.5)
Nausea	162 (6)	228 (2)	3.2 (2.6 to 3.9)	1.5 (1.1 to 2.1)
Fracture	159 (6)	201 (2)	3.6 (2.9 to 4.6)	3.1 (2.3 to 4.2)
Joint pain	118 (4)	358 (3)	1.5 (1.2 to 1.8)	1.6 (1.2 to 2.2)
Combined bone pain	108 (4)	112 (0.7)	4.3 (3.3 to 5.6)	2.1 (1.4 to 3.1)
Weight loss	107 (4)	86 (0.7)	5.6 (4.2 to 7.1)	3.0 (2.0 to 4.5)
Rib pain	80 (3)	47 (0.4)	7.7 (5.4 to 11.0)	2.5 (1.5 to 4.4)
Nosebleeds	76 (3)	78 (0.6)	4.4 (3.2 to 6.0)	3.0 (1.9 to 4.7)

	Investigations						
	Cytopenias	1309 (4)	1109 (9)	5.3 (5.0 to 5.7)	5.4 (4.6 to 6.4)		
	Raised inflammatory markers	1146 (42)	753 (6)	6.8 (6.3 to 7.4)	4.9 (4.2 to 5.8)		
	Raised creatinine	648 (24)	1021 (8)	2.9 (2.6 to 3.1)	1.8 (1.5 to 2.2)		
	Raised MCV	347 (13)	250 (2)	6.2 (5.3 to 7.3)	3.1 (2.4 to 4.1)		
	Hypercalcaemia	246 (9)	44 (0.35	26 (18 to 35)	11.4 (7.1 to 18)		

Table 9-5: Theme 3 How do myeloma patients present for diagnosis?

Author/year	Context of route or frequency analysed	Association reported
Elliss-Brookes et al., 2012	Referral pathway used from primary care to secondary care in myeloma patients to a diagnosis N= 11221 screen detected = 0; Two Week Wait (TWW) 11%; GP referral 27%; other outpatient 13%; inpatient elective 6%; emergency presentation 37%; Death Certificate Only (DCO) 1%; unknown 6%	Higher number of referrals seen for myeloma, than other cancers analysed, through an emergency route this translated into poorer survival in this group of patients (reported in survival analysis)

<table>
<tr>
<td>Friese et al., 2009</td>
<td>Patients diagnosed during an inpatient stay were significantly less likely to experience a delay in diagnosis - OR 0.73 (95% CI 0.64-0.84)

Increased physician (OR 1.05 (95% CI 1.05-1.06) or hospital visits (OR 1.07 (95% CI 1.2 – 1.13) in the preceding year of diagnosis increased the likelihood of delay</td>
<td>+ve association of diagnosis made as inpatient reduces time to diagnosis

+ve association of increased visit to physician or hospital leading to delay in diagnosis</td>
</tr>
<tr>
<td>Kariyawasan et al., 2007</td>
<td>N= 103

51 patients (55%) presented to GP -56% had an interval <6 months (>12 months in 33%) before specialist referral

3 patients presented to haematologist – diagnosed within 3 months of first symptom

An overall delay of >6 months between first symptom and definitive diagnosis was seen in 43 patients , 29 (67.4%) initially presenting to GP

5 17%) patients who presented to GP were reported to have delayed own presentation whereas 29 (79%) visited a GP within 2 weeks of the onset of symptoms

Increased time to diagnosis principally due to increased time to specialist referral

Interval before diagnosis, according to the presenting physician:

<table>
<tr><td>Interval</td><td>All</td><td>0-3</td><td>3-6</td><td>>6</td></tr>
</table>
</td>
<td>+ve association for increased time to diagnosis for patients who have a delayed referral to specialist services. Despite figures given for receiving referral speciality no analysis based on onward referral in secondary care given</td>
</tr>
</table>

months				
GP	51	11	11	29
Haematologist	3	3	0	0
Rheumatologist	4	0	2	2
Nephrologist	6	2	1	3
Neurologist	3	2	0	1
Orthopaedic	4	1	0	3
A&E	8	3	3	2
Homeopath	1	0	0	1
Oncologist	3	2	1	0
ENT	1	0	0	1
Physician	8	4	3	1

Excluded surveillance patients from analysis as presumed 0 days wait for diagnosis

92 patient de Novo 11 patients surveillance

2 smoldering

6 MGUS

	3 plasmacytoma – account for lost to follow up and GP representing	
Li et al., 2012	N= 167 – 109 with renal disease and therefore grouped into Group I presented to nephrologist (n=29) Group II presented to a haematologist (n=62) 18 patients presented via other routes including bone surgery, cardiovascular medicine, and respiratory medicine (not further quantified). Group I median TTD 6 months Group II 0.5 months (p=<0.001) Conclude that renal damage may occur 1-6 months prior to clinical manifestations therefore in a quarter of patients renal impairment may be an initial presentation and easy to misdiagnose as renal disease	+ve association of patients who have renal disease and present to nephrology having a longer time to diagnosis
Lyratzopoulos et al., 2012	Visiting a general practitioner 3 or more times prior to referral to secondary care for myeloma= OR 3.32 (95% CI 2.70.-3.95) obtained by multivariate analysis adjusted for age, sex, deprivation and ethnicity	+ve association for visiting a general practitioner three or more times prior to referral to specialist care for myeloma patients

Table 9-6: Theme 4 Stage, complications and survival

Author/year	Context of analysis	Association reported:
Ellis-Brooke et al.,2012	One year relative survival reported by route of referral to secondary care for myeloma All routes survival 70% (95% CI 69-71) Two week wait survival 82% (95% CI 80-85) GP referral survival 81%(95% CI 79-82) Other outpatient survival (95% CI 75-80) Inpatient survival 79% (95% CI76-83) Emergency presentation survival 51% (95% CI76-83) Unknown route survival 80% (95% CI 76-83)	+ve association with decreased relative 1 year survival for myeloma patients who referred via an emergency route
Friese et al., 2009	Logistic regression – patients diagnosed during an inpatient stay more than twice as likely to experience a complication as those diagnosed as an outpatient OR 2.53 (95% CI 2.22-2.88) Significant predictors of complications included chemotherapy within 6/12 after diagnosis OR 1.40 (95% CI 1.24-1.59), more inpatient stays in year preceding diagnosis OR 1.06 (95% CI 1.01-	+ve association of complications for patients diagnosed as in patient; requiring chemotherapy within 6 months of diagnosis; having had inpatient stays in year preceding diagnosis = likely to reflect the poor health status or burden of myeloma

<table>
<tr><td></td><td>1.12) – may reflect the individuals poor health status and higher severity of myeloma</td><td></td></tr>
<tr><td>Kariyawasan et al., 2007</td><td>N= 103 - 92 analysed

45.5% of those diagnosed within 3 month – Stage I (Durie Salmon) disease and 7% stage III compared to 16% and 28.5% respectively of those patients diagnosed at >6months (p= 0.04 X^2)

Median number of complications for males = 2 for females = 1

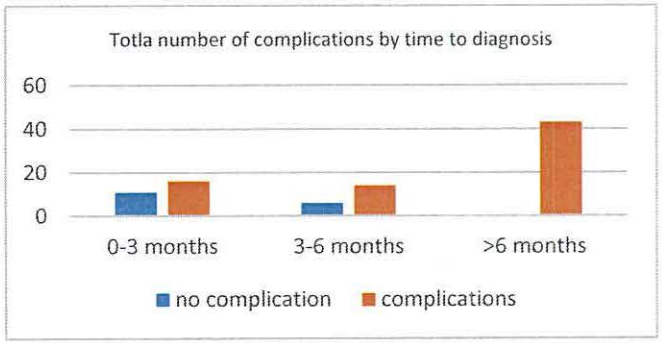
At diagnosis 18 patients had no complications vs 74 who did

Most frequent complications seen were anaemia (50/92, 45%) and renal impairment (34/92, 36%)

<table>
<tr><td>Delay in diagnosis (months)</td><td colspan="6">Durie-Salmon stage</td></tr>
<tr><td></td><td>Ia</td><td>Ib</td><td>IIa</td><td>IIb</td><td>IIIa</td><td>IIIb</td></tr>
<tr><td>0-3</td><td>12 (42%</td><td>1 (3.5%)</td><td>10 (36%)</td><td>3 (11%)</td><td>1 (3.5%)</td><td>1 (3.5%)</td></tr>
<tr><td>3-6</td><td>8 (38%)</td><td>0 (0%)</td><td>8 (38%)</td><td>2 (9.5%)</td><td>3 (14.2)</td><td>0 (0%)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td><td>+ve association with longer diagnostic journey and presentation with higher stage prognostic disease score

+ve association of longer diagnostic journey with the presence of complications</td></tr>
</table>

>6	6 (14.2%)	1 (2.3%)	14 (33%)	9 (21.4%)	8 (19%)	4 (9.5%)	



	Kaplan Meier analysis of overall and disease free survival – log rank test revealed significant benefit impact on delayed diagnosis group on disease free progression (p= 0.003 and original symptoms (p= 0.043 but no significance on overall survival	+ve association with influence of delay on disease free survival – shortening the length -ve association of delay on overall survival – no effect on shortening or lengthen survival
Li et al., 2012	Group 1 presentation to nephrologist Group II presentation to haematologist	+ve association with lower level of clinical manifestations of myeloma when presenting to nephrologist – making misdiagnosis easier and lengthening journey to diagnosis

<table>
<tr><td></td><td>Group 1 – had significantly lower incidence of bone pain (p = <0.01) and worse renal failure (p= >01.05) on presentation

Group1 patients mainly present with proteinuria

Slightly higher levels of Hb and lower incidence of moderate to severe anaemia seen in patients in group I than in Group II – these differences were insignificant (p= 0.05)</td><td></td></tr>
<tr><td>Ong et al., 21995</td><td>Stage at diagnosis:

<table>
<tr><td colspan="5">Durie Salmon Prognostic Score</td></tr>
<tr><td></td><td>I</td><td>II</td><td>III</td><td>p</td></tr>
<tr><td>Diagnosis delayed (n= 47)</td><td>13</td><td>10</td><td>24</td><td><0.001</td></tr>
<tr><td>Diagnosis immediate</td><td>8</td><td>3</td><td>69</td><td></td></tr>
</table>

<table>
<tr><td colspan="4">Number of lytic lesions</td><td></td></tr>
<tr><td></td><td>0</td><td>1</td><td>≥2</td><td>p</td></tr>
</table>
</td><td>-ve association with no differential diagnosis made at initial presentation impacting on stage of disease and number of lytic lesions</td></tr>
</table>

	Diagnosis delayed	27	2	18	<0.001		
	Diagnosis immediate	19	11	50			

Table 9-7: Theme 5 Factors associated with processes and intervals to diagnosis – Multi-morbidities

Author/year	Context of comorbidity analysis	Association reported
Friese et al., 2009	Predictor for being in delayed group for diagnosis of myeloma (journeys over the median time to diagnosis of myeloma) = ≥1 or more comorbidity present. Charlson score = p0.0001 When ≥comorbidity exists with 1- Anaemia or back pain OR 1.4 (95% CI 1.2 – 1.6) 2- Anaemia/PRBC + back pain OR 1.5 (95% CI 1.25 – 2.00) 3- No anaemia/PRBC + back pain OR 1.37 (95% CI 1.18 – 1.59)	+ve predictor for one or more comorbidity for a delay in diagnosis
Ong et al., 1995	Category collected as "other symptoms" due to comorbidity (any complaint not associated with myeloma) was present in significantly more patents in the "delayed" diagnosis group (group where differential diagnosis did not include myeloma)	+ve association of presence of comorbidity delaying a suspicion of myeloma

Table 9-8: Themes 5 Factors associated with processes and intervals to diagnosis – Age

Author/year	Context of age analysis	Association reported:
Abel et al., 2015	Effect of age on the risk of presenting as an emergency for diagnosis	Risk of presenting as an emergency for diagnosis of myeloma initially is decreased by younger age and then seen to increase with age with the oldest patients being at most risk
Din et al., 2015	Effect of age on myeloma diagnostic interval	-ve association – no significant difference in myeloma and mean change per 10 year increase in age using multivariate analysis
Friese et al., 2009	Duration of delay in diagnosis – significant differences reported – patients in delay group on average 1 year older- No sign or symptom reported (n = 1652) - 75.9 ± 6.4, no delay group (n= 1913) - 75.7 ± 6.4, delay group (n= 1918) - 76.9 ±6.6 p= 0.0001	+ve association on the length of diagnostic journey
Howell et al., 2013	Influence of age on time to diagnosis -	+ve association – patients aged 80 or over were observed to have longer diagnostic journeys. This was not further quantified
Keeble et al., 2014	Prompt presentations (patient interval) influence of age	+ve association –younger patients have more prompt presentation to health-carer
Ong et al., 1995	Influence of age on delayed journey by differential diagnosis of myeloma not being made	-ve association – age did not affect length of journey when differential diagnosis of myeloma not made in initial workup

Table 9-9: Theme 5 Factors associated with processes and intervals to diagnosis – Gender

Author/year	Context of gender analysis	Association reported
Abel et al., 2015	Effect of gender on the risk of presenting as an emergency for a diagnosis of myeloma	-ve association of gender and the risk of emergency presentation for myeloma
Din et al.,2015	Influence on diagnostic interval – myeloma at 5% significance level no evidence of an effect- pooling results of all cancers studied did show an effect.	-ve association – no effect of gender observed on diagnostic journey interval
Ong et al., 1995	Influence on having longer journey due to myeloma not being in the differential diagnosis	-ve association – no difference observed for gender (Mann-whitely or Chi square
Friese et al., 2009	Significant difference observed for gender between no delay and delay groups. Male no symptom (n = 1652) 854 (51.7), no delay (n= 1913) – 973 (50.9), delay 805 (42.0) Females – no symptoms 798 (48.3), no delay 940 (49.1), delay 1113 (58.0) (p= <0.0001)	+ve association for women experiencing delay in journey to diagnosis

Table 9-10: Theme 5 Factors associated with processes and intervals to diagnosis – Ethnicity

Author/year	Context of ethnicity analysis	Association reported
Friese et al., 2009	Predictive value of lengthened diagnostic interval by ordered logistic regression based on ethnicity Non- white race/ethnicity odds ratio 1.19 (95% CI 1.02 – 1.39)	+ve association for non- white ethnicity groups to have increase length to time to diagnosis

Table 9-11: Theme 5 Factors associated with processes and interval to diagnosis – deprivation

Author/year	Context of ethnicity analysis	Association reported
Abel et al., 2015	Effect of deprivation on the risk of presenting as an emergency for a diagnosis of myeloma	+ ve association of risk of presenting as an emergency for diagnosis in most deprived groups – this was in keeping with the majority of cancers studies (24/27)

Table 9-12: Theme 5 Factors associated with processes and intervals to diagnosis – Geography

Author/year	Context of geographical analysis	Association reported
Friese et al., 2009	Narrative text says significant differences seen for geographical region and diagnostic journey interval but this is not substantiated in the statistical data Region of residence, n (%) Northeast – No sign or symptom 308 (18.6) No delay 347 (18.1) Delay 315 (16.4) South No sign or symptom 180 (10.9) No delay 230 (12.0) Delay 216 (11.3) Midwest 407 (24.6) No delay 506 (26.5) Delay 549 (28.6) West no sign or symptom 757 (45.8) No delay 830 (43.4) Delay 838 (43.7) p=0.10 Urban resident No sign or symptom 1508 (91.3) No delay 1738 (90.1) Delay 1725 (90.0) p = 0.36	-ve – no association between geographical region and diagnostic journey duration

Table 9-13: Theme 5 Factors associated with processes and intervals to diagnosis – Diagnostic workup

Author/year	Context of analysis of diagnostic workup	Association reported
Friese et al., 2009	N = 2953 Half patients had claim for protein electrophoresis of urine or serum, 37% had BM biopsy and 42% had either bone scan or skeletal survey Less than a quarter of study patients received both protein electrophoresis and BM biopsy and only 17% received all three diagnostic tests. This was further analysed in relation to complications at diagnosis but not quantified for diagnostic delay	No association but an observation that only a quarter of patients received full diagnostic workup in this study
Ong et al., 1995	N = 945 134 out of the 945 participants on reanalysis did not fit criteria for diagnosis of myeloma as all necessary tests were not performed. 10 patients were diagnosed as not having myeloma despite having met the Durie Salmon criteria. 3 were diagnosed as having solitary plasmacytoma; 1 as having smoldering myeloma and three as having MGUS and one was suffering from Non-Hodgkin's lymphoma whilst in 2 the diagnosis was uncertain. Incomplete testing leads to misdiagnosis – a comprehensive diagnostic workup is essential in establishing a diagnosis	+ve association for incomplete testing leading to missed diagnosis

Table 9-14: Theme 5 Factors associated with processes and intervals to diagnosis – Barriers to help-seeking

Author/year	Context of analysis	Association reported
Howell et al., 2015	N = 150 (100%) Analysis of the reasons for delay in help-seeking Number with symptoms in study 118 (78.7%); total number with symptoms that reporting putting off going to the doctor 51 (43.2%). Barrier reasons given: - Did not realise symptom was serious 30 (25.4%) - Worried about wasting doctors time 4 (3.4) - Too many other things to worry about 6 (5.1%) - Too busy to go to doctor 3 (2.5%) - Worried what the doctor might find 4 (3.4) - Difficult to make an appointment 1 (0.8) - Doctor difficult to talk to 2 (1.7) - Other 1 (0.8)	+ve association for the risk that 'not realising symptoms serious' for a delay in help-seeking

Table 9-15: Main recommendations of included studies

Author and year	Main recommendations made by authors
Abel et al., 2015	• Risk of emergency presentation by sex age and deprivation group varies by cancer type • Study shows risk persist even after adjusting for age sex and deprivation • Emergency presentation is multifactorial but may provide a marker for diagnostic difficulty – apparent in harder to suspect cancer i.e. myeloma • Sociodemographic variables are more influential the authors expected – interventions should aim to reduce the proportion that can be attributable to either heath care focus • This research can be used to target policy decision for adjusting sociodemographic influence
Din et al., 2015	• Disparity highlights the need for deeper understanding of the gender differences to tailor interventions according to patients • Symptoms should not be overlooked by healthcare professionals based on patients gender only
Elliss – Brookes, et al 2012	• Methodology for categorising a Route to Diagnosis using routine collected available health service dataset can be applied in an automated fashion to all patients diagnosed with cancer in England that are recorded on cancer registries and enables research to be undertaken to understand differences within these groups
Friese et al., 2009	• Delays between diagnosis and treatment may have significant associations with outcomes and warrants further investigation • Findings of in frequent use of diagnostic testing is provocative. Low use of protein electrophoresis by PC physicians also may point to the need for adoption of diagnostic guidelines which may help in the identification of aggressive myeloma and initiation of treatment earlier • No consensus for determining clinically significant time between myeloma diagnosis and evaluation for a related sign and symptom. • Methods may not be ideal but use of mean, median and quartile categories, the tenth percentile and a continuous measure can obtain similar results
Howell et al., 2013	• No symptom signatures associated with haematological malignancies – making them difficult to diagnose • UK referral guidelines for urgent suspected cancer require refinement at the very least distinguish between myeloma, lymphoma and acute and chronic leukaemia's • Colleting self-reported symptoms allow elicitation of the patient experience giving social and contextual basis

Howells et al., 2015	• Public awareness campaigns around symptom awareness may be more challenging in haematological malignancies due to the lack of symptom signature but would be a useful step in raising awareness of these cancers – any intervention must be balanced against finite resource. • Importance of avoiding prolonged time to diagnosis of haematological malignancies to ensure earlier stage of disease at diagnosis and accrue survival advantage is still not clear – likely that tumour subtype and biology impact on outcomes in some subtypes than time to diagnosis • Presentation to doctor is just one aspect of the time taken to diagnosis - further research is needed alongside primary care practitioners to identify mechanism by which patients can be identified as early as possible and routes to haematology and diagnosis can be seamless as possible
Kariyawasan et al., 2007	• Effect of prolonged time to diagnosis on disease free survival implies an impact on the durability of remissions achieved after a delay in initial diagnosis and commencement of treatment • Data does not show a significant difference in overall survival but there was a trend to reduce overall survival from diagnosis in the group with the longest delay – this needs confirming in a larger cohort, longer follow up and co-analysis of other biological factors • Needs to be increasing awareness of myeloma and related conditions within medical communities and the general public • Further study planned in UK Myeloma UK
Keeble et al., 2014	• Aim of public awareness campaigns is to decrease patient interval – strong advocate to conduct regular survey of patient intervals in representative samples to help monitor impact • Appreciating variations in the promptness of presentations can help better targeted and tailored interventions • Recommend in overcoming difficulties of object measurement of patient interval both review of case information and interviews used – survivor attrition may bias this • Further research of timeliness of presentation among broader populations of patients with symptoms likely to be cancer related required
Li et al., 2012	• Caution required and awareness in nephrologists – when renal damage is severe and systemic symptoms are slight or moderate patients would be presented to nephrology. When this occurs it will be difficult to exact the cause of the renal damage and diagnosis of myeloma will be ignored • Earlier diagnosis and responding therapy will improve long term prognosis of patients with myeloma caused by renal damage – this early clinical clues and myeloma laboratory analysis are important. • History and cytology of the bone marrow, serum free light chains and bone image will be helpful in the diagnosis of myeloma patients with renal disease

Lyratzopoulos et al., 2012	• In PC awareness that myeloma patients are more likely to have 3 or more visits before hospital referral • Women and younger patients more likely to have greater number of visits • Findings only applicable to tax paying healthcare systems but also with a strong primary care gatekeeper function but this has implications for the diagnosis of cancers in the community • Strongly encourages research to understand better cancer signs and symptoms in women and younger patients and ethnic minority groups • Policy research should focus on cancers with a non- specific symptom signature and greater number of pre-referral consultations • Research and policy (to cope with such complex issues) should explore and assess physician level of educational interventions, further development of point-of-care decision aids, risk calculators and diagnostic tests, and system redesign to enable more appropriate and timely use of specialist diagnostic tests (e.g. imaging or endoscopy)
Lyratzopoulos, et. al. 2013	• A more liberal policy for referral and investigation of patients with non- specific symptoms may increase the number of cancer patients being diagnosed after one or two consultations; expense of additional patient anxiety and healthcare utilisation costs for patients who will be investigated but found not to have cancer needs to be considered • Wider access to PC is being advocated – there is a need to monitor the impact of GP led investigations on the promptness of diagnosis of cancer (and other pathologies) and on resource us this may be achieved by PC audit that encompasses use of diagnostic testing. Point of care diagnostic technologies can have a part in reducing the number of consultations before referral, and such tests merit further development and evaluation • Findings support the effort to improve timeliness of diagnosis by improving the sensitivity of the appraisal of cancer symptoms by GPs e.g. decision tools • Raising awareness of the importance of persistent symptoms among patients may also help reduce untimely diagnoses • Research and policy initiatives can be further prioritised focusing on patients with cancers that are more 'difficult to suspect' which are typically associated with longer PC intervals and greater pre-referral consultations
Lyratzopoulos et al., 2015a	• The appreciation of the length of the patient and primary care interval and the relative length can inform priorities for future early diagnosis research and policy strategies helping to optimally use either community based or a healthcare system based focus or their combination as applicable for all cancers
Neal et al., 2014	• NICE referral guidance has had impact on interval duration in a number of cancers but not myeloma • Overall modest reductions in diagnostic interval impacts on stage of disease and survival

	• Soft symptoms may go investigated because of guidance and fast track referral for alert symptoms – may disadvantaged these patients • There is variability across cancer types and the stages of diagnostic intervals • Identifying red flag symptoms is relatively straightforward but identifying non red flag symptoms remains a challenge for clinicians
Ong et al., 1995	• A delay in the diagnosis of myeloma is made when presenting signs and symptoms are not recognised at initial presentation • When testing is incomplete a diagnosis may be missed; a comprehensive diagnostic workup is essential in establishing a diagnosis
Shephard et al., 2015	• Findings should influence the new NICE diagnostic guidance for referral – no single symptom is a strong indicator of myeloma, repeated occurrences of back pain or back pain combined with nosebleeds or rib pain suggest initial testing of inflammatory markers, at the discretion of the GP; the risk of myeloma increases greatly with the presence of hypercalcaemia; joint pain and rib pain in conjunction with leukopenia or hypercalcaemia also signify a high risk of myeloma

9.5 Appendix 5: Dissemination protocol

Diagnostic Journeys in Myeloma (DJiM): Dissemination and knowledge mobilisation strategy

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School: Healthcare Sciences

Institution: Bangor University

Strategy for dissemination and knowledge mobilisation

It is the intention of the studentship supervisory team, the PhD candidate, The North Wales Centre for Primary Care Research (NWCPCR); Tenovus Cancer Charity (TCC) and Bangor University (BU), that the outcomes of this research project are widely disseminated. With this at the forefront of the project, a commitment to dissemination was made.

The dissemination plan is outlined below.

This document will aim to:

- Provide an understanding of the benefits of research dissemination
- Outline the strategy for dissemination of the research outcomes to include
    - Project overview
    - Dissemination goals
    - Target audience
    - Key messages
    - Sources/messenger
    - Dissemination activities, tools, timing and responsibilities:
    - Engagement
    - Budget
    - Evaluation
- Dissemination log
- Lessons learnt
- Dissemination outcome evaluation

Definition

For the purposes of this document, dissemination is defined as a term meaning communication, or the flow of information so that learning can be used to influence change and make an impact. Dissemination activities will aim to move beyond publishing and attendance at academic conferences, and seek to connect with appropriate stakeholder groups in order to engage them with the research implications and learning. Through a collaborative approach, between researchers and decision makers, it is anticipated that a greater impact will be achieved by

working towards problem solving through the sharing and exchanging of information and activating knowledge mobilisation.

Dissemination Overview

The dissemination plan aims to transfer useful and useable knowledge to appropriate and targeted audiences. The audience for this project will include: research communities, healthcare practitioners, in primary and secondary care, the public, policy makers, regulatory bodies and third sector organisations. The plan will specifically address the needs of each audience by creating tailored key messages to appropriately position the learning and encourage engagement.

1. Project overview

Myeloma is a rare, mature B cell malignancy which has longer diagnostic journeys than most other cancer types. Multiple factors are seen to contribute to longer diagnostic intervals. These include: higher numbers of primary care consultations prior to referral to specialist care; greater frequency of emergency presentation; late stage disease, poor outcomes in longer intervals to diagnosis; vague, non-specific symptoms. The full picture of journeys to diagnosis in myeloma is under researched. There is, therefore, limited ability to identify influences within journey duration or display the relative contribution of identified variables currently understood as significant. The result is a lack of policy informing literature on the timely diagnosis of myeloma, and a failure to influence practice and policy. There has been no consideration of the personal or social contextual experiences of the patient or family, health practitioner within the journey to diagnosis in myeloma. This fails to contribute to the understanding of "why" journey duration differs in myeloma and limits research for policy development.

The overall aim of this research project is to describe, in detail the journeys to diagnosis of newly diagnosed myeloma patients across Wales. The measurement of the intervals to diagnosis and treatment will be calculated. The factors associated with individual pathways will be determined, displayed and significance measured. The behavioural and contextual issues surrounding the individual journey to diagnosis will be explored. Both quantitative and qualitative methods will be used. Factors which contribute to more timely diagnosis of myeloma will be identified and inform recommendations for policy and practice.

Findings will inform practitioners involved in the diagnosis of patients with myeloma. Results are anticipated to be most impactful for primary care practitioners who, in general, are the first healthcare professionals who interact with patients who have symptoms. Secondary care clinicians, haematologists and other speciality groups will also receive disseminated finings. Practitioners outside the speciality of haematology are considered important to target as they receive referrals from general practitioners where a differential diagnosis of myeloma may be made.

Policy makers influencing cancer care will receive disseminated findings. These policy decision makers, will primarily be based in cancer services and national strategic groups in the Welsh Government and NHS Wales. These groups influence policy direction, resource and Public Health.

Third party sector representatives and funding groups, will receive disseminated findings. These groups will include the major haematological cancer charities such as Myeloma UK, Bloodwise. Additionally, national cancer charities such as MacMillan, Cancer Research UK/Cymru and Tenovus Cancer Care will receive disseminated findings. The charitable body funding the studentship, Tenovus Cancer Care, will receive additional dissemination as part of the feedback of study progression. These groups are influential collaborators in policy decision making, and their engagement is important to the dissemination process. These groups also, importantly, provide an interface between the public and researchers and can potentially contribute to dissemination to the public more widely.

Public Patient Involvement (PPI) groups will receive disseminated findings, these groups who actively participated in reviewing content for the study will receive feedback on the outcome of their contribution by way of study success and findings thereby completing their cycle of engagement.

2. Dissemination goals

The major goal for dissemination of the work is to inform policy and practice; making recommendations on how to diagnose myeloma more timely.

Additionally, dissemination will aim to raise awareness, generally, of the condition myeloma, in both the public and clinical domains.

Additionally the design of the study and the effectiveness of the methods adapted with be disseminated to the research community to reflect on the success of the

study and the usefulness of engaging these methods in further research of rare difficult to diagnose cancers.

3. Target audience

A priority group will be targeted which will reflect the key partners in dissemination. This group will include those concerned with applying the findings of the research in clinical practice, or those applying findings to policy developments. Dissemination in this primary audience will commence at conception of the study and continue, by way of continuous feedback of early findings and recruitment updates, throughout the study duration. As some of these key partners will influence the success of recruitment and data completion within the study, early engagement and understanding of study aims, is of great importance.

A secondary audience will be targeted who will receive findings at a later stage of the project, where results are more fully reported. This group will principally be an audience that has less immediate influence in the diagnostic pathway of myeloma, but may care for myeloma patients more generally. Disseminated results for this group are likely to be of interest to their practice i.e. practice nurses, physiotherapists; osteopaths etc.

Primary audience	Secondary audience
General Practitioners	Patient public Involvement Groups i.e. Involving People, North Wales Cancer Patient Forum
Decision/policy makers – e.g. Public Health, Cancer Services	Allied health carers – e.g. nurses in primary and secondary care settings; physios, OTs, osteopaths
Haematologists	Public and patients involvement groups
Hospital clinicians (other than haematologists)	Early Diagnosis of Cancer Researchers
Third sector charities – e.g. Tenovus Cancer Care, Myeloma UK, Bloodwise (formerly Leukaemia and Lymphoma Research) Cancer Research UK	Media
Research workforce: research nurses/officers, Health Board R and D departments, ethics	

4. Key messages

- Recommendations for the more timely diagnosis of myeloma for practice and policy
- A description of the factors and influences affecting intervals to diagnosis and treatment in myeloma
- A description of the personal, social and contextual differences in patients with prompt and longer diagnostic journeys
- The difficulties reported by GPs of diagnosing myeloma in primary care and their contributions to prompt and longer intervals to diagnosis
- The strengths and limitations of evaluating diagnostic journeys in myeloma in a single population of patients in a prospective manner
- Recommendations for research of timely diagnosis of myeloma and other rare cancers

5. Sources/Messengers

The key messenger will be the student researcher and dissemination will be a high priority throughout the project duration. The student researcher will be the primary messenger for clinicians in primary and secondary care settings; the research community, key partners in the study and the wider community with an interest in early diagnosis of cancer.

Key engagement partners in dissemination roles, will include the third party sector, particularly those with a remit in haematological malignancies such as Myeloma UK and Bloodwise. Engagement may take the format of providing articles for newsletters; briefing notes; attendance at development meetings discussing early diagnosis initiatives; presenting posters or plenary/ workshop sessions at conferences hosted by them of early findings and full results. Chief Executive Officers, information consultants and event's organisers will form the main contact for these organisations.

Policy makers within the cancer networks and strategic planning groups and public health will be sent briefing notes to highlight findings and recommendations.

The supervisory committee for the study, are also key messengers and their responsibility will be to, at available opportunities, impart key aims of and messages

from the study. The diversity of clinical and academic backgrounds of the supervisory committee are likely to ensure a wide audience.

6. Dissemination activities, tools, timing and responsibilities

Dissemination will commence at the start of the project, with the engagement of key partners in the research, GPs, secondary care clinicians; MDT coordinators; research workforce; Research and Development departments of the local health boards; ethics committees for University and the NHS groups. Through personal e-mail or face to face meetings (in person or via skype, video conferencing – when possible) or presentations to groups at local meetings to these key partners. Where opportunities are given for a two way exchange of information these will be prioritised (i.e. telephone/video conferencing). This importantly gives partners an opportunity to contribute to the formation of the research at a planning level, but also at a level of contributing to the research questions and outcomes themselves.

Through e-mail communication and teleconferencing, the student researcher will contact third sector organisations with an interest in haematological malignancies and early diagnosis of cancer to introduce the study. This contact may promote access to public and patient dissemination also, through news articles within third sector bulletins and presentations within public and patient roadshows. Cancer information services will be contacted to include study information on trial portfolio lists, this is likely to extend the audience reach and the level of knowledge transfer.

Every opportunity will be taken to submit abstracts, present posters or oral presentations at local, national and international conferences during the running of the study and as analysis progresses. Abstracts will be submitted from all stages of the study from underpinning methodology to results. Local conferences may include University research showcases, interdepartmental sharing of work; health board research seminars, MDT meetings in secondary care or GP workshops. This will be an important undertaking in the dissemination of early findings. In the groups associated with recruitment, this activity is likely to encourage continued engagement. Where recruitment is lower than anticipated or data returns are poor, the researcher will target these groups for presentations. National conferences, such as the early diagnosis group NAEDI/Early Diagnosis and the national cancer conference, NCRI, will be targeted. The researcher will look for collaboration with

and present to third sector group meetings and workshops associated with other interested groups of researchers and clinicians such as the London Cancer Alliance, Myeloma UK and Bloodwise. International conferences such as CaPRI (Cancer in Primary Care) will have abstracts submitted.

Social media such as Twitter, Linkedin, Researchgate will be used to highlight the study reporting and profiling for specialist events such as myeloma awareness week. The student researcher through these social media sites, will engage through activities such as "following" and "tagging" to disseminate study details and findings.

At commencement of recruitment all staff associated directly with the recruitment process i.e. research nurses/officers, haematologist, all Wales GPs, will be circulated 2 monthly newsletters. Newsletters will convey: recruitment information; questions and answers regarding trial recruitment/eligibility/data collection issues; recruitment rankings; details of publications/presentations, copies of poster presentations. This strategy has a three-way effect, firstly it maintains a high profile of the study, and secondly, it encourages recruitment by promoting healthy competition between sites, by way of recruitment league tables. Thirdly, this allows feedback of early findings which to research partners of early findings following of their valuable contribution which may encourage continued engagement.

The student researcher will submit news bulletins to media and if given the opportunity engage with interviews with the media. This allows a wider audience coverage.

Briefing document will be prepared and sent to cancer network leads, cancer strategic planning group, policy makers and Welsh Government Health Department.

End of study reports summarising major findings and recommendations will be sent out to all partners in the primary and secondary audience groups.

7. Budget

There is no specific budget for dissemination, much of the proposed actions will fall into the overall budget for the DJiM project. This is felt not to be detrimental to the implementation of the disseminating plan. The travel budget will allow travel to events to collaborate with key partners and present findings. The stationary budget will be utilised to send paper information where appropriate, but the use of web mail to disseminate newsletters etc. and maintain contact with key partners will be the

primary way of disseminating knowledge. The stationary budget will also allow the production of professional poster presentations. The telephone conference budget will support the availability of two way dialogue sessions with partners via telephone and skype, alternatively videoconferencing facilities at the University will be utilised which will reduce budget expenditure.

8. Evaluation

Evaluation will be informed through the maintenance of a dissemination log which will allow reflection of the overall process and plan. Feedback will be logged alongside the dissemination log highlighting good and less successful practices. A small number of key partners will be asked to feedback at the end of the project their engagement activity and impact through evaluation questionnaires. This will include preliminary engagement, engagement and feedback through the recruitment phase and feedback and engagement following analysis and result reporting.

9. Dissemination activity log

Stage of project	Target audience	Activity	Outcome observed	Date
Planning	Haematologist – lead clinicians MDT	E-mails to lead haematologists for MDTs across Wales outlining study aims and detailing operational needs. Follow up tele-conferencing with individual haematologists for clarification and engagement with more reluctant clinicians	Engagement – assessment of level of interest in this clinician group was positive. Valuable information relating to outcome measurement and appropriate recruitment methods for individual sites gained. Reviewing of specialist questionnaires for content and face validity – amendments made following feedback	Oct 2013 - Feb 2015
Myeloam UK Patient Info day	Networking re new study and discussion with patients regarding their interest	Poster presentation and networking	Good engagement witnessed form the patient group and clinicians attending the meeting	Nov 2013
Planning	All Wales GP	GP flyer/briefing introducing aims and objectives of the study along with details of level of participation required in primary care - to GPs in Wales region (All Wales GP circulation list). Feedback welcomed through e-mail dialogue	Engagement – no negative feedback received about methods or level of commitment required in primary care. Evaluation of questionnaires for content and face validity. Valuable feedback and amendments made to primary care questionnaires based on feedback	May 2014
Planning	All Wales MDT coordinators	E-mail communication detailing proposed study and requirements to collect all Wales figures for newly diagnosed myeloma, detailed discussions via e-mail and teleconferencing undertaken as to how best to collect this	Engagement – commitment to provide all Wales registration of newly diagnosed myeloma for study at the planning phase. Trials of the best methods of capture via activity logs	Oct 2013
Planning	Research workforce Wales – network leads	E-mails to team leads then follow up telephone conferences with individual sites for feasibility assessments	Engagement – discussion re recruitment methods and commitment to the study and best methods for completion of research data collection. Commencement of good working relationship vital for the study success with recruitment	Oct2013 – Feb 2014

Planning	Third sector organisations – Myeloma UK	E-mails and teleconferences introducing study and main aims	Presented study outline at Myeloma UK Patient Forum Valuable sharing of activities within the organisations on current priorities and strategies being undertaken Opportunity to raise awareness in the patient group and general public	Nov 2013
Planning	Research groups – known interest in topic area York (Debra Howell/Eve Bowman). Edinburgh Sara Morgan (myeloma UK research group)	E-mails and telephone conferences	Collaboration with other research groups working within the field. Sharing of some difficulties experienced with collecting similar open ended questions re data and styles of questionnaires.	Jan 2014 May 2014 Feb 2015
Planning	Involving People PPI group and North Wales Cancer Patient Forum	E-mail communication with Involving People network and Patient Cancer Groups and individual patients	Engagement- General feedback on study design and user friendliness of patient information – specific evaluation of the patient questionnaires from multiple individual patients. Useful comments and amendments made following feedback	Nov 2013 – Feb 2014
Planning	Wales REC 5	E-mails and face to face meetings	Engagement-Discussions about feasibility and ethical applications. Useful comments made about information needs of participants	Dec 2013 – May 2014
Planning	Local R and D departments within 6 Health Boards	E-mails and telephone conferences to R and D leads	Engagement – collaboration and approvals	Jan2014 – Feb 2015
Planning	NCRI conference – clinicians, researchers, policy decisions makers, public patient involvement groups, third	conference poster presentation	Study aims and objective and methodological consideration presented. Opportunity to personally introduce study to fellow researchers, clinicians, patient representatives and charities Tweets sent disseminating presentation.	November 2014

	sector organisation with an interest in cancer		**Early career bursary award granted**	
Recruitment	MDT lead clinicians and research workforce, all Wales GP	Two monthly electronic newsletters	Feedback on recruitment at individual sites, promoting good practices and successful recruitment strategies in use. League tables for top recruiters added to later editions promoting healthy competition or a "name and shame" policy to encourage meeting of targets. Frequently occurring questions from research workforce and issues answered by study researcher. As early findings were presented these were highlighted in the newsletters giving dates and venues. Posters with early results were additionally added to the newsletters as available after publishing to demon stated early dissemination and presentation of work and encourage continued engagement. Feedback from sites was very positive about receiving early analysis findings – posters were reported to be used as a learning tool for haematology and research staff and thanks giving for sharing early reports	October 2014 – Every two months
Recruitment	London Cancer Alliance – group of clinicians, haematologists and GPs and allied healthcare professionals with a remit to support early detection on blood cancers in the London and South East region	Oral presentation	Presentation of preliminary findings, first 30 patients Well received and collaboration then asked for on other grant applications. Opportunity to network with fellow researchers presenting – discussions about the progress of the DJiM project and sharing of information with York Group	February 2015 (Oral workshop presentation)

Recruitment	NAEDI national conference	Poster presentation of early findings – first 30 participants and methods	Presentation of preliminary finding to group of researchers and academics and third sector charitable groups Cancer Research UK and Bloodwise. Tweets sent disseminating presentation.	March 2015
Recruitment	York research group Stella Bowman, Simon Stern and Stephen Oliver-grant proposal for further investigations in diagnostic pathways in myeloma	E-mail dialogue	Collaborative on grant applications whilst using the experiences from the DJiM project to inform the trial design	November 2015
Recruitment	Bangor Showcase	Oral presentation of findings from the first 50 participants in Phase I	Presentation of preliminary findings to wider group of academics and researcher plus local health board clinicians, R and D personnel and policy makers. Chief Medical Officer Wales in attendance	September 2015
Recruitment	PRIME initiation meeting	Poster presentation	Poster presented in my absence to audience of policy makers and primary care leads, academics and researchers at new network launch	September 2015
Recruitment	Bloodwise – UK national blood cancer charity	Meeting with head of research and author of a published abstract of interest	Collaborative meeting – sharing of research aims and objectives and plans for future research	December 2015
Recruitment	Questionnaire analysis	Processing of data	Feedback from clinicians regarding the experience of completing the questionnaire – revealed that the process acting as a learning aid, highlighting areas of their practice where they could improve the diagnostic pathways of patients. A clinicians revealed that the experience had been beneficial and led to greater awareness and desire to revise their knowledge of myeloma and blood cancers more generally.	February 2016

			This was also reflected in the GP interviews where GPs expressed a desire to learn more about the disease and sought clarification of symptoms and referral processes	June 2015 – August 2015
Recruitment	Tenovus showcase of mobile units and attendance of HRH The Princess Royal patron of the charity	Personal introduction to HRH The Princess Royal	Opportunity to discuss briefly the DJiM project and early diagnosis of cancer research and being a grant holder with The Princess. Also networked with other patrons and committee members to discuss the study. Tweets sent about the event and discussions surrounding DJiM project	November 2015
Recruitment	Bangor Institute of Medical Health Research launch	Poster presentation preliminary findings	Poster presented to clinicians, academics, allied healthcare workers and policy makers in public health and NHS. Chief Medical Officer and Chief Scientific Advisor for Wales in attendance. Poster information highlighted by plenary speaker to audience	February 2016
Analysis	INSIRE departmental meeting	Oral presentation	Dissemination of findings from the DJiM systematic revew to fellow academics' colleagues and PhD students	April 2016
Analysis	INSIRE departmental meeting	Oral presentation	Dissemination of findings from the Qualitative Patient Interview study to fellow academics' colleagues and PhD students	April 2016
Analysis	CaPRI conference Boston USA	Oral presentation	Dissemination of findings of the DJiM systematic review. International audience of primary care clinicians, cancer policymakers and early diagnosis researchers	April 2016
Analysis	CaPRI conference Boston USA	Poster presentation with guided tour and 2 minute accompanying talk	Dissemination of findings from the qualitative patient interview DJiM study. International audience of primary care clinicians, cancer policymakers and early diagnosis researchers	April 2016
Analysis	CaPRI conference Boston USA	Networking	Active networking and dissemination of initial findings and promotion of forthcoming results. Fruitful engagement and encouraging feedback	April 2016

Analysis	School Health Care Sciences Postgraduate Research Conference	Poster presentation	Dissemination of qualitative patient interview study to fellow postgraduate researchers and school researchers and leads	May 2016
Analysis	Tenovus Cancer Charity research Engagement Officer and Storyteller	Meeting with Tenovus representatives to give an overview of the research project and findings "so far". Short biography of myself and a plan for dissemination of findings for the future and particularly through Myeloma Awareness week drawn up. Photo short for social media presentation	Series of early tweets discussing research Article for Daily Mail Wales – focus on aims of the study diagnosing myeloma early	June 2016
Results	Tenovus Lovelight Concert	Host for the evening for the annual concert for cancer survivors family and friends	Host for the event and asked to give a short report on the cancer research funded by Tenovus. Past and present research highlighted including the DJiM study. This was a public event and gave an opportunity to raise the awareness of myeloma and engage with the patient and public group	December 2016
Results	North Wales Haematologists meeting	Asked to join a meeting regarding standardisation of diagnostics for myeloma	Opportunity to contribute some of the DJiM findings to the main discussion and following this discussions with an advisory group member from Myeloma UK group	January 2017
Results	CRUK Early Diagnosis Conference London	Abstract submission for the dissemination of the Phase I survey study	Asked to combine to abstracts for one oral presentation – Oral presentation to main conference body (300+ delegated). Dissemination of main findings for the overall study Good response and dissemination seen through Twitter Excellent networking following presentation **Early career bursary award granted**	Feb 2017
Results	CRUK Early Diagnosis Conference London	Abstract submission for the dissemination of Phase II qualitative patient and GP interview study		

Results	Pending submission to BJC	Systematic review paper	Pending modification post review by authors	Pending
Results	Personal contact with local GPs	Requests from individual GPs for information on findings – prompting discussions	Dissemination of findings through sharing of presentation slides with local GPs and explanation of some of the findings in relation to case reports from their own practices.	April 2017 - continuous
Results	CaPRI conference 2017 Edinburgh	Abstract submission for the dissemination of the Phase I and II studies	Oral presentation of main findings to international audience in themed session **Cancer research UK early career award**	April 2017
Results	Myeloma UK Early Diagnosis Advisory Committee	Invited to speak and join this advisory group	Oral presentation of main findings	May 2017

10. Lessons learnt

Early engagement is paramount to the success of recruitment and running of the project and also excite and set the stage for dissemination. Third sector organisations are incredibly active in dissemination and essential key partners for successful dissemination.

11. Dissemination outcome evaluation

The table shows an active engagement and dissemination process throughout the duration of the study. There has been a diverse range of dissemination techniques used from informal networking and public engagement to international and national conference presentations.

12. Evaluation form

To be completed following final dissemination of published scientific papers

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9.6 Appendix 6: study questionnaires

Diagnostic Journeys in Myeloma: how long does it take to diagnose?

Patient questionnaire

Thank you very much for taking the time to fill in this questionnaire- it is quite comprehensive and should therefore take between 20- 30 minutes to complete.

Our aim is to gain a better understanding of the process by which people have their myeloma diagnosed. We would like to find out more about the symptoms they experience (if any), and the pathways they follow from first symptoms to treatment of their myeloma. This will help to identify ways in which myeloma can be diagnosed quickly and effectively.

Thank you once again for your time.

This information is confidential and will not be disclosed to anyone involved in your treatment

May we contact you if we need to clarify or check any of your answers in the questionnaire? If you are happy for us to contact you please supply contact details i.e. telephone number or e-mail address.

Name:

Date of birth:

Address:

Gender:

Telephone number ..... E-mail address.....

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1. Please can you confirm the details of your GP/Practice (name, practice address- as best you can remember): Please give the GP you would say provides the majority of your care, particularly relating to your diagnosis of myeloma.

Name of doctor

Name of practice

Address

Town

Postcode

---

2. Which of the following best describes the events which led to the diagnosis of your myeloma? (please tick only ONE answer)

√

I had symptoms/I noticed a bodily change and went to see my doctor/GP	
I had symptoms/I noticed a bodily change and went/was taken to Accident and Emergency (A&E)	
I had seen a doctor/GP with symptoms, but went/was taken to Accident and Emergency (A&E) when the condition got worse	
I was being investigated by my doctor(s) for another problem during which time the myeloma was diagnosed	
I was being monitored by my GP/hospital doctor having previously been diagnosed with "high proteins" (Monoclonol gammopathy of undetermined significance MGUS), and was then diagnosed with myeloma	
was having routine tests and I was referred for further investigation and diagnosed with myeloma	
I was being monitored by my GP/hospital doctor having previously been diagnosed with a plasmacytoma (a cancer lesion within the bone or soft tissue) and was then diagnosed with myeloma	
Other (please describe)	

3. The following health concerns or symptoms are commonly experienced in myeloma (please tick if you had the symptoms listed below before being diagnosed with myeloma- you may tick more than 1). We are interested in those symptoms that were unusual, above your normal level of health or new to you, that you think were related to the beginning of your myeloma

√

Fatigue/tiredness, above the norm for you	
Bone pain, new or unusual	
Anaemia, determined from a blood test	
Infection, returning, repeated or recurring	
Breathlessness, above the norm for you	
Loss of appetite	
Musculoskeletal pain (joints, muscles, bones etc), new or unusual	

Please also tell us of any other symptom(s) health concern(s) that you also had that we have not listed in the box above. Please list any/each additional symptom(s), health concern below- you may have more than 1

Or

√

This does not apply to be me- I did not have any symptoms- please tick	

4. Please write down your best estimate of the date you noticed the **first** of these health concern(s) or symptom(s) before you were diagnosed? If you cannot remember exact dates, please try to fill in the month and year.

Date of first symptom	Which symptom(s)/health concern(s) did you first experience?
DD/MM/YY	…… …… ……

Or

√

This does not apply to me- I did not have any symptoms	

5. Approximately how long did you have health concern(s) or symptom(s) before seeking attention/seeing a doctor? (Please think of the first consultation with a doctor/health professional) Please tick one answer.

√

Less than a week	
1-2 weeks	
3-4 weeks	
5-7 weeks	
2-5 months	
6-12 months	
Over 1 year but less than1 ½ years	
Over 1 ½ years but less than 2 years	
More than 2 years	

Or √

This does not apply to me - I did not have any symptoms/see my doctor/health professional	

6a Once you decided to seek advice regarding your health concern(s) or symptoms(s), how long did it take you to get an appointment with a doctor? (Please think of the first visit to the doctor to discuss your health concern(s) or symptoms(s))

Please tick only ONE answer.

Same day/next day	
Within 1 week	
1-2 weeks	
3-4 weeks	
Longer than 4 weeks	

Or

There was no waiting time because Please specify..... (e.g. you went/were taken to A&E/other reason), please tick this box	

Or √

This is not applicable to me- I had no symptoms please tick/did not see my doctor	

6b What was the date you first saw a doctor/health professional about your health concern(s) or symptom(s)? This may be your family doctor or a doctor from out of hours service or A&E. If you cannot remember the exact date, please try to fill in the month and the year.

DD / MM / YYYY

Or √

This is not applicable to me- I had no symptoms/did not see my doctor/healthcare professional	

7 How many times did you see the following after you first noticed symptoms until you were diagnosed? If you saw more than one healthcare professional please fill in EACH OF the professionals you saw.

	Please write down the number of consultations
GP	
Hospital consultant	
Consultant/specialist outside of the hospital e.g. private or NHS physiotherapist/Osteopath etc	
Other please specify	

Or

This is not applicable to me- I had no symptoms/ I did not see my doctor or others listed above, please tick	

8a If you were referred by your GP to a specialist, how long did it take you to get an appointment?

Please tick ONLY one answer. √

Less than 1 week	
1-2 weeks	
3-4 weeks	
5-7 weeks	
2-3 months	
4-5 months	
6-9 months	
9 -12 months	
Over 12 months	

Or

This is not applicable to me- I was not referred by GP- please tick		

8b. Who is the consultant doctor who has taken the responsibility for diagnosing and or treating or monitoring your myeloma? This is likely to be a haematologist and you may have been referred directly from your GP or from another speciality within the hospital.

Name of consultant:
Hospital name:
Hospital department:

8c What was the date of your first appointment with the doctor or doctors team (named above).

If you cannot remember the exact date, please try to fill in the month and the year.

DD / MM / YYYY

9. What was the date you were told you had myeloma? If you cannot remember the exact date, please try to fill in the month and the year.

DD / MM / YYYY

10. When you were given your diagnosis can you tell us whether you were taking any pain killers/relief? We are interested in knowing about the pain medication you were taking before you received any treatment for your myeloma

√

Yes	No

If the answer is YES please can you tell us what type of pain relief you were taking? If you were taking more than one type of pain killer please fill in all the boxes that apply. If you are not sure of what group the pain killers you were taking falls into please just add to the "other" box

√

Type of pain killer/relief	
Simple analgesics- usually taken for simple headaches, everyday pain and generally available at chemists or supermarkets "over the counter" e.g. paracetamol, nurofen/brufen/Ibuprofen, naproxen diclofenac/voltarol	
Weak opioids- more likely to be taken after the pain killers in the previous group if the pain doesn't go away. May need to be prescribed by your GP or purchased at the chemist e.g. tramadol, codeine/co-codamol/zapain	
Strong opioids- pain killer taken for quite severe pain that is not relieved by the other two groups of pain killers. Would be prescribed only by your GP **e.**g. oramorph/MST, oxycontin/oxynorm, fentanyl	
Adjuvant drugs- medication given sometimes alongside pain killers and often used to relieve special types of pain such as nerve pain e.g. amitriptyline/gabapentin, pregabalin	
Other- Please specify.....	

11. Have you had any of the treatments listed below for your myeloma? If so please can you estimate the date this treatment started? Please tick ALL that apply to you. You may be having more than one treatment. If you cannot remember the exact date, please try to fill in the month and the year.

Type of treatment	√	**Date of treatment** (give first date if you have more than one)
Spinal surgery- surgery on your back		DD / MM / YYYY
Chemotherapy- this may be tablets or intravenous (drip)		DD / MM / YYYY
Radiotherapy-given to parts of your body in a scanner type machine		DD / MM / YYYY
Bisphosphonate therapy- treatment for your bones to protect and keep healthy - either given as tablets or a drip		DD / MM / YYYY
Renal dialysis- usually involves 3 visits a week to be linked onto a blood cleaning machine		DD / MM / YYYY
Stem cell transplant- this is a procedure where your cells after chemotherapy are collected and then given back to you after you have received more treatment as a "rescue"		DD / MM / YYYY
Treatment not started yet/ under surveillance only/other- Please specify		

Please can you tell us some more general questions about your health?

12. Looking back over the last 2 years before you were diagnosed with myeloma, would you say your general health was (Please tick only ONE answer):

√

Very good	
Good	
Fair	
Poor	
Very poor	

13. Have you been treated for any long standing health conditions (some examples are listed below). If you have been treated for more than one condition please tick ALL the conditions you have been treated for.

If there is another condition you have been treated for that is not listed below please write in it the row marked other.

Heart disease- please specify ……	
Stroke	
Lung disease please specify ……	
Diabetes	
Other- please specify …… …… ……	

Myeloma is associated with a greater prevalence in certain ethnic groups. We would therefore like to describe the ethnic background of people in this research study.

13. Which of these best describes your ethnic group? (Please circle one choice, as appropriate). If you are descended from more than one ethnic or racial group, please tick the group you consider you belong to.

Please circle your selection

White

1 Welsh/English/Scottish/Northern Irish/British

2 Irish

3 Gypsy or Irish Traveller

4 Any other White background, please describe

.....

Mixed/Multiple ethnic groups

5 White and Black Caribbean

6 White and Black African

7 White and Asian

8 Any other Mixed/Multiple ethnic background, please describe

.....

Asian/Asian British

9 Indian

10 Pakistani

11 Bangladeshi

12 Chinese

13 Any other Asian background, please describe

.....

Black/African/Caribbean/Black British

14 African

15 Caribbean

16 Any other Black/African/ Caribbean background, please describe

.....

Other ethnic group

17 Arab

18 Any other ethnic group, please describe

.....

15. To help us further describe our population of patients could you please also provide your employment status?

Please tick only ONE answer

	√
Employed for wages	
Self-employed	
Out of work and looking for work	
Out of work but not currently looking for work	
A homemaker	
A student	
Military	
Retired	
Unable to work	
I would rather not answer	

16. Further comments

Please add anything else that you would like to tell us about your myeloma diagnosis.

Thank you very much for taking the time to complete this questionnaire.

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Primary care questionnaire

Diagnostic Journeys in Myeloma (DJiM): how long does it take to diagnose?

Primary care questionnaire

Thank you very much for taking the time to fill in this questionnaire- it should take about 20 minutes or less to complete. As part of an all Wales study examining differences in patient pathways to diagnosis of myeloma, we are sending this questionnaire to GPs of patients who have consented to participate in this study and have given their permission for us to approach their primary care doctors.

Our aim is to gain a better understanding of the process by which people have their myeloma diagnosed: the symptoms they experience, and the pathway they follow from onset of first symptom to treatment of their myeloma. This will help us in identifying ways in which myeloma can be diagnosed and treated quickly and effectively.

Thank you once again for your time.

Please can you refer to your patient's notes in completing the questionnaire as this will help in obtaining data on the time points.

Your patient named below has agreed to participate in this study. We enclose a copy of the patients consent for your records

Patient information

Study ID-number:

Full name

Address

Postcode:

Date of birth:

1. Duration of symptoms

Please estimate how long your patient had symptom(s), attributable to myeloma, before attending your practice (or other health service).

We appreciate that identifying a date of first symptom is not always straightforward- particularly when there are multiple and/or chronic symptoms. Nevertheless, we hope you can provide a "best estimate"

Estimate of symptom duration (please tick one):	√	What were or what are the symptoms?
Less than 1 week		
1-4 weeks		
5-7 weeks		
2-5 months		
6-12 months		
12-18 months		
18-24 months		
More than 24 months		
Not possible to estimate		
No symptoms (e.g. identified through monitoring program or incidental finding)		

2. Pathway of presentation-through what route did the patient **first** present? Please tick ONE. We appreciate it may not be easy to determine but we would like you to make a judgement as to what presentation related to your patients first symptom attributable to myeloma

√

Your patient presented to primary care within normal practice hours		Please can you provide your best approximation of the date of this primary care visit DD/MM/YYY
Your patient presented to primary care out-of hours services		Please can you provide your best approximation of the date of this primary care visit DD/MM/YYY
Your patient first presented to A&E (with or without your involvement)		Please can you provide your best approximation of the date of this hospital visit DD/MM/YYY
Your patient first presented to primary care, but then at a later date presented to A&E as an emergency (with or without your involvement)		Please can you provide your best approximation of the date of this primary care visit DD/MM/YYY
Your patient's myeloma was diagnosed within a follow up monitoring program		
Other-please describe		

2.1 Number of pre-diagnosis visits

How many consultations did your patient receive and/or make in the primary care setting for symptom(s) relating to/attributable to myeloma? Please count ALL visits made to the surgery to any healthcare professional, home visits etc.

Number of consultations to practice or home visits	
Does not apply to my patient- if this does not apply please specify why-	

2.2 How many **different** doctors or nurses did the patient see from the primary care team during the period from first symptom to diagnosis

GPs	
Other healthcare professionals (i.e. practice nurse/pharmacist/physio)	
Does not apply to my patient-if this does not apply please specify why	

3. What test/investigations did you order/do in response to symptom(s)

Test/investigation ordered	√	Date requested	Was the test significantly abnormal? Yes/No	Did you repeat the test? Yes/No	Number of times the test was repeated
FBC					
ESR					
Plasma viscosity					
Chemistry profile					
C Reactive protein					
Protein electrophoresis (PEP)					
Serum free light chains or Bence Jones protein					
X-rays of symptomatic areas					
Physical exam performed- with assessment of hepato-splenomegaly					
Does not apply to my patient I did not see or investigate the patient					

4. What date did you first suspect your patient had myeloma? This may be hard to define but please think about the date you received abnormal test results or saw your patient again and the patient's condition prompted your suspicions.

DD / MM / YYYY

√

Does not apply to my patient I did not see/ investigate the patient	

5 Referral to specialist medical services

What date did you first refer the patient to hospital or another specialist transferring the responsibility for on-going investigation/treatment to other medical services?

DD / MM / YYYY

Does not apply to my patient I did not refer the patient	

6 Do you know the date that the patient was seen for this referral?

Yes	DD / MM / YYYY	
	√	
No		

√

Does not apply to my patient I did not refer the patient	

6.1. If you did make a referral to specialist services, which of the following best describes the nature/characteristics of this referral? Please tick one.

√

Emergency admission: a referral to A&E/ED (or equivalent) for immediate assessment/admission	
An urgent referral for assessment of cancer symptoms/signs/test results (Note this will be within 2 weeks for Wales)	
A less urgent referral in which cancer is raised as a possibility (Note this will be greater than 2 weeks in Wales)	
A more general referral for investigations and assessment without cancer mentioned	
No referral made- please specify ……	
Other- please describe- ……	

6.2 If you made a referral which hospital speciality did you refer the patient to e.g. haematology/orthopaedics/nephrology

Speciality referred to	
Multiple referrals to specialist- please specify Each speciality referred to	

7 Additional information- comorbidities

We are interested to know what other conditions your patient has, and the severity of these conditions

Have you and/or any of your partners treated this patient (or has the patient been to hospital) for any of the following conditions? Please tick no if the condition is not present, or give in your opinion the severity of the condition, if it is present

Co morbidity present	No	Mild	Moderate	Severe
Cardiovascular disease				
Stroke				
Lung disease				
Diabetes				
Other –please specify				

8 Access to primary care

We are interested in understanding changes in patterns of access to primary care services prior to the patient developing symptoms attributable to myeloma and being diagnosed. Working back from the point of diagnosis please tell us the number of monthly consultations the patient received from your practice. This may include consultations at the GP practice or home visit, with the practice nurse GP or other.

Month	2012	2013	2014	2015	2016
January					
February					
March					
April					
May					
June					
July					
August					
September					
October					
November					
December					

9. Additional information

Looking back at this patient's pathway is there anything that could/should have been done to reach the diagnosis more quickly?

Are there any other comments you would like to make about this patients diagnostic journey?

10. Finally we are interested in knowing how many patients with myeloma you have seen/been involved with their care. This may relate to any period or stage of their care

Number of myeloma cases	Years of practice

Name (and title):

Signature:

Date:

Thank you very much for taking the time to complete this questionnaire

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Diagnostic Journeys in Myeloma: how long does it take to diagnose?

Specialist care questionnaire

Thank you very much for taking the time to fill in this questionnaire- it should take about 15-20 minutes to complete. As part of an all Wales study examining the differences in patient pathways to diagnosis in myeloma we are sending the questionnaire to healthcare providers of a sample of patients with myeloma.

Our aim is to gain a better understanding of the process by which patients have their myeloma diagnosed- the symptoms they experience, and the pathway they follow from onset of first symptoms to the treatment of their myeloma. We hope you can help us with the information on this patient's journey to diagnosis once they were referred to specialist cancer services. This will help in identifying ways in which myeloma can be diagnosed and treated quickly and efficiently

Thank you once again for your time

Please can you refer to your patient's notes in completing the questionnaire, as this will help in obtaining accurate data on time points.

tenovus your cancer charity

Your patient named below has agreed to participate in this study. We enclose a copy of the patients consent for your records

Patient information

Study ID-number:

Full name

Address

Postcode:

Date of birth:

---

1. Date patient first attended hospital with symptoms related to their myeloma diagnosis. We appreciate this date can at times be difficult to identify, particularly when there have been multiple visits in the lead up to definitive diagnosis. Put another way, it's the date that the hospital assumed responsibility for the on-going investigation/treatment for the patient. This may not be haematology but another speciality but we would appreciate information on the patient's journey from first contact with secondary care.

DD / MM / YYYY

2. Who was the patient referred to for this first consultation at the hospital?

Speciality i.e. orthopaedics, rheumatology, renal physicians	.....
Multiple referrals- please specify specialities	.....

3. Who made this referral to hospital/secondary care?

Referred from- please specify	.....

4. What date was the patient first seen by haematology/oncology for investigation of their symptom(s), (if the patient was referred directly to haematology and you have filled in question 1 and given details in question 2, please skip this question

DD / MM / YYYY

Who referred the patient to haematology/oncology? Please tick and specify the department/team that best describes the referral. You may tick more than one team if appropriate.

√

GP		Laboratory following identification of monoclonal band or other abnormal results- please specify ……	
External (out of area) e.g orthopaedic or neuro surgical centre- please specify ……		Medical speciality-e.g. renal. rheumatology, acute medical admissions please specify ……	
Surgical speciality- e.g. orthopaedics, acute surgical admissions- please specify ……		Was already under surveillance- please specify ……	
A&E (ED)		Other- please specify ……	

5. What date was this referral to haematology/oncology made?

DD / MM / YYYY

6. Diagnosis tests and dates performed

This can be decided in different ways.

Please tick **ALL** tests performed and complete as many of the following dates as possible.

	√	Test date DD/MM/YYYY
Date of report of bone marrow aspirate		
Date of report of bone marrow trephine		
Date of report of skeletal survey		
Date of report of serum electrophoresis		
Date of report of serum free light chains/Bence Jones protein		
Date of baseline blood tests: FBC ESR U&Es Ca^{++} Beta ^{2} microglobulin		
Date of MDT confirmation of diagnosis		
Date the patient was given their diagnosis		
Other-please specify		

8. Type of monoclonal paraprotein detected

√

Ig G	Ig A	Ig M	IgE	Ig D	Light chains

8.1 Sub classification

√

Kappa	
Lamda	

9. Date treatment for myeloma commenced

DD / MM / YYYY

Patient not commenced treatment- specify why e.g. asymptomatic myeloma moving into surveillance, poor prognosis for palliative treatment	

10.. Treatment choice- please specify the pathway of treatment

√

Intensive pathway		Non-intensive pathway		Palliative		Surveillance	

10.1 What determined your choice of treatment? If there were a number of factors please tick **ALL** the factors that influenced your decision.

√

Age- please specify	
Pre-existing co-morbidities- please specify	
Burden of disease at presentation and associated complications- please specify	
Eligibility criteria related to clinical research study available at site- please specify	
Not fit for autologous stem cell transplant	
Patient choice- please specify	
Guidelines for treatment/surveillance e.g asymptomatic myeloma requiring monitoring	
Other-please specify	

11. Was the patient eligible for a clinical trial open to recruitment at your centre? Please tick

√

Yes	
No	

11.1 If the answer was yes did the patient enter the study? Please tick

√

Yes	
No	

11.2 If the answer was no to question 6.1 please specify reason

Reason for not entering study	....

12. Decision to treat

Please indicate organ related disease at presentation for symptomatic myeloma patients

√

Monoclonal plasma cells in the bone marrow > 10% and/or presence of a biopsy-proven plasmacytoma	
Monoclonal protein present in the serum and/or urine	
1. Myeloma-related organ or tissue impairment (ROTI) **[C]** Corrected serum calcium elevation > 10mg/L (0.25 mmol/L) above the upper limit of normal or>110mg/L (2.75 mol/L) **[R]** Renal insufficiency Creatinine >20mg/L (173 mmol/L) **[A]** Anaemia Haemoglobin < 20g/L below the lower limit of normal or haemoglobin <100g/L **[B]** Lytic bone lesions or osteoporosis with compression fractures **Other** symptomatic hyper viscosity, amyloidosis, recurrent bacterial infection (>2 episodes in 12 months) Does not apply to my patient –asymptomatic myeloma diagnosed	√

12.1 International Staging System- please indicate

√

Stage I: β_2-microglobulin (β2M) < 3.5 mg/L, albumin ≥ 3.5 g/dL	
Stage II: β2M < 3.5 mg/L and albumin < 3.5 g/dL; or β2M 3.5–5.5 mg/L irrespective of the serum albumin	
Stage III: β2M ≥ 5.5 mg/L	

13. Chromosomal abnormalities

High risk: presence of t(4;14) or deletion 17p13 detected by FISH	
Standard-risk: t(11;14)detected by FISH	
Normal	
Not done	
Performed within a clinical trial and not known to the treating clinician	

14. If your patient has finished induction chemotherapy what response did they achieve? Please tick

√

Complete response		Partial response	
Very good partial response		Progressive disease	
Minor response		No change	

15. Finally any further comments

Looking back at this patient's pathway is there anything that could/should have been done to reach the diagnosis more quickly? Are there any other comments you would like to make about this patient's diagnostic journey?

Name (and title):

Signature

Date:

Are you a… (Please tick below):

√

Haematologist	
Medical oncologist	
Clinical oncologist	
Clinical nurse specialist	
Clinical research nurse/officer	
Other- please specify ……	

Thank you very much for taking the time to complete this

9.7 Appendix 7: Data hierarchy for quantitative analysis

Data coding DJiM Phase I:

Age determination at diagnosis:

Primary data – DOB patient questionnaire = date of diagnosis secondary care questionnaire

- Where secondary care data is not available use date of diagnosis from patient questionnaire
- Where there are dates for diagnosis for MGUS/asymptomatic myeloma and myeloma use date of myeloma diagnosis

Stage of disease:

International staging score	Code
No staging performed	0 Regression (4)
Stage I	1
Stage II	2
Stage III	3

- Primary data source = SC questionnaire
- Where no SC data is available mark as missing data
- When SC questionnaire records stage not performed record as category 0 – no staging performed (important to acknowledge incomplete testing or assessment)
- Where SC questionnaire records as non- applicable or not relevant in this category mark as 0 test not performed

Monoclonal paraprotein type:

Paraprotein type	Code
IgG	1
IgA	2
Light chain myeloma	3
Non secretary myeloma/no abnormal bands	4
IgM	5

- Primary data source = SC questionnaire
- When monoclonal paraprotein is reported alongside light chains (i.e. both boxes are ticked) record the identified paraprotein as the class of paraprotein seen i.e. IgG, IgA etc.
- When section is answered no abnormal bands record this as non-secretory myeloma
- When not specified in monoclonal paraprotein section but marked as lambda in the sub classification record as serum free light chain disease

Sub classification of paraprotein:

Sub classification	Code
Kappa	1
Lamda	2
Non secretary myeloma	4

- Primary data source = SC questionnaire
- Where a monoclonal paraprotein is recorded as non-secretary or no abnormal bands and sub classification is left blank record as non-secretary myeloma not missing data

Comorbid features: List of comorbid features:

Condition
No comorbidity
Other/previous malignancy
Hypertension
Cardiovascular disease
Diabetes
Osteoporosis
Previous MGUS
Osteoarthritis
Lung disease
Stroke
Depression
Chronic retention of urine
Temporal arteritis
Chronic kidney disease
Anaemia
Hypothyroidism
Vit B12 deficiency
Sleep apnoea
Polymyalgia-rheumaticia
Post-traumatic stress disorder
Oesophageal reflux
Irritable bowel syndrome
ITP
Splenectomy
Epilepsy
Fibromyalgia
Spinal injury
Hypercholesterolemia
Vasculitis

Comorbidity present	Code
Yes	1
No	0

Comorbidity 1 previous malignancy	Code
Yes	1
No	0

Comorbidity 2 hypertension	Code
Yes	1
No	0

Comorbidity 3 cardiovascular disease	Code
Yes	1
No	0

Comorbidity 4 diabetes	Code
Yes	1
No	0

Comorbidity 5 osteoporosis	Code
Yes	1
No	0

Comorbidity 6 MGUS	Code
Yes	1
No	0

Comorbidity 7 osteoarthritis	Code
Yes	1
No	0

Comorbidity 8 lung disease	Code
Yes	1
No	0

Comorbidity 9 stroke	Code
Yes	1
No	0

Comorbidity 10 depression	Code
Yes	1
No	0

Comorbidity 11 chronic retention of urine	Code
Yes	1
No	0

Comorbidity 12 temporal arteritis	Code
Yes	1
No	0

Comorbidity 13 chronic kidney disease	Code
Yes	1
No	0

Comorbidity 14 anaemia	Code
Yes	1
No	0

Comorbidity 15 hypothyroidism	Code
Yes	1
No	0

Comorbidity 16 Vit B12 deficiency	Code
Yes	1
No	0

Comorbidity 17 sleep apnoea	Code
Yes	1
No	0

Comorbidity 18 polymyalgia-rheumatica	Code
Yes	1
No	0

Comorbidity 19 post-traumatic stress disorder	Code
Yes	1
No	0

Comorbidity 20 oesophageal reflux	Code
Yes	1
No	0

Comorbidity 21 irritable bowel syndrome	Code
Yes	1
No	0

Comorbidity 22 ITP	Code
Yes	1
No	0

Comorbidity 23 splenectomy	Code
Yes	1
No	0

Comorbidity 24 fibromyalgia	Code
Yes	1
No	0

Comorbidity 25 spinal injury	Code
Yes	1
No	0

Comorbidity 26 hypercholesterolemia	Code
Yes	1
No	0

Comorbidity 27 vasculitis	Code
Yes	1
No	0

- Primary source data = PC questionnaire – when PC data is unavailable code comorbidity from the patient data- coded from PC data preferentially as likely to code in a more meaningful way to assist in analysis and implications for practice
- If coded from patient questionnaire and the section is not filled in mark as missing data

Length of time to help-seeking:

Duration	Code
Did not seek help	0 (Regression 9)
Less than a week	1
1-2 weeks	2
3-4 weeks	3
5-7 weeks	4
2-5 months	5
6-12 months	6
Over 1 year but less than 2 years	7
More than 2 years	8

- Primary source data = patient questionnaire
- Where category is not completed mark as missing data

Time to get a GP appointment:

Duration	Code
No waiting – planned visit (surveillance/incidental finding)	0
Same day/next day	1
Within a 1 week	2
1-2 weeks	3
No visit no symptoms	4
No waiting – Emergency admission	5

- Primary data source = patient questionnaire
- Where category is not completed mark as missing data

Gender classification:

Gender	Code
Male	1
Female	2

- Primary data source = patient questionnaire
- If gender not specified interpret from name where possible
- If name is unisex count as missing data

Ethnicity:

Ethnicity	Code
White British	1
Mixed/Multiple ethnic group -white and black African	2

- Primary data source = patient questionnaire

Work status:

Status	Code
Retired	1
Employed for wages	2
A homemaker	3
Out of work and not currently looking for work	4
Self employed	5
Unable to work	6

- Primary source data = patient questionnaire
-
- Where two categories are reported i.e. a homemaker + unable to work take the category which reflects ill health status
- Where two status are reported that reflect the status from working to retired take first status as this is likely to refer to employment at diagnosis

Welsh Index of multiple deprivation:

Deprivation category	Code
10% most deprived	1 (5 regression)
10-20% most deprived	2 (4 regression)
20-30% most deprived	3 (3 regression)
30-50 % most deprived	4 (2 regression)
50% least deprived	5 (1 regression)
Score unavailable = English address	0 (removed for regression)

- Primary data source = DJiM registry
- Where postcode not given – search by address in Post Office address tracker
- Where address is in England mark as 0 - this is not directly comparable to Welsh Index Scoring
- Where postcode is only measurable from the first two letters and two digits within the WIMD interactive tool use score for the wider postcode field examined

Health status:

Status	Code
Very good	1
Good	2
Fair	3
Poor	4
Very poor	5

- Primary source data = patient questionnaire

Analgesics taken pre-diagnosis:

Analgesic taken in pre-diagnostic stage	Code
Yes	1
No	2 (Regression 0)

Analgesic category used pre-diagnostically:

Class of analgesic	Code
No analgesia	0
Simple analgesia	1 (2 regression)
Weak opioids	2 (3 regression)
Strong opioids	3 (4 regression)
Adjuvant therapy	4 (I regression)

- Where more than one category of analgesics are reported, record the highest strength analgesic group. We are interested in knowing not just whether analgesics were required but the level of pain relief required
- If patient states elsewhere (not in this section) that they are receiving medication possibly for pain management but does not include in this category then leave as nil taken- likelihood that this could be long standing medication for another condition
- Where patient ticks no to receiving pain medication and then completes the box below listing medication taken –mark first box as analgesics taken
- Where other non-analgesic medications are reported ignore category
- Where the box is left uncompleted but patient records no analgesic taken in previous category record 0 no analgesic taken group

Symptoms:

Symptom number:

- Primary data source: Patient questionnaire
- Calculate the number of recorded symptoms given within the predefined symptom category and additional symptoms
- Where no symptoms are reported mark as 0

Symptom onset date:

- Primary data source = patient questionnaire. Secondary data source = PC questionnaire
- Record as a date
- Where month and year given record as the middle of the month i.e. 15th
- Where year only given record the middle day of the year
- Where a dates are provided in the symptom categories record the earliest date given against the symptoms

- Where participant reports no symptoms record as 0
- Where dates are given for symptoms related to an MGUS diagnosis add this as missing data
- Where symptoms are given but no date is recorded use data given re symptom duration from primary care data. Within this data if a range given for symptom duration record the middle point of the duration

Symptoms present:

Category	Code
Symptoms present	1= Yes 0 = no

First symptom experienced:

- Primary data source – participant questionnaire
- Where participant offers more than one symptom along with a series of dates – use the symptom with the first date
- Where participant acknowledged symptoms in previous category but ticks box that says "does not apply to me- no symptoms" mark as missing data
- If two symptoms given for the first symptom experienced – code as a category
- When just a date is given record as missing data

First symptom experienced	Code
No symptoms	0
Back pain	1
Chest infection	2
Back pain and # rib	3
Fatigue, muscle pain, trouble passing water	4
Pain buttocks and groin	5
Leg pain	6
Pain in ribs	7
Pain in toe	8
Back pain and loss of appetite	9
# shoulder	10
Neuropathy	11
Pain in hip	12
Pain in chest	13
Back and hip pain	14
Pain muscles and ribs	15
Pain in side	16
Awkward getting out of bed	17
Fatigue	18
Back pain and sciatica	19
Musculoskeletal pain	20
Fatigue and breathlessness	21
Back and shoulder pain	22
Sciatic pain	23
Pain in chest and fatigue	24
Bone pain	25
Arm pain	26
Fatigue and constipation	27
Back pain and nausea	28
Shoulder pain	29
Pain in legs and back	30
Back bone pain and fatigue	31

Exclude from regression

Symptom type	Code
No symptoms	0
Fatigue	1
Bone pain	2
Anaemia	3
Infection	4
Breathlessness	5
Loss of appetite	6
Musculoskeletal pain	7
Additional symptoms reported	
Weight loss	8
Skin irritation	9
Urinary problems (trouble passing water)	10
Bowel problems (constipation)	11
Locomotive problems (trouble standing up/straight)	12
Specified back pain	13
Mouth ulcers	14
Neuropathy	15
Sciatic pain	16
Allergy (insect bites)??check coding RN	17
Feeling generally unwell	18
Vomiting or nausea	19
Raised blood sugars	20
Cognitive problems (memory loss) check with RN	21
Unsteady on feet getting out of bed	22
Loss of movement of legs	23
Chest infection	24
Trouble laying down	25
Muscle spasms	26
Shingles infection	27
Gall bladder problems	28
Hip pain	29
Generalised pain which moved around	30
Reduced mobility (walking with sticks)	31
Protein high in blood	32
Pain in side of body	33
Cold sores on mouth	34
Burning top of back	35
Stiffness in back	36
Pain in shoulder	37
Chest pain	38

Symptom presents	Code
Yes	1
No	0

Symptom 1 - fatigue	Code
Yes	1
No	0

Symptom 2 bone pain	Code
Yes	1
No	0

Symptom 3 anaemia	Code
Yes	1
No	0

Symptom 4 Infection	Code
Yes	1
No	0

Symptom 5 breathlessness	Code
Yes	1
No	0

Symptom 6 loss of appetite	Code
Yes	1
No	0

Symptom 7 musculoskeletal pain	Code
Yes	1
No	0

Additional symptoms:

Symptom 1(8) weight loss	Code
Yes	1
No	0

Symptom 2 (9) skin irritation	Code
Yes	1
No	0

Symptom 3 (10) Urinary problems (trouble passing water)	Code
Yes	1
No	0

Symptom 4 (11) Bowel problems (Constipation)	Code
Yes	1
No	0

Symptom 5 (12) Locomotive problems (trouble standing up/straight)	Code
Yes	1
No	0

Symptom 6 (13) specified back pain	Code
Yes	1
No	0

Symptom 7 (14) mouth ulcers	Code
Yes	1
No	0

Symptom 8 (15) neuropathy	Code
Yes	1
No	0

Symptom 9 (16) sciatic pain	Code
Yes	1
No	0

Symptom 10 (17) allergy insect bites	Code
Yes	1
No	0

Symptom 11 (18) feeling generally unwell	Code
Yes	1
No	0

Symptom 12 (19) Vomiting or nausea	Code
Yes	1
No	0

Symptom 13 (20) raised blood sugars	Code
Yes	1
No	0

Symptom 14 (21) Cognitive problems (memory loss)	Code
Yes	1
No	0

Symptom 15 (22) Unsteady on feet getting out of bed	Code
Yes	1
No	0

Symptom 16 (23) loss of movement of legs	Code
Yes	1
No	0

Symptom 17 (24) chest infection	Code
Yes	1
No	0

Symptom 18 (25) trouble lying down	Code
Yes	1
No	0

Symptom 19 (26) muscle spasms	Code
Yes	1
No	0

Symptom 20 (27) shingles infection	Code
Yes	1
No	0

Symptom 21 (28) gall bladder problems	Code
Yes	1
No	0

Symptom 22 (29) hip pain	Code
Yes	1
No	0

Symptom 23 (30) generalised pain which moved around	Code
Yes	1
No	0

Symptom 24 (31) reduced mobility (walking with sticks)	Code
Yes	1
No	0

Symptom 25 (32) protein high in blood	Code
Yes	1
No	0

Symptom 26 (33) pain in side of body	Code
Yes	1
No	0

Symptom 27 (34) cold sores on mouth	Code
Yes	1
No	0

Symptom 28 (35) burning top of back	Code
Yes	1
No	0

Symptom 29 (36) stiffness in back	Code
Yes	1
No	0

Symptom 31 (37) pain in shoulder	Code
Yes	1
No	0

Symptom 32 (38) pain in chest	Code
Yes	1
No	0

Symptom 33 (39) pain in legs	Code
Yes	1
No	0

- Primary data source = patient
- Where symptoms are given in the additional symptom section that match exactly to the symptoms within the "symptom" section do not count these i.e. anaemia
- Symptoms reported in the additional symptom category are reported as individual symptoms

Date of presentation to primary care:

- Primary data source = patient questionnaire
- Where participant does not give date within patient questionnaire take date given in primary care questionnaire when available
- Where participant gives a date that is incomplete check primary care record and if available to clarify patient record with this date i.e. participant writes June 2014 – check PC questionnaire GP record visit as 12/6/2014 – use this data. If these dates to not correspond i.e. participant gives date as June 2014 and GP record 19/9/2014 modify participant date as below
- Where a month and year is given use the middle point of the month to establish a date
- Where the participant or GP reports no consultation with patient record as 0
- Where date given by participant or GP relates to the diagnosis and follow up surveillance of MGUS record but exclude from analysis

Number GP visits:

- Primary data source = patient
- When box is ticked for attended GP but number of visits is unspecified count 1 visit: important to acknowledge involvement of GP but cannot assess number
- When term "couple" count 2 visits; when term "few" count 3 visits.
- When the term numerous/loads is used use number 5
- When a number is given such as 8+ or more than 4 count the figure given. This is likely to ensure no over estimation
- When a range of figures is given count the highest figure given i.e. 4-5 use 5
- When dates are given but no figure count the dates as one even t

Other healthcare seen in primary care interval:

Type as specified	Code
No visits to other health carers in PC	0(excluded for regresssion
Osteopath/physiotherapist unspecified	1
Non NHS consultant	2

- Primary source = patient
- Separate number of GP visits into a separate category
- Where hospital consultant visits are recorded these are removed as they relate to visits where transfer of care has been made to secondary care by primary care
- Where patient record category does not apply to them – record as no visits made

Number of different GPs seen in PC:

Category	Code
Record number specified	1 - 5
Does not apply to my patient	0 (excluded for correlation and regression
GP states impossible to determine	10 (excluded from regression and correlation)

Primary data source = PC questionnaire

Number of different healthcare professionals seen in PC (excluding GP):

- Where only one answer is given report this as the number of different GPs seen

Category	Code
Record number specified	1 - 5
Does not apply to my patient	0 (0 remove for regression
GP states impossible to determine	10 (remove from regression)
No healthcare professionals seen	11 (0 for regression)

Primary data source = PC questionnaire

- Where the GP responds to number of GPs seen but leaves the healthcare professional section black record this as no healthcare professional seen

Patient data events leading to diagnosis (Patient data):

Event	Code
Symptoms and PC presentation	1 (5)
Symptoms and presentation as emergency to SC	2 (6)
PC presentation then presentation then emergency presentation to SC	3 (7)
PC presentation and investigation for another problem (incidental finding)	4 (3)
Monitored by GP/hospital for MGUS and diagnosed with myeloma	5 (1 regression)
Routine testing prompted investigation and diagnosis	6 (2)
Monitored for previous plasmacytoma then diagnosed with myeloma	7 (1 regression)
Referral from allied health carer	8 (4)

- Primary data source = patient
- Where two events are described use the broader descriptive category i.e. "I had symptoms and went to GP", given alongside "I was being investigated for another problem". Priority here is to include interaction with GP, therefore, use "I went to GP" category
- Where the description of events is given in the "other" grouping but fits a category already specified i.e. I was taken to AE by my wife after being seen by GP and been given painkillers – use the wider category pre-defined.
- Where data cannot be interpreted clearly i.e. "does not apply to me I was diagnosed in hospital" that does not allow analysis of whether this was a follow up/surveillance or emergency presentation. Review the description of events within the questionnaire and within the other questionnaires and interpret a "best fits" category

Presentation to PC (PC data)

Category of presentation	Code
Presented within normal working hours	1 (2)
Presented to out of hours services	2 (4)
Presented to AE (with or without your involvement)	3 (6)
Your patient presented to PC then went onto present as an emergency (with or without your involvement)	4 (5)
Patient was within a surveillance program	5 (1)
Other	6 (3)

Primary data source = PC questionnaire

- Where two answers are given tot eh question include the answer that depicts the GP involvement i.e. if presented to PC and diagnosed within a surveillance program are given as answers use presented to PC as this reflects an involvement of the GP

Tests performed in PC:

Category	Code
Clinical investigations performed in primary care	1= yes 0 = no

Tests ordered in primary care
No tests ordered
FBC
ESR/PV
U&Es
LFTs
X-ray symptomatic area
PEP
SFLC/BJP
Microscopic haematuria
Physical exam
CRP
MRI/other radiological assessment

Test ordered	Code
FBC	Test performed = 1 Test not performed = 0

Repeated for each individual test

- Primary data source – Primary care questionnaire
- Code radiology other than plain x –ray together
- Where ESR or Plasma viscosity recorded code together
- CRP and U&Es coded separately0

Abnormal tests recorded:

Abnormal tests recorded	Code
Test performed but no tests reported as abnormal	1
Abnormal tests recorded	2
No tests performed	0 (removed for regression)

Test performed	Code
FBC	2 = abnormal 1 = not abnormal 0= test not done (removed for regression0 4 = lab error (removed for regression)

Repeated for each individual test recorded

- Where tests are reported abnormal individually record the tests specified as completed but not reported as normal as "not abnormal"
- Where category ordered tests is complete but section specifying abnormal tests and reordered test remain empty count this as missing data
- Where tests are reported as completed but no answer is given as to whether abnormal or not then record as missing data
- Where tests are not performed record this as tests not performed rather than missing data

Repeated investigations:

Test category	Code
Test repeated	2
Test not repeated	1
No tests performed	0 (removed for regression)

Test repeated

Test category	Code
FBC	Yes = 2 No = 1 Not performed = 0 original test not performed (removed for regression)

Repeated for individual tests

- Where the categories have been completed for tests performed and abnormal test but section left blank for repeated investigations record this as no investigations reordered

Date of first investigation in PC:

- Primary data source = PC questionnaire
- Use first date given for investigations of FBC, PV, ESR, U&E LFT X ray
- If month and year given use middle of month i.e. 15th
- Where the date or year is unclear and another date is available for a different test use this test date
- Record 0 if nil performed

Date of MM specific investigation in PC:

- Primary data source = PC questionnaire
- Use first date given for either PEP or serum BJP/SFLC
- If month and year given use middle of month i.e. 15th
- Record 0 if nil performed

Date GP first suspected a myeloma diagnosis:

- Primary data source = primary care questionnaire
- Record 0 when GP marks as non-applicable patient within a surveillance program. This will be checked by referring to category pathway of presentation within the primary care questionnaire
- Record 1 for GP who reports category non applicable because they did not see or investigate the patient. Pathway of presentation will be used to judge the authenticity of the statement
- Record 2 to GP who reports investigating patient but not suspecting myeloma before the diagnosis was made
- Where a month and year is reported but no day take the middle point of the month given

Date referred to SC by PC: Date referred to haematology in SC= to allow primary care interval determination

- Primary data source = primary care questionnaire
- Where PC questionnaire is not available use date of referral to haematology in the SC questionnaire to enable analysis of primary and secondary care intervals
- Where two dates are available one for MGUS diagnosis and one for MM diagnosis use the later set of dates that depict the time intervals for diagnosis of myeloma
- Where only one set of dates appear for referral and this relates to the diagnosis of MGUS and the commencement of surveillance – record this date but exclude from analysis
- Where month and year only are entered take the midpoint of the given month
- Where there is more than one referral made or the level of referral changed use the date of the original referral made

Type of referral instigated from primary care:

Referral Type	Code (regression coding)
No referral made by GP	0 (7)
Two week wait – urgent ref cancer	1 (2)
Urgent referral without cancer (non-cancer speciality team)	2 (3)
A less urgent referral in which cancer is raised as a possibility	3 (4)
More general referral for investigations and assessment without cancer mentioned	4 (6)
Emergency admission	5 (1)
Re-referral	6 (5)

- Primary data source = PC questionnaire
- Where GP describes a telephone referral – report as TWW or urgent non cancer referral depending on who referral made to i.e. haematology = TWW; nephrology = urgent but no mention of cancer likely
- Where two referral routes are given take the earliest referral route given
- Where GP marks referral category as non-applicable mark as no referral made

Date first seen in secondary care:

Primary data source = SC questionnaire

Date first seen by haematology:

Primary data source = SC questionnaire

- Where a month and year only are given take the midpoint date within the month
- Where two dates are given relating to two separate diagnostic workups record the latter date which relates to the workup where the patient entered the study
- Where presentation relates to diagnosis of MGUS and the commencement of surveillance mark this section as 0 – surveillance
- Where the referral was direct to haematology and presentation to SC was with haematology record date of presentation to SC if absent in the presentation to haematology section

Referral of care from PC to SC:

Team referred to:
No referral made
Haematology
Urology
COTE
ENT
General Medicine
Surgical
Respiratory
Oncology
Orthopaedics
Nephrology
Cardiology
Osteoporosis clinic
Under surveillance
Musculoskeletal team
Emergency medicine

Referred from PC to haematology:

Referral made to:	Code (Regression)
Haematology	1 = Yes (1) 2 = No (0) 0 = no referral made (removed)
Urology	1 = Yes (1) 2 = No (0) 0 = no referral made (removed)

The repeated for each team as above

Multiple referrals made	1 = Yes (1)2 = No(0) 0 = no referral made (removed for regression)

- Primary source date = PC questionnaire
- Where surveillance is reported alongside an emergency admission record as an emergency

Symptom start date:

- Primary data source = patient data
- If patient data does not specify a symptom start date then check symptom duration category in primary care data and use this
- If month and year given – use middle date of month as start date
- If Year only given use middle point of year
- If a time frame is given with a specific date i.e. presentation to primary care date and symptoms acknowledge as present 2-5 months previous to presentation, calculate midpoint of time interval and subtract this from the start date

Number of myeloma patients seen (GP)

- Primary data source = PC questionnaire
- Where a figure is given i.e. less than or more than use the exact figure written
- If marked unsure with no figure then mark as missing data
- If ambiguous statement given but says several record 5, few record 3, couple record 2
- Where a range is given i.e. 4-5 use the upper limit figure
- If incidence reported as a number per year calculate annual number for years of doctors medical service

GP years of practice:

- Primary date source = PC questionnaire

SC referral taken from:

Referring clinician/team	Code
No referral – in surveillance	0
GP	1
Self-referral ED attendance	2
Out of area referral	3
Internal referral	4
Non NHS discipline i.e. ophthalmology	5

Primary data source = SC questionnaire **Haematology referral received from:**

Referring clinician/team	Code (Code for regression)
GP	1 – referred 2 – no referral (0)
Laboratory identification	1 – referred 2 – no referral(0)
Renal medicine	1 – referred 2 – no referral(0)
Surgical speciality	1 – referred 2 – no referral(0)
Radiology	1 – referred 2 – no referral(0)
Under surveillance	1 – referred 2 – no referral(0)
Acute medical admissions	1 – referred 2 – no referral(0)
Orthopaedics	1 – referred 2 – no referral(0)
Acute surgical admissions	1 – referred 2 – no referral(0)
External referral out of area (Orthopaedics)	1 – referred 2 – no referral(0)
General medicine	1 – referred 2 – no referral(0)
Respiratory medicine	1 – referred 2 – no referral(0)
Rheumatology	1 – referred 2 – no referral(0)
Anaesthetics	1 – referred 2 – no referral(0)
External out of area (Oncology)	1 – referred 2 – no referral(0)
Pain Team	1 – referred 2 – no referral(0)
External out of area – non specified	1 – referred 2 – no referral(0)

Gateway access to SC:

Number teams seen:

Measure the number of teams/departments recognised within the SC questionnaire as being involved in the diagnostic journey

Data hierarchy= SC questionnaire

- Where surveillance program is given count as one department separate from haematology – we cannot ascertain if this surveillance is in primary or secondary care. Additionally surveillance in haematology may be as within a different team or hospital

Team referred to in SC	
gastro, ED, haematology	1
lab haem	2
renal haem	3
gastro lab haem	4
urology renal haem	5
radiology via GP request lab/haem	6
surveillance program haem	7
haem	8
haem	8
lab surveillance haem	9
haem	8
COTE renal haem	10
haem	8
acute medical admissions haem	11
gastro acute medicine lab haem	12
ortho haem	13
ortho oncology haem	14
surveillance lab haem	9
acute surgical admissions haem	15
haem	8
haem	8
lab haem	2
acute medical admission ED haem	16
orthopaedics out of area haem	17
ED acute surgical admission orthopaedics/trauma haem	18
orthopaedics haem	17
haem	8
haem	8
general med, acute medical admission haem	18
acute medical admissions haem	11
orthopaedics haem	17
haem	8
haem	8
renal haem	3
musculoskeletal orthopaedic haem	18
surveillance lab haem	9
haem	8
acute medicine lab haem	19

ED general medicine haem renal lab	20
general medicine haem	21
haem	8
respiratory haem	22
lab haem	2
haem	8
haem	8
lab renal haem	23
general physician haem	21
renal cardiology haem	24
orthopaedics minor injuries unit haem	25
metabolic clinic respiratory rheumatology haem	26
ED orthopaedics haem	27
lab haem	2
acute medical admissions haem	11
haem	8
haem	8
general medicine lab haem	28
orthopaedics surveillance haem	29
ED acute medicine general medicine haem	30
haem	8
ED acute medical admission haem	16
acute surgical admissions orthopaedics haem	31
haem	8
haem	8
haem	8
anaesthetists/radiology haem	32
ED orthopaedics haem	27
ED renal haem	33
haem	8
respiratory haem	22
haem	8
ED orthopaedics oncology haem	34
haem	8
haem	8
surveillance haem	7
acute medicine haem	11
surveillance haem	7
musculoskeletal early intervention team PSIN team haem	35

haem	8
lab haem	2
orthopaedics haem	17
haem	2
ophthalmology haem	36
lab haem	2

- Primary data source = SC (more complete list available and several categories capture the referral process)
- Secondary source – if not clear in SC data PC, then patient data to be used
- The use of several categories of evidence areas strengthens the interpretation of the pathway used. i.e. domains of team referred to in SC; team first seen in SC, who made referral to SC

Test performed in SC:

Test	Code
Bone marrow aspirate	1
Bone marrow trephine	2
Protein electrophoresis (serum)	3
SFLC/BJP	4
FBC	5
ESR/PV	6
U&Es	7
Calcium	8
Beta 2 micro-globulin	9
Skeletal survey	10
Other radiological assessment MRI, bone scan	11
Bone biopsy	12
CRP	13

Test performed coding:

Test performed	Code (Regression coding)
BM aspirate	1 = yes 2 = not performed (0)
BM trephine	1 = yes 2 = not performed(0)
Protein electrophoresis serum	1 = yes 2 = not performed(0)
SFLC/BJP	1 = yes 2 = not performed(0)
FBC	1 = yes 2 = not performed(0)
ESR/PV	1 = yes 2 = not performed(0)
U&Es	1 = yes 2 = not performed(0)
Calcium	1 = yes 2 = not performed(0)
B2M	1 = yes 2 = not performed(0)
Skeletal survey	1 = yes 2 = not performed(0)
Other radiological assessment	1 = yes 2 = not performed(0)
Bone biopsy	1 = yes 2 = not performed(0)
CRP – removed from analysis as info not collected from all participants	1 = yes 2 = not performed

Cytogenetic assessment:

Result	Code (Regression coding)
High risk: presence of t(4:14) or deletion 17p13 detected by FISH	1 (3)
Standard risk t(11:14) detected by FISH	2 (2)
Normal	3 (1)
Not done	4 (5)
Performed within a clinical trial and not known to the treating clinician	5 (4)
Unsure	6 (removed)
Sample failed	7 (removed)

- If results marked as "waiting" – enter as missing data – it did not influence treatment decision making

Treatment commenced date:

- Primary data source = SC questionnaire
- Where secondary care questionnaire missing collect from patient questionnaire
- If patient/SC questionnaire gives month year only take middle day of month and record as a date
- Where patient/SC questionnaires gives month and year and states the beginning or end of the month use 1st and 30/31st as date
- Where patient has not commenced treatment record 0
- Where dates are given for both radiotherapy and chemotherapy for myeloma use the earliest date for either treatment
- Where date for radiotherapy is given for treatment of plasmacytoma and another date for treatment of myeloma use the date of commencement from the myeloma treatment

Decision to treat (ROTI/CRAB) based on:

Category present	Code
Monoclonal plasma cells in bone marrow >10% and/or presence of a biopsy proven plasmacytoma	1
Monoclonal protein present in the serum and/or urine	2
C – corrected serum calcium elevation > 10mg/L (0.25mmol/L) above the upper limit of normal or>110mg/L (2.75mol/L)	3
R – renal insufficiency Creatinine >20mg/L (173 mmol/L)	4
A – Anaemia haemoglobin < 20g/L below the lower limit of normal or haemoglobin <100b/L	5
B – Lytic bone lesions or osteoporosis with compression fractures	6
Other symptomatic hyper viscosity, amyloidosis, recurrent bacterial infection (> 2 episodes in 12 months)	7
Does not apply to my patient - asymptomatic myeloma	0

Category	Code (Regression coding)
e.g. Monoclonal plasma cells in bone marrow >10% and/or presence of a biopsy proven plasmacytoma	1 = present (1) 2 = not present (0)

Repeated for all individual categories

Treatment choice:

Pathway	Code
Intensive	1
Non intensive	2
Surveillance	3

- Primary data source = SC questionnaire

Treatment decision based on:

Reason	Code
Age	1
Pre-existing comorbidity	2
Burden of disease at presentation	3
Eligibility for clinical trials	4
Not fit for ASCT	5
Patient choice	6
Guidelines for treatment/surveillance	7
Other	8

- When data added to other but fits into an existing category such as complications or comorbidity – count within this category

Category	Code (regression coding
e.g. Age	1 = present (1) 2 = not present (0)

Repeated for all individual categories

Eligible for clinical trial:

Eligible	Code (regression coding)
	0
Yes	1 (0)
No	2 (1)

Entered a clinical trial:

Eligible	Code (regression coding)
	0
Yes	1 (1)
No	2 (0)

Reason for not entering:

Reason	Code
NA entered study	0
Patient choice	1
Clinician choice due to clinical condition	2
No trial at site	3
Rapid deterioration in clinical condition	4

Response to treatment:

Response measured	Code
Complete response (CR)	1
Very good partial response (VGPR)	2
Partial response (PR)	3
Minor response (MR)	4
Progressive disease (PD)	5
No change	6

- Where clinician adds currently on treatment – mark as missing data

Date of diagnosis:

Primary data source = secondary care questionnaire. Secondary source data = patient questionnaire

- SC date hierarchy for date of diagnosis:
    - BM aspirate report date
    - Skeletal survey report date
    - PEP or BJP/SFLC report date
- If two clinical diagnostic workup dates are reported one for MGUS or asymptomatic MM and one for diagnosis of MM take the dates for the workup for myeloma
- In absence of secondary care data take date of diagnosis from patient data
- In absence of date of diagnosis being completed in patient data – mark as missing date
- Where bone marrow performed as part of diagnosis of asymptomatic myeloma/MGUS or solitary plasmacytoma and further investigation has been performed such as skeletal survey or PEP to identify ROTI (CRAB) and diagnosis of myeloma made use the date of the investigation performed to confirm ROTI

Access to primary care:

Primary data source = PC questionnaire

- Calculate point of diagnosis from secondary care data if not acknowledged on form by GP completing questionnaire and work back for 24 months from the point of diagnosis
- Where the GP completes boxes with a number but leaves other boxes empty record this as 0 visits
- If no number is given just a tick in each box count this as one visit
- If visits specify a difference between the healthcare professional seen during consultation i.e. nurse or GP count the total number of visits within each box i.e. GP x 2 Nurse x 1 = 3 visits

Survival analysis:

Death of participant:

Collected directly from sites on the survival analysis CRF and intended to display overall survival (OR). Date from diagnosis to death of participant

- Collect as a date DD/MM/YYYY
- Participant alive mark as A

Time to next treatment (TTNT):

This is a pragmatic attempt to capture disease progression in the participant to measure disease free progression. Rather than use a complicated criteria to assess clinical progression which may results in poor data production: clinicians deciding participant does not require treatment and therefore be misrepresentative: the data be incorrectly applied due to the research nurse being asked to use a complicated criteria to assess this variable; a more practical approach was adapted. Collected from sites was the date the patient first received treatment for progression of disease. This is an unusual category as myeloma treatment does not follow the same expected trajectory as solid tumours and therefore requires specific survival analysis. The model for this survival analysis rather than replicating the hierarchy of data in the Aarhus statement (Weller et al., 2014) applied the format adopted in Kariyawasan et al., 2007 and He et al., 2012.

- Collect as a date DD/MM/YYYY
- Where month and year given use the midpoint of the month i.e. day 15
- Qualify with sites if stem cell transplant or maintenance treatment is added to the form and ask for the CRF to be recompleted.
- Participant not progressed mark as NA

9.8 Appendix 8: Ethical application

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters) Diagnostic Journeys in Myeloma (DJiM)

1. Is your project research?

◉ ○

2. Select one category from the list below:

○ Clinical trial of an investigational medicinal product

○ Clinical investigation or other study of a medical device

○ Combined trial of an investigational medicinal product and an investigational medical device

○ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice ○ Basic science study involving procedures with human participants

◉ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

○ Study involving qualitative methods only

○ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

○ Study limited to working with data (specific project only) ○ Research tissue bank

○ Research database

2a. Please answer the following question(s):

	○	◉ No
a) Does the study involve the use of any ionising radiation?	○ Yes	◉ No
b) Will you be taking new human tissue samples (or other human biological samples)?	○ Yes	◉ No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

☐ England
☑ Scotland
☐ Wales
☐ Northern Ireland

○ England

○ Scotland

◉ Wales

○

○ Northern Ireland

This study does not involve the NHS

4. Which review bodies are you applying to?

☑

☐ NHS/HSC Research and Development offices Social

☑ Care Research Ethics Committee Research Ethics

☐ Committee

National Information Governance Board for Health and Social Care (NIGB)

For NHS/HSC R&D offices, the CI must create Site-specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ○ No

Please describe briefly the involvement of the student(s): this research project forms part of a PhD programme

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ Yes ○ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

○ Yes ◉ No

Integrated Research Application System

Application Form for Research administering questionnaires/interviews for quantitative analysis or mixed methodology study

NHS/HSC R&D Form (project information)

Please refer to the Submission and Checklist tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms) Diagnostic Journeys in Myeloma (DJiM)

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Diagnostic Journeys in Myeloma (DJiM): Why are they so long and what may facilitate earlier diagnosis?

A2-1. Educational projects

Student 1

	Title Forename/Initials Surname Mrs Tania D Seale
Address	The Old Rectory Llanddona Beaumaris Isle
Post Code	of Anglesey LL588UR
E-mail	t.d.seale@bangor.ac.uk
Telephone	

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree: PhD

Name of educational establishment:

Name and contact details of academic supervisor(s):

Academic supervisor 1

	Title Forename/Initials Surname Prof Richard D Neal
Address	North Wales Centre for Primary Care Research
	Bangor University, Gwenfro Unit 5
	Wrexham Technology Park, Wrexham
Post Code	LL13 7YP
E-mail	r.neal@bangor.ac.uk
Telephone	01978 725328
Fax	

Academic supervisor 2

	Title Forename/Initials Surname Prof Lynne Kennedy
Address	Head of Department of Clinical Sciences & Nutrition
	University of Chester
	Parkgate Road, Chester
Post Code	CH1 4BJ
E-mail	l.kennedy@chester.ac.uk
Telephone	01244 513054
Fax	

Academic supervisor 3

	Title Forename/Initials Surname Prof Christopher Fegan
Address	Director of Research and Development, Honorary Consultant Haematologist Cardiff University/Cardiff a
	Institute of Cancer & Genetics Cardiff University School
	Institute of Medical Genetics Building Heath Park Cardiff
Post Code	CF14 4XN
E-mail	christopher.fegan@wales.nhs.uk
Telephone	
Fax	

Please state which academic supervisor(s) has responsibility for which student(s):

Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Mrs Tania D Seale	☐ Prof Richard D Neal Prof Lynne Kennedy Prof Christopher Fegan

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

◉ Student

○ Academic supervisor

○ Other

A3-1. Chief Investigator:

	Title Forename/Initials Surname Mrs Tania D Seale
Post	Postgraduate Researcher & PhD S tudent
Qualifications	BSc (Hons) Bio medical Science, Diploma of Professional Practice, Haematology Nursing, Registered General Nurse, Certificate of Higher Education
Employer	Institute of Medical and Social Care Research, Bangor University
Work Address	North Wales Centre for Primary Care Research Bangor University, Gwnefro Unit 5 Wrexham Technology Park, Wrexham
Post Code	LL13 7YP
Work E-mail	t.d.seale@bangor.ac.uk
* Personal E-mail	tania_seale@hotmail.com
Work Telephone	01978726651
* Personal Telephone/Mobile	07879779259 Fax

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?

	Title Forename/Initials Surname Prof R T Woods
Address	Insitute of Health and Social Care Research Ardudwy Building, Normal Site, Bangor University, Bangor LL57 2PX
Post Code	b.woods@bangor.ac.uk 01248383719
E-mail	

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):

Sponsor's/protocol number: Protocol Version: 1.1

Protocol Date: 09/05/2014

Additional reference number(s):

Ref.Number Description	Reference Number

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.*

Primary outcome: to describe in detail diagnostic journeys in myeloma
Research questions:

- How do diagnostic journeys occur in myeloma patients across Wales?
- What factors, interactions and experiences influence the pathway to individual diagnosis?
- What factors can facilitate timely diagnosis?

Background:

There is a dearth of information relating to the diagnostic journeys of myeloma patients. Myeloma is a rare cancer and is 'hard to diagnose', it is characterized by non-specific and vague presenting symptoms and is mainly a disease of the elderly, where comorbidities may mask its presentation. Its rarity (myeloma accounts for 1.5% of all newly diagnosed cancers in the UK) results in primary care physicians having little exposure to the disease and higher levels of GP consultations are seen with longer time intervals to diagnosis. The general hypothesis of earlier diagnosis of cancer is that timely diagnosis decreases burden of the disease and elicits better outcomes.

Methods: This is a prospective mixed methods designed study protocol.

Phase 1: Collection of data through myeloma specific questionnaires directly from the patient, the GP and diagnosing specialist (usually a haematologist) will produce data on complex pathways components and intervals. Prospective recruitment reduces recall bias in patient and clinicians. Questionnaires, additionally, through open ended questions collect narrative data of perceptions and experiences which informs Phase 2
Phase 2: A qualitative study, using individual semi structured interviews from a purposively selected group of patients, is proposed to explore in more detail patients individual and subjective experience and understanding of the diagnosis journey for myeloma. This will include consideration of the interaction between patient, health professional (GP) and health services associated with the diagnosis of myeloma.

190 Patients will be recruited from across the 7 health boards in Wales through the established MDT infrastructure, facilitated by the research network workforce NISCHR CRC.

Eligibility

- Patient over 18 years of age
- Able and willing to give informed consent
- Able and willing to complete the study interventions complete questionnaire

• Has been diagnosed with asymptomatic or symptomatic myeloma as defined by the MDT
• Diagnosed within 6 months of study registration

Exclusion criteria

• In the last few days/weeks of life and too unwell to complete questionnaire

Results: Results will be used to inform practice and policy

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

We consider this study to have a low risk ethical component, but some aspects are considered below.
Risks to patient include distress caused by recalling their diagnostic journey and we have measures in place (discussed later) to ensure the interviewer has a solid skill base to conduct interviews and sign post to appropriate services if distress occurs (e.g. GP/Research Nurse/hospital team). The experience in the similarly structure questionnaire study ICPB Module 4 being conducted in Wales, is that over 200 participants have been recruited in Wales and to date there have been no concerns raised about the design of the questionnaire. Additionally the study researcher has had questionnaires piloted by the Involving People Network and the North Wales Cancer Research Network Forum group and modified the questionnaires based on their feedback to ensure the design and style of questions are user friendly and not distress provoking.

The organizational conduct of the study is considered also to be low risk as the study recruits through the established infrastructure within the secondary care hospitals, utilizing MDTs to identify patients and confirm eligibility and research network workforce staff to approach patient protecting identity of the patient from the researcher until the patient voluntarily gives informed consent. Additionally operational handling of data will be conducted by staff familiar and trained in GCP and ensure quality of the research and data generated in the early recruitment phase.

Management of the study: The study researcher is GCP trained and has established research project management skills. A robust system of Supervision is in place for the student as part of the PhD supervisory process. Additionally the Supervisory Committee members are experienced independent researcher as well as being experienced supervisors to current and previous PhD students

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐
- ☑ Case series/ case note review
- ☐ Case control
- ☐
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study

☐ Feasibility/ pilot study

☐ Laboratory study

☐ Metanalysis Qualitative

☑ research

☑

☐ Questionnaire, interview or observation study

☐ Randomised controlled trial

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The primary aim of this research study is to describe, in detail, the diagnostic journeys of patients with myeloma and determine potential interventions to prevent unnecessary delays in diagnosis. That is we wish to describe, in depth, the way people come to be diagnosed with their illness, describing the interval in the different stages of the pathway, the symptoms suffered by individuals and the health care professionals patients may see along this route to diagnosis. This forms the quantitative phase of the research. Additionally we will conduct a qualitative interview study where we will aim to describe in-depth the patients' individual and subjective experience and understanding of the diagnosis journey for myeloma. Through describing these pathways we aim to determine factors which facilitate earlier referral and diagnosis and commencement of treatment as well as determining factors which have influenced and effected the length of time to diagnosis that those factors which have caused delay.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

- What factors, interactions and experience influence the pathway to individual diagnosis?
- What factors can facilitate earlier diagnosis?

Please see above for explanation

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

The general hypothesis of early diagnosis of cancer is that earlier diagnosis decreases burden of disease and elicits better outcomes. Myeloma diagnostic journeys are known to be longer than other cancers.
Myeloma is a rare cancer and is 'hard to diagnose' and yet there is a dearth of information relating to pathways to its diagnosis.
Myeloma it is characterized by non-specific and vague presenting symptoms and is mainly a disease of the elderly, where comorbidities exist at presentation. Myeloma is rare (it accounts for 1.5% of all newly diagnosed cancers in the UK) and in primary care physicians little exposure to the disease occurs and higher levels of GP consultations are seen in myeloma presentations.
A prospective study of newly diagnosed myeloma patients which describes each component and interval within the diagnostic journey and further describes the individual and subjective understanding around diagnosis will elicit new information about the processes of diagnosis and aim to inform practice and policy with recommendations of factors that can influence the earlier diagnosis of myeloma and improve outcomes.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

This research aims to describe the way people living in Wales are diagnosed with myeloma. Little is currently known about the symptoms that patients have, how long they have had them before being diagnosed and how long it takes for them to receive a diagnosis. The research will describe how people come to be diagnosed with myeloma by collecting information directly from the patients and the clinicians who were involved in investigating their illness. By collecting information about the way patients are diagnosed recommendations for improvements may be made, this will help in the more timely diagnosis of myeloma and help clinicians to start treatment more quickly.

Patients across Wales will be invited to participate in the research; 190 patients will be included in the study. By inviting patients across the whole of Wales we aim to recruit a truly representative patient group.

Methods: This study will recruit patients soon after a diagnosis of myeloma is made by their hospital doctor. This will help patients and doctors remember the details of being diagnosed more easily. The research will be in two parts.

2 Interviews will be conducted with a small number of the patients who have already completed questionnaires. In interviews the discussion will be around their feelings and interactions with health professionals during the process of being diagnosed. This will allow us to collect more in-depth information about how and what affects the time it takes to be diagnosed.
Phase 1: Each patient will receive a pack from a nurse at their local treating hospital. This pack will contain a patient information sheet, consent form, invitation letter (in Welsh and English) and a patient questionnaire. The patient information sheet will give details of the research being undertaken, the reasons why it is being done, and gives the patient a clear idea of what would be asked of them if they decide to take part. The invitation letter explains to the patient what to do if they wish to participate. Patients who are willing to take part will be asked to sign the consent form and complete the "patient questionnaire". The patient questionnaire will ask specific questions about the symptoms experienced prior to the diagnosis of myeloma, and the number and type of health care workers the patient visited on the route to diagnosis. There will be some additional questions that will be asked which will help us describe the patients who took part in the study (questions relating to socio-economic grouping and ethnicity). The patient will be asked to identify in the questionnaire the GP and hospital doctor who was involved in their care and diagnosis. All completed forms will be sent back to the researcher. The researcher on receiving the forms will send a questionnaire to the patient's GP and hospital doctor. These questionnaires will ask similar questions about symptoms and routes followed and some specific questions about the tests ordered to help with a diagnosis. All information given in questions by patients or health care workers are treated with confidence and not shared with anyone.
Phase 2: A small number of patients (24-30) will be invited to participate in an interview with the researcher. Interviews will be offered either in the patients' own homes or in the hospital where they receive treatment for myeloma. Patients will be able to specify a preference. The patient group invited to interview will be chosen from the responses given to the questionnaires used in Phase 1. Three specific groups will be chosen and eight to ten patients from each of the three groups will be invited to interview. The three groups:

1 Patients who have shown a shorter pathway to diagnosis
2 Patients who have had a longer pathway to diagnosis
3 Patients who have been diagnosed without any symptoms of the illness.

These groups of patients are expected to provide the best quantity and quality of information to assist the researchers in determining which indicators provide the best opportunity for timely diagnosis of myeloma. Consent will be discussed before the interview is commenced and the patient will be asked to give written consent before the interview starts. The interview will be conducted by the researcher and will be recorded. The interview will follow a semi-structured format, with the researcher having a small list of questions relating to how the patient felt about their "journey to diagnosis". The interview will encourage a discussion about the patient's observations and interactions between themselves and the health carers that they saw along the pathway. The patient will be encouraged to expand and lead the conversation as much as they wish to. If the interview goes off the topic of discussion the researcher will bring the questions back to topic by using questions from the list of pre-defined questions. The interviews will last approximately 30 minutes.
At the interview a small number of patients, 2-3 from each group interviewed, will be asked if they would be willing to look at a summary of the themes that the researcher has picked from the information collected. This will help determine that the topics identified by the researcher relate back to the topics the patients feel they were discussing.
The study will invite patients to participate over an 18 month to 2 year period. Patients will not be invited to participate if they have had myeloma for more than 6 months. Questionnaires will be completed when patients decide they wish to participate. Interviews will take place with the chosen patients within 6 months of completing their questionnaires.
This research study will publish its results in medical journals. Anonymity will be guaranteed and the patient will be unidentifiable from the published results. The research study will also be written up as a PhD and be available from Bangor University Library. The Supervisory Committee led by leading experts in early diagnosis of cancer research and haematology, will monitor of the research. The Supervisory committee meet every 6-8 weeks and at these meetings the study progress will be discussed.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

☑
☐ Design of the research
☑ Management of the research
☑ Undertaking the research
☐ Analysis of results Dissemination
☐ of findings None of the above

Give details of involvement, or if none please justify the absence of involvement.

Network hosted by NISCHR CRC and by the North Wales Cancer Patient Forum. Additionally primary care and specialist questionnaires have been evaluated by clinicians across Wales representing each group. The questionnaires were further modified based on the feedback received

In the process of application for funding from the Tenovus Cancer Charity for a PhD studentship, this study received peer and lay/service user review.

Patients participating in the qualitative analysis (small number 2-3 in each of the 3 groups) will be asked at interview if they would be willing to review the summarized main themes generated from reviewing the core data to check it is representative to

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [x] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

- Able and willing to give informed consent
- Able and willing to complete the study interventions complete questionnaire
- Has been diagnosed with asymptomatic or symptomatic myeloma as defined by the MDT
- Diagnosed within 6 months of study registration

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Exclusion criteria
- Life expectancy less than 3 months- as determined by clinician
- Mentally incapacitated
- Not at liberty

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol.
These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Approach by Research Nurse to offer participation	1	0	20 mins	Research Nurse assigned to Haematology MDT to
Completion of Informed consent forms and questionnaires and return of these documents in a prepaid postal envelopes	1	0	30-45 mins	The patient would complete these documents at home once they have read through and digested the information given
A small number of participants (24-30) would be requested to attend for qualitative interviews to explore individual perceptions of their pathway to diagnosis	1	0	1 hour	Study researcher would conduct the interview and this would be conducted in a place of the patients choosing ie with in the patients' home or in the local hospital where the patent is receiving treatment
2-3 patients from each sample group in the interview study would at interview be verbally asked if they would be willing to review the summarised themes generated from the data	1		15	Study researcher would send via e-mail/post if e- mail not available main themes from analysed data. No identifiable information from summarised or interview transcripts would be included just main codes and

A21. How long do you expect each participant to be in the study in total?

Participants will be recruited within 6 months of diagnosis and questionnaires will be completed at recruitment along with consent and returned to the research unit. Participants will then be approached within 3-9 months of returning questionnaires for interview where appropriate. Interviews will be conducted within 6 months of invitation.
Therefore the majority of patients (~160) will be in the active part of the study for no longer than 9 months and a minority of patients (~30) be in the active part of the study for no longer than 18 months.
6-9 patients will at interview be asked to review summarized data and check for representativeness of the data given at their interview and summarized by the researcher. This is to increase validity and occur within 3 months of the interview.
All patients will be requested to provide consent to be followed up via the NHS cancer database at the start of participation for survival analysis, but this will happen remotely and will not require active participation by the patient or form analysis for the PhD thesis.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

As this is a study using questionnaires and interviews only to collect data, we therefore anticipate no adverse effects from participating in the research. The researchers recognise however, that the process of recalling journeys to diagnosis may evoke personal and distressing feelings in individuals' participating. The questionnaires used for this project have been adopted for the patient population specifically and reviewed by service users to reduce the possibility of asking questions in an insensitive manner The questionnaires were modified from questionnaires being used in a study iof a similar design currently recruiting in Wales, the International Cancer Benchmarking Partnership Module 4, and the current recruitment of 200 has not led to any concerns or complaints regarding causing distress in patients.. The study researcher is appropriately trained in communication skills and has experience of working with cancer patients (see CV T. Seale) and will personally conduct qualitative interviews and is aware of the framework of support available for patients if referral is necessary and will signpost individuals as necessary.

Additionally the patients will have access to their usual support mechanisms within cancer services at their treating hospitals. The choice to present the study to patients via the established MDT framework and research network workforce is important in

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

◉ Yes ○ No

If Yes, please give details of procedures in place to deal with these issues:

The study researcher is appropriately trained in communication skills and has experience of working with cancer patients (see CV T. Seale) and will personally conduct qualitative interviews and is aware of the framework of support available for patients if referral if necessary will sign post to these support networks. Additionally the patients will have access to their

A24. What is the potential for benefit to research participants?

There are no direct benefits anticipated for patients participating in this study. However it is anticipated that this project will through describing the journeys of some 190 patients with myeloma in Wales, lead to the research team identifying areas that affect intervals to diagnosis and this will inform practice and policy decision making.

A26. What are the potential risks for the researchers themselves? *(if any)*

A potential risk to researcher exists in visiting patients for qualitative interviews when the request is made for this to occur in the patient's own home. To reduce the risks to interviewer, interviews will only be conducted within the working week and within the working day time schedule. The researcher will invoke the Bangor University Lone Worker Policy adopted for use for this study.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? *For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential patients will be identified through the established MDT infrastructure across the 7 health boards in Wales at first registration of myeloma. MDTs are supported by a research network workforce of skilled research nurses and research officers. Patients presented to the MDTs for discussion of their diagnosis of myeloma will be identified by NISCHR CRC (WCRN) staff (in the absence of research staff the MDT coordinator will identify patients- this is expected to be minimal) and the Consultant in charge will be asked to confirm diagnosis and approach to patient at the

Patients hospital medical notes by the NISCHR CRC workforce staff and the patients will be approached at their next clinic appointment. Patients will be given information packs and asked to read the information contained in the pack at home. Research nurses will offer to discuss study participation if the patient wishes

Research staff at site will be requested to complete a screening log with anonymised patient details and fax this to the trial unit when a patient is approached. This will allow the trial team the ability to track patient activity and, in the absence of a return of the consent and questionnaire within 4 weeks, the researcher will ask the research nurse at site to give a reminder letter to the patient at the next scheduled hospital appointment. If no response is received at the study centre the patient will be considered to have declined.

National MDT coordinators will be asked to complete a monthly anonymised myeloma registration log, allowing staff to identify areas of poor recruitment and give a statistical analysis of the incidence, numbers of patients approached and numbers of patients recruited during the study period.

NISCHR CRC resource is provided centrally through the national research budget and therefore does not impact on individual health boards' service support costs. Consultants from health boards will be asked to confirm an approach to the patient is appropriate and therefore resource is not considered.

National MDT coordinators have confirmed their willingness to provide monthly figures for registration of myeloma cases in Wales and as this is part of their standard database management resource in terms of sending one e-mail a month to give figures is of significance only.

Approach for Phase 2 of the study will be made by the researcher team as consent to approach the patient for interview if selected will be given in the consent for Phase 1. To ensure the patients are only approached if applicable the researcher will make contact with hospital research staff to confirm approach is appropriate.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

(●) Yes ( ) No

Please give details below:

NISCHR CRC research staff will screen patients case notes to confirm eligibility for the study prior to approaching patients. NISCHR CRC staff are integrated into the MDT infrastructure and are contracted NHS personnel. No identifiable data will be

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants. *Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Patients will be identified via screening case notes by their own clinical teams i.e. Consultants, MDT coordinators and/or research nurses. An approach to patient via the research nurse integral to the clinical team will be made.
Data released to the research unit i.e. screening logs, will be anonymized by the clinical team, protecting identity of the potential participant.
Patients that consent to participation and return questionnaires freely give their details to the research team and their permission to approach their GP and Hospital Consultant and in the process identifying themselves to the research team. Identifiable details are stored on a standalone password protected database within the research unit at the University.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

( ) Yes (●) No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

( ) Yes (●) No

A29. How and by whom will potential participants first be approached?

Potential patients will first be approached at their scheduled outpatients appointment at their treating hospital by the research

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material).

Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Phase 1 consent
The process of informed consent will start with the approach of the potential participant by the clinical team's research nurse at a scheduled hospital appointment. The research nurse will offer the patient a copy of the patient information sheet, consent form and invitation letter to read and take away. The research nurse will offer to discuss the research study with the patient. The patient may decline this and take information away to read or discuss study participation with the research nurse. The patient information sheet is sufficiently robust to ensure full informed consent is conducted. Additionally the information sheet offers the patient the opportunity to contact the research team if they Wish to give an opportunity to extend the informed consent process if patient wishes.
The patient will be encouraged to take their time to think about the participation, discuss with their GP their participation; This is documented in the patient information sheet.
The invitation letter will direct the patient to consent to the study participation by signing the consent form and completing the patient questionnaire if they wish to participate and return the documents in a pre-paid envelope to the research unit completing the informed consent process.
Phase 1 patient information also discusses Phase 2 of the study and asks patients to consent to be sent information about Phase 2 interviews if they are selected for an interview.
Phase 2 consent
Patients selected for interview will only be approached after the clinical team have confirmed suitability for approach. This will be facilitated by the study researcher contacting the research nurse at site and confirming the patient is well enough to be approached. Information will then be sent in the post to the patients this fully details the Phase 2 study and is sufficiently robust to ensure informed consent occurs. Patients will be asked to return a reply slip of they do not wish to participate in the study and if no reply form is received within 2 weeks the study researcher will contact patients directly via the details given in Phase 1.
At interview prior to any data collection the study researcher will go through the information sheet and consent form and with the patients consent take written consent.

Information sheets for Phase 1 and 2 will be given in English and Welsh to patients and copies of consent forms will be made available to patients for their personal records

If you are not obtaining consent, please explain why not.

NA

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

Patients will be recruited within 6 months of diagnosis as part of the eligibility. The approach to patients will be made following an MDT and at a scheduled hospital appointment and will involve patients taking information away to read and consider. This will ensure a minimum time window is achieved of 24 hours.

We anticipate that the process of patients taking information away with them will allow them to consider participation in an

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters)*

Translations of the patient information sheet, consent, invitation letter and reminder letter will be translated into Welsh. Patients will be given packs that contain both Welsh and English versions of consent forms (see additional comments below).
Patients with other language needs or special needs will be given information and they may seek help within their own support networks in their home environment to complete the forms.
Patients who cannot provide their own signature will not be able to participate in this study however.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

Translations of the patient information sheets, consent forms and, invitation letters for Phase 1 and 2 and the reminder letter for Phase 1 will be translated into Welsh. Patients will be given packs that contain both Welsh and English versions of the patient information consent forms or send these through the post for Phase 2 participation. Translations will be done centrally by the Bangor University translation services and made available in packs for local sites. They will be available for review by the R and D committees for the 7 Health Boards in Wales that plan to participate in the research study

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

◉ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

○ The participant would continue to be included in the study.

○ Not applicable – informed consent will not be sought from any participants in this research.

Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

It is not anticipated that this will be a common occurance. We have identified and requested consent to the use of data given prior to incapacity on the phase 1 and 2 consent forms. A patient invited to interview will have a status check with the local research nurse prior to invite and if incapacity reported no approach will be made.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

☐

☐

☐ Access to medical records by those outside the direct healthcare team Electronic

☐ transfer by magnetic or optical media, email or computer networks Sharing of

- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [x] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [x] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [x] Manual files including X-rays
  - [ ] NHS computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:

Patients consent to enter the study freely give their personal details on the patient questionnaires. These questionnaires will be stored securely at the North Wales Centre for Primary Care Research at Bangor University and only be available to study researchers. Department where storage is to occur have access codes protecting entry and within these departments questionnaires will be stored with in locked filing cabinets.
Patients on entry will be given a unique trial activity number and this will be used in any further correspondence with site staff in any form of communication i.e. letter e-mail. Additionally data extracted from the analysis of questionnaires will be stored and tracked against the unique trial number.
Recordings of qualitative interviews will identify patient with their unique trial number and any direct quotes published will be anonymized, protecting participant's identity.
Non anonymized data will be securely stored under the custodianship of Bangor University on a standalone database

A37. Please describe the physical security arrangements for storage of personal data during the study?

Data with participants' personal details will be stored with in the North Wales Centre for Primary Care Research. This unit has a pass code protected entry system. Cabinets where the data will be stored will be locked.
Electronic data will be stored on a standalone computer database under the custodianship of Bangor University. All files will be password protected and only accessible to study personnel. All University computers require secure log in. Any lap top is encrypted and requires password access.

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

The SOP for confidentiality for research data from Bangor University will be adhered to throughout the management of the trial.

http://www.bangor.ac.uk/imscar/nworth/documents/4.07Dat aProtectionandConfidentialityv2.pdf][#'

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Study researchers named in this application will have access to the personal data of participants.
On request from the regulatory authorities of the sponsor Bangor University the R and D committees of the 7 Health Boards and MHRA information will be made available by the study researchers for audit and review as requested.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Data generated from the study will be analysed by the study researcher and stored and analysed within the North Wales Centre for Primary Care Research Bangor University.

Non anonymised data will be uplifted onto a standalone computer data base password protected under the custodianship of Bangor University. On a weekly basis non analysed date will be transferred to secure databases.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title Forename/Initials Surname Mrs Tania D Seale
Post	Postraduate Researcher PhD Student
Qualifications	BSc (Hons, Cert Ed,Diploma, Professional Practice, RGN, GCP
trained Work Address	North Wales Centre for Primary Care Research
	Bangor University, Gwenfro Unit 5
	Wrexham Technology Park, Wrexham, North Wales
Post Code	LL13 7YP
Work Email	t.d.seale@bangor.ac.uk
Work Telephone	01978 726651
Fax	

A43. How long will personal data be stored or accessed after the study has ended?

- ○
- ○ Less than 3 months 3
- ○ – 6 months
- ○
- ◉ 6 – 12 months
- 12 months – 3 years
- Over 3 years

If longer than 12 months, please justify:

A44. For how long will you store research data generated by the study?

Years: 15
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

Study data will be archived at the North Wales Centre for Primary Care Research and remain under the custodianship of Bangor University

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in thisresearch?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ○ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

◉ Yes ○ No

Please give details, or justify if not registering the research.

We will seek adoption to the NISCHR portfolio. a dialogue has already been established with the adoption team at NISCHR CRC regarding the research study.

Registration of research studies is encouraged wherever possible.

You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

☑

☑ Peer reviewed scientific journals internal

☑ report

☑

☐ Conference presentation

☑ Publication on website Other

☐ publication

☐ No plans to report or disseminate the results Other

☐ (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Patients/participants will not be identified in published reports

A53. Will you inform participants of the results?

◉ Yes ○ No

Please give details of how you will inform participants or justify if not doing so.

Patients/participants will retain the researcher's details for communication.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

☑

☐ Independent external review Review

☐ within a company

☑

☐ Review within a multi-centre research group

☑ Review within the Chief Investigator's institution or host organisation Review

☐ within the research team

Review by educational supervisor

Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

☐

☑ Review by independent statistician commissioned by funder or sponsor Other

☐ review by independent statistician

☐

☐ Review by company statistician

☐ Review by a statistician within the Chief Investigator's institution Review by a

☐ statistician within the research team or multi-centre group Review by

☐ educational supervisor

Other review by individual with relevant statistical expertise

No review necessary as only frequencies and associations will be assessed – details of statistical input not required

	Title Forename/Initials Surname Dr Jim Turner
Department	Senior Research Fellow/Clinical Audit & Effectiveness Betsi
Institution	Cadwaladr University Health Board
Work Address	Wrexham Maelor Hospital Clinical Audit & Effectiveness Wrexham Medical Institute,Wrexham Technology Park Centre, Wrexham LL13 7YP
Post Code	
Telephone	
Fax	jim.turner@bangor.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Primary outcome of the study is to describe how diagnostic journeys of 190 patients with newly diagnosed myeloma occur in Wales. This will be completed in Phase 1 of the project and will involve statistical description:
Statistical analysis Phase 1 study:
Firstly, all numerical data will be summarized to describe the sample population with descriptive characteristics. Following this, the type and distributional characteristics of the data will determine whether parametric or non-parametric analysis will be used. If the former, then analysis of variance (ANOVA), regression and survival analysis may be possible; alternatively, non-parametric versions of these tests could be used where appropriate.

A58. What are the secondary outcome measures? *(if any)*

The secondary outcome measures are to describe:
- What factors, interactions and experiences influence the pathway to individual diagnosis?
- What factors can facilitate earlier diagnosis?

This analysis is likely to take a more narrative description of the data collected from Phase 2 qualitative interview data. However the findings of both qualitative and quantitative data will be examined collectively to identify routes of diagnosis demonstrated in this Welsh population. These data are likely to be described with a narrative statistical description.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 190

Total international sample size (including UK): Total in European Economic Area:

Further details:

Sample size calculation:

Sample size To determine the sample size required from a pool of 375 (the anticipated incidence in Wales over a 18 month period), with a 5% margin of error and 95% confidence intervals, 190 responses are needed. Another way would be to assume a small effect size of 0.2 and preliminary analysis would consist of t-tests on mean differences:

t tests - Correlation: Point biserial model Analysis: A

priori: Compute required sample size Input: Tail(s) =

Output: Non-centrality parameter δ = 2.8210518

Critical t = 1.9725951 Df
= 189

Total sample size = 191

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Independent review by statistician to give sample size calculation:
Sample size To determine the sample size required from a pool of 375 (the anticipated incidence in Wales over a 18 month period), with a 5% margin of error and 95% confidence intervals, 190 responses are needed. Another way would be to assume a small effect size of 0.2 and preliminary analysis would consist of t-tests on mean differences:

t tests - Correlation: Point biserial model

Analysis: A priori: Compute required sample size

Input: Tail(s) = Two
Effect size |ρ| = 0.2
α err prob = 0.05
Power (1-β err prob) = 0.80

Output: No centrality parameter δ = 2.8210518

Critical t = 1.9725951
Df = 189

Total sample size = 191

A61. Will participants be allocated to groups at random?

○ Yes ◉ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Statistical analysis for Phase 1: Statistical
analysis Phase 1 study:

Firstly, all numerical data will be summarized to describe the sample population with descriptive characteristics. Following this, the type and distributional characteristics of the data will determine whether parametric or non- parametric analysis will be used. If the former, then analysis of variance (ANOVA), regression and survival analysis may be possible; alternatively, non-parametric versions of these tests could be used where appropriate.

Missing data will be handled accordingly depending on the extent of data missing, this will be analysed at the end of data collection

Phase 2: Qualitative study

Several steps have been built into the research design to enhance the methodological rigour of the analysis. First, obtaining data from multiple sources across 3 patient groups those with prompt diagnostic pathways and those with delayed diagnostic pathways and those with asymptomatic presentations, will allow us to explore how length of diagnostic interval/symptomatic presentations and social and cultural context may influence diagnostic intervals.

Second, a member checking protocol will be used. A small sample of participants in each of the 3 patient groups will receive a summary of the findings and be asked to evaluate whether the analysis reflects their personal experiences. Finally, the interview sample size is substantial and will enhance our ability to attain data saturation, which will allow us to draw meaningful conclusions from the data.

7.0 Data synthesis

Findings from the analysis of the quantitative and qualitative data will be examined collectively to identify the routes of diagnosis demonstrated in this Welsh population of myeloma patients. Data will be synthesised and analysed to demonstrate intervals from first symptom to diagnosis as a total and then categorised for patient, GP and secondary care interval. Synthesis will include the grouping of patient's in terms of diagnostic journeys and these groups will be compared to categories of data collected i.e. patient characteristics, symptoms experienced, routes of presentation/referral etc. This is likely to be a narrative

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title Forename/Initials Surname Prof Richard D Neal
Post	Professor of Primary Care Medicine, Director of the North Wales Centre for Primary Care Research
Qualifications	FRCGP 2009 PhD, University of Leeds 2000 Postgraduate Certificate in Teaching and Learning in Higher Education, University of Leeds 1999 MRCGP 1994 DRCOG 1992 DFFP 1992 MB ChB, University of Birmingham 1988 GMC 3303029 GCP trained
Employer Work Address	University of Bangor North Wales Centre for Primary Care Research University of r.neal@bangor.ac.uk
	Title Forename/Initials Surname Prof Lynne Kennedy
Post	Head of Department Clinical Sciences and Nutrition
Qualifications	PG Cert Teaching & Learning. (Distinction) PhD M Phil BSc. (Hons): Food Science & Applied Nutrition: 2:1
Employer	University of Chester

	University of Chester
	Parkgate Road Chester
Post Code	CH1 4BJ
Telephone	01244513054
Fax	
Mobile	
Work Email	l.kennedy@chester.ac.uk

	Title Forename/Initials Surname Prof Christopher Fegan
Post	Clinical Professor Institute of Cancer and Genetics
Qualifications	MB, MD, FRCP, FRCPath
Employer	Cardiff University School of Medicine
Work Address	Institute of Cancer and Genetics
	Cardiff University School of Medicine
	Institute of Medical Genetics Building, Heath Park, Cardiff
Post Code	CF14 4XN
Telephone	
Fax	
Mobile	
Work Email	christopher.fegan@wales.nhs.uk

	Title Forename/Initials Surname Dr Emma Litt
Post	Clinical Lecturer in Palliative Medicine
Qualifications	
Employer	Glyndwr University
Work Address	North Wales Centre for Primary Care Research
	Gwenfro Unit 5 Wrexham Technology Park
	Wrexham
Post Code	LL13 7YP
Telephone	
Fax	
Mobile	
Work Email	e.litt@bangor.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Status:
- ○ NHS or HSC care organisation Academic
- ◉
- ○ Pharmaceutical industry
- ○ Medical device industry Local
- ○ Authority
- ○ Other social care provider (including voluntary sector or

Commercial status: Non-Commercial

○ Other

If Other, please specify:

Given name	Institute of Health and Social Care Research (IMSCaR) Prof R
Family name	T Woods
Address	Ardudwy Buidling Normal Site Bangor University Bangor
Town/city	Gwynedd
Post code	LL57 2PX
Country	
Telephone Fax	
	b.woods@bangor.ac.uk

Is the sponsor based outside the UK?

○ Yes ◉ No

A65. Has external funding for the research been secured?

☑

☐ Funding secured from one or more funders

☐

What type of research project is this?

○ Standalone project

○ Project that is part of a programme grant Project

○ that is part of a Centre grant

◉

○ Project that is part of a fellowship/ personal award/ research training award Other

Please give details of funding applications.

Organisation	Tenovus
Address	9th Floor
	Gleider House
	Ty Glas Road, Llanishan, Cardiff
Post Code	CF14 5BD
Telephone	

Email Anita.howman@tenovus.org.uk

Funding Application Status: ◉ Secured ○ In progress

Amount: £65,178.00

Duration

Years: 3

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project? PhD funding

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

○ Yes ◉ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title Forename/Initials Surname
	Dr Rossela Roberts
Organisation	Betsi Cadwaladr Universit Health Board
Address	Ysbyty Gwynedd
	Penrhosgarnedd Bangor
	North Wales
Post Code	LL572PW
Work Email	rossela.roberst@wales.nhs.uk
Telephone	01248384877
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 02/06/2014
Planned end date: 30/09/2016
Total duration:
Years: 2 =Months: 3 Days: 29

A71-1. Is this study?

○

◉ Single centre

A71-2. Where will the research take place? *(Tick as appropriate)*

☐

☐ England

☑ Scotland

☐ Wales

☐

Northern Ireland

Other countries in European Economic Area

○

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? *Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:*

☐ NHS organisations in England NHS

☑ organisations in Wales NHS 17

☐ organisations in Scotland

☐

☐ HSC organisations in Northern Ireland GP

☐ practices in England

☐ GP practices in Wales GP

☐ practices in Scotland

☐

☐ GP practices in Northern Ireland

☐ Social care organisations Phase 1

☐ trial units

☐

☐ Prison establishments

☐ Probation areas Independent

☐ hospitals Educational

Total UK sites in study: 17

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Monitoring and auditing the study will be conducted by NHS research departments as is required and requested. Bi annual R and D reports will be completed by the study researcher as requested by the hosting R and D committees. The study documentation will be made available to the regulators for auditing as requested

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐

☑ NHS indemnity scheme will apply (NHS sponsors only)

☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐

☑ NHS indemnity scheme will apply (protocol authors with NHS contracts only) Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where nonNHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☐

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only) Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

◉

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites.
For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

Research site		Investigator/ Collaborator/ Contact	
Institution name	Betsi Cadwaladr University Health Board	Title	Dr
Department name	Ysbyty Gwynedd (West Division) Haematology Department	First name/ Initials	Jim
Street address	Penrhosgarnedd	Surname	Seale
Town/city	Bangor North Wales		
Post Code	LL57 2PW		
Institution name	Betsi Cadwaladr University Health Board	Title	Dr
Department name	Ysbyty Glan Clwyd (Central Division) Haematology Department	First name/ Initials	Earnest
Street address	Sarn Lane	Surname	Heartin
Town/city	Bodelwyddan North Wales		
Post Code	LL18 5UJ		
Institution name	Betsi Cadwaladr University Health	Title	Dr
Department name	Wrexham Maelor Hospital (East Division) Haematology Department	First name/ Initials	David
Street address	Croesnewydd Rd	Post Code	LL13 7TD
Town/city	Wrexham North Wales	Surname	Watson
Institution name	Cardiff and Vale University Health Board	Title	Professor
Department name	University Hospital Wales Haematology Department	First name/ Initials	Chris
Street address	Heath Park,	Surname	Fegan
Town/city	Cardiff Wales		
Post Code	CF14 4XW		
Institution name	Cardiff and Vale University Health Board	Title	Professor
Department name	Llandough Hospital Haematology Department	First name/ Initials	Chris
Street address	Penlan Road Llandough	Surname	Fegan
Town/city	Penarth South Glamorgan Wales		
Post Code	CF64 2XX		
Institution name	Aneurin Bevan University Health Board	Title	Dr
Department name	Royal Gwent Hospital Haematology Department	First name/ Initials	Nilma
Street address	Royal Gwent Hospital Cardiff Road	Surname	Parry-Jones
Town/city	Newport Gwent Wales		
Post Code			

Post Code	NP20 2UB

Institution name	Aneurin Bevan University Health Board	Title	Dr
Department name	Nevill Hall Hospital Haematology Department	First name/ Initials	Nilma
Street address	Brecon Rd, Abergavenny, Monmouthshire	Surname	Parry-Jones
Town/city	Monmouthshire Wales		
Post Code	NP7 7EG		

Institution name	Cwm Taf Haelth Board	Title	Dr
Department name	Prince Charles Hospital Haematology Department	First name/ Initials	W M
Street address	Gumos Road	Surname	Bashi
Town/city	Merthyr Tydfil Mid Glamorgan Wales		
Post Code	CF47 9DT		

Institution name	Cwm Taf Health Board	Title	Dr
Department name	Royal Glamorgan Hospital Haematology Department	First name/ Initials	Husni
Street address	Ynysmaerdy,	Surname	Habboush
Town/city	Pontyclun Mid Glamorgan Wales		
Post Code	CF72 8XR		

Institution name	Abertawe Bro Morgannwg University Health Board	Title	Dr
Department name	Princess of Wales Hospital Haematology Department	First name/ Initials	Vinod
Street address	Coity Rd	Surname	Devalia
Town/city	Bridgend Wales		
Post Code	CF31 1RQ		

Institution name	Abertawe Bro Morgannwg University Health Board	Title	Dr
Department name	Neath Port Talbot Hospital	First name/ Initials	Vinod
Street address	Baglan Way	Surname	Devalia
Town/city	Port Talbot Wales		
Post Code	SA12 7BX		

Institution name	Abertawe Bro Morgannwg University Health Board	Title	Dr
Department name	Morriston Hospital Haematology Department	First name/ Initials	Saad
Street address	Heol Maes Eglwys Morriston	Surname	Al-ismail
Town/city	Swansea Wales		
Post Code	SA6 6NL		

Institution name	Abertawe Bro Morgannwg University Health Board	Title	Dr
Department name	Singleton Hospital Haematology Department	First name/ Initials	Saad
Street address	Sketty Lane Sketty	Surname	Al-ismail
Town/city	Swansea Wales		
Post Code	SA2 8QA		

Institution name	Hywel Dda University Health Board	Title	Dr

Department name	Prince Phillip Hospital Haematology Department	First name/ Initials	Peter
Street address	Bryngwyn Mawr Dafen		
Town/city	Llanelli Carmarthenshire Wales	Surname	Cumber
Post Code	SA14 8QF		

Institution name	Hywel Dda University Health Board	Title	Dr
Department name	West Wales General Hospital Haematology Department	First name/ Initials	Peter
Street address	Dolgwili Rd Town Centre,		
Town/city	Camarthan Wales	Surname	Cumber
Post Code	SA31 2AF		

Institution name	Hywel Dda University Health Board	Title	Dr
Department name	Withybush Hospital Haematology Department	First name/ Initials	Peter
Street address	Fishguard Rd, Haverfordwest,		
Town/city	Pembrokeshire Wales	Surname	Cumber
Post Code	SA61 2PZ		

Institution name	Hywel Dda University Health Board	Title	Dr
Department name	Bronglais General Hospital Haematology Department	First name/ Initials	Peter
Street address	Caradog Road		
Town/city	Aberystwyth Wales		
Post Code	SY23 1ER		
Surname	Cumber		

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

   - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
   - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
   - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
   - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
   - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication *(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- (●) Chief Investigator
- ( ) Sponsor

○ Study co-ordinator

○ Student

○

○ Other – please give details

Access to application for training purposes *(Not applicable for R&D Forms) Optional*

– please tick as appropriate:

☑

I would be content for members of other RECs to have access to the information in the application in confidence for training

This section was signed electronically by Mrs Tania Seale on 04/06/2014 11:17.

Job Title/Post:	Postgraduate researcher/PhD student
Organisation:	Bangor University
Email:	t.d.seale@bangor.ac.uk
Signature:	.....
Print Name:	TANIA SEALE
Date:	17/03/2014

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co–sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken

This section was signed electronically by Robert Woods on 05/06/2014 12:20.

Job Title/Post:	Acting Head, IMSCAR
Organisation:	Bangor University
Email:	b.woods@bangor.ac.uk

D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

Job Title/Post:	Professor
Organisation:	Cardiff University
Email:	christopher.fegan@wales.nhs.uk

Academic supervisor 2

Job Title/Post:	head of department
Organisation:	University of
Email:	l.kennedy@chester.ac.uk

Academic supervisor 3

Job Title/Post:	Professor of Primary Care Medicine
Organisation:	Bangor University
Email:	r.neal@bangor.ac.uk

9.9 Appendix 9: Interview topic guide –patient interviews

In-depth Interview/topic guide DJiM study

The Research Inquiry:

The second phase of the DJiM study is designed to answer the research question:

- What factors, interactions and experiences influence the pathway to individual diagnosis?

and contribute, along with data from phase one, to answer:

- What factors facilitate timely diagnosis?

Currently little is known about the personal experiences, perceptions and interactions around the individual journey to diagnosis of myeloma, making qualitative methods most appropriate for investigation; additionally, qualitative methods allow exploration of these areas, but avoid imposing hypotheses formed by a professional understanding (Joubish et al., 2011).

The choice of qualitative tool is based on the ability of the tool to elicit the type of information required to answer the research question. The Health Technology Assessment guidelines on Qualitative Research (Murphy et al., 1998) put the question of judging what information you wish to obtain from participants very simply - "If you want to understand what people do, believe and think, ask them".

The Qualitative Inquiry Method:

A variety of qualitative inquiry methods are available (Mason 2002):

- Focus groups
- In-depth interview
    - Structured interview
    - Unstructured interviews
    - Semi-structured interviews
- Participant observation

Each method has been assessed to judge for the likelihood of soliciting the desired information from participants for the purpose of this particular qualitative study.

Patient observation does not allow for the researcher to address specific topics with individuals through discussion and dialogue, the primary object being to observe the

participant in their normal environment and record how they react and behave. Researchers may enter in to conversation and be an active part of the environment but the context remains natural. Whilst observation has its own merits and produces natural uncontrived behaviour for observation in a way interviews do not, essential to the DJiM study is the solicitation of the personal opinions and reflections of the participants which can only occur through direct dialogue/questioning (Murphy et al., 1998).

Focus groups allow the questioning and soliciting of in-depth personal perceptions and perspectives required for this qualitative inquiry. They draw a group of participants together which can have both advantages and disadvantages to the qualitative work. Crucially focus groups require a homogenous population of participants matching power, age, cliques and sometimes gender to ensure equity in opportunity of expression of perceptions. The population of recruits for the DJiM study will be purposefully selected to identify information rich pathways for discussion from a large geographical region. The opportunity to draw a homogenous group of individuals from such a group is very limited. Additionally it was recognised when designing the study that recall of the diagnostic journeys for patients may be emotive and cause distress, and consideration of these factors makes personal interviewing a more favourable method of inquiry (Eliot 2005)

The interviews will to be discursive in nature. The aim of the researcher not to lead the participant, but to engage in and encourage open dialogue and focus in on some of the interesting and richer experiences the individual introduces. This allows exploration and reflection the properties of good qualitative research (Richie and Lewis 2003). This is a move away from the more structured interview style which operates a question and answer architecture, restricting a divergence from the questions asked. The unstructured interview affords no structure, with usually just one opening question, which has limitations in its use for naïve researchers and is less able to ensure consistency with coverage of recognised themes with participants. The use of a semi- structured interview schedule allows the researcher to maintain some structure and adherence to the topic in question, with the formation of a "guide or aide memoire", but does not restrict the flow of the conversation, encouraging the dialogue and openness in the participant and therefore facilitating

the ability to expand on themes introduced by the participant (Richie and Lewis, 2003).

The use of semi-structured interviews with the support of an interview/topic guide is the chosen method of qualitative inquiry for the second phase of the DJiM study.

Development of an interview/topic guide:

An interview/topic guide offers a tool to enhance the consistency in data collection. It allows the formation of general topics/questions for discussion to be placed in a logical order and gives the researcher a reference to take into the fieldwork with him (Richie and Lewis 2003). The topic guide can be seen as a mechanism for steering the interview but caution is taken in its formulation that the guide does not make the interview restrictive and discourage the patient introducing themes important to them and stop reflection occurring. It serves as an aide memoire during interview ensuring the consistency of covering topic with all participants.

By using general headings rather than specific questions the researcher has the ability to phrase questions differently reacting to the individual participants experience and understanding. The broader titles or headings encourage the interview to follow a conversational style, reducing rigidly associated with the reading of longer structured questions (Richie and Lewis 2003).

The interview guide will provide the evidence of fieldwork activity and will support any published research papers relating to the qualitative inquiry, providing a written record, giving transparency and rigour.

The interview guide will allow consultation and discussion in the form of peer review in the early stage of development and be documented evidence of the development of the interviewing as the research progresses (Mason 2002; Richie and Lewis 2003).

The interview/topic guide has been developed in line with the structure and process recommended by Richie and Lewis 2003.

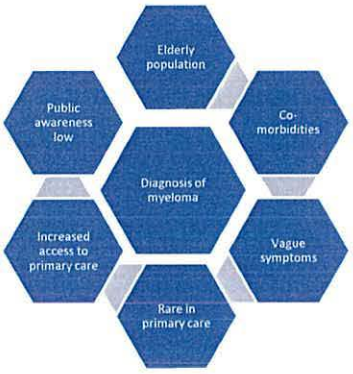
Subject coverage: identifying the themes for discussion

Themes for discussion have been identified from multiple sources:

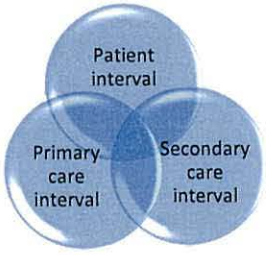
- review of the current literature
- analysis of the patient questionnaires from recruited patients
- Myeloma UK patient stories

The review of this data allows the formation of broad headings and categories for the interview/topic guide.

What are the influences affecting timely diagnosis of myeloma described as described in the current literature?



Literature recognises 3 distinct areas where influences occur:



These identified areas will be used to structure the interview dialogue, giving a logical progression of time and place for the participant to recall the process of diagnosis but equally a reference point for the data.

The gift of having a participant give their time for interview is recognised and therefore only the topics that will clarify data given in phase one or topic themes emerging from data and questionnaire review will be covered to ensure "old ground" is not covered. Careful consideration of what data has been collected in the questionnaire study ensures repetition does not occur. Participants may be unwell or receiving current treatments and time is limited for long discussions therefore a priority will be given to information that is novel or unexplored.

Interview guide will be divided in to 3 headings

- Patient interval topics
- Primary Care Interval topic
- Secondary Care interval topics

Patient interval:

Questionnaires draw:

- Time lines first symptom to help-seeking
- Routes of presentation
- Frequency of access to HCP (type of HCP)
- Pre-diagnosis symptomology
- Comorbidities
- Health status pre symptoms
- Ethnicity and work status

Themes emerging from returned questionnaires and literature: (this is ongoing as more patients are recruited and will be constantly revisited)

- Highlight of tolerance of symptoms for lengthy periods (?more so in the elderly)
- Denial of symptoms even on recognition of possibility of myeloma/serious illness
- No recognition of influence of help-seeking behaviour in literature- new unique perspective
- No recognition of lay advice- new unique

Topic areas for discussion focus around:

- First symptoms/feeling of being unwell
    - Response to symptoms (tolerance/delayed help-seeking/didn't acknowledge as serious/sought help immediately)
    - Prompts for help-seeking
    - Other influences in life at this time (family/work)

- Advice/reassurance seeking (significant others including frontline health workers)
    - Who?
    - Why?
    - Effect of advice (delay or prompt medical help)?

- Reflection- doing things differently
    - Timing- good/poor
    - Seeking help
    - Understanding symptoms/health/illness
    - Good and bad things

Primary care interval:

Questionnaires draw:

- Time frames for the primary care interval
- Number of pre-referral visits to GP or HCP
- Type and number of HCP visited
- Investigations ordered as a result of symptoms, results and response to results
- Referral process initiated
- Date the GP first suspected something serious was wrong
- Comorbidities
- Changes in access to PC services
- Reflection from GP

Themes emerging from returned questionnaires and literature:

- Repeated visits to GP highlighted in literature and returned questionnaires
- Changes in access patterns to primary care
- Different doctors respond differently to patients same symptoms
- Reassurance at initial consultations
- Availability of appointments- putting people off
- No reference in literature to the interaction between patient and clinician- new and unique

Topic areas for discussion focus around:

- About the first visit to GP/or other service experience
    - What happened?
    - Understanding
    - The interaction (explanation of symptoms/hurried/related)
    - Concurrence
    - Reflection
- After the visit
    - Feelings (anxious/reassured/fearful/understanding)
    - Reflection (good and bad)
- Other visits
    - Alternative pathways experienced
    - Interactions with others lay/healthcare
    - Reflection (what went well/not so well)

Secondary care interval:

Questionnaires draw:

- Time from referral to be seen/diagnosis to other team+ haematology;
- Number of specialities seen within secondary care
- Criteria fulfilled for diagnosis of myeloma and staging
- Reflection from haematologist

Themes emerging from returned questionnaires and literature:

- Referral pathways longer when channelled through wrong speciality
- Number patients presenting through ED
- Perceptions of what is prompt/longer journey different for patient and haematologist

Topic areas for discussion focus around:

- First visit to hospital experience(haematologist)
    - What happened?
    - Understanding
    - The interaction (explanation of symptoms/situation/hurried/related)
    - Concurrence
    - Reflection
- After the visit
    - Feelings (anxious/reassured/fearful/understanding
    - Reflection (what went well/not so well)
- Other visits- the experience
    - Alternative pathways
    - Interactions with lay/healthcare
    - Reflection (what went well/not so well)

Additionally, a formal introduction takes place ensuring identify and affiliations are acknowledged. Study aims and objectives are revisited to ensure informed consent occurs. Explanation of the reason for recording the interview and permission is sought, confidentiality procedures discussed.

Introductions:

- Researcher introduces herself/the study
    - Thank for participating
    - Name and job title and University affiliation
    - Study outline and aims
    - Brief about the interview length and reason for doing it
    - Recording equipment and why- confidentiality
    - Consent

A warm up question is used to put the participant at ease but also draws on the personal circumstance of the individual giving context to the researcher.

To warm up: Life history

- Ask participant to tell you something about them selves
    - Background
    - Family
    - Employment
    - Interests

At the end of the interview to acknowledge the interview is drawing to a close a thank you will be said and the participant will be given a chance to ask any questions. Confidentiality will then be reiterated

Ending/Sum up:

- **Reassurance**
    - Thank you
    - Any questions
    - Confidentiality check

The researcher will take fieldnotes to add to the depth of the data collection recording the situation, context and experience of the interview

Fieldnotes:

- Record the observations outside the immediate context of the researcher
    - What is seen/heard
    - Thoughts on the dynamics of the encounter
    - Issues appropriate in further fieldwork
    - Issues for analytical consideration

Summary Interview guide: theme testing DJiM study- for fieldwork

Before the interview:

- Researcher to familiarise themselves with the information given by the participant in Phase I questionnaire
- Test equipment

TURN TAPE ON

Introductions:

- Researcher introduces herself/the study
  - Thank for participating
  - Name and job title and University affiliation
  - Study outline and aims- emphasise participation is NOT based on their being errors/fault in the journey experienced
  - Brief about the interview length and structure/housekeeping (breaks etc) i.e. some questions but very conversational. Warm up question to settle us both
  - Recording equipment and why- confidentiality
  - Release of information/referral on in event of danger to vulnerable person or distress to interviewee
  - Consent

To warm up:

- Something about themselves
  - Settle and open channels of communication
  - Build trust
  - Positioning of participant

Topic guide around patient interval:

- First symptoms/feeling of being unwell

- Other people have said they felt their symptoms were not serious enough to take them to the doctors? (AWARENESS/PHYSICALITY?RATIONALISING))
- Other people have said they felt too unwell to navigate through the GP appointment systems – initially/again? (SYSTEMS/AWARENESS)

- Advice/reassurance seeking (significant others including frontline health workers)
  - Other people have said the GP reassurance led them to take longer to go back when symptoms persisted (REAPPRASAL AWARENESS)
  - Other people said they didn't want to go back (making a fuss/being a burden) when the doctor had reassured them their symptoms were down to A B C (SYSTEMS/TRUST/NEGATIVITY)
  - Other people said they were reassured by family that the doctor knows best and felt they shouldn't go back (LAY INFLEUNCE/AWARENESS/REAPPRAISAL)
  - Other people say they were encouraged to go back by relatives/friends and this prompted their representing to the doctor (LAY INFLEUNCE/AWARENESS/REAPPRAISAL)
  - Other people said they have a very negative feeling toward doctors (GP or general) (TRUST/REAPPRAISAL)
  - How did this influence your returning to your GP (ALL)
- Reflection- doing things differently
  - Other people have said when they look back after their diagnosis was made they can identify symptoms that may be related to myeloma earlier than when they went to their GP – how would you see that in relation to your diagnosis?

Topic guide GP interval and subsequent visits:

- Accessing GP services
  - Can you tell me how you found making appointments to see your GP (SYSTEMS/APPRAISAL/ AWARENESS/CANIDACY/HEALTH LITERACY)

- Other people have discussed having to go through receptionists difficult (SYSTEMS/APPRAISAL/AWARENESS?HL/CANDIDACY))
- Other people have found the system making appointments ringing in the morning difficult (SYSTEMS/APPRAISAL)
- How did these factors influence you seeing your GP? (ALL)

- After the visit
  - What was your understanding of the plan of action you needed to follow after visiting your doctor? (SAFETY NETTING/PLANNING/JOINT CARE)
  - Other people have said they found it difficult to get back to or go back to see their doctors after visiting the first time – what was your experience? (SYSTEMS/REAPPRAISAL/TRUST)
  - Other people have said that they feel they have lost trust or faith in their GPs – in your experience did this have an effect on your going back to see your doctor? (TRUST)

Topic guide secondary care interval:

- First visit to hospital experience(haematologist)
  - Other people have said they felt communication between PC and SC wasn't great? What was your experience of this? (SYSYEMS COMMUNICATION EQUIPMENT PATHWAYS/TRUST)
  - What was your experience of the communication between your family doctor and the hospital teams during diagnosis? (COMMUNICATION/TRUST/SYSYTEMS)
  - Did you feel reassured by your doctor's treatment of your symptoms and investigations
- After the visit
  - Now that you have been diagnosed a while what do you feel about your journey to diagnosis? Would you do or have anything done anything differently (ALL)
  - Reflection – how do you feel looking back now – will this affect you in the future?? (ALL)
  - Anything you would like to add that I haven't covered?

- Finally - What do you think could be done to make myeloma diagnosis as timely as possible?

Ending/Sum up:

- **Reassurance**
  - Thank you
  - Any questions- Confidentiality check

TURN TAPE OFF

If time and situation allows this may be recorded on the tape after the interview has ended

Fieldnotes: Enter into log book

- Record the observations outside the immediate context of the researcher
  - What is seen/heard
  - Thoughts on the dynamics of the encounter
  - Issues appropriate in further fieldwork
  - Issues for analytical consideration

Additional notes:

Dealing with complaints/concerns

It is feasible, and to be taken into consideration, that some patients may have complaints/concerns they wish to raise about care/treatment. A plan of action as to how to respond to these concerns has been addressed here and gives guidance to the researcher:

- Listen and acknowledge the participants concerns and distress
- Sign post to appropriate services (NHS concern teams) if appropriate and apologise that this is not the forum to discuss or help with the concern
- Discuss with Supervisor if issues raised or of a serious, illegal or negligent nature

9.10 Appendix 10: Interview guide GP interviews

Diagnostic journeys in myeloma (DJiM). Interview/topic guide primary care physicians

Introduction:

- Researcher introduces herself/the study
    - Thank for participating
    - Name and job title University affiliation
    - Study outline and aims
    - Brief about the interview length
    - Recording equipment and why- confidentiality

Topic guide around the individual patient at the practice

- Experience and observations of diagnosing your patient and their journey
    - Good or bad
    - Prompt or long
    - Usual/different from other experiences
    - Particular factors in this patient that made a difference
    - Difficulties with systems/referrals/practice
- With hindsight would there be anything to change
    - Responding to symptoms
    - Route of referral
    - Investigation profile/repeating of investigations/reaction to reports/other test requested

Topic guide around general diagnosis of myeloma:

- General perspective on diagnosing myeloma in primary care
    - Difficulties/challenges in diagnosing the disease
    - Experience/background/knowledge base

What could be done to promote earlier diagnosis?

- Opinion – identify two areas where you thin improvements could be made

Opportunity to add anything:

- Anything we haven't covered? Anything to add?
    - Picking up of anything we night not have thought of/captured/considered

Ending/Sum up

- Confidentiality check
- Concerns/complaints
- Further information/expected publications timelines/feedback for policy makers

Fields notes:

- Record the observations outside the immediate context of the researcher
    - What is heard/experienced
    - Dynamics of the encounter
    - Issues appropriate in further fieldwork
    - Issues appropriate for analytical consideration

9.11 Appendix 11: Protocol Diagnostic Journeys in Myeloma (DJiM)

Diagnostic Journeys in Myeloma (DJiM): how long does it take to diagnose?

Protocol Version 2, 27th June 2014

Study staff

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List of Contents

1.0 Introduction- setting the context

1.1 Incidence/prevalence:

Myeloma is a rare cancer of the plasma cell of the bone marrow. Myeloma accounts for 1.5% of all newly diagnosed cases of cancer in the UK (www.cancerresearch.org). It is the second most common haematological malignancy accounting for 10-15% of newly diagnosed haematological cancers. (Group IMW 2003). In 2009, newly diagnosed myeloma figures for the UK recorded an incidence of 7.1 for males and 4.3 for women per 100,000 population. Figures in Wales for 2010, registered 245 cases of newly diagnosed myeloma (www.cancerresearch.org).

Death from myeloma accounts for 2% of all deaths from cancer in the UK and 15-20% of deaths related to haematological malignancy. Myeloma affects predominantly the older population. The median age of diagnosis is 70 years, with only 15% being diagnosed in adults under 60 and 2% in adults under 40 (Bird et al., 2011). Incidence is two times greater in men than in women, exclusive of ethnicity, and twice as prevalent in Afro-Caribbeans and Afro-Americans (Waxman et al., 2010; Alexander et al., 2007).

There is now a body of thought that almost all cases of myeloma are preceded by an asymptomatic state, monoclonal gammopathy of undetermined significance (MGUS) (Weiss et al., 2009; Ludwig et al 2010). Guidelines for monitoring patients who have been diagnosed with MGUS are well established and exist to ensure a rapid diagnosis of MGUS evolving into myeloma (Smith et al., 2005; Bird et al., 2011). The majority of cases of myeloma, however, present *de novo* (Bird et al., 2011) to clinicians.

1.2 Clinical course of myeloma:

The clinical course of myeloma evolves from an accumulation of cancerous plasma cells in the bone marrow secondary to their malignant proliferation. These plasma cells produce a monoclonal antibody, a paraprotein, which lead to organ damage and destruction. Malignant proliferation is seen to take two courses. In asymptomatic myeloma (also referred in the literature as smoldering or indolent myeloma) proliferation follows a slow steady course and bone marrow plasma cells and the monoclonal protein are raised but organ and

tissue damage are not seen clinically. Progression occurs to symptomatic myeloma requiring treatment but this is not uniform in time but is reported to be 10% per year for the first 5 years following diagnosis (Bird et al., 2011). Asymptomatic myeloma accounts for 10-15% of myeloma incidence (Blade et al., 2009). In symptomatic myeloma a progressive systemic disease is seen and characterised by raised bone marrow plasma cells, monoclonal protein and organ and tissue disease with bone marrow failure, and accompanying anaemia and infection, hyper viscosity and renal impairment, lytic bone lesions, pathological fractures and hypercalcaemia). Symptomatic myeloma requires systemic treatment (Smith et al., 2013).

1.3 Outcomes in myeloma:

Myeloma patients' treatment options and outcomes have seen improvements in the last decade with patients now having a median predicted survival of 5 years (Bergsagel et al., 2013; www.cancerresearch.org). A number of clinical and laboratory interventions have been given as influences for the improvement in morbidity and mortality rates.

Improvement in survival outcomes has been attributed to high dose chemotherapy and stem cell transplant programmes (ASCT), as demonstrated and reported in the MRC Myeloma VII trial. A greater CR in the intensively treated ASCT arm of the study was reported demonstrating CR responses of 44% vs 8 % in the standard therapy arm (Child et al., 2003) for younger fitter patients. ASCT has become the standard treatment for younger fitter patients following induction regimens (Kumar et al., 2008; Ludwig et al., 2010; Smith et al., 2013).

Improvements to supportive care measures in terms of bone prophylaxis with widespread use of bisphosphonate treatments, growth factor support, radiotherapy and knowledge and access to specialist departments (Snowden et al., 2011; Kumar et al., 2008) have been given as influences in improved outcomes in terms of morbidity and mortality.

The development of novel therapies such as Thalidomide, Lenolidamide and Bortezomib and their availability in the relapse setting have contributed to better survival outcomes (Kumar et al., 2008). Kumar attributes trending survival

improvements since 1994 to a variety of improvements (supportive and ASCT programmes) but remarks on the "striking" improvements since 2000 being largely attributable to the novel agents. As the novel therapies move forward in multi-centre studies in induction treatment regimens, the monitoring of primary outcomes in terms of survival remain a focus (Ludwig et al., 2010; Auguston et al., 2005). Second generation protease inhibitors and third generation immune-modulatory drugs are now being evaluated in clinical trials with agents such as carfilzomib (Siegal et al., 2012; Jakubowiak et al., 2012), Vorinostat (Cambell. 2010; Bandros et al., 2009) and Pomalidomide (Lacy et al., 2009; Escoubet-Lozach et al., 2009). Analysis of their benefits in survival outcomes in time will become available.

The identification of the cytogenetic abnormality basis of myeloma has deepened the understanding of the disease and allowed the identification of a population of high risk patients based on their chromosomal disorder. Chromosomal translocations and trisommies that correspond with poorer outcomes are now acknowledged and treatment pathways personalised based on these abnormalities, this has and continues to have, an impact on improved outcomes (Smith et al., 2012; Bergsagel et al., 2013; Kumar et al., 2012). Reviews of RCTs have looked at how cytogenetic abnormalities may also be influenced by the novel therapies (Bergsagel et al 2013). Further research is called for in this newer area of investigation to fully understand the benefits of targeted treatment due to the heterogeneity of the genetic variants (Kumar et al., 2012).

Despite improvements in outcomes for the younger fitter patient group treatment outcomes for patients over 70, the largest proportion of the myeloma population, have remained stable with no significant improvements reported (Brenner et al., 2008).

Myeloma remains an incurable disease. Patients relapse following cytotoxic chemotherapy, immune-modulatory drugs and protease inhibitors, in a cyclical pattern. In the absence of treatment the prognosis for patients is very poor.

Given that improvements have been slow but steady in the clinical treatments for myeloma and new clinical treatments continue in their evaluation, what other

avenues may be explored to potentially improve outcomes in myeloma? Can looking at the evidence base accumulating exploring poor outcomes in cancer survival provide insight for improving outcomes in myeloma?

2.0 Diagnosing cancer earlier- the evidence

The UK Government and NHS have been focused and committed to promoting and improving early diagnosis of cancer (DOH 2011; Richards 2009). The initiatives have arisen from the now generally accepted knowledge that the UK has some of the poorest survival outcomes in Europe, and that late diagnosis of cancer is seen to be a major contributing factor in these poor outcomes (Berrino et al., 2007; Richards, 2009). The National Awareness and Early Diagnosis Initiative hypothesis is that delays lead to patients being diagnosed with more advanced disease and negatively impacts 1 and 5-year survival results. (Richards, 2009). A body of work has been undertaken to investigate and describe the process of diagnosis and consequences of longer intervals in these pathways to diagnosis for specific cancers and explores areas of facilitating earlier diagnosis and improving outcomes.

Pathways to diagnosis described in the literature uniformly comment on the process being highly complex and that delays are multi-factorial. Authors have described delays in terms of components. There is generally a feeling that delays occur within the domains of patient, referral interval, doctor diagnostic interval and within the healthcare system (Round et al., 2013; Tørring et al., 2011; Kostopoulous et al., 2008; Neal et al., 2007; Corner et al., 2005, Neal, 2009, Rubin, 2011, Richards, 2009)

2.1 Patient referral intervals

Patient related delay has been observed generating from patients' attitudes with reluctance to access GP services based on fears of an impending cancer diagnosis or a feeling that they are "bothering" or "wasting" their GP's time (Robb, et al 2009). This leads to longer intervals in presenting to GP and extends the period of time between first symptoms to presentation to health professional. Public awareness of cancer has demonstrated a poor recall of alert symptoms and exposes a gap in the knowledge of patients and raises concern that patients do not access GP services because they are unaware of

alert symptoms of cancer (Stubbings et al., 2009; Robb et al., 2009). Differences across cancer sites are observed with breast cancer, where public awareness is high, having significantly shorter diagnostic intervals (Allgar et al., 2005). Several authors have discussed the disparities in outcomes and pathways to diagnosis found in different demographic groups. Round (2013) discusses the higher mortality rates in areas of deprivation such as Tower Hamlets in London and Rubin (2011) highlights the increases in diagnosis pathway intervals for groups from ethnic minorities and comments on there being interplay between demographics, patients and outcomes in terms of age, ethnicity and socioeconomic grouping. Patients with comorbidities who present with symptoms attributable to cancer have been reported as having longer diagnostic intervals with referral to secondary care being increased, due to symptoms attributed to pre-existing conditions. When symptoms are vague and non-specific delays are observed in referral times to specialist services (Allgar et al., 2005; Torring et al., 2011; Round et al., 2013) and an increase the primary care referral interval.

2.2 GP diagnostic intervals-

GPs see 80% of patients who go on to have a diagnosis of cancer (Allgar et al., 2005) making the interaction between GP and patient crucial to the process of timely diagnosis. Patients are said to like continuity in their family doctors (Ridd et al., 2006) but there is evidence that patients who bypass their GP are diagnosed faster (Allgar, 2005). Misdiagnosis of cancer by GPs influences primary care referral pathways increasing the interval to specialist care referral (Round et al., 2013; Kostopoulou et al., 2008). Misdiagnosis may be rooted in comorbidities, a lack of alert symptoms at presentation to GP, the rarity of the cancer in terms of lack of doctor exposure/knowledge/experience, or an asymptomatic presentation of the cancer (Neal, 2009; Round et al., 2011; Corner et al., 2005; Tørring et al., 2011, Kostopoulou et al., 2008). GPs in England see approximately 7-8 new cases of cancer each year (Richard, 2009) but will see hundreds of other conditions. The low incidence of cancer in primary care challenges GPs in terms of maintaining education in order to assess and refer potential cancer patients promptly and appropriately. Round et al. (2011) believes a lack of education can reduce awareness and surveillance

skills in GPs, this coupled with a stretch on services and difficulties for GPs accessing training further impacts and increases primary care intervals states Round. GPs are guided by the NICE referral guidelines for alert symptoms of cancer, but they are reported as having a low predictive value and are non-specific and often equally represent symptoms from chronic less serious conditions (Neal, 2009), making the use of the guidelines imperfect.

Work defining and regulating the systems for referral of suspected cancer patients has been initiated, and Richards, (2009) reports on the now more streamlined and effective systems in place when referring from primary to secondary care services. However Neal, (2009) reports of diagnosis pathways in secondary care being longer when patients are referred and investigated by the wrong speciality group the consequence being an increased secondary care diagnosis interval.

2.3 Healthcare system influence on diagnostic interval

Debate about the gatekeeper role of GPs within the healthcare system in the UK has raised concerns about the negative impact of its effect on the early diagnosis of cancer. Vedsted, (2011) describes the impact of the GP gatekeeper system reducing 1-year survival outcomes for cancer and describes the pressure for gatekeepers to use resource correctly, impacting negatively on the responsiveness of GPs to patients' needs and concerns. Vedsted describes the system of gatekeeping by GPs as "too rigid" for cancer care due to the need for more interplay of primary and secondary care systems in diagnosis and treatment. Other authors also recognise the gatekeeper system working against more fluid referral to hospital diagnostic services. Neal, (2009) highlights the difficulties for GPs to access diagnostic tests. Round. et al. (2011) reports that his experience of fragmented services that GPs deliver care from, with increasing numbers of sessional and part time workers, leads to loss of continuity and poor communication, making gatekeeper roles extremely difficult. Round et al. (2011), states GPs become incapable of using gut feelings about patients who are more familiar to them and the non-urgent referral waiting times mean GPs are often inclined to follow up their own patients rather than refer on and wait a long time for appointments from hospital specialists. Round et al. (2011) also discusses his experience of the sessional basis of practice doctors

making accessing training difficult for them and leaves the clinicians isolated from professional services. With 24% of cancers being diagnosed in the ED (emergency departments) as emergency presentations (Elliss-Brookes et al., 2012), the gatekeeper role of GPs has come under criticism for failures to diagnose cancer in primary care (Round et al., 2011), and has led to recent discussions in the medical literature (McCartney, 2013). McCartney, (2013) argues that analysis of the data on ED presentations is incomplete and no reference is given for GP interplay in referral to the ED. Given that the NAEDI hypothesis that late presentation equates to poorer outcomes the emergency presentation of cancer to the ED department is to be avoided. The most endorsed barrier to presenting to GPs given by patients in a qualitative study though was the difficulty in obtaining an appointment at their surgeries (Robb et al., 2009), a serious health system failure.

3.0 Early diagnosis in myeloma:

What is known about the processes of diagnosing myeloma?

Very little work has been undertaken to describe the pathways to diagnosis of myeloma patients. A small number of studies exist which look at different elements of the pathway but there are no studies to our knowledge that describe and contextualise all the components of diagnostic intervals and delay in myeloma.

In studies looking at presenting signs and symptoms in myeloma there is consensus that symptoms are non-specific and sometimes vague (Friese et al., 2009; Kariyawasan et al., 2007; Kyle et al.,2008; Blade et al., 1996; Howell et al 2013) irrespective of the age of the patient. Symptoms ranging from pain, fatigue, deranged blood (haematology/chemistry) laboratory tests, breathlessness, low energy, anorexia, sweating, oedema, bruising, numbness, gastrointestinal, genitourinary to collapse where all reported as presenting symptoms in 847 registry patients with myeloma (Howell et al., 2013). Some but not all of these symptoms are demonstrated in varying amounts in a number of retrospective studies describing presenting signs and symptoms of newly diagnosed myeloma patients (Friese et al., 2009; Kariyawasan et al., 2007; Howell et al., 2013; Ong et al., 1995; Kyle et al.,2008). This serves to

underline the difficulties in assessing alert symptoms associated with myeloma and eliciting rapid referral to specialist care and diagnosis. This difficulty in aligning symptoms and promoting prompt referral to specialist care replicates the same difficulties demonstrated in the oncology setting (Neal, 2009), and is underlined by the evidence for misdiagnosis seen in myeloma (Ong et al., 1995) and the higher number of pre-referral GP consultations demonstrated in myeloma patients (Lyratzopoulos et al., 2012). Further confounding difficulties exist in myeloma with a proportion of patients who require treatment and are diagnosed with symptomatic myeloma, presenting to secondary care with no symptoms (Ong et al., 1995; Howell et al., 2013). Ong. et al. (1995) noted that 15% of patients in this study presented with no symptoms and Howell et al. (2013) documented no symptoms in 152 out of 341 patients presenting with myeloma in their study. Ong et al. (1995) went on to describe a large proportion of patients (51%) that demonstrated a high stage burden of disease despite not presenting with any symptoms.

Kariyawasan et al. (2009) described an interval of greater than six months from first symptom attributable to myeloma and diagnosis in 67.4% of cases. 33% of this total had a referral time greater than 12 months. Other studies are comparable; Friese et al. (2009) described a significant delay in 40% of new diagnoses in a US study and described an average of 1 year in time to diagnosis in the "delayed" group. Breaking the delay group down further, delays were described as influenced by age, ethnicity and co-morbidities. A recently published study of newly registered patients with myeloma has shown diagnostic intervals to be of long durations with a median interval to diagnosis of 163 days and the interquartile range of 84-306, from first symptom to diagnosis (Howell et al., 2013). Longer intervals has been correlated with greater complications at diagnosis with disease being recorded at increased stages, the burden of disease increasing in patients who have commenced treatment later (Kariyawasan et al., 2007; Friese et al., 2009; Ong et al., 1995). The consequence of delay in commencement of treatment and outcomes was addressed in a Cochrane review (Yulong et al., 2012) with conclusion that progression free survival is decreased in patients who have delay in the commencement of treatment. Overall survival in the review was not altered. A

correlation between burden of disease and early mortality has also been described in a review of patients entered into the MRC trials (Augusten, et al 2005).

Evidence presented from retrospective reviews demonstrates a lack of uniformity in the diagnosis of myeloma. This lack of uniformity bridges both primary and secondary care. Patients have been observed to have shorter diagnosis intervals when diagnosed as an inpatient (Kariyawasan et al., 2007) and this may be influenced by rapid access to diagnostic tests. Kariyawasan et al. (2007), Friese et al. (2009) and Ong et al. (1995) all present evidence that diagnostic testing to determine myeloma is not consistent with differing percentages of patients having full criteria fulfilled having presented through primary care and referred to secondary care or presenting directly to secondary care.

Given the scarcity of information available on the pathways to diagnosis and elements of diagnostic intervals and delays in myeloma cases, this study will draw together the components of diagnostic intervals that are recognised in terms of the patient referral, GP diagnosis and healthcare services and describe in details what occurs in the population of Welsh patients presenting with newly diagnosed myeloma.

4.0 Aims and objectives:

The primary aim of this study is to describe in detail the diagnostic journey for patients in Wales with newly diagnosed myeloma and determine potential interventions to prevent unnecessary delays in diagnosis.

1 Prospectively recruit new patients with myeloma in Wales, and obtain data relating to their diagnostic journey, and obtain data from their GPs and diagnosing clinicians

2 From these data, identify patients who have had either prompt or longer diagnostic journeys or asymptomatic presentations of myeloma and undertake semi-structured interviews with a sample of these patients, and with their GPs, to explore the social and contextual factors associated with diagnostic intervals, and identify potential actions or interventions that may hasten myeloma diagnosis in the future

Research questions:

- How do diagnostic journeys occur in myeloma patients across Wales?
- What factors, interactions and experiences influence the pathway to individual diagnosis?
- What factors can facilitate timely diagnosis?

5.0 Eligibility

190 participants will be recruited over a period of 18 months.

Inclusion criteria

- Patient over 18 years of age
- Able and willing to give informed consent
- Able and willing to complete the study interventions-complete questionnaire
- Has been diagnosed with asymptomatic or symptomatic myeloma as defined by the MDT
- Is fully aware of their diagnosis and nature of the disease as defined by the treating clinician
- Diagnosed within 6 months of study registration

Exclusion criteria

- In the last few days or weeks of life and too unwell to complete questionnaire- as determined by clinician
- Mentally incapacitated
- Not at liberty
-

6.0 Methods:

This is a prospective mixed methods study that will define the pathway to diagnosis of a cohort of newly diagnosed myeloma patients across the Welsh nation. The study aims to recruit 190 participants. In order to facilitate rapid and full recruitment the study will utilise the established clinical and research

infrastructure in Wales. Multi-disciplinary Teams (MDT) throughout the 7 health boards in Wales will be asked to identify patients. The MDTs are well established and the current systems in place in recording diagnosis and registering patients are fluid and will complement the structure of this study. Identifying the patient for research at the first documented time point of myeloma diagnosis will ensure a prompt approach to patients occurs. If then recruited, this timely process will minimise the potential for recall bias for patient, GP and hospital specialist. MDT clinicians will be asked to confirm eligibility of individual patient and approach.

The study will utilise the support of the national research network dedicated research workforce NISCHR CRC (WCRN). NISCHR CRC (WCRN) nurses or research officers will screen patients against the eligibility criteria and approach the patient giving written information for the patient to take away and read. This will ensure dedicated and trained research staff approach patients at this difficult time around diagnosis in a sympathetic and appropriate manner. Additionally, the use of this dedicated research workforce will ensure the management and collection of data in terms of confidentiality and integrity.

6.1 Phase 1

Sampling, recruitment and data collection from patients and clinicians

Patient recruitment and data collection:

All new diagnoses of myeloma will be identified through the haematology MDT meetings in Wales at registration of the condition asymptomatic or symptomatic myeloma. Research nurses/officers (from the NISCHR CRC workforce) and clinicians will identify patients as potential participants (in the absence of a research nurse linked to the MDT, MDT coordinators will be asked to identify patients with clinicians) and provide patient information packs to patients, this is expected to be a small number of MDTs). Clinicians present at the MDT will confirm eligibility for the study and confirm approach can be made to patient. Potential patients will be then screened via hospital healthcare records against the eligibility criteria listed in the protocol.

If eligible, research nurses will approach patients at their next scheduled hospital appointment and offer participation in the study. The research nurses will discuss the study with patients, if the patient wishes, and provide the patient with a pre-prepared pack (Pack A), which will have been provided by the research team on completion of approvals to run the study. This pack will contain the informed consent literature (ICF) available in English and Welsh (Appendix 1) an invitation letter (Appendix 2) available in English and Welsh and the study specific patient questionnaire (Appendix 3), and a stamped self-addressed envelope.

The patient will confirm willingness to participate in the study by completing the informed consent (patient information sheet and consent) form and study specific patient questionnaire, returning it to Bangor University in the pre-paid addressed envelope. Two copies of the ICF will be given in patient packs and the patient will be asked to retain one copy for their own records.

Research nurses/officers will be asked to fill in a study recruitment log, anonymous for confidentiality, (Appendix 4) and scan and e-mail to study researcher when a patient is offered participation to allow study staff to track activity for reminders.

If the research team does not receive a reply from the patient within 4 weeks the study researcher will inform research nurses at site and ask research nurses to provide a reminder letter for the patient at their next scheduled hospital clinic appointment (Appendix 5).

Patients that do not respond to the reminder letter will receive no further communication but will be considered to have declined participation.

National MDT coordinators for Wales will provide monthly anonymised activity logs for total numbers of myeloma diagnosis by each MDT. This will allow the study researcher to assess the recruitment activity at individual sites and provide early intervention to promote better recruitment in poorly recruiting areas and also describe recruitment activity in terms of national incidence at the end of the study (Appendix 6).

GP and hospital specialist data collection:

MDT lead clinicians across Wales will have been approached personally regarding the study prior to recruitment and agreed to participate. GPs will be sent through the GP mail system in Wales notification about the aims and objectives for the study prior to receiving questionnaires (Appendix 7).

Individual GPs will be sent study specific primary care audit questionnaires with covering letters (Appendix 8 and 9) requesting their cooperation in completing questionnaires, of the recruited patients once the patients have returned questionnaire and consent. Copies of patient consent forms will be sent with the packs to ensure clinicians are aware of patient's consent to disclose information. Hospital specialists will be sent study specific secondary care audit questionnaires and covering letters (Appendix 10 and 9) along with copies of patient consent forms in the same manner.

GP and hospital specialists who do not return the questionnaire will be sent a reminder two weeks after the dispatch of the questionnaire by the research team (Appendix 11). A further reminder will be sent if the questionnaires are not returned in another 2 weeks, after this no further reminders will be sent.

In the event of poor returns the trial steering committee will seek support from NISCHR CRC nurses in primary and secondary care to complete questionnaires on behalf of GPs and hospital specialists. This will be possible as data from GPs and specialists will be generated from patient medical notes. It is most desirable to have the data generated from the primary source i.e. the treating clinician but in the event that data is not forthcoming from these sources the importance of collecting data from a secondary source via medical notes will be considered in the interest of analysis of the study

Questionnaire design:

The questionnaires have been adapted from the International Cancer Benchmarking Partnership (ICBP) Module 4 questionnaires for patient, GP and hospital specialist. These questionnaires (Vedsted personal communication) were piloted for use in other cancers and are in use in the currently recruiting trial in Wales and have not experienced any major difficulties operationally (Law personal communication).The questionnaires have been adapted for use in the

myeloma setting by the study researcher and piloted and evaluated by patients through the Involving People Network and the North Wales Cancer Patients Forum and through clinicians in primary and secondary care throughout Wales. Questionnaires were then modified based on the feedback received.

Data Management: entry and analysis for quantitative study

Personal details and completed questionnaire data will be entered on a stand-alone centrally supplied database at Bangor University. On a weekly basis data without personal identifiers will be transferred to a locally held secure database within the University. The data management system will be under the custodianship of Bangor University, sponsor of the study.

Statistical analysis Phase 1 study:

Firstly, all numerical data will be summarized to describe the sample population with descriptive characteristics. Following this, the type and distributional characteristics of the data will determine whether parametric or non-parametric analysis will be used. If the former, then analysis of variance (ANOVA), regression and survival analysis may be possible; alternatively, non-parametric versions of these tests could be used where appropriate.

Sample size To determine the sample size required from a pool of 375 (the anticipated incidence in Wales over a 18 month period), with a 5% margin of error and 95% confidence intervals, 190 responses are needed. Another way would be to assume a small effect size of 0.2 and preliminary analysis would consist of t-tests on mean differences:

t tests - Correlation: Point biserial model

Analysis:	A priori: Compute required sample size
Input:	Tail(s) = Two
Effect size |ρ|	= 0.2
α err prob	= 0.05
Power (1-β err prob)	= 0.80
Output:	Non-centrality parameter δ = 2.8210518
Critical t	= 1.9725951
Df	= 189
Total sample size	**= 191**

6.2 Phase 2- Semi-structured Interviews

A qualitative study, using individual semi-structured interviews, is proposed to explore in more detail patients individual and subjective experience and understanding of the diagnostic journey for myeloma. This will include consideration of the interaction between patient, health professional (GP) and health services associated with diagnostic pathways, both prompt and delayed.

Qualitative data will be collected from a sample of myeloma patients recruited in Phase 1 and their GPs. Qualitative methods are most suitable where there is little known about the area of study, and where there is a need to solicit the perspectives/perceptions of participants rather than impose hypotheses formed from professional understandings (Joubish et al., 2011)

Advice from user representatives (see below) will guide choice of research tools (e.g. individual interviews). Individual interviews will be used because these afford privacy and may be less threatening for respondents.

A Framework method approach will be taken for Phase 2. This is a method recognised as valuable in healthcare research and particularly valuable where research builds from one phase to the other The Framework approach ensures integrity of data but allows a complete view of perceptions and experience that answers the research questions but maintains a rigorous analytical process (Smith et al 2011).

Recruitment Process

Prior to approaching patients for the qualitative interviews the study researcher will contact via telephone or e-mail research nurse attached to the MDT, to ask for confirmation that the patient is well enough to be approached for interview. If patients are well enough to attend for interview a Patient Information Sheet for Phase 2 of the study with consent form and invitation letter (Appendix12 and 13) will be sent to the patients' home address (given in original returned patient questionnaire). Once the patient has read the patient information sheet the patient will be advised to return the reply slip if they **do not** wish to be contacted for interview. Patients that return the reply slip will not be contacted again. If there is no response from the patient after 2 weeks the study researcher will telephone or e-mail the patient to arrange an interview date.

Sampling

A purposeful sampling approach will be used, a strategy that is designed to identify the most information rich cases from which to learn about issues that are fundamental to the purpose of the research (Suri, 2011).

Purposive sampling will initiate the selection of participants: sample of 24-30 patients (three groups of 8-10) and 10-15 of their GPs selected from data retrieved from Phase 1 questionnaire. Selected patients will be identified by the research team from a group that demonstrate prompt/longer or asymptomatic presentations of myeloma. Interviews will be conducted and recorded with patient consent.

There will be four respondent samples:

a. Sample of (n=8-10) patients reporting diagnosis time within the upper quartile sample range. The sample will be purposive to include a representative sample number of asymptomatic myeloma patients

b. Sample of (n=8-10) patients reporting diagnosis time within the lower quartile range. The sample will be purposive to include a representative sample number of asymptomatic myeloma patients

c. Sample of (n=8-10) asymptomatic presentation of myeloma, The sample will be purposive to include a representative sample of asymptomatic myeloma patients

d. GP's (10-15)

Until recruitment reaches a stage where a distribution can be described data from existing published research (Howell et al., 2013) will be used to calculate the upper and lower quartile ranges in myeloma patients in order to identify sample a and sample b.

Face to face interviews with patients will be conducted in the environment preferable to the patient, this may be a home visit or at the hospital where they receive treatment for their myeloma. GP interviews will be conducted via telephone. Where there is a home visit involved the researcher will invoke the study specific lone worker policy adopted by the NWCPCR from the Bangor

University lone worker policy, and interviews will be conducted within working hours to facilitate implementation of the policy.

Methods

Some 24-30 face-to-face semi-structured interviews are planned. The semi-structured interview helps to ensure that the breadth of data collection is achieved whilst enabling topical trajectories in the conversation to be followed when appropriate (DiCicco-Bloom and Crabtree, 2006). Further interviews may be required if saturation has not been achieved, this is subject to time constraints to collect and analyse further data. The format of semi structured interviews is mainly discursive allowing respondents to develop their answers in their own terms and at their own length and depth; unlike some research methods, semi-structured interviews address specific study questions whilst also allowing both the respondent sufficient freedom to digress and the researcher to 'delve' further to seek clarification or elaboration of the phenomenon (DiCicco and Crabtree, 2006). Interviews will be 30 to 60 minutes in length and will be digitally recorded using digital voice recorders. An interview schedule will be devised generating a series of open-ended questions about factors related to the research questions.

A topic guide will be developed to address the primary and secondary research questions. This will be piloted before use. The interviews will explore the patient's perceptions and interactions around self-referral, primary and

secondary care diagnostic experiences and intervals, so that diagnostic journey components and intervals can be discussed in relation to their own particular social and cultural contexts. Discussion around myeloma diagnosis and diagnostic intervals will be allowed to emerge inductively although interest in this agenda will be apparent from the outset of the interviews.

ll interviews will be transcribed in full, by the researcher (or using transcription service within the NWCPCR) and data analysis will commence following the first formal interview; the data analysis will be guided by the principles of Framework Analysis and traditional 'thematic analysis'; this follows a constructivist approach whereby patients meaning structures around myeloma diagnosis and what influences the diagnostic journey, in the broad context of their social situation

and relationships with health professionals, health services and family or social networks (significant others) are explored through an understanding of their everyday lives.

Transcripts will be anonymised for names, places and critical events e.g. family, staff or clinical sites.

For the next phase in the analysis, transcripts will be analysed using framework analysis Transcripts and fieldnotes will be read independently by the two RAs on the project. Independently, the RAs will devise an index of all the key issues, concepts and themes drawing on a priori issues linked to the aims and objectives of the study as well as issues expressed by the participants themselves. The researchers will then come together to verify the consistency of their thematic framework.

Several steps have been built into the research design to enhance the methodological rigour of the analysis. First, obtaining data from multiple sources across 3 patient groups those with prompt diagnostic pathways and those with delayed diagnostic pathways and those with asymptomatic presentations, will allow us to explore how length of diagnostic interval/symptomatic presentations and social and cultural context may influence diagnostic intervals. Second, a member checking protocol will be used. A small sample of participants in each of the 3 patient groups will receive a summary of the findings and be asked to evaluate whether the analysis reflects their personal experiences. Finally, the interview sample size is substantial and will enhance our ability to attain data saturation, which will allow us to draw meaningful conclusions from the data.

7.0 Data synthesis

Findings from the analysis of the quantitative and qualitative data will be examined collectively to identify the routes of diagnosis demonstrated in this Welsh population of myeloma patients. Data will be synthesised and analysed to demonstrate intervals from first symptom to diagnosis as a total and then categorised for patient, GP and secondary care interval. Synthesis will include the grouping of patient's in terms of diagnostic journeys and these groups will be compared to categories of data collected i.e. patient characteristics,

symptoms experienced, routes of presentation/referral etc. This is likely to be a narrative statistical description.

Findings will also be used to identify potential interventions that could reduce time to diagnosis

8.0 Study outcomes and dissemination of findings

Study findings will be disseminated via publication in peer-reviewed literature, conference presentation and newsletters. Findings will be shared locally within the North Wales Centre for Primary Care Research and IMSCaR and the wider Bangor University academic and NHS communities and with the project research funder Tenovus and other charitable organisations. This research will also become a PhD thesis and will be publicly available through Bangor University

9.0 Confidentiality and data security

Participants will be assigned a unique study identification number upon registration which will be used for identification purposes throughout the study for all research activity and analysis.

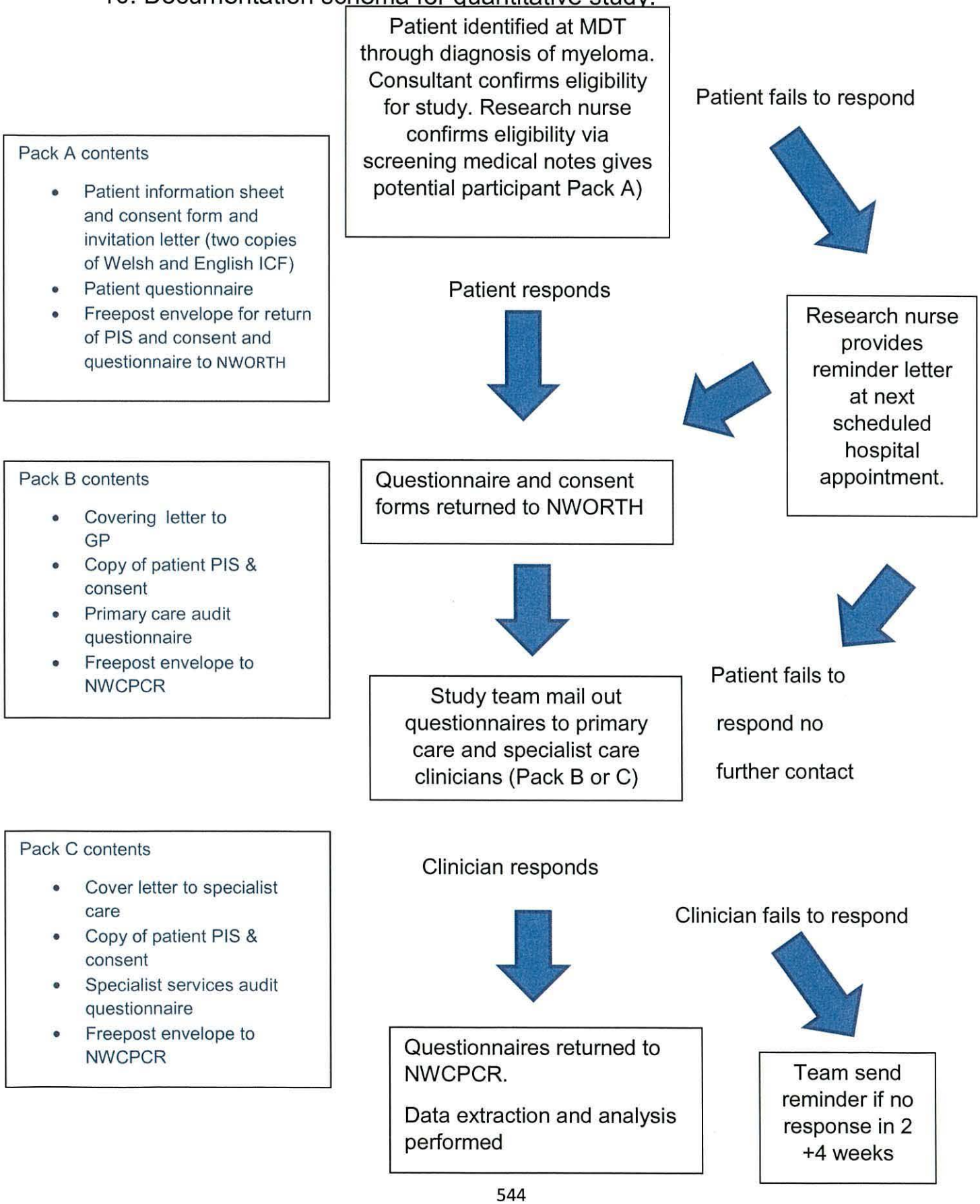
Participant non-anonymous data will be stored on a stand-alone system under the custodianship of Bangor University. Additionally, a database secured and stored under the custodianship of Bangor University will be stored within the electronic database systems, which will be password protected.

All hard copy documentation, case report forms, questionnaires and transcripts will be stored securely within the facilities provided by Bangor University. Paperwork will be stored within locked cabinets within a locked secured building. Access to this building is restricted to staff members with photographic identification and entry doors pass codes.

Documentation for the study, following successful completion of study and PhD, will be archived with NWCPCR, Bangor University.

Diagnostic journeys in myeloma (DJiM): why are they so long and what may facilitate early diagnosis.

10: Documentation schema for quantitative study:



9.12 Appendix 12: Details of the interview study population:

IDENTIFIER/ TRIAL NO.	GENDER/ ETHNICITY	AGE AT DIAGNOSIS	INTERVIEWED ALONE YES/NO	SAMPLE GROUP	MARITAL STATUS	DERIVATION QUINTILE	HEALTH BOARD	STAGE OF TREATMENT
SAM 004	Male/ White British	46	Yes	Longer	Married	50% least deprived	Betsi Cadwaladr	Post induction/post ASCT
CARYS 006	Female/ White British	62	Yes	Prompt	Married	50% least deprived	Betsi Cadwaladr	Post induction/awaiting ASCT
ARTHUR 013	Male/ White British	82	No	Longer	Married	50% least deprived	Betsi Cadwaladr	Surveillance
AUDREY 017	Female/ White British	61	No	Prompt	Married	50% least deprived	Cardiff and Vale	Post induction/awaiting ASCT
DAPHNE 018	Female/ White British	84	No	Prompt	Widow	20-30% most deprived	Hywel Dda	Post induction treatment/stable disease
TOM	Male/	65	No	Longer	Married	50% least deprived	Aneurin Bevan	Post induction/stable disease

19	White British							
JOHN 027	Male/ White British	59	Yes	Prompt	Married	20-30% most deprived	Hywel Dda	Post induction/progression/acutely unwell
CHARLIE 030	Male/ White British	70	No	Longer	Married	50% least deprived	Hywell dda	Post induction/stable disease
SHAN 034	Female/ White British	56	Yes	Asymp-tomatic	Married	30-50% most deprived	Hywel Dda	Post induction/stable disease
HARRIET 041	Female/ White British	64	Yes	Longer	Married	50% least deprived	Hywel Dda	Post induction/palliative
TREFOR 042	Male/ White British	73	No	Longer	Married	20-30% most deprived	Aneurin Bevan	Post induction/stable disease
JAN 044	Female/ White British	77	Yes	Prompt	Widow	50% least deprived	Cardiff and Vale	Post induction/stable disease