MASTERS BY RESEARCH

Developing Core Outcome Sets for Pleural Interventional Trials

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‘Yr wyf drwy hyn yn datgan mai canlyniad fy ymchwil fy hun yw’r thesis hwn, ac eithrio lle nodir yn wahanol. Caiff ffynonellau eraill eu cydnabod gan droednodiadau yn rhoi cyfeiriadau eglur. Nid yw sylwedd y gwaith hwn wedi cael ei dderbyn o’r blaen ar gyfer unrhyw radd, ac nid yw’n cael ei gyflwyno ar yr un pryd mewn ymgeisiaeth am unrhyw radd oni bai ei fod, fel y cytunwyd gan y Brifysgol, am gymwysterau deuol cymeradwy.’

Rwy’n cadarnhau fy mod yn cyflwyno’r gwaith gyda chytundeb fy Ngrichwyliwr (Goruchwylwyr)’

‘I hereby declare that this thesis is the results of my own investigations, except where otherwise stated. All other sources are acknowledged by bibliographic references. This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree unless, as agreed by the University, for approved dual awards.’

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Bangor University

Masters by Research (MRes)

Developing Core Outcome Sets for Pleural Interventional Trials

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Abstract

Heterogeneity in outcome measures in clinical interventional trials cause a vast amount of research waste. Endpoints of studies in what they set out to measure to judge efficacy of one treatment vs another, i.e. outcome measures, can vary hugely, making it difficult for these studies to be compared and contrasted in larger scale analysis. This leads to perfectly well-designed studies not being incorporated into systematic reviews due to the inconsistency in outcome measures. The variability in outcome measures chosen by researchers can be explained by a number of reasons. A lack of consensus of what the best outcome measures are, can sometimes be the cause. Other causes are slightly more sinister, with researchers cherry picking certain outcome measures which bolster the significance of their findings. This is known as outcome reporting bias. This variability of outcome measures, or lack of consensus of a number of key outcome measures within a particular clinical field, has become a recognised problem in research. This conundrum also affects the research in pleural medicine and pleural interventional trials with a particular lack of patient centred outcome measures. This study aims to develop a set of core outcome measures to be used by pleural interventional trials, as a bare minimum, in order to tackle this problem. Achieving a consensus on a minimum set of outcome measures deemed to core by relevant stakeholders to a particular field, will reduce this variability which causes issues to synthesis of reliable evidence from large scale analysis.

A long list of outcome measures was constructed through a scoping review of the literature, complemented by thematic analysis of semi-structured interviews with key stakeholders. This long list was streamlined in a meeting with four independent reviewers and entered into a modified two stage Delphi process. The Delphi process included both patients and practitioners scoring each included outcome measure on a 9-point scale. Participants were given an opportunity to advise on the list of outcome measures enrolled into the Delphi, ensuring it was an iterative process.

The synthesis of a ‘long list’ of outcomes elicited 9 outcome measures, entered into a Delphi process with a total of 78 participants. The Delphi process refined the long list into a core outcome set, consisting of 4 outcome measures. The Delphi process is a well-known consensus forming process used in the literature.

An all-encompassing core outcome set was developed, tailored to the key stakeholders pertaining to pleural interventions. The aim is for this core outcome set to be incorporated as a minimum to relevant research projects of the future within pleural interventional research and will be a step towards the standardisation of outcome measures, allowing for meaningful synthesis of evidence from the comparison and analysis of independent studies.

Further work must be done to assess the uptake and efficacy of these outcome measures.

Developing Core Outcome Sets for Pleural Interventional Trials

Preamble

Reflexive Account

Reflective practice, articulated as a concept primarily by Schon in 1984, states it is a type of reflection in a professional context. (Schon 1984) Reflexivity is often used interchangeably with the term reflective practice. It can be described as a process through which individuals intentionally explore their feelings and experiences in regard to a certain aspect of their professional conduct, in order to further their development and future actions. (Tremblay et al. 2013) Reflexivity is a crucial factor in enabling practitioners integrate knowledge, theory and practice. There is a consensus that reflexivity endorses professional development, allowing practitioners to transform their experiences into learning.

Reflexivity also has a significant part to play in the professional conduct of research. Reflexivity is described by Schaklock and Smyth as the justification of a methodological approach through the conscious revelation of underlying beliefs. This has the potential benefit of alerting a researcher to potential biases in their work, and whether their methodology is affected. (Schacklock and Smyth 1998)

A reflexive account is viewed as an important piece when judging analysis of qualitative research and the reliability of their findings. (Reid et al. 2018) The position of a researcher is unique, as they tend to have a working knowledge of the particular field of interest. They also have relationships with participants both in their capacity as an investigator and often in a non-analytical role, such as a practitioner. They are often savvy to competing priorities and the cogs in the machine that drive the research work forward and the obstacles that can hinder it. This position of insight can often serve as a tool for efficiency, or be the cause of incrementing bias, unbeknown to them. (Reid et al. 2018) The practitioner-researcher position becomes a heightened version of this position of insight; it's vital these professionals are able to effectively manage these multiple roles, power relations in order to avoid harming the reliability of their research. (Reid et al. 2018)

This reflexive account summarises my personal path and insights on the thesis research undertaken. My research study focused on developing core outcome sets in pleural interventional trials. The research undertaken allowed both patients and clinicians to reflect on pleural procedures experienced and undertaken respectively, helping formulate the desired core outcomes. I would like to begin this reflexive account on my personal experience as a practical technician in this field as a junior doctor, exploring my own interactions with patients and obstacles as a clinical operator.

Patient contact as a junior doctor exposes you to innately difficult situations, from raw emotions and disgruntled family members to handling deteriorating physical and mental health. The interpersonal skills you develop to tackle these issues naturally heighten your receptiveness to patient emotions. (Gunderman 2017). I have been fortunate enough to develop this emotional receptiveness particularly in my two medicine-based placements as an F1 and F2, which both happened to be based in Respiratory Medicine. This had not been something I had paid much thought to which I will go on to explore in further detail. Nevertheless, the general consensus amongst junior doctors remains that their time spent in medical rotations is often where they are able build their interpersonal skills. (Takeda et al. 2013) This concurred with my personal experience of medicine and the skill I was able to exercise and develop in the communicative domain. Exposure to palliative medicine allowed me to tackle patient issues in a largely holistic manner, contrasting from the goal driven care provided in my previous surgical specialties. (Bowman et al. 2019)

Treating patients with chest pain and dyspnoea on the respiratory ward gave me a comprehension of the tumultuous effect it had on their activities of daily living, impairing both their physical and mental health. (Talwar et al. 2015) The most dramatic resolution to dyspnoea that I had witnessed on the ward was due to a chest drain being inserted for a pneumothorax, causing almost instant relief. I was thoroughly impressed by both the therapeutic punch the small drain packed, along with its swift and apparent ease of insertion, with the use of the seldinger method by an experienced technician. Having only previously ever witnessed insertion of a surgical trauma drain, the seldinger technique, with preliminary pleural ultrasound, appeared to be a cleaner and more precise method. (Argall 2003)

My peaked interest meant I was observing every procedure I was able to, assisting and learning the method and process as best I could. This culminated in being invited to observe a medical thoracoscopy under sedation, a pleural intervention which involves induction of a pneumothorax to visualise and biopsy the pleura. (Yildrim 2013) This solidified my growing ambition to become competent at pleural procedures starting with the simple chest tube.

Focus and structured based courses have been designed with the primary aim of developing confidence in foundation year trainees with invasive medical procedures, with some success. (Garrood at al. 2010). Though self-reported confidence in these procedures improves with such

courses, realistically only a small proportion of foundation trainees have managed to complete these in clinical situations. A study reviewing NHS trusts across England found that a low proportion of foundation trainees had ever carried out an invasive medical procedure. Moreover, it found that only a third of foundation trainees had ever attempted a chest drain, with the average confidence score being markedly low. (Lim et al. 2014) Overall, this is an accurate reflection of my own personal experience with medical procedures. However, my interest and desire to become competent in pleural procedures with the abundance of supportive senior staff I was able to become self-sufficient. I was able to refine my skills at procedural courses, becoming increasingly confident with pleural ultrasound.

Becoming competent with this medical procedure gave me a confidence I was able to wear, in handling my duties as a junior doctor. On the respiratory ward, I felt a valued member of the team; middle grade doctors felt comfortable in allowing me to complete pleural taps, whilst nurses felt reassured in asking me questions regarding care for chest drains. This confidence extended into other rotations, most notably my placement in intensive care where the mainstay of the day-to-day duties involved medical procedures. I was able to volunteer confidently to carry out chest drains in intensive care under supervision. I found this allowed senior staff to be more willing to teach, opening up opportunities to carry out medical procedures less accessible to other foundation trainees. (Lim et al. 2014)

Nevertheless, chest drains remained my favourite procedure due to the effective relief it provided my patients both in the emergency and in elective setting. To this day, the most satisfying moment of my medical career was my first chest drain for a pleural effusion; simultaneously watching the pale yellow, opalescent pleural fluid flowing through the tube into an underwater seal and the marked discomfort of dyspnoea slowly dissipating from the patients face.

The combination of technical ability to complete a multifaceted procedural task along with providing almost instantaneous symptomatic relief resonated with me. I had always enjoyed surgical procedures for this very reason, from simple abscesses to hip replacements. Before starting my first respiratory placement, I had laid down roots in surgery having taken my surgical speciality exams. I entered my respiratory placement quite unaware of what to expect. Through medical school, I had always been quite interested in cardiothoracic surgery, but had never appreciated the association between the surgical specialty and that of respiratory medicine. Their association was made apparent at my first aforementioned experience of a medical thoracoscopy, accelerating my newfound interest in pleural procedures. I quickly realised the amount of information that was shared between the two specialities and had the pleasure of attending a cardiothoracic clinic. As I became more accustomed to pleural procedures, my affinity for the practice grew; I felt I had found an overlap between medicine and surgery allowing me to further my knowledge in both fields.

The conception of this project lay in my consistent conscious effort to become as skilled in pleural procedures as possible. The evolving role of the indwelling pleural catheter in treating malignant pleural effusion meant its frequency as choice of therapy in lung cancer patients slowly increased. (Wahidi et al. 2017). Witnessing increasing numbers of indwelling pleural catheters inserted I felt like I had observed enough to attempt one myself. However, the transition into attempting one was more difficult than I had experienced before for a number of reasons. 1) Opportunities were scarce due to select patients deemed to be able to benefit from IPCs long term 2) Only a select number of senior staff felt comfortable in supervising insertion of an IPC as most consultants have only experience of a handful. 3) Middle grades proved resistant to junior staff seeking opportunities for IPC insertions; partly due to scarcity of chances to do so and partly due to determination to ensure they were the ones to gain experience initially.

In my effort to seek an opportunity, I ensured I was present to every scheduled IPC insertion as they were more often than not, an elective procedure the patient was well enough to come in for. In making myself available, I came into contact with all the potential patients who mostly had had some experience of a type of pleural procedure. Through my conversations, I was able to gage their previous experiences with details of positives and negatives, what they were expecting from their next procedure and where this ranked in terms of their overall experience with pleural interventions post-procedure.

In my patience to carry out this technical procedure I studied the literature in its slow transition in favour of indwelling pleural catheters. I came across evidence in reported papers that in effect propped up the use of IPCs over other pleural interventions in certain situations but wasn't completely content with the way in which interventions were compared. I noticed the heterogeneity in the way in which authors went about comparing the efficacy of pleural interventions, with some giving more importance to stats and others putting greater emphasis on patient related outcome measures.

On further research, it came to my attention this was a common problem in clinical efficacy trials and researchers had already developed a database in order to combat the problems of heterogeneity of outcome measures – COMET initiative. (Williamson and Clarke 2012) A thorough search of the database revealed the absence of a representation of pleural interventions, conceiving this project as its objective to ensure this was no longer the case. Several months down the line, I was able to finally complete my first IPC under ultrasound guidance and under senior supervision. I felt proud of this achievement due to the grief and perseverance I had shown in order to achieve it. I felt an accomplished practitioner, demonstrating the skill in inserting the most up to date evidence-based intervention in treating malignant pleural effusion. However, I was prouder of the project that I had originated in my quest to complete an IPC insertion. I felt excited that if completed correctly, I would be able to develop a consensus of core outcome sets for pleural procedures, which could be

used to objectively compare indwelling pleural catheters to the next developed pleural intervention of the future.

Chapter One

Introduction and Policy Context

The short reflexive piece projects my personal relevant experience and the background for the proposed thesis. In the account I tie my affinity for the procedural efficiency of pleural interventions and a current and problematic issue affecting researchers across the whole stratosphere of research evidence-based practice; heterogeneity in outcome sets in particular clinical fields impeding the reliability of evidence gleaned from meta-analysis of randomized trials. A method of combating this issue is the development of a consensus on core outcome sets in clinical subareas in order to resolve the existing heterogeneity. This can be done through the incorporation of input from relevant stakeholders, including patients and practitioners, through validated processes, producing reliable core outcome sets. Research to produce core outcome sets is required to enable a standardised set of primary outcomes to be used in trials pertaining to a particular clinical field resolving the issues currently impeding meta-analysis.

The pleura is a thin layer of body tissue that envelopes the lungs completely. On top of the pleura is a second layer of cells called the mesothelium. (Williams et al. 1989)

The pleura itself is a serous membrane which folds back on itself forming two layers. One layer known as the visceral pleura, closely adheres to the lung. This layer is anatomically at one with lung tissue and contains no sensory innervation. On the contrary, disturbance of the parietal pleura often causes pain for patients, as it has rich sensory bed of nerves. The parietal pleura is often known as the ‘outer’ pleura and adheres to the chest wall via the mesothelium. (Charalampidis et al. 2015) The mesothelium is as uniform layer of cells lining the pleura. Their primary function is to provide a slippery and non-adhesive protective layer, allowing the expansion of the lung within the chest wall to occur seamlessly. (Mutsaers 2004)

Though one structure the visceral and parietal pleura receive their blood supply from two distinct sources. (Charalampidis et al. 2015) The potential space between the visceral and parietal pleura is known as the pleural space. This cavity helps the transfer of forces, from the movement of the chest wall to the lungs. (Charalampidis et al. 2015)

This space can often contain a few millilitres of fluid in a healthy lung, termed pleural fluid. (Hooper et al. 2010) A 'pleural effusion' occurs when there is an excessive accumulation of this fluid, caused by either excessive pleural fluid production or lack or altered fluid resorption (Karkhanis and Joshi 2012) This can pose a diagnostic conundrum for medical professionals as there are over 50 documented causes; from local pleural complications to systemic conditions (Light and Porcel 2008). Interestingly, it is more common for pleural effusions to be a direct cause of pulmonary and extrapulmonary causes, rather than primary pleural disease. It is the most common manifestation of pleural disease and can cause symptoms such as chest pain, dyspnoea and dry cough. (Dancel et el. 2018)

Pleural effusions are not the extent of pleural disease with rates of other pleural related conditions on the rise such as pneumothorax, empyema and pleural malignancy. (Finley et al. 2008) Pneumothorax is the occupation of the pleural space with air secondary to the damage of the chest wall or the lung itself. (Zarogouldis et al. 2014) Empyema is a collection of pus in the pleural space and associated with infective pneumonia. (Ahmed and Yacoub 2010)

Generally, in order to treat pleural conditions, this will involve the insertion of an intercostal chest tube or a therapeutic thoracentesis, with visualisation of the parietal pleura and potential biopsy. (Bhatnagar et al. 2016) These pleural interventions include medical thoracoscopy, pleural biopsy, temporary drainage procedures for both air and fluid. (Bhatnagar et al. 2016) Depending on the nature and requirements of a patient a novel technique is the Indwelling pleural catheter (Chalhoub et al. 2018). This pleural intervention aims to improve the quality of life for patients by allowing thoracentesis, without the need for a painful procedure each time. It has emerged as an efficacious adjunct in the fight against recurrent pleural effusions. Studies have shown it can reduce the number of days patients are hospitalised, positively and significantly impacting the quality of life for patients. (Thomas et al. 2017)

Pleural interventions lie in the peculiar field of responsibility, of both medical and surgical specialities. (Bhatnagar et al. 2016) Traditionally, pleural interventions were carried out by thoracic surgical personnel or interventional radiologists. Due to the recent advancement of bedside technology, the onus has been put on to "interventional pulmonologists" to provide a specialist pleural service. This means the boundaries have now shifted drastically, clouding the distinctions that were once made between medical and surgical professionals. (Hooper et al. 2010) My reflexive account provides a background on my personal experiences embedded in the conception of this project.

Background: Pleural intervention

There have been a countless number of advances over the past few decades in gaining access to the pleura by practitioners, including incorporation of new insertion techniques, to more readily

available imaging options. Once a specialised procedure largely carried out intraoperatively by thoracic surgeons, it has evolved into an accessible procedure for clinicians to utilise to intervene in acute situations. (McElnay and Lim 2016)

Intercostal pleural drains are quite an invasive procedure, often done with little supervision. Complication rates remain just under 10%, with most being manageable phenomenon such as pain and discomfort and dislodgement (Porcel 2018). However, catastrophic complications such as organ injury are extremely conceivable scenarios (Porcel 2018). There are certain fail safes in place to ensure dire complications are not encountered, such as imaging and technique options. However, this highlights the need for the practitioners to be able to choose the most appropriate intervention for each patient. This decision is normally in the hands of the most experienced and senior practitioner or clinician, as evidence has naturally shown complication rates are significantly lower in experienced hands. (Porcel 2018)

With the continued advancement of medical technology and adjuncts, there seems to be an interminable scope for progression; from new techniques to completely novel interventions. At the forefront of all practitioners' minds, needless to say all governing bodies, is the delivery of high quality and safe patient care. The responsibility of allowing the safe introduction of novel treatments or procedures lies with both practitioners at the duty of care and with regulatory agencies (Patelarou et al. 2017).

Aforementioned, indwelling pleural catheters are a good example of a novel method, where initial studies have depicted their efficacy. In order to warrant seamless amalgamation into the options available to healthcare professionals, further work must be done.

The way in which new methods are incorporated into medical practice is based on analysis of the available literature. This analysis, and the problems heterogeneity of primary outcomes poses, is the specific problem that I aim to address, within the constraint of the particular clinical field of pleural disease.

Reviewing the Evidence: Rationale for study

The safe vetting process in which clinicians rely on is the process of practicing evidence-based medicine. The four stages of a treatment or procedure undergoing evidence-based accreditation is as follows:

- Formulation of a research question
- Access relevant literature
- Appraisal of the literature
- Application of the findings to affect practice

The breadth of the research that is reviewed must be wide enough to ensure all relevant literature is included, once a research question is formed. The appraisal of literature is referred to often as meta-analysis and, quite literally, involves a systematic review of the outcomes in order to establish evidence-based practice and resolve the issue of contradicting research outcomes. (Patelarou et al. 2017). Meta-analysis from its origins in the 1970s has had a ground-breaking effect on the essence of evidence-based practice. It allows the systematic review of the results of relevant studies in order to achieve a holistic understanding of a particular issue or topic. (Gurevitch et al. 2018)

Until recently this was done using a narrative method with each study being summarised to be objectively compared. It quickly became apparent that this had its limitations; summarising and analysing huge numbers of articles in this style often caused discrepancies in the quality and objectivity of analysis. A more robust, scientific and reproducible method was required to ensure results from various studies were meta-analysed with minimal bias. (Gurevitch et al.2018)

The incorporation of formal reproducible protocols allowed this to happen, effectively being able to analyse considerable numbers of primary studies. This allows researchers to understand the magnitude of any conclusions drawn from the evidence, identifying trends and anomalies in the data. (Gurevitch et al. 2018)

This systematic protocol developed out of a desire for consistency also has its downfalls. The reproducibility and prestige they have attained has meant a surge in the number of quantitative systematic reviews produced more recently. This has often caused a dramatic drop in the quality of systematic reviews with overly ambitious authors compromising the quality of the studies used for publishable units. (Ioannidis 2016)

Nevertheless, the efficacy of quantitative meta-analysis should not be abandoned, with a focus and drive to encourage an improved method and quality of reporting. A shift in the culture is required, with increased training of practitioners in the rationales of meta-analysis with further issues addressed appropriately when systematic review studies are drawn up. (Hillebrand and Cardinale 2010)

A significant well-documented issue with quantitative meta-analysis is the heterogeneity between the studies selected for meta-analysis. The differentiation process of meta-analysis now accounts for these, incorporating methods of assessing publication bias, power and precision between studies. (Egger et al. 1997) These heterogeneity tests appropriately account for the weighting of each study in the meta-regressive process. This cumulative meta-analysis allows the detection of temporal trends and publication bias, enhancing the reliability of the results from meta-analysis. (Leimu and Koricheva 2004) Recent further studies have depicted the need for researchers to be aware of publication bias, as empirical evidence has clearly shown the association of apparent significant results with publication.

The heterogeneity in relation to outcome reporting has been an issue receiving attention from researchers more recently. Outcome reporting bias has been recognised as a potential threat to the reliability of meta-analysis. Recent studies have depicted that outcomes that show a statistically significant result are more likely to be fully reported with other outcomes not reported as comprehensively. (Dwan et al. 2008) A study carried out in 2006 comparing protocols within trial publications, discovered to up to 60% of trials changed, introduced or omitted one primary outcome at the very least. This clouded ethos amongst researchers in order to become published authors, has most probably spiralled worse out of control, up until more recent awareness of outcome reporting bias. (Dwan et al. 2008)

This form of outcome reporting bias can be categorised into three, known as selective reporting bias; based on either 1) the selective reporting of only a few of the outcomes tested and other analysed results left out 2) inconsistent reporting of a certain outcome 3) Incomplete reporting of a specific outcome. (Kirkham et al. 2010)

Studies with aims to identify prevalence of outcome reporting bias, state the substantial nature of this issue with both independent trials and the meta-analysis of systematic reviews. Confounding the problem, studies selected for meta-analysis often use varying outcome measures. (Kirkham et al. 2010) This inevitably raises the likelihood of outcome reporting bias to be a major concern in the context of meta-analysis of selected studies. (Kirkham et al. 2018)

The ORBIT study carried out in 2010, reporting on the outcome bias in trials, elicited the issue of outcome reporting bias in 34% of Cochrane systematic reviews. (Kirkham et al. 2010) A study following on the work from this, focusing on harm outcomes, depicted the presence of outcome reporting bias in over 75% of systematic reviews. (Saini et al. 2014)

The ORBIT study developed a matrix tool in order for reviewers to easily identify outcomes that are partially reported in studies. Mapping out the outcomes reported from related studies in a simple table, providing a transparent method of depicting potential outcome reporting bias, allowing systematic reviewers to account for this and to justify the exclusion of certain outcomes from meta-analysis. (Kirkham et al. 2010) There is a free to use template for researchers to construct such a matrix online and reviewers should be encouraged to export this to include in their systematic review articles. (ORBIT Matrix Generator 2018)

A key method in which authors are able to combat this significant issue to meta-analysis, streamlining the work of systematic reviews, is to collectively work towards developing a consensus on outcomes that are considered to be core for all interventional or efficacy trials. (Kirkham et al. 2018) Developing a standardised set of outcome measures for particular fields by incorporating input from all relevant stakeholders, will promote good quality meta-analysis of data produced from

clinical trials. This would make a considerable change to the quality of the conclusions drawn from systematic reviews, significantly rectifying this issue which often leads to waste in research.

Systematic reviewers aim to address uncertainties by turning to a composite of clinical trials, in order to carry out evidence-based practice. The current inconsistent nature of outcome measures impedes their ability to resolve the qualms they wish to address. It becomes important that researchers are made aware that there are solutions to this issue that they can be responsible for. The more researchers become involved in the development of core outcome sets, and use them as a foundation for their studies, the easier the task of rigid meta-analysis becomes. (Williamson and Clarke 2016)

This is not to suggest that authors should limit their studies by incorporating a cap on their outcome measures to match core outcomes. On the contrary, researchers should be encouraged to include as many outcomes they are able to measure and report competently. However, a greater effort should be made by researchers to include a bare minimum of particular core outcome sets in efficacy trials in clinical subset areas. This would ensure that inappropriate outcomes are not solely relied on reducing the utility of studies, increasing the statistical power of systematic reviews, as fewer studies are excluded. (Sinha et al. 2008)

In light of this, there have been a number of initiatives and organisations mandated to organise the efforts of researchers in developing a universally accessible database, populated with deduced core outcome sets for all clinical specialties. This began with certain specialties investing research efforts to collect core outcomes to utilise themselves, setting an example for other specialities to follow suit.

This was done in exemplary fashion by the OMERACT process in rheumatology. Their aim was to improve endpoint outcome measurement data, on the principles of truth, discrimination and feasibility. A powerful and pioneering strategy of the OMERACT initiative was the incorporation of patient input at each step of the OMERACT process for core outcomes in rheumatology. (Tugwell et al. 2007)

The importance of incorporating patients into the consensus process is a step all researchers participating in establishing similar approaches in other fields should emulate. I drew from the approach in this study and planned to ensure patients are healthily represented and accounted for when formulating the method of consensus for my study. Patient involvement in research has been a growing theme since the introduction of the INVOLVE programme in 1996 and overtaken by the National Institute for Health Research (NIHR) in April 2020. (Brett et al. 2014) The essence of the initial initiative was to increase the overall patient involvement with all stages of research. This includes consulting patients when designing research projects and whilst carrying out the methodology. In theory, increased patient involvement in research design, conduct and implementation improves the focus of the overall process, producing a higher quality end product.

Patient involvement in health care research can be viewed as a positive feedback mechanism. The end product is ultimately to improve healthcare for patients, and if patients are involved in the process from the early stages, theoretically this should help identify research priorities and affect research design in a positive manner. (South at al. 2016)

As well as being involved in the early stages of research development, there is a growing notion of increased patient and public involvement in the overall conduction of projects and how they are governed. Patient involvement has now moved into the mainstream of research development, to the extent that it is now a prerequisite for research funding across the globe. This is understandable when in fact most of this funding often comes from public sources. It seems fitting that patient and public involvement be stipulated into the terms of these funds being granted. (Wilson et al. 2015)

There are however some drawbacks with ubiquitous patient involvement in the development of research. Tokenistic patient involvement in expert areas, in which patients would struggle to positively contribute to can introduce a waste of limited resources of time and personnel. (Domecq et al. 2014)

Nevertheless, the involvement of patients and the public has been shown to be generally beneficial to research development, particularly patient facing elements, and I plan for it to play an important role in the completion of this study.

The establishment of OMERACT, involving leaders in the clinical field of rheumatology from America, Europe and Australasia, has naturally taken a consistent effort, with specialists understanding the nature of issues they aim to combat. OMERACT emphasis that these efforts can often take a huge length of time; other clinicians in other fields shouldn't expect consensus of standardised outcomes to happen overnight. The organisation of such a logistically difficult task is a huge obstacle for researchers to overcome. (Tugwell et al. 2007)

Fortunately, there has been an organisation taking on this huge feat, aiming to ensure there is a tangible space for researchers taking on this work to be able to consolidate and confluence their work. The COMET initiative is an online database for work done on the development of standardised outcomes, allowing researchers to easily search their field of interest for validated studies. This initiative was funded by the MRC North West Hub for Trials Methodology (NWHTMR) in 2010. With the backing of trialists, systematic reviewers, health service users, journal editors, policy makers, trials registries and regulators, there was a growing demand for such an initiative. This not only allows accessibility through the database but raises further awareness to the unrelenting issue of heterogeneity in outcome measures in efficacy trials. (Williamson et al. 2012)

This issue has been recognised as a multi-faceted problem, affecting a wide range of clinical specialties. The pleural community have also recognised the way in which the research in this particular clinical area has also suffered due to this ever-reaching problem.

This has become more apparent with the development of novel pleural interventions and the efficacy trials developed in order to assess their validity and applicability. The indwelling pleural catheter is a new intervention that patients can be selected for as a reliable method of dealing with chronic pleural effusions, whilst being able to keep their hospitalisation days to a minimum. A huge contributing factor to why it has taken so long for valid efficacy trials to be definitive in their assessment of IPCs is due to the variety and inconsistent nature in which outcome measures have been defined and measured in this population. Evidence collated from systematic reviews in this field has therefore suffered the same issues, impeding the reliability of conclusions gleaned from meta-analysis. (Ost et al. 2014)

Another issue highlighted in the recent research into the efficacy of Indwelling Pleural Catheters was the importance of incorporating patient related outcome measures. Clinical trials are slowly migrating towards patient centred outcomes as a whole, with pleural interventional trials also following suit. Patient views have been successfully incorporated into the development of core outcome sets in other clinical specialties; this should be a key objective of researchers in pleural studies to ensure the patient perspective is healthily considered in the development of a consensus for core outcome sets. A multidimensional, patient focused approach to defining and measuring outcomes of pleural disease treatments is essentially required.

The incidence, mortality and morbidity for pleural disease are extremely high. Over 15 % of patients with an underlying cancer suffer with malignant pleural effusion, with mortality rates at 30 days 22% and 74 % at one year. It is a pathological phenomenon associated with both poor short-term outcomes and chronic health deterioration. A generally poor outcome increases the importance of ensuring there are effective outcome measures assessing the efficacy of pleural interventions, in order to avoid unnecessary interventions and the incorporation of effective treatment methods in this predominantly palliative population. (Markatis et al. 2022)

Indwelling pleural catheters are an example of a relatively novel intervention within a number of tools in the management of malignant pleural disease; the significant burden of mortality and morbidity this disease exerts on populations across the world, it can be expected that further research and clinical trials will be completed to evaluate newer methods in treating this disease in the coming years. Ideally, these will be investigated with new randomised controlled trials. The absence of a core outcome within this clinical field will theoretically impede the evidence synthesised, and ultimately affect the quality of evidence-based practice gleaned from this.

Healthcare workers caring for these patients require a core outcome set to be able to gage the efficacy of their interventions. Only more recently have researchers started to incorporate the effect of pleural interventions on the symptomatic benefit of patients. This indicates the lack of a consensus of the best outcome measures to effectively assess the merit of certain pleural procedures. The aim of this study is to incorporate the new trend towards patient centred outcome

measures, with the previously practitioner targeted elements, to produce a holistic set of core outcomes which can then be used to assess the overall efficacy of named pleural procedures.

A lack of a core outcome set which engulfs both these fronts, leaves researchers at risk of being negligent of certain important aspects to either practitioners or patients, in efficacy trials of pleural interventions. To consider a wider range of outcome measures when deducing a core outcome set is important. It is simplistic to imagine there is a single intervention available that is the best for every patient suffering with pleural disease, as the varying prognosis of patients means that practitioners have particular treatment goals for each patient. A core outcome set that would address, if not all, but the majority of these, would contribute to the effective selection of appropriate interventions for certain patients, avoiding unnecessary procedures.

There are various methods of achieving consensus, with modern methods incorporating traditional methods with more rigid and reliable frameworks. The Delphi method has been a process with a long history of use in health and medical research, first being established in 1948. (Fink et al. 1984)

The process through which this method is applied can often rely on scoring methods, which can often have their own shortcomings. An organisation founded to tackle this issue is the GRADE working group: The Grading of Recommendations Assessment, Development and Evaluation. This initiative is the collaboration of people to address the quality of rating systems within health care and research. Moreover, they are instrumental in assessing the quality of research and strength of recommendations based on that research. (Guyatt et al. 2011)

Modern consensus methods rely on scales validated by organisations such as the GRADE working group (GRADE 2000), along with traditional processes such as the Delphi Method, often made up of more than one round, to achieve its goal. (Millar et al. 2017) Other methods used involve focus groups, individual interviews, semi-structured interviews and anonymous questionnaires. Whichever methodological approach used, the key congruent concept remains that the views and ideas of all key stakeholders are to be included when making the final decisions in regard to a consensus. Researchers should remain cognisant of the methods used and the way in which these can affect their results and the potential biases that can occur. Within the COMET initiative there is currently ongoing research into ways in which this process can be perfected. (Williamson et al. 2012)

COMET are consistently updating their database with ongoing research being vetted for inclusion. There remains no current study into core outcome sets for pleural disease or intervention. There are currently no studies present on the database in regard to or relating to thoracentesis, pneumothorax or malignant pleural effusion. Often assessing and eliciting gaps in the literature can be a difficult concept, without the benefits of a thorough literature review. This is an important step in the justification of research efforts in a particular clinical field, often merely based on the climate of opinion at the time. With the help of the COMET database, along with the ever-emerging problem of

heterogenic outcomes used in clinical trials, the gap in the literature for Pleural Interventional COS should be addressed. The disease burden that malignant pleural effusions put on health care systems across the globe, with over half of malignancies being complicated by one, it is safe to say it is an area that can no longer go on to be neglected. (Baas and Burgers 2018)

There have been efforts by researchers, which appreciate the fact, that often the treatment intent for pleural procedures is symptom amelioration. A recent pioneering study carried out by researchers took it upon them to shift the focus on to patient related outcome measures (PROMS), in relation to various pleural interventions. It can be argued that this a welcomed change of direction for outcome sets for pleural interventional trials, focusing on the symptomatic aspect of patients' experience to evaluate novel pleural treatments. On the other hand, this can be seen as a narrowminded approach in the opposite direction, dismissing other important outcome measures such as repeat intervention rate and hospitalisation days. (Psallidas et al. 2017)

This further supports the requirement for a confirmed consensus in the pleural interventional field, allowing for a core outcome set that inhabits the middle ground, including outcome measures important to all stakeholders involved.

Summary

Arguably, the tangible impedance, to the eliciting of reliable conclusions from the meta-analysis of powerful studies that the heterogeneity of outcome measures causes, is having a continuous negative effect on the quality of care delivered to patients. Its restrictive effect on the growth of good evidence-based practice has become a phenomenon that all researchers must strive to fight.

The small, but important, area of pleural disease, is no exception to this rule, and efforts to align this clinical field with the others addressing this problem, is a goal of this thesis. Structures such as the COMET initiative are in place to facilitate such work to be carried out. (Williams and Clarke 2006) The guidelines set out by COMET present standards, that I will work towards meeting, whilst ensuring a thorough and holistic approach to this well recognised problem. The ultimate aim of my thesis is to be able to contribute to the database for core outcome sets, establishing a consensus for the pleural community that would aid future trials to come.

Structure of Thesis

The structure set out follows a systematic four step process. Step one is the justification of the research project, including the pre-amble and issues discussed in this chapter. It is important for me to be able understand the importance of the efforts and aims of organisations such as COMET, allowing me to potentially consolidate their work against a database of previous research. This not only induces morale to be able to effectively tackle a problem of this magnitude, but also provides me with a potential framework to organise my attempt.

The following chapter is an iterative scoping review of both primary and other outcome measures used in pleural interventional trials. The scoping study will allow me to review numerous relevant studies in the effort to build up a cohort of outcome measures used by researchers and clinicians in the recent past. The review will also allow me to gain an insight into the method of how outcome measures were gaged. Moreover, the literature review will allow me to form a judgement on the importance of each outcome to researchers and clinicians of the recent past, in this particular clinical field of pleural disease and intervention.

I will also use the scoping study to review the various stakeholders detailed in previous studies; analysing the extent of their input to the primary and secondary outcome measures used.

After discussion with my supervisors, a scoping review was deemed to be the best method of reviewing the literature for this thesis. Firstly, a scoping review has been the method to review the literature in the development of core outcome sets in various other clinical disciplines. (Tugwell et al. 2007) The purpose of the scoping review, in this context, is essentially to develop a long list of outcomes as a step in the process of eliciting a core outcome set. The flexibility, breadth and iterative nature of a scoping review allowed me to ensure this list of outcomes produced was extensive as possible. However, this in itself can be interpreted as a limitation, with the lack of methodological steps and boundaries meaning key studies may go missed. The iterative and flexible nature of a scoping review meant I was able to review outcome measures from the literature swiftly. This however meant key studies were missed, and to be able to take full advantage of the iterative nature of a scoping review, greater time and resources are required.

Following on from this will be chapter 3, entailing the empirical work in two stages. The first stage will be semi-structured interviews with both practitioners and patients. Practitioners will be interviewed at all levels including: Consultant Respiratory Physicians, Consultant Intensivists, Specialty Respiratory Doctors in training, Junior Doctors and Specialist Nurse Practitioners. These practitioners will be the subject of the semi-structured interviews as they are the clinicians most likely to carry out pleural procedures in my health board.

Semi-structured interviews will also be carried out with patients, encompassing most common indications for a pleural procedure. This will also include patients with pneumothorax, empyema, and pleural effusion, including both cancer and non-cancer causes.

Interviews will mainly be carried out post-procedure, but an effort will be made to also carry out pre-procedure interviews in patients with mild symptoms that are able to consent appropriately. Patients undergoing all pleural interventions will be drafted and consented for interview including Intercostal pleural drains, Indwelling Pleural Catheters, Pleural Biopsy and Medical Thoracoscopy.

Semi-structured interviews will centre around what the interviewee consider to be the most important aspect of pleural procedures. These semi-structured interviews will be transcribed and thematically analysed. (Braun and Clarke 2006)

Semi structured interviews are based on a predetermined guide, which is a framework of questions and key points that aimed to be explored. The benefits of an interview guide allow researchers to explore detail with interviewees, whilst keeping the process focused on the desired track of questioning. This method of qualitative research is a step not taken routinely in previous research projects developing core outcome sets. However, I felt, the potential for semi structured interviews to empower participants to reveal underlying themes could be integral to the process. This encouragement of a two-way conversation is an advantage of semi structured interviews, ensuring participants have the ability to lead the conversation to new territory, in particular the patient cohort.

The introduction of this extra step of qualitative data analysis did however mean a further stretch of limited resources available to me. The issues of interviewer bias, choice of sampling and reaching saturation had to be considered and will be discussed in more detail in the appropriate chapter.

Informed by the scoping study and the thematic analysis from semi-structured interviews, this will allow the development of a list of outcome measures to be contended. This list will then be used in the second stage of the empirical work.

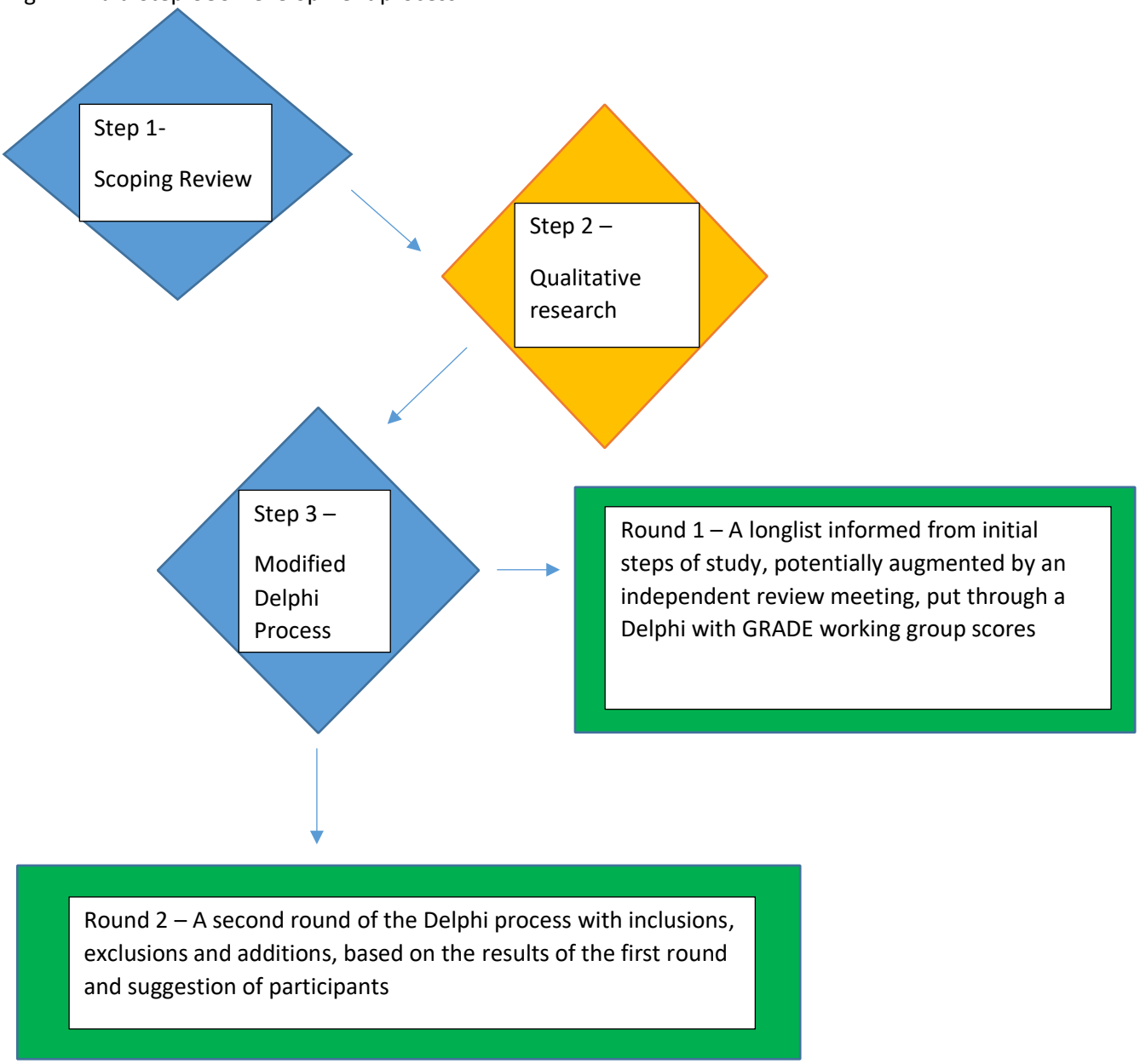
Clinicians and Patients alike will be drafted to take part as panel in a Delphi process in order to illicit a consensus on the primary outcome measures for pleural interventions. Clinicians will be invited to take part via email link, and patients approached in person on the relevant hospital wards or clinics.

Panellists will be instructed to score the importance of each outcome on a Likert Scale ranging from 1-9. Scores from 1-3 indicating outcomes of 'limited importance', 4-6 as 'important but not critical' and 7-9 as 'critical'. This scoring system has been used widely by COMET and other core outcome set developers, gleaned from the recommendations made by the GRADE working group. (Guyatt et al. 2011)

This Delphi process will be designed to be an iterative process with feedback being encouraged between the two rounds. Data analysis from the surveys will allow a development of a consensus for the outcome measures in pleural interventional trials. I gleaned from the literature the importance and contribution a face to face meeting can provide for the consensus process.

Many studies incorporate an ultimate consensus discussion, or an independent review meeting prior to the Delphi process in order to guide the process. (Watson et al. 2020)

Fig 1 – Multi Step COS Development process



Chapter Two

Scoping review

Background

Clinicians and academics alike strive to practice and develop evidence-based medicine. The most coveted evidence is widely considered to be systematic meta-analysis of the available relevant studies surrounding a topic or issue. This applies universally; from deciphering most effective treatment arms to a certain condition or clinical situation, choosing the most efficient diagnostic test to cost-effectiveness research.

This highest level of evidence is birthed out of systematically analysing relevant trials. However, it becomes difficult to pool and meta-analyse findings from different studies when they don't use similar primary outcome measures. This is now recognised as a substantive problem for the paradigm, meaning that it can often be difficult to draw firm conclusions, making the implementation of research findings into clinical practice problematic. (Saldanha et al. 2020)

I have experience working in the clinical specialty of respiratory medicine. Whilst working in this specialty I developed an interest in the practical skill of pleural interventions, becoming independent in this procedure. I found this skill hugely satisfying for the relief it brought to patients. The field of pleural interventions is a dynamic and evolving field with new types of interventions being developed and offered. It's been a staple of palliative cancer treatment since its inauguration, with malignant pleural effusions occurring in up to 15% of patients with malignancies. (Antony et al. 2001)

Upon a review of the recent literature pertaining to pleural interventions, it became apparent that trials in this field also suffer from the same problem; there is a lack of a consensus on the primary outcomes to be measured when comparing different modalities of pleural intervention. (Clive et al. 2016)

Moreover, patients' expectations and preferences have not been taken into consideration, with studies largely being driven by clinicians and researchers producing a range of mostly non-holistic outcomes. (Clive et al. 2016) In 2016, a Cochrane meta-analysis of pleural interventions for malignant pleural effusions found side effects, quality of life and patient satisfaction were reported inconsistently. (Clive et al. 2016) If patient related outcomes are assessed in studies it becomes difficult to evaluate comparative effectiveness due to how outcomes are measured and defined. A systematic review pertaining to tunnelled pleural catheters found the way that symptomatic benefit

was recorded varied hugely. Some studies used validated scales, others using non-validated ones along with some studies simply stating symptomatic improvement. (Ost et al. 2014)

This heterogeneity also spills into other common outcomes often reported in studies relating to pleural interventions such as pleurodesis. Some studies have considered pleurodesis to be the case under radiological guidance whilst others report it as the absence of the need for re-intervention. (Meter et al. 2011)

There is a lack of consensus relating to outcomes. Though studies in the past have not always included patient related outcomes in the past, more recent studies have advocated the need for a multidimensional, patient centred approach to defining and measuring outcomes of pleural interventions. (Ost et al. 2014)

The growing problem of increasing heterogeneity between outcomes reported by trials has been addressed collectively with the growing interest in the development of Core Outcome Sets (COSs) (Williamson et al. 2012) COSs are a set of outcome measures that are designed to be collected in all trials undertaken in a specific clinical discipline in order to allow the results to be meaningfully pooled and meta-analysed. There have been increasing numbers of examples where COSs contrived from qualitative research have made a meaningful impact to clinical practice, including rheumatoid arthritis and cardiac care. (Fried et al 2002).

To facilitate the collation and standardisation of these COSs, an initiative known as 'COMET' (Core Outcome Measures in Effectiveness Trials) has been established. This organisation aims to record the number of COSs in use and facilitate their agreement across a broad range of stakeholders. (Williamson and Clarke 2012)

The inclusion of all stakeholders is a pillar that allows the development of COSs through consensus developing methods. Prior to this stakeholder prioritisation, candidate outcomes are to be identified from both stakeholder interviews and also an inclusive literature scoping review looking at all trials pertaining to pleural interventions, including both systematic reviews and other comparative study designs.

Reviewing the literature in the holistic manner of a scoping review will allow me to be able to identify all relevant outcomes without discrepancy, ensuring the stakeholders are presented with an inclusive and wide variety of relevant outcomes.

Scoping reviews have been favoured over other literature reviews when developing core outcome sets by previous authors. (Tritschler et al. 2020) This could potentially be due to the fact that a scoping review would decrease the likelihood of less commonly used outcome measures within the literature to be missed. This inclusive take on the literature when formulating a long list of outcome measures for refinement into a core outcome set, gives the author more power to ensure even the

least popular outcomes are considered into the overall investigation. When embarking on a study to define a core outcome set, it is more thorough to assume all outcome measures previously adopted by researchers are of equal value until proven otherwise. In contrast, a more rigid outlook on a literature review, such as a systematic review, would narrow the inclusion of outcome measures existing on the fringe of studies pertaining to that clinical field. I believe, the inclusive and eclectic nature of scoping reviews conform to the requirements of a literature review in the development of core outcome sets. This is supported by the successful application of scoping reviews of past authors in the preamble of previous development of core outcome set studies, in other clinical fields. (Visser et al. 2022)

Aims and Objectives

The primary aim of this review is to map out the primary and secondary outcomes measured in pleural intervention clinical trials.

I aim to illicit how they are measured, identify discrepancies and to evaluate consistent themes that arise from the review.

Moreover, I aim to compare outcomes of a patient centred nature to those outcomes advocated by researchers and clinicians alike.

Finally, we aim to illicit any gaps in the array of outcomes pertaining to pleural interventional trials, either suggested by studies or from analysis performed.

Methods

This scoping review was designed on published and authenticated methodological guidance. (Levac et al. 2010) Scoping reviews are unique in the way they allow a picture of the existing evidence base, without maintaining quality of evidence as an initial priority. This inclusive criterion allows the development of a broad understanding of the evidence surrounding a topic whilst providing sufficient depth. (Arksey and O'Malley 2005) The review adopted a narrative approach, allowing it to be populated with a range of literature.

Data extraction and charting were done in two separate phases to allow time to become familiar with the research content. I was able to tabulate the data through a continuous iterative process, refining the objectives and research questions as much as possible. The data was collated, summarised and reported henceforth.

1. Develop the research question

2. Formulate a search strategy A) Identify relevant terminology

b) Identify Inclusion and exclusion criteria 3.Data

Sifting

a) Title

b) Abstract

c)Full text

d) Initial data tabulation

4. Refine objectives and research questions

a) Further data tabulation

5) Collating, summarising and reporting results

Primary Research Question

1. What are the primary and secondary outcomes measured in pleural interventional trials?
2. What are the ways in which how these outcomes are measured, i.e. the different ways in which studies have measured similar or identical outcomes?
3. What patient centred outcomes have been utilised in pleural interventional trials, focusing on the frequency and extent at which they are used?
4. What are possible outcomes, if any, that have not been considered in trials pertaining to pleural interventions?

Search Methods

Articles were collected from four major health science, social and welfare databases; MEDLINE via Ovid (biomedical science), EMBASE (Biomedical science and pharmacology), PUBMED, (biomedical science and life sciences). In order to achieve a holistically inclusive scope of the literature the data base PSYCHINFO (psychology) was also used to collect studies. The approach to use PSYCHINFO database was taken in light of one of the key underlying aims of the scoping review; to investigate whether there had been sufficient representation of patient centred outcomes in the primary measures of pleural interventional trials. Although I took the initiative to ensure my search revealed studies with patient centred outcomes, more attention should have been paid to recent randomised controlled pleural interventional trials. Negligence of this meant that key literature such as the recent AMPLE trial (Thomas et al. 2017) were not included in the review. A principal objective for the development of the core outcome set in this study, was to be able to provide outcome measures for pleural interventional trials of the future. Not evaluating the outcome measures used in important pleural interventional trials of recent, retracts from the overall validity of the process. I have recognised this as a limitation of the scoping review and the consequences this had on the overall project.

A criterion was assembled to harvest a cohesive collection of articles. This included simple options such as accepting articles only in English and only including articles addressing the treatment of 18 years and over (adults). A time period of 5 years was added to the search criteria, to be able to assess up to date studies and evaluate the direction in which the literature has been moving to the present day.

In hindsight this was a tactical error which significantly hindered the yield of the scoping review. In my own deliberation in the aims of this study, I emphasised the need for the consideration of a holistic set of outcomes when deducing a core outcome set. This would ensure the inclusion of previously popular practitioner targeted outcome measures in the literature, along with the more recent trend towards patient related outcome measures. By instilling a time period of 5 years my scoping review was flawed as it meant outcome measures deemed significant in past literature would not be included. It can be argued this was a significant error in judgement and detrimental to the whole process. The process of deducing a core outcome set relies on the accurate harvesting of the most significant outcomes from a diverse pool of potential outcomes. If the pool of outcomes is strangled by unnecessary and stringent restrictions this can reduce the accuracy and reliability of the whole process. When reviewing the core outcome set finalised by the empirical work of the study, it can be argued they are heavily one-sided towards a patient centred framework. This error of introducing a 5-year timeline could have been the root cause of this and is something I have learnt from the process.

Secondly, the implication of a time frame on the scoping review meant that key literature pertaining to pleural interventions were neglected. Pleural medicine as a subcategory of Respiratory medicine is a novel progression and has contributed hugely to the recent advancements of pleural interventions available. However, there are key studies that were carried out examining the efficacy of some of the interventions focused on in my study, such as medical thoracoscopy, dating back to 1995. (Harris et al. 1995) In summary, the progression of pleural interventions as an entity and a practice of medicine date back up to decades before the time frame I subjected my own study to. This negatively affected the scoping review in itself and consequently the reliability of the findings of the empirical work to follow which was based on this.

This is an important learning point I take away from the process. I endeavour to ensure I complete accurate research into the history of any field of medicine I will complete research in the future, before embarking on a design of a literature review. This was my first attempt at a scoping review and in hindsight should have made more use of my clinical supervisors when designing the review, instead of my academic supervisors who have less experience in this particular field. In doing so, I ended up using a formula which focused on the feasibility of completing the scoping review within the time constraints of a MRes. In hindsight, the inclusion

of keystone literature of the past 3 decades was integral to the process and not something I should have sacrificed for practicality. Nevertheless, completing the process of the scoping review was beneficial for my own development; I became familiar with the steps involved and picked up invaluable skills such as getting accustomed to the use of referencing management software, such as Endnote; skills I am putting to use currently through a systematic review I am completing in my current field of surgery.

Inclusive search terms were selected to ensure maximum yield of relevant studies. Mesh terms were reviewed and selected to ensure all types of pleural intervention were represented. Comprehensive results were ensured using OR and AND to connect search terms. Once again specific mention of patient centred outcomes was detailed using the advanced search options. These thoughts were structured using the PICO framework of developing a search strategy. (Schardt et al. 2007)

(Table 1)

P	Population and their problem	Malignant Pleural Effusion OR Pleural Effusion OR Pneumothorax OR Empyema AND Pleural Biopsy
I	Intervention	Thoracentesis OR Pleural Catheter OR Indwelling Pleural Catheter OR Chest Drain OR Medical Thorocoscopy OR Thoracic Ultrasound
C	Comparison, Control, comparator	n/a
O	Outcome	Patient centred outcomes OR Patient related outcome measures

The development of the search strategy was an iterative process; starting off with broad searches enabling me to navigate and redefine the search to the final included terms. I often found these steps had to be repeated at different stages of this flexible process to ensure literature wasn't missed or left out. This fine tuning of the search strategy to ensure inclusive data is recommended by Arksey and O'Malley. (Arksey and O'Malley 2005)

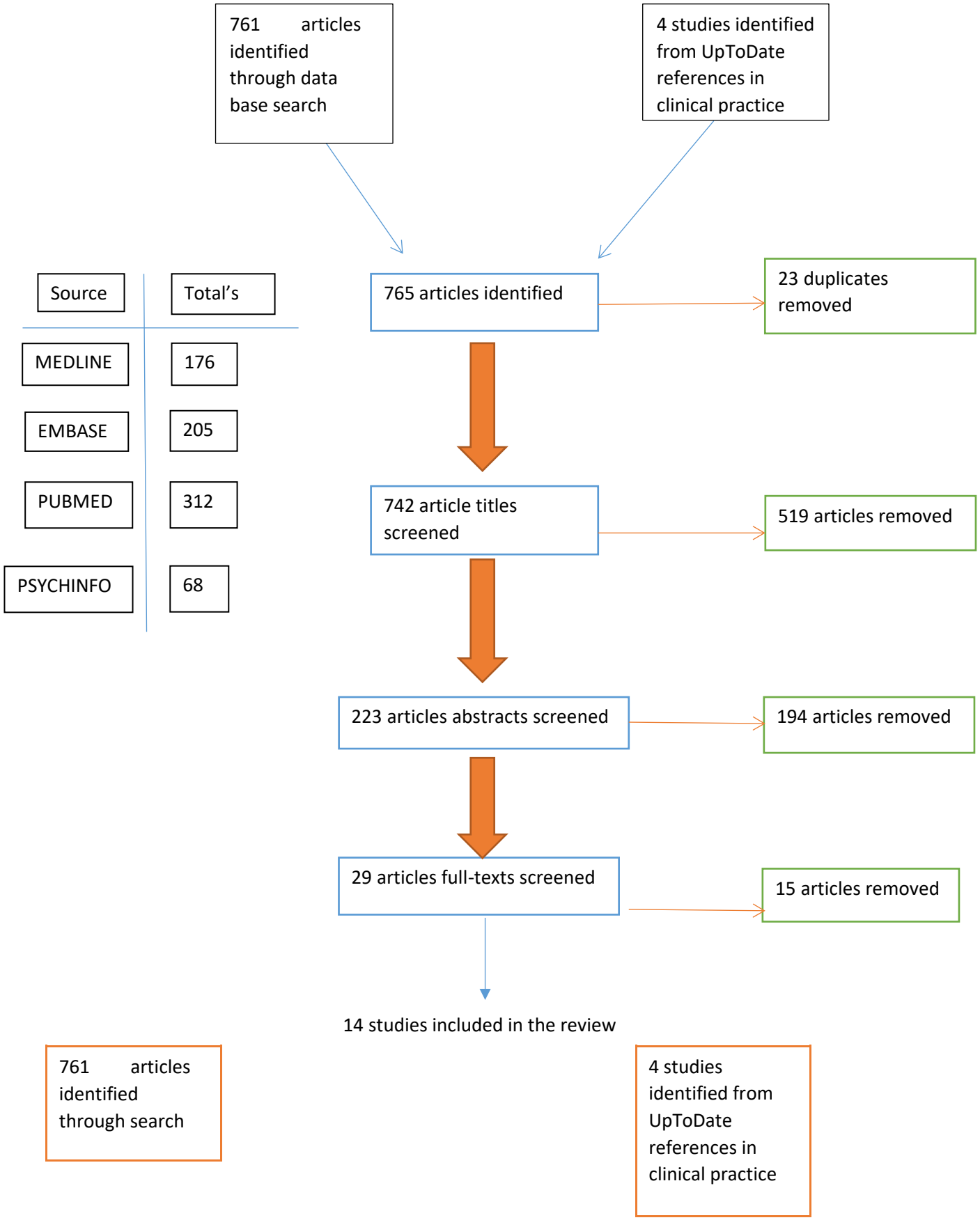
Citations were directly imported from the databases into the bibliographic manager EndNote and duplicates were removed. No exclusions were made based on the quality of evidence or methodology.

Data Sifting

Once the selected literature had been gathered, a total of 765 studies, I firstly began sifting through the titles, excluding studies not deemed to be relevant. The second stage was screening through abstracts to gage relevance to the research question. Irrelevant surgical studies pertaining to complex cardiothoracic surgery, upper GI interventions along with lymph node dissection were swiftly removed from the list. Studies pertaining to biological therapy for numerous lung cancers, lymph node biopsy and histopathology of malignant cells were similarly screened and removed.

Studies with relevant abstracts were then selected to be read in full detail. Once the databases had been thoroughly searched, the reference lists of relevant studies were scanned for additional potential publications.

Figure 2 Data Sifting



Initial data extracting and charting

Information and data were extracted from the literature taking care to re-analyse it whilst populating a table. This ensured an organised narrative of re-analytical data, segmented into columns to depict key issues and themes. (Davis et al. 2009) Whilst becoming increasingly familiar with the selected studies, it was beneficial for the research question to underpin the reanalysis of raw data.

This iterative process would have the potential to refine a research question and objective if the area of interest was broad and expansive. This is reported in some of the literature addressing the construct of a scoping review and the benefits of the iterative process it involves. (Levac at el. 2010) However the current research questions posed, which stem this scoping review have a certain and concise purpose. Nevertheless, efforts were made to offer refinement of the study objectives.

(Table 2)

Citation Info	**Methodology**	**Aims of the study**	**Outcome measures**	**Important Results**	**Specific Info/Useful Info**
Ault, M. J., et al. (2015). "Thoracentesis outcomes: a 12-year experience." Thorax A	The cohort study was undertaken over a period of 12 years. Data was collected prospectively at the time of the procedure, with all procedures included carried out or supervised by a single clinician. This is also recognised as a limitation as complications reported by the single operator may have been understated. Patients were followed for 24hours post	The aim of the study was to question the existing assumptions and beliefs amongst practitioners that dictated the clinical guidelines and practice patterns. This included evaluation of the specific demographics and clinical indicators associated with well-known complications of chest drains, including iatrogenic	Iatrogenic pneumothorax, re expansion pulmonary oedema and bleeding.	9320 inpatient chest drains were placed for 2426 patients. 91 complications were recorded including 57 iatrogenic, 10 re expansion pulmonary oedema, 17 bleeding episodes, 1 splenic laceration and 6 vaso-vagal reaction.	The study refers to a possibility, volume is likely to play less of a role in the formation of REPE than a number of other factors which include pleural and lung elastance, chest cavity volume and degree of visceral pleural disease.

	procedure to account for any complications.	pneumothorax, re-expansion pulmonary oedema and bleeding.			Moderately strength of evidence.
Azzopardi, M., et al. 2019 "Protocol of the Australasian Malignant Pleural Effusion-2 (AMPLE-2) trial: a multicentre randomised study of aggressive versus symptom-guided drainage via indwelling pleural catheters B	This will be a multicentre open labelled RCT.	The large study aims to determine the best manner in which to drain fluid from cancer patients whom have had an indwelling pleural catheters; aggressive vs symptom guided.	Primary end point is proposed as degree of breathlessness (VAS scale), with secondary outcomes being physical activity measured by accelerometer and quality of life measured with a EQ 5D 5L and VAS scale. Spontaneous pleurodesis and hoospitilisation are also secondary outcome points. Moreover, there is an element of economic evaluation proposed to work out the difference between the cost-effectiveness between the two studies. This is to be done by working out cost-effectiveness ratios by using quality adjusted life years extrapolated from EQ 5D 5L scores	n/a	n/a
Boshuizen, R. C., et al. (2017). "A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14)." Lung cancer (Amsterdam, Netherlands)	This was a study based on a multicentred randomized control trial comparing talc pleurodesis through an ICD with the insertion of an indwelling pleural catheter.	This was a treatment efficacy study to compare IPC with chest drain and TALC aiming to determine the best treatment arm.	The outcomes are of interest for the scoping review. The primary end point was an improvement from baseline in modified borg scale 6 weeks after intervention. Secondary endpoints included hospitalisation days, re-interventions and adverse events	The outcomes from the study depict both interventions as an effective treatment for pleural effusion, with no difference between dyspnoea scores (primary outcome). Secondary endpoints	n/a randomized rct with excellent quality of evidence.

C				however favoured indwelling pleural catheters over talc pleurodesis.	
Walker, S. et al. 2016. A prospective study of patient centred outcomes in the management of malignant pleural effusions. International Journal of Palliative Nursing D	This prospective cohort study compared four treatment options for malignant pleural effusion including VATS, Chest tube, Indwelling pleural catheter (IPC) and VATS Talc poudrage	It measured the efficacy of each treatment option by measuring patient centred outcomes over 6 weeks post procedure.	The primary end point was patient satisfaction based on the FACIT-TS questionnaire, with quality of life, dyspnoea and length of hospital stay being secondary outcomes. These were assessed using the reliable and validated questionnaires and assessment tools. 1. Functional assessment of chronic illness therapy – Treatment satisfaction (FACIT-TS)- essentially a recommendation score form the patient 2. Functional assessment of chronic illness therapy palliative (FACIT-Pal)- assessment in categories of physical wellbeing, social/family well being and functioinal wellbeing 3. FACIT Pal shortness of breath scores 4. London chest activity of daily living scale -	The study found no statistically significant difference between the four treatment options, with a trend towards VATS and pleurodesis in improved patient satisfaction and overall dysnpea. Interestingly, length of hospital stay showed a significantly lower average stay in the IPC and VATS and pleurodesis group respectively.	The main discussion points in the study emphasize the importance of length of hospital stay in palliative MPE patients when deciding the intervention. With all four treatment options showing a similar benefit in patient centred outcomes, patients with poor performance status and limited life expectancy, simple chest drain may be appropriate. Limitations of the study include lack of randomization and lack of outcomes related to mortality; an outcome so often associated

			5. Eastern Cooperative Oncology Group functional status 6. Pain score 1-10		with efficacy of treatment.
Thomas, R., et al. 2015. Intrapleural fibrinolysis for the treatment of indwelling pleural catheter symptomatic loculations. CHEST E	This retrospective study assessed the efficacy of treatment and patient outcomes for intrapleural fibrinolysis through indwelling pleural catheters for loculated effusions	To determine efficacy and safety of intrapleural fibrinolysis through IPC for loculated effusions.	Interestingly the study had a wide range of clinical outcome data. Their primary outcomes included cumulative volume drained at 24 hours and 72, subjective response in breathlessness, recurrence of loculations, need for further interventions. There are some limitations to the dyspnea assessment as it is based on a purely subjective assessment of breathlessness inferred from the patient's medical records. Secondary outcomes focused on length of hospital stay and adverse events.	The study found the intervention improved symptoms and outcomes significantly, with a small risk of intrapleural bleeding.	Radiological response was assessed for some patients, based on pre and post treatment chest x-rays. This was done using a previously validated method of measuring the change in pleural opacity on CXR. (Rahman NM, Maskell NA, West A, et al: Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med 2011; 365: pp. 518-526
Dhaliwal, I., et al . 2016. Management of Malignant Pleural Effusion with ASEPT Pleural Catheter: Quality of feasibility, and	This was a single centre prospective study taken at a single centre with a total of 50 patients.	Its aim was to assess the efficacy of a newly introduced ASEPT pleural catheter which offered a luer lock system with a smaller external draining requiring a smaller dressing	The primary outcome was to assess the self-rated quality of life Quality of Life assessment at baseline, 2 weeks, and 6 weeks was performed using well-validated European Organization for Research and Treatment of Cancer Quality of Life	The outcomes were found significantly significant improvement in all quality of life scores in a similar fashion to other IPCs, cementing	n/a

patient satisfaction. In Canadian Resp Journal F.		for patients for an IPC resolution to MPE.	Questionnaire (EORTC QLQ30) and Lung Cancer (LC-13) specific Quality of Life scores [1, 10]. Dyspnoea measurement was performed at the same intervals using Baseline Dyspnoea Index (BDI) on initial visit followed by Transitional Dyspnoea Index (TDI) to evaluate for improvement.	previous studies to depict IPC as the ideal therapeutic modality in treating MPE.	
Feller-Kopman, D.J., et al. 2018. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical practice guideline. In American Journal of Respiratory and Critical Care Medicine. G	This was an up to date multidisciplinary collaborative effort to provide evidence based recommendations to guide treatment for MPE..	It aimed to combine systematic reviews to be systematically reviewed in producing recommendations for treatment	. It addressed 7 different issues, using the GRADE approach to formulate clinical questions in the PICO format.	The key findings from the systematic review included suggestions to focus on patient centred outcomes such as dyspnoea, recurrent admissions and hospitalisation as primary outcomes over secondary endpoints such as radio graphical improvement.	n/a
Lorenzo, M.J., et al. 2014. Quality of life assessment in malignant pleural effusion treated with indwelling pleural catheter: A	This was a multicentre observational study conducted in patients with recurrent MPE treated with an indwelling pleural catheter.	The primary aim was to assess quality of life. Quality of life was assessed at three stages using version 3 of the European organisation for research and treatment of cancer quality of life questionnaire.	The questionnaire used EORTC QLQ-C30 contains 5 functional domains including physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. It also included three symptom scales including pain, dyspnoea and nausea. Patients with confirmed	They key findings were that a month after ipc insertion there was a significant improvement in symptoms according to qlq-c30 from baseline. It found it was	The study also found its efficacy in reducing hospitalization in recurrent mpe. A demise in physical function, debilitating dyspnea and reduced short

prospective study. In Palliative Medicine H		Patency time of the drain, and overall survival were secondary outcomes.	lung cancer were assessed with a supplementary questionnaire regarding lung-cancer symptoms including three items solely assessing dyspnoea.	an effective way of resolving symptomatic dyspnoea and palliating symptoms.	life expectancy were recognized as key issues to be addressed when assessing treatment options for recurrent MPE.
Ost,. D.E. et al. 2014. Quality adjusted survival following treatment of malignant pleural effusions with indwelling pleural catheters. In CHEST I	This was a prospective observational study, to describe patient centred outcomes for patients with malignant pleural effusions undergoing IPC placement.	The goal of this study was to prospectively describe patient-centred outcomes and their associated risk factors for patients with MPE undergoing IPC placement.	Their primary outcome was quality adjusted survival, along with secondary outcomes of dyspnoea, complications and repeat procedures. The authors were able to assess quality adjusted life days via the information attained from self-reported SF-6D questionnaires. The authors strongly felt quality adjusted survival was the most accurate way of reporting efficacy of pleural interventions, especially in relation to malignant pleural effusions.	Although dyspnea improved significantly, median quality-adjusted survival was only 95 QALDs, and there were only modest improvements in utility, with the greatest improvements being observed in patients who were more short of breath at baseline and in those who received radiation or chemotherapy after IPC placement. Overall 7.8% of patients required a repeated intervention after IPC removal. A greater proportion of	They also felt studies had focused too much on pleurodesis. The heterogeneity in which this could be measured had clouded the quality of previous data sets. The authors felt that this should be assessed by measuring time to recurrent malignant pleural effusion requiring repeat pleural intervention.

				these repeat interventions were required for patients that had the IPC removed due to complication.	
Potechin., R. et al. 2014. Indwelling pleural catheters for pleural effusions associated with end stage renal disease :a case series. In Royal Society of Medicine. J	This was a case series of a cohort of patients identified to have resistant pleural effusion due to end stage renal disease	Its aims were to analyse and evaluate the efficacy, safety and feasibility of using an IPC in pleural effusions for patients on haemodialysis.	The primary outcome was the improvement of dyspnoea, assessed via dyspnoea index. Secondary outcomes were lung re expansion, change in serum albumin, catheter removal and fluid recurrence, depletion of protein stores, and the need for a secondary pleural intervention	The data shows the use of IPCs for refractory effusions associated with ESRD is effective in relieving dyspnea in selected patients. Lung re-expansion with pleural apposition >80% was achieved in the majority of patients and the catheter could be removed without recurrence of the effusion in some patients. The complication rate was very low; particularly there was no occurrence of infection of any kind.	n/a
Rahman., N.M. et al. 2015. Effect of opioids vs nsaids and Larger vs	This study was a multicentre randomised controlled trial with superiority and non-	To assess the effect of chest tube size and analgesia (NSAIDs vs opiates) on pain and clinical efficacy related to	The 2 co–primary outcomes were a superiority comparison of pain scores and a noninferiority comparison of the	The study found that there was no statistically significant difference between the	There was an overall greater VAS scores for pain for patients with larger drains.

Smaller chest tube size on pain control and pleurodesis efficacy among patients with pleural effusion. The TIME 1 randomized clinical trial. In JAMA. K	inferiority end points	pleurodesis in patients with malignant pleural effusion.	occurrence of pleurodesis failure. The study assessed pain using VAS scales at different time points whilst the drain was in situ. Pleurodesis failure was defined as re-intervention within three months on the same side as the drain placed.	use of opiods vs NSAIDS, though NSAIDS required a greater proportion of rescue doses. This could be related to the unblended nature of the study where NSAID patients felt as if they needed greater break through doses. The study found no difference in pleurodesis rates between the opiod vs NSAID groups.	However pleurodesis rates seemed to be negatively affected by the use of smaller drains in comparison to larger drains.
Raman,. T and Meena., N. 2017. A single institution experience for the management of recurrent pleural effusions with tunnelled pleural catheter and its evolution. In Royal Society of Medicine.	This was a large retrospective observational study. Records of patients who had tunnelled pleural catheters from 2009 – 2016 were reviewed	This study aimed to determine if spontaneous pleurodesis rates could be improved using TALC pleurodesis via IPC during time of insertion. The aim of the study was to provide descriptive data on the utility of IPCs in this manner, factoring in complication rates numbers needed to harm.	n/a	The study found that IPCs with TALC pleurodesis meant a shorter amount of time the catheter was in place, compared to no TALC pleurodesis, however was associated with more complications	It was also noted when TALC pleurodesis was avoided, regular and more aggressive drainage led to a faster spontaneous pleurodesis with the added benefit of fewer complications, when compared to liberal less frequent drainage.

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Thomas., R. et al. 2017. Effect of an indwelling pleural catheter vs TALC pleurodesis on hospitalisation days in patients with malignant pleural effusion. In JAMA. M	This multi-centred randomized clinical trial was a highly anticipated study, comparing the efficacy of two established treatments for malignant pleural effusion	To determine whether indwelling pleural catheters are more effective than talc pleurodesis in reducing total hospitalization days in the remaining lifespan of patients with malignant pleural effusion.	. There have been 3 RCTs in the past comparing the two treatment modalities, the consensus being equipoise. This study was the first to have days spent in hospital from remaining lifespan in cancer patients the primary outcome. Secondary outcomes included symptoms such as breathlessness and need for repeat interventions.	The study found that the patients randomised to the IPC group recorded a median of 2 days less spent in hospital compared to TALC pleurodesis. The importance of this value clinically is still debateable.	The IPC group depicted some advantages over TALC in a few areas.

Collating, Summarising and reporting the results

Though the descriptive analysis was phased towards the research questions, the most important aspect of this step was to become familiar and at ease with the direction in which the literature seemed to be flowing. Once the descriptive analytical data had populated a standardised table, this allowed the studies to be compared and contrasted in order to gage categories and themes.

The themes appraised in this manner were then depicted to directly answer the refined research questions. Results were organised under the research questions. Grave importance was not ascribed to the impact or quality of evidence, due to the nature of the scoping review. The aim was to portray an encompassing depiction of primary studies.

1. What are the primary outcomes measured in pleural interventional trials.

   Primary outcomes from the selected studies were categorised and counted. They were organised and displayed into a table.

2. What are secondary outcomes measured in pleural interventional trials?

Secondary outcomes were counted and collated in the same manner. There were often notably a number of outcomes deemed to be secondary. These secondary outcomes however were not always reported in equal detail. Nevertheless, no discrepancy was made on the quality of the reports on each secondary outcome. The studies were taken at face value when setting out there aims and outcomes to be measured.

3. What are the ways in which how these outcomes are measured, i.e. the different ways in which studies have measured similar or identical outcomes?

   Outcomes that featured in more than one study were identified. Analysis on the way in which they were reported and measured was an important step in understanding the true heterogeneity within outcome measures. Ways in which they could be compared along with congruency was discussed in our analysis.

4. What patient centred outcomes have been utilised in pleural interventional trials, focusing on the frequency and extent at which they are used?

   Patient centred outcomes were collated in comparison to other outcomes measured. An assessment on how these patient related outcomes were measured was interesting to analyse as there doesn't seem to be guidelines on the best way forward in this respect.

5. What are possible outcomes, if any, that have not been considered in trials pertaining to pleural interventions?

   A discussion was also formulated in regard to possible gaps in the literature in appropriate outcomes to measure.

6. Finally, what are the main outcomes gaged from the review that will form parts of the Delphi Survey? Which outcomes are to be under review pending semi structured interviews with clinicians and patients?

Articles at this stage populated a busy table. Arksey and O'Malley's framework recommend using excel to chart each paper. Daudt et al. 2013 suggested a key step in organising the data, would be to give each paper a unique reference number or letter. This was adopted in this case once the final studies had been selected so reference in text could be made with ease. (Daudt et al. 2013)

Table 3- Primary Outcomes

Primary Outcomes	**Frequency**
Complication rates	1
Dyspnoea	3
Quality of life	4
Volume drained	1
Repeat intervention rate	2
Pain	1
Hospitalisation	1

Table 3 shows the collation of primary outcomes measured through the selected literature. It is important to note that not all studies were presented as studies investigating treatment efficacy. There were a few studies reporting local statistics and narrating on common themes relevant to pleural interventions.

Quality of life and breathlessness were amongst the most common primary outcome, signifying the awareness amongst researchers regarding the importance of patient centred outcomes in regard to pleural interventions. This seemed to be the natural progression of the literature in moving this way. In fact, there was a direct correlation with the more recent studies and their likelihood in adopting a patient centred outcome such as dyspnoea or quality of life. Regardless of this shift in climate for outcome measures in pleural trials, “pain” featured only the single time as a primary outcome. Moreover, when it did feature it was only “co-primary outcome”. (Rahman et al. 2015) This represents the possibility for further progression towards more holistic outcomes and a key point that I’d like to explore in developing the process of drawing consensus in this matter.

In the frequency tables, repeat intervention rate is mentioned as a primary outcome in table 3. This is an outcome definition that has in itself held some heterogeneity throughout many studies pertaining to pleural interventional trials. (Meter et al. 2011) Pleurodesis is the obliteration of the pleural space by way of adhesion between the parietal pleura and the visceral pleura, often via an induced inflammatory reaction. (Shaw and Agarwal 2004) Some studies have short-sightedly simply termed this outcome measure as “pleurodesis” or “spontaneous pleurodesis”, defined by a radiological criterion. However, this can be extremely misleading. The fact that there has been temporary radiological evidence of pleurodesis negates the fact, that the chance of re-occurrence of pleural effusion is quite substantial, depending on the modality of

pleurodesis. (Xia et al. 2014) As we move towards patient centred outcomes at the forefront of outcome measures, pleurodesis should be captured within the outcome of time or rate of repeat intervention. It is a sensible and pragmatic approach to measure the success of pleural interventions with the rate of repeat intervention, taking into consideration the palliative nature of these patients.

Table 4 – Secondary Outcomes

Secondary Outcomes	**Frequency**
Spontaneous Pleurodesis	1
Hospitalisation	5
Repeat intervention rate	4
Complications	3
Quality of Life	1
Dyspnoea	5
Pain	1
Lung re-expansion	1
Albumin	1
Serum Protein	1

Table 4 shows the collation of the secondary outcomes utilised by the studies. Interestingly dyspnoea and hospitalisation are joint modes of the set, with repeat intervention coming up a close second. In a similar fashion to primary outcomes, pain represents a small portion of the secondary outcomes used, as mentioned above, warranting further exploration as to the reason behind this.

In contrast to the primary outcomes, “quality of life” is only recorded the once as one of the secondary outcomes used. This can either be interpreted as one of two ways; Quality of life is moving to be a key outcome measure in the design of pleural interventions and is being drafted as an integral primary outcome, causing its appearance in secondary outcomes to dwindle. Alternatively, it could be interpreted as something for researchers to address, as quality of life is surely a valued outcome measure in this line of medical procedure.

On designing an interventional trial an investigator has to choose appropriate outcome measures that will be able to effectively evaluate the treatment arms of a study. Consideration of the most appropriate outcomes can be gaged from those deemed most important to multiple stakeholders. As well as this, the fiscal confinements of the study must also be taken into account to ensure the outcome measures are able to be accurately used.

Moreover, an instrumental factor that is to be considered by researchers when selecting outcome measures is their validity and variability. When selecting outcomes, researchers have to evaluate their reproducibility and work out the best method of actually measuring their outcomes of choice.

Reliability of an outcome measure is based on the reproducibility. Validity is based on the ability of an outcome measure to actually measure what it intends to. When discussing patient related outcome measures the responsiveness of an outcome measure is also evaluated in its ability to be sensitive to change over a period of time. These are all considerations to be made about specific ways in which outcomes are measured. It can be argued the accuracy in which outcomes are measured can in itself contribute to which outcomes are chosen by researchers. (Velentgas et al. 2013) This will be discussed in greater detail for some of the dominant outcomes that emerged from the scoping review, analysing outcomes and how they are measured.

Quality of life is measured in a variety of ways through the selected literature.

The most common method was the use of the European Organisation for Research and treatment of cancer (EORTC) Quality of life Questionnaire. This is a questionnaire with an eminent history in the oncological assessment of quality of life. In 1986 the European Organisation for Research and Treatment initiated a research project to evaluate quality of life on an international scale. Interestingly its initial birth and development centred on assessing the quality of life of patients with non-resectable lung cancer, before and during treatment. (Aaronson et al. 1993) It can be argued that this allows this quality of life assessment tool to be completely adaptable to the target population of patients enduring pleural interventions with malignant pleural effusions forming the mainstay of indications for pleural procedures. This convenience is a complete coincidence, as the EORTC went onto complete further work to develop and complete questionnaires for site specific cancers such as gastric, breast and lung questionnaire tools. (El-Fakir et al. 2014) The EORTC QLQ30 takes a broad approach in assessing quality of life with nine multi item scales. Five of these scales pertain to physical, role, cognitive, emotional and social functional scales. Three scales refer to symptom scales of fatigue, pain and nausea and a single global health and quality of life scale. The tool has been showed to be able to be translated and adapted to cultures from both in and outside Europe, supporting its potential use for a wide array of patients. Moreover, it has been validated against the Eastern Cooperative Oncology Group (ECOG) performance status scale. The functional and symptom scales of EORTC QLQ30 showed to comprehensively differentiate between patients defined to be in varied clinical states by the ECOG performance status scale. (Aaronson et al. 1993)

The ECOG performance status is another well documented and validated tool of quantifying functional status of cancer patients. It was published in 1982 (Oken et al. 1982) and endorsed by the ECOG group, an organisation started in 1955, as the first publicly funded group to perform multicentre clinical trials for cancer research. The ECOG scale is simple and patients are easily

categorised based on their ambulatory function. Grades range from 0-4, with 0 being a patient fully active as normal and 4 being someone completely unable to care for themselves. Studies have shown the score to be extremely reliable and consistent with inter-observer variability studies recording minimal fluctuation. (Sorensen et al. 1993) The score is used by clinicians all over the world due to its ease of use and applicability. Its main caveat is due to its nonspecific nature, and for our purpose of measuring pleural intervention, it could cause problems in differentiating between patients' satisfaction with their own life. It wasn't surprising for me to see its use in assessing quality of life in pleural interventional trials, in a completely complimentary way in one of the selected studies. (Walker et al. 2016) This study focused on treatment satisfaction and quality of life, relying on the FACIT TS and FACIT Pal questionnaire tools. The functional assessment of chronic illness therapy (FACIT) system is a competent and inclusive set of health-related quality of life measures. (Webster et al. 2003) It consists of a general 27-item tool, which can be coupled with disease or treatment specific sub-tools. This is very similar to the additional cancer type specific questionnaires offered by the EORTC tools. (El-Fakir et al. 2014)

The FACIT ethos is to capture the quality of life of a patient in four domains, physical, social, emotional and functional well-being. (Lyons et al. 2008)

The FACIT tool has been continuously adapted and developed since its establishment. As the literature's affinity for patient centred outcomes grows, a new FACIT tool was created in 2013 called the FACIT – TS (treatment satisfaction) used in article "D". This FACIT tool was created in conjunction with a patient satisfaction tool, with its aim to overall evaluate current treatment. Its premise was to assess patient satisfaction with treatment under five subscales; 1) Physician communication 2) Treatment staff communication 3) Technical competence 4) Confidence and trust 5) Nurse communication. The study found that all five of the FACIT TS scales met psychometric standards for internal consistency reliability (>0.70). One of the limitations of the study elicited was due to the very high proportion of patients that had lung cancer when the questionnaire was tested in its development. It can be argued, this peculiar coincidence would benefit our cause, as the study found the FACIT-TS was valid for use across a number of chronic conditions, especially lung cancer. (Peipert et al. 2013)

The various adjuncts and tools used through the selected literature have their strengths and weaknesses. I feel The FACIT and EORTC QLQ30 offer similar advantages in their multi domain approach and disease specific assessment. However, the quality of life assessment used in article "I", seemed to be the most progressive and appropriate.

Article "I", whilst taking into account dyspnoea, focused its primary outcome on quality adjusted survival. Its take on quality of life in patients requiring pleural interventions was refreshing and unique when compared to other studies reviewed, whilst after contemplation, seemed the most sensible. A large proportion of patients requiring pleural interventions have malignant pleural

effusions and fall into the palliative category; it would be appropriate for any construct assessing efficacy of treatment in these patients to include a validated measure of quality adjusted survival. (Ost et al. 2014) This is mainly due to the reality that various pleural interventions may affect mortality and quality of life conversely. It can be argued this brings in a balanced view which is imperative. (Ferguson et al. 2013) Quality adjusted life survival was extrapolated from the SF-6D. This tool generates a utility score from 0 to 1. Integrating scores over a period of time allows quality adjusted survival to be extrapolated and calculated as quality adjusted life years. For article "I" and for the use of other pleural interventional trials, this would be and is expressed as quality adjusted life days. (Ost et al. 2014)

Cost-utility analysis is one of the most common methods of economic evaluation for various treatment regimes. It's often based on the unique and precise measures of quality adjusted life years. Its applicability to various treatments allows it to be used ubiquitously and has been endorsed by NICE as the most important indicator of health-care intervention effectiveness. (Rawlins and Culyer 2004)

Taking this into consideration one would expect there to be a number of studies that exist using a variable of quality adjusted years as a primary or secondary outcome in relation to pleural intervention. However, in a systematic review done in 2006, it found that quality adjusted survival was not a common outcome measure selected, with absolutely no evidence of any pleural interventional trials reporting quality adjusted survival based on pre-treatment and post treatment measures. (Rasanen et al. 2006) In the scoping review of the literature over the most recent five years, there was just a single study identified. Quality of life is an undoubtedly significant outcome measure for pleural intervention. A discrepancy in the ways in which it has been measured has added to the problem of heterogeneity between outcome measures in pleural interventional trials. I feel this is an issue to be tackled head on. Further research should be carried out to determine the most appropriate way in which quality of life is to be measured, should it come to fruition as a core outcome. A suggestion would be that the seemingly unpopular method of quality adjusted survival be a consideration.

Dyspnoea is a key outcome measured throughout the selected literature, and similarly is measured with a number of methods. Three of the most common methods are the visual analogue scale, BORG scale of dyspnoea and the London Chest Activity of Daily Living Scale, measured pre and post treatment. Dyspnoea is a difficult entity to measure as it involves converting a subjective feeling of a person into a numerical value. (Mahler et al. 1992)

The Modified BORG scale includes descriptors of dyspnoea against a graded scale and has been validated in the use of patients with respiratory disease, namely emphysema. (Mador et al. 1995) It was updated in 1994 in the form it is known of and used today stemming and adopted from the CR 10 in 1982. (Mahler et al. 1992) It is respected and has been used in countless respiratory clinical

trials. Variations of “2” grade points on the scale from baseline have been validated as significant changes in perceived improved or worsening of dyspnoeic symptoms. (Ries 2005)

The Visual Analogue scale has similarly been well validated and used as a succinct outcome measure; especially as in response to an intervening process i.e. exercise, potentially making it a good option for pleural interventional trials. (American thoracic society 1999) It was first described in 1969 but adapted to dyspnoea much later. (Aitken 1969) It involves a line drawn with two extremes at either end. The patient subject is instructed to indicate a point on the line which matches up to their symptoms at a specific time. Its drawback is based on the assumption that the patient completing the VAS scale has a sufficient ability for abstract thinking, which isn’t always the case.

The third most common tool used is the London Chest Activity of Daily Living Scale, which again has been validated and commonly used in trials pertaining to respiratory diseases such as COPD. (Garrod et al. 2002) Where this scale holds its value for the cause of pleural interventions is, its assessment of dyspnoea in direct relations to performance of daily activities. It triangulates on the effect of significant limitation in an individual’s functional capacity and the social deprivation the dyspnoea causes. This directly quantifies the effect of dyspnoea on quality of life and can be deemed a comprehensive assessment.

All three tools hold their own value in describing and measuring dyspnoea, providing the nature of pleural interventional trials is taken into consideration. An example of an unreliable and difficult to interpret method would be the way in which article E reports dyspnoea. Its use of subjective deductions from reports of breathlessness documented in medical notes is highly unmeasured and could easily skew results.

The natural progression of outcome measures towards patient centred outcomes in pleural interventional trials is palpable by the trends in the scoping review; both in the time spent becoming familiar with the literature and the message it conveys and within the frequency of outcome measured deemed to be patient related.

Though there were only three out of the seven primary outcomes collated central to patient outcome measures, namely, Dyspnoea, Quality of life and pain, these made up more than 60% of the total outcome measures counted. Secondary Outcomes were less emphatically patient related with the same three patient related outcomes forming 30% of the total detected. It can be argued hospitalisation days can be outfitted to be a patient related outcome due to its inferred effect on quality of life. The reciprocal that can be calculated from this stat has been validated as a patient related outcome measure, as days alive at home. (Myles et al. 2017) This is something that needs further research as a potential gap in the literature, as it would seem a credible patient outcome measure to assess the efficacy of pleural interventional trials.

Throughout the scoping review, I assessed the potential for gaps in the literature, and aspects of pleural studies that could be explored in terms of outcome measures. The sense was that the most effective avenues had been handled sufficiently, especially with the trend towards patient related outcome measures. Another potential gap in the literature however is the lack of discussion on the diagnostic value a pleural procedure can hold. From the complex tissue sampling of pleural biopsy to the simple identification of the colour of fluid harboured in a patient's thorax, the diagnostic value of pleural interventions is a significant entity not reflected in the outcome measures used in the selected literature.

Table 5- Overall frequency of outcome measures

Outcome Measures	**Frequency**
Complication rates	4
Dyspnoea	8
Quality of life	5
Volume drained	1
Repeat intervention rate	6
Pain	2
Hospitalisation	6
Spontaneous Pleurodesis	1
Lung Re-expansion	1
Albumin	1
Serum Protein	1

Table 5 was drafted in hand with the continuous analysis of common themes within the literature to produce a list of outcomes to be considered in the next steps of developing a consensus in outcome measures.

As the cumulative table of outcome measures suggests, dyspnoea, repeat intervention rate and hospitalisation record the highest number of selections. Repeat intervention is an outcome measure that is directly related to the successful rates of pleurodesis, an important aspect of pleural procedures. Hospitalisation is also an understandably popular outcome measure; it ties in with both a validated patient related outcome measure and the facts and figures most valued to leading physicians on the wards in hospitals.

"Pain" as an outcome forms a ultimately disappointing tally. Nevertheless, it falls into the appropriately trending patient centred outcome group and therefore should hold weight when outcome measures are being considered for pleural procedures. It is a key outcome when

considering treatment satisfaction. Further research should be undertaken to understand the best way and time point to measure pain.

In conclusion, the scoping review, allowing for its limitations, has allowed me to develop a better idea about the most valuable outcome measures pertaining to pleural procedures. It is valid analysis to suggest the most important outcomes in regard to pleural interventional trials lay with the patient related items. The methods in which these patient related outcomes are measured have been explored and prioritised in position of efficacy, with suggestions on the direction in which research should be undertaken. The information and insight analysed and gathered here will be further built on in the process of developing a consensus for core outcome sets. I have been able to gather a list of the outcomes deemed to be core to the issue of pleural procedures by the researchers and clinicians over the last five years. The application of a five-year time limit on the scoping review was introduced, predominantly to make the task of thoroughly reviewing the literature more manageable. It was implemented without the review of my clinical supervisors and was possibly suggested by my academic supervisor out of reflex from his previous experience of coaching novice investigators though the masters by research. This was a significant, avoidable limitation of the review, hindering the general reliability of my review and will be discussed in more detail.

Another more subtle limitation, is in regard to the focus of a large proportion of the studies, on the efficacy of indwelling pleural catheters, in comparison to other pleural interventions. An effort was made to be inclusive as possible, as per the guidelines of the scoping review. Nevertheless, the introduction of the IPC in most recent years seems to have taken the pleural intervention realm by storm, emerging as the most effective procedure in managing malignant pleural effusion in selected patients. This, in fact, is directly related to the miscalculation of implementing a 5-year constraint on the review. If this has not been the case, there would have been less risk of the studies reviewed, to be skewed in this manner. This trend in the literature was noted and I am cognisant of the limitations on the conclusions able to be drawn from this review.

Chapter Three
Thematic Analysis

Although semi structured interviews have not routinely been used by previous researchers in the development of core outcome set development, they are considered to be a staple of qualitative data attained for health services research. Organising and holding flexible but structured conversations provide an opportunity for researchers to delve deeper into the thoughts and perspectives of key stakeholders. This is done with a method of designing interview protocols supplemented by iterative follow up questions at the discretion of a trained interviewer. (Jamshed 2014)

Following discussions with my academic supervisor, I felt semi structured interviews would add an extra layer of empirical work to support the literature review to attain a long list of outcome measures. This would in theory support the validity of the Delphi process to follow, which would draw from a list of outcome measures attained from two distinct research methods.

In order to be able to complete these semi structured interviews, I had to under-go training in the form of tutorials from my supervisor Sion Williams in order to equip myself with the skills for not only conducting the interviews but in order to thematically analyse the data based on the methods of Braun and Clark. (Braun and Clark 2006). By attaining the data in transcript form, this revealed an issue of ensuring a password protected Dictaphone was provided by the University, for the production of verbatim transcripts.

From the tutorials with my academic supervisor, we discussed the planned approach to the interviews. Firstly, the purpose and aims of the interviews was established. This was to be an exploratory process to elicit potential themes and patterns which could be analysed and summarised as potential outcome measures. I planned to generate abstract themes from the attained qualitative data to supplement the long list of outcome measures to be entered into the later empirical work of the study. This can be described as an inductive approach to semi-structured interviews, where the purpose of the data gathered is to map out observations to identify the emergence of new information. This approach involves the interviewer behaving as a blank canvas, interpreting the qualitative data with no preconceived theory. Unfortunately, due to limited resources, I was planning on completing the interviews myself, and interviewer bias was almost an unavoidable phenomenon. However, awareness of this and using an inductive approach to the interviews, I believe, reduced the risk or extent of this.

(Young et al. 2020) This framework and general approach towards the interviews fit the purpose they were to play in the study. I felt this approach provided the best opportunity to empower the stakeholders involved to convey their perspective, and for this to have the greatest impact on the overall process. Moreover, I felt an inductive approach to elicit subtle and less investigated themes within the most important outcomes, provided a suitable contrast to the literature review completed, as an overall collective method of producing a long list of outcome measures.

The next step was to decide on who should be invited to participate as part of the interview process using the principles of purposive sampling in qualitative research. This is opposed to randomised sampling, which in theory reduces the risk of selection bias. Purposive sampling allows researchers to select participants that are able to provide the greatest amount of information pertaining to the area of interest. This is done by selecting participants that have a special knowledge and are able to provide researchers with a deeper understanding. (Patton 2002) The main benefit of this for my study was the increased yield of desirable data to the limited resources available to me. In theory the plan in terms of sampling was simple; to include all relevant key stakeholders. In practice this was more complicated due to the range of sub-groups of practitioners and patients. I wanted to ensure a diverse range of practitioners and patients were included. Maximising a range in such fashion would allow identification of distinctive themes amongst certain subgroups, whilst ensuring important patterns applicable across variations were recognised. This stratified purposeful sampling method is a documented technique used in implementation research and was suitable for the aims of the process. It is a combined method to assess the values across a range, allowing contrast, whilst focusing on similarities and common themes. (Patton 2002)

When evaluating how many interviews should take place within each group and subgroup there were two factors to consider. More pressing was the awareness of the limited resources I had available to complete the interviews within a set deadline. The interviews were to occur over a four-month period whilst completing my F2 rotation in respiratory medicine. The second factor involved the phenomenon of theoretical saturation in qualitative research, and its use in dictating the sample size of semi structured interviews. Simplistically, the thematic saturation point is where further interviews do not reveal any new information. This is dependent on the pillars of the study including aims, the similarity of the participants and the quality of the interview process and analysis which follows. Malterud et al. 2016 suggest the greater the relevant information held within a participant sample, the fewer the participants required to achieve saturation. (Malterud et al. 2016)

On review of the time available and the limited resources, using a stratified purposeful sample, my initial sample size was estimated to be 16, focusing on a diverse range of subgroups. This was to be an iterative process and for more or less interviews to be included depending on the extent of thematic saturation. This iterative design of sample sizing in this context has been described in the literature as a viable method of ensuring the further interviews are only carried out when productive to the end goal

of the process. (Guest et al. 2006) In identifying a diverse subgroup of practitioners I set out to include an eclectic mix; this included junior doctors and advanced nurse practitioners to consultant intensivists and respiratory physicians. I wanted to include decision makers and skilled practitioners carrying out demanding pleural procedures such as medical thoracoscopy and complex drains, as well as the health care staff on the ground responsible for the day to day care of these patients. I managed to discuss this range of practitioners with my clinical supervisor before embarking on the organisation of these interviews. My clinical supervisor suggested to also include a medical registrar within these interviews, as he informed me, they are required to gain the competencies in ward based pleural procedures as part of their specialty training.

For the patient cohort, I planned a diverse criterion to cover with my supervisors to ensure a stratified sample. I wanted to include as much of a diverse range of pleural procedures as possible and for as many indications as possible. Along with this I came up with the idea of making the effort to interview patients in regard to their pleural intervention at different time points, pre and post procedure. I felt this would add to the depth of information attained from this group of interviews and also provide an opportunity to elicit any contrasting or hidden themes between these subgroups of patients. I understood this would require an extra logistical barrier to overcome, in terms of planning the interviews for pre-procedure patients, but I felt securing a small number of participants in this fashion was beneficial for the overall project. There were ethical issues to consider here and these were pre-empted and discussed at my tutorials centred on this stage of the empirical work of the study. Regardless of who was being interviewed, a respectful and sensitive approach was to be adopted, but this felt absolutely crucial for the interviews carried out with patient's pre-procedure.

In terms of approaching participants, I was able to recruit some help from research nurses. This was a significant helping hand in terms of reducing the overbearing workload of organising the semi-structured interviews, as well as acting as a gatekeeper to protect the participants, namely the patients. Building a rapport with the research nurses at this stage was important for the later stages of the study, as I would again require their assistance in approaching patients for the Delphi survey.

Once patients had received the PIS and agreed to participate I had to consider a time and place for the interviews to take place. For post-procedure patients that had been discharged, this could be arranged over the phone or for when patients had pre-planned visits to out-patient clinic. It was relatively easy for me to ensure I wasn't disturbed whilst interviewing patients over the phone, and out-patient clinic provided a quiet, private and patient friendly setting for the process to run smoothly. For the practitioner interviews I was able to recruit the help of the local north wales clinical school, who were able to provide me with a quiet and uninterrupted space. This is documented in the literature as an ideal setting for interviews, and significantly adds to the quality of them. (Edwards and Holland 2013) As previously mentioned the university provided a password protected Dictaphone for the interviews to be recorded on. This allowed for me to be able build a rapport with the participants instead of

incessant note taking. An important aspect of my tutorials with my supervisors regarding the interviews was the development of an interview protocol. This was my first time completing a piece of qualitative research in this fashion and I wanted to be confident in the style of questioning. It was assumed from the beginning that the questions for both practitioners and patients would only be slightly different but contrasting enough to have separate interview protocols. An introductory question would be followed up with questions relating to what the participants deemed the most important outcomes. There were more targeted questions relating to indication of the pleural procedure for practitioners and greater exploration of experiences with the patient cohort. Moreover, language was modulated for suitability for each cohort, a recurring theme within the study. I have attached an interview protocol that was used for the study in the appendices to follow.

I was tutored to ensure I conducted the interviews in a conversational tone and to ensure I kept the participant, namely the patient cohort, at ease throughout the process. Methods of doing this were discussed in my tutorials, such as the art of active listening and gestural cues. (Anderson and Jack 1991)

Themes

Interviews were carried out with both patients and practitioners to illicit underlying themes to be studied, relevant to the development of a core outcome set. Thorough case analysis highlighted a range of themes pertaining to various aspects of the pleural procedure for both patients and clinicians. It highlighted some themes along with delineating more subtle and complex ones.

Each theme was considered along with the respective subthemes.

Contexts

Interviews with practitioners of various grades and experience were utilised to essentially gage their views on the most pertinent outcomes for pleural procedures. The questions used formed a consistent structure; delving into the different stages of the procedure along with taking into account the personal circumstance of either the practitioner or patient.

An effort was made to focus questions for patients on the procedure itself, keeping the conversation away from any potential difficult discussions regarding prognosis of the condition or diagnosis they were suffering with. This was done firstly to stop emotional responses to cloud the data, and in order for the well-being of patient participants to be held in the highest regard. Nevertheless, in the effort to ensure a thorough data set was achieved I ensured different types of patients were recruited for interview. This included both cancer and non-cancer patients, and also patients undergoing a pleural procedure for pneumothoraces. Moreover, interviews with patients qualifying for a medical thoracoscopy were also undertaken to give the data sufficient depth in terms of the variety of pleural procedures. There was a further initiative taken to include patients being selected for Indwelling pleural catheters. (IPCs) This was done in light of the trend discovered in the scoping

review, towards the increased use of IPCs in the management of chronic malignant pleural effusion. This vetting process was often done well in advance, allowing interviews to be set up with relative ease, with candidates for IPC admitted as elective patients. Patients receiving specialist interventions such as IPCs or medical thoracoscopy were labelled as such, as opposed to the standard ICD procedure.

Interviews with patients were sub-categorised into pre-procedure and post procedure. The interviews conducted pre-procedure were either effectively immediately before the procedure or as soon as patients were notified, they were to have a procedure that same day. It was difficult to identify patients for this category of interview; it was a rarity to identify patients who immediately before the procedure had symptoms that were controlled well enough to be comfortable to participate in an interview. Nevertheless, there were some patients who qualified for elective procedures who consented and provided a unique insight into the thoughts of a patient immediately before the procedure.

Patients were further categorised by the indication for the intervention into cancer and non-cancer. This was under the presumption that all interviewed cancer patients would have 'malignant pleural effusions' as the indication for procedure, as was the case. Patients classified into non cancer would either have a pneumothorax, empyema or parapneumonic effusion. However, I felt it was only significant to record non-cancer pneumothorax patients as a separate entity, due to the different physiological implications, procedural technique and definitive management of these patients.

Core Theme: Patient outcomes- '*See what's most important from where we sit on the table'*

Theme 1. Shortness of breath

Dyspnoea, as expected, is a common theme throughout the patient transcript data set. It's often referred to as a prominent symptom. In other interviews its mentioned as something that patients have been suffering with chronically, with an acute deterioration causing them to present and require the procedure.

> "Well… [pause] this all started when I was struggling with my breathing, I needed first some oxygen and then that horrible machine for hours." (Patient #2 Post Procedure Cancer).

Patient #3 – Post procedure, Cancer, drain insitu

"I couldn't speak I was so breathless, still am, the drain helped a lot with it but now I've got this cough, and with the bit of soreness from where it is, I'm not in a good way"

It's important to note the patients requiring pleural procedures will more than likely be accustomed to dyspnoea as part of their day to day battle with certain respiratory diseases. The fact that, in general, they reported a positive effect on their breathlessness is a telling aspect to pleural procedures, in what they are able to offer dyspnoeic patients. This essentially depicts shortness of breath as a valid measurable outcome that should be considered for pleural interventional efficacy trials.

Sub themes

Fluid off

From the interviews it became apparent that patients associated their symptoms with the accumulation of fluid in the chest. This is to be expected as this is the most common indication for a chest drain.

Patient #5 Post procedure Cancer

"I was told draining the fluid would help me feel better, which it did, though it was extremely painful."

"Well obviously it was how much it was going to help my breathing, and getting the bad fluid out of my lungs."

Describing pleural effusions as "fluid on the chest" that sequentially "needs to be drained", adequately simplifies the process of malignant pleural effusion giving the patient an idea as to why they are experiencing symptoms. They are able to often understand the simple biomechanics that this implies and provides them with hope that once they are free of the fluid through the chest drain, their symptoms will improve. As practitioners we should be more observant in the way in which we describe certain conditions and processes to patients, with the aim to provide patients with accurate information to achieve informed consent.

Lung up

This subtheme of the 'lung coming up' is very similar to the previous subtheme recognised within the transcript data. It stems from the language used in order for the patient to understand why the pleural intervention would benefit them and their symptoms.

"I think it was important for my breathing that the fluid was removed so my lung could come up and so I could breathe normally again"

Anxiety

It is common for patients to be extremely anxious before the procedure. Though they have consented and understood the potential risks, the procedure itself can be daunting from beginning to the end depending on the skill and experience of the technician. This angst being driven by the procedure itself can often heighten the sense of dyspnoea a patient feels, as they are hyperventilating.

Patient #8 Post-Procedure -Medical Thoracoscopy

"Like I said, I think I was most concerned with getting the fluid off. I wasn't exactly dying for my breath as I'm quite used to being breathless. But I was extremely eager to see how much having this fluid off would improve my breathing. I felt like the start of the procedure would ease my anxiety."

This links in with another theme to be considered on the level of information the patient receives. It is the duty of the practitioner to ensure they are doing their utmost throughout the whole procedure to ensure the patient is as relaxed as possible. This naturally starts with a good introduction of themselves and a thorough explanation. However, it is important for the practitioner to engage the patient throughout the procedure, keeping their anxiety under control.

Theme 2. Pain and Discomfort

Discomfort is something practitioners have to manage when carrying out pleural procedures. This is portrayed by the frequency and regularity it was mentioned by practitioners in the interviews when discussing potential core outcome sets. Theoretically pain should be kept to the minimum with competent and liberal application of local anaesthetic. However, as depicted by the recurring theme throughout the patient interviews, it's often an unavoidable consequence of gaining access to the pleura.

Patient #4 Post Procedure drain in situ Noncancer Pneumothorax drain insitu

"The pain, oh god yeah the pain. I'm in enough pain as it is already with my chest normally, fighting for every breath. The tube helps with the breathing, but I don't look forward to the pain"

Patient #5 Post procedure Cancer

"I was told draining the fluid would help me feel better, which it did, though it was extremely painful."

The experiences of the patients depict clearly the relevancy of pain and discomfort, as an innate by product of the procedure. It's frequently described in parallel to the benefit the patients receive from the procedure with other symptoms, as its own independent entity. Moreover, the discomfort of having a procedure lasts a considerable time after the procedure has been completed. Pain during

the procedure is normally handled well, but as the local anaesthetic wears off, patients complain of discomfort that requires generous dispensing of analgesia for it to be sufficiently controlled.

Practitioner #2 Medical Registrar, interventional fellow

"After the procedure is completed, I think pain control is really really important, because chest drains cause a lot of pain and discomfort in a lot of people."

Practitioner #4 Consultant Intensivist

"I'd say resolution of clinical symptoms firstly, for example dyspnoea and pain. Following this Radiological Evidence of resolution of pleural effusion/ pneumothorax."

Practitioner #5 – Consultant respiratory physician

"Yes, I'd say with procedures done on the ward pain often is a mainstay of the whole procedure. Assessing for pain, warning the patient during the procedure is quite important, In contrast in theatres or endoscopy suites we are able to provide sedation for the patient and it's not something that the patients actively complain about. It doesn't impede the procedures success. As long as you're liberal with the PRN analgesia after the fact."

Interviews with practitioners revealed that the pain and discomfort of the patient was a relevant issue in terms of core outcome sets. It was emphasised that a key role of the practitioner is to ensure the patients are pain free for a considerable time after the procedure, to enhance recovery and promote rehabilitation.

Subthemes

Discomfort of the tube

The discomfort experienced by the patients in the aftermath of the procedure is mostly caused by the presence of a tube in the chest and its attachment to the underwater seal via a conduit. The inconvenience of being attached to an appendage makes mobilisation and simple trips to the bathroom a chore. This can affect the mental wellbeing of patients and generally reduce their confidence in their independency.

Patient #8 Post-Procedure -Medical Thoracoscopy

"Good question, I think a bit of both, though pain killers seem to settle the pain quite nicely. I have to think twice about doing things with it which is normal I think for someone of my fitness. But I feel maybe I think thrice now before doing anything."

It's important that patient's chest tubes and reviewed regularly by medical staff, to ensure they are still indicated. It is also important that nursing staff monitor patients with ICDs regularly to ensure

they are receiving the appropriate care as often a patients' needs can change whilst being inconvenienced with a chest tube in situ.

Sleep

Another subtheme identified under the wider theme of discomfort, was the lack of sleep patients were able to achieve in the days after the procedure. This has much to do with the aforementioned discomfort patients experience impeding them of a good night sleep. Particular reference was made to the inconvenience of the chest tube for the lack of sleep.

Patient #2 Post Procedure Cancer

"It's quite uncomfortable to sleep since it's been in as I tend to lie on my right side but I'm sure I will get used to it"

Patient #7 Non-Cancer Post procedure

"A tube so thick, I didn't think it was going to be as big. It stopped me from sleeping for about a week."

Patient #8 Post-Procedure -Medical Thoracoscopy

Nights with it are awful and I haven't had a good night's sleep since I've had it in. Might be this place though."

Naturally, this may affect the mental health of patients and is a further pertinent reason to ensure patient's pain is well controlled.

Theme 3. Length of stay

A recurring major concern for patients in both cancer and non-cancer cohorts, was their overall hospitalisation. A lot of the patient interviews were done on patients whilst already in hospital, and their cumulative days in hospital were predictably on the forefront of their mind. In gaining consent the patients for the procedure, they are informed of the likelihood that they will be in hospital for an extra couple of days. This seemed to be the most common issue raised once the procedure was over and done with. Pre procedure, the larger concerns seemed to be either symptoms endured, or level of information provided.

Patient #5 Post procedure Cancer

"No not really, just when I'd be able to go home. Once the drain was out it was a fight to get off the oxygen and that became my focus"

Patient #7 Non-Cancer Post procedure

"[Pause] How long it'd be until I could get home really. I was feeling on the mend before it was even put in so I felt it kept me in for longer than I should."

Hospitalisation days as a potential outcome repeatedly cropped up in the practitioner interviews. Length of stay and hospitalisation are essentially synonymic, as days in hospital for the patient are evidently equally important to pleural interventionists.

This depicts 'hospitalisation' as occupying some elemental common ground between the two main stakeholders in regard to this issue. The analysis of the transcript data is evidence of its relevance to the patient cohort used in this part of the study; simultaneously 'hospitalisation' measured in number of days provides a quantitatively based core outcome for practitioners and researchers, providing a well-balanced outcome measure of efficacy in pleural interventional trials.

'Hospitalisation' forms an excellent 'bridging' outcome, evidently appearing in both sets of transcript data. This outcome measure shares this quality with the themes 1. Shortness of breath and 2. Pain/ discomfort. Thematic analysis of our data depicts the relevance of these underlying themes to the main stakeholders, as potential appropriate primary outcome sets.

Guided by the knowledge attained through the scoping research done into this issue, and the nature in which these themes have been elicited through stakeholder interviews, these potential outcomes have become key considerations for the next stage in the compilation of consensus.

Subthemes

Getting back home/family

The amount of time ultimately spent in hospital was not only a concern with the patient cohort but was repeatedly flagged by their families. This was either offered willingly by the interviewee, or after probing on the thoughts of those closest to them. This is elicited as subtheme of hospitalisation, and as a possible explanation as to why days in hospital were so relevant to patients.

Patient #5 Post-procedure Cancer

"What do you think was the most important aspect in regard to the drain for your husband?"

"The same as me, how long it would until I was able to go home, because I'd finished my course of antibiotics whilst the drain was still in,"

Patient #1 – Post-Procedure Non-Cancer

"What was the most important aspect reported by your family do you think with the procedure?"

"Time again. I'd say how long it'd keep me away from home. Also If the fluid was to do with the pneumonia I had or some other problem"

Patient #2 Post-Procedure Cancer

"What do you think was your wife's biggest concern?"

"How soon I would be home after this since I had got back to normal, feeling more like myself"

Patient #3 – Post-procedure Cancer

"What do you think is your family's greatest concern is now in regard to this chest tube?"

"They're not worried about the drain; think they just want me home as soon as possible but I don't think I'm going to make it out anytime soon"

Family members, as expected were innately concerned with the amount of time their loved ones would remain in hospital. This, as demonstrated, influenced the patients to also raise their concerns about hospitalisation. This is a pattern that is repeated in themes yet to be discussed, with the concerns of the family becoming the concerns of the patient.

Theme 4. Level of patient information

The level of patient information provided was another underlying theme amongst the patient cohort of interviews. There was certainly an expressed desire for patients to know exactly what was going to happen with the procedure itself and the accompanying complications, along with information in regard to immediately after the procedure.

Patient #1 – Post-Procedure Non-Cancer

"so, what was the most important aspect to your well-being, BEFORE you had the drain? Would you say?"

"explanation of what he was going to do and why, really?"

"What was the most important aspect *after* you'd actually had the procedure? What was the most important thing to yourself?"

"Same again really, another explanation of what would happen and how Long it would take. I didn't really understand how long it was going to be then, was about 10 days in the end"

Patient #4 Post-Procedure drain in situ Non-cancer Pneumothorax

"Did the doctor explain the procedure sufficiently?"

"As always the doctors were wonderful, really got nothing but good things to say about the way things are handled round here"

There was, on overall balance, positive appreciation for the effective communication of practitioners and their conduct. Effective communication and comfort of the patient was equally recognised in the practitioner cohort of interviews, as a significant issue.

Practitioner #1 ANP

"…Ok so measuring the efficacy of drains, [pause] I think patients need to be assessed properly before the chest drains are put in, it's about quality of life, having been a lung cancer nurse for so long… And how they're put in as well, often an experienced person can make the patient feel at complete ease and often someone with less skills and experience can often make the experience for the patient more traumatic than it needs to be"

The effective communication and information provision are paramount to the safe administration of any pleural procedure, or any procedure in fact. Patient satisfaction can be upheld quite vivaciously with small efforts made by the practitioner, as depicted by the transcript data.

The subthemes found within the concerns for information, are as follows.

Subtheme

Risk of Complications

In discussing the information the practitioners provided the patients before the procedure, there was a concern in regard to the possibility of complications. This is an important aspect of the consenting process for the procedure but naturally seemed to stir patients. This is where effective communication comes to the forefront to ensure patients concerns are put at ease.

Patient #7 Non-Cancer Post-procedure

anything else you were thinking about?"

"Well my breathing too, but it'd become much better. Must have been the antibiotic kicking in, I was also worried it was going to go you know, wrong and there'd be a risk of things going wrong like Ambu said may happen"

Patient #6 Pre-procedure Cancer

"Yeah, my sons are great. They want me to come home, like normal. They're worried about any complications Ambu talked about,"

Hospitalisation

This is a theme that has presented itself throughout the interviewing process. The most common piece of information patients would seek once the procedure was complete, was the unrelenting question of how long they'd have to live with a chest tube and underwater seal appendage. Moreover, how long it would be until they could go home now that the procedure had been done successfully.

Patient #4 Post Procedure Non-Cancer Pneumothorax drain

"What would you say is the most important aspect of your care now in regard to this drain you have in now?"

"How long this is all going to take, I really think I need to be sent in to Liverpool and have something done about this. I don't think this drain can come out now until something is done, it's just not going to heal by itself."

It's clear the amount of time to be spent in hospital is a grounding concern for all patients for pleural procedures. This could be due to the nature of the underlying diagnosis or fears the procedure itself will further delay a planned day of discharge. When discussing expected days to discharge, its important the practitioner is tactful in the way he predicts this. This is to ensure the practitioner does not unduly raise the patient's expectations, as the possibility for re-intervention due to failed pleurodesis can be quite high in certain patients.

Patient #9 Post-procedure Non-Cancer

- "The second one hurt like hell mind you. I guess it always was going to with it being so much bigger."

Theme 5. Pace and Getting it done

Interviews were carried out both pre and post procedure with patients, with pre procedure interviews being more difficult to come by. I did the utmost to include these patients to ensure any underlying themes were not missed.

There was congruency between most of the themes already discussed between pre and post procedure interviews. The most strikingly unique theme to the pre procedure interviews was the increased urgency expressed by the patient for the procedure to be done. Once the patient was notified that a procedure could possibly improve their symptoms, it became apparent that the swift initiation of the procedure was at the forefront of the mind of the patients.

Patient #6 Pre-procedure Cancer

"What needs to happen for this drain to be a success for you?"

"For [pause] it to happen, quickly, make my breathing easier and I get home as soon as possible to my wife and family,"

The cause for this urgency can be interpreted as the patient's willingness for symptom resolution. I was mindful to ensure that patients included in pre procedure interviews weren't compromised by their symptoms.

Core Theme: Professional outcomes – 'I'd lean towards patient comfort and patient symptoms'

The following sets of themes elicited from the interviews from both sets, tick more boxes and hold more relevance with the practitioner cohort of participants.

As discussed previously, often the concerns of the family uphold the significance of certain issues in the minds of patients. This was previously depicted in the issue of hospitalisation days and is again the principle in which the following theme of diagnostic value is elicited.

Theme 6. Diagnostic Value

Subtheme- Family interest in diagnostic value

From the interviews carried out with patients, an underlying theme in regard to the interest of the families was discovered. This involved the diagnostic value of the procedure itself. Some inference was made here, as the term 'diagnostic value' is not used by the families; however, patients reported their families questioning whether the procedure itself would indicate diagnosis, prognosis, or length of hospitalisation.

Patient #1 – Post Procedure Non-Cancer

"What was the most important aspect reported by your family do you think with the procedure?"

"Time again. I'd say how long it'd keep me away from home. Also If the fluid was to do with the pneumonia I had or some other problem"

Patient #7 Non-Cancer Post-procedure

"My wife was asked if the fluid drained off may tell us why exactly it was there?"

Patients also expressed their hope in this regard. The following patient voiced his reasoning for electing for a medical thoracoscopy, based on the potential for its diagnostic value to his condition. This is a trend elicited in the interviews done with patients who had undergone a medical thoracoscopy. This could very well be due to the extra diagnostic ability of a medical thoracoscopy, relayed to patients in the consenting process for this procedure.

Patient #8 Post-Procedure -Medical Thoracoscopy

"…So that's probably most important. I'd say I hope the fact that I picked a more complicated and lengthy process, that this will pay off in A) stopping this from happening again and B) the samples Ambu took can get to the bottom of why this happened. As Ambu explained it this fluid Is a symptom of a cause and I think finding the cause is important to me."

Through the scoping research carried out, it was interesting to note that diagnostic value of pleural procedure was not an outcome measure that appeared frequently. In the interviews with practitioners however, it appeared as an underlying theme. This I felt was something to be considered, in determining the most appropriate outcome sets.

Practitioner #3 Junior Doctor

"…I'd lean towards patient comfort and patient symptoms as my primary outcome, with quality of life a close second. I'd also want to mention diagnostic value to the patients work up as something else that I probably haven't mentioned enough over this discussion."

Through this set of interviews, the importance of the diagnostic value of a pleural procedure becomes apparent; to patients, their families and practitioners. This insight validates diagnostic value as an outcome that should be taken a step further, as a potential core outcome set. I also feel it is important to consider the reasoning behind its scarcity in appearance in the scoping review and the fact it has been elicited as major concurrent theme throughout this set of semi-structured interviews.

Theme 7. Quality of Life

I expected this to be an important underlying theme, throughout both interview sets. However, this theme pre-dominated the interviews with practitioners, indicating its relevance to efficacy trials. Quality of life, if recorded accurately and precisely, is appreciated by practitioners as a measurable outcome in pleural efficacy trials.

Practitioner #4 Consultant Intensivist

"What do you think is the most important outcome for people requiring chest drains?"

"I'd say for those that are awake the relief of dyspnoea, for those that are sedated I'd say quality adjusted survival,"

Practitioner #3 Junior Doctor

"overall what do you think are the most important outcome measures in pleural international clinical trials?"

"This isn't something I've had to think about before but from our discussion today I think I'd lean towards patient comfort and patient symptoms as my primary outcome, with quality of life a close second.

The scoping research carried out delved into the ways in which quality of life was assessed, looking into various measuring tools and their validity. The need for a well-balanced and inclusive assessment of quality of life is elicited from an interview with an experienced practitioner.

Practitioner #5 – Consultant respiratory physician

"…I think it'd be wiser to assess cancer patients with a more holistic quality of life index rather than a particular symptom."

After an evaluation of the various quality of life indices, it became apparent that quality adjusted survival was an appropriate way in which to measure quality of life. This seemed to be best tailored for measuring quality of life associated with pleural procedures, due to the palliative nature they are carried out in. More often than not, the goals of the procedure are to manage an acute to sub-acute

manifestation of a chronic palliative disease. This element of pleural procedures is reiterated throughout the interviews with practitioners and is elicited as a subtheme.

Subtheme – palliative procedure

As mentioned, practitioners discuss quality of life in conjunction with the mortality ratios of patients; putting an emphasis on comfort in survival, rather than survival alone.

Practitioner #2 Medical Registrar, interventional fellow

"… Most of these patients have high mortality ratios for their admission into hospital, whether it be a malignant pleural effusion, or it be a pneumothorax secondary to COPD… it becomes about the comfort and quality of life for that patients remaining lifespan often…"

In this given example the practitioner makes the valid point of allowing for the concurrent significant morbidities these patients have, along with their need for a pleural intervention. Co-morbidities such as COPD, can often have dire consequences on a patient's overall prognosis, and must be considered by pleural procedural practitioners when assessing the interests of patients.

Practitioner #1 ANP

"Ok so measuring the efficacy of drains, [pause] I think patients need to be assessed properly before the chest drains are put in, it's about quality of life, having been a lung cancer nurse for so long, chest drains are put into patients that are inappropriate and say , it doesn't really matter about age or anything like that but if the patients is end of life and they're not going to gain symptomatic benefit. For example, if a patient is nursed in bed and they're not going to be getting up and walking around the fact they've got a massive pleural effusion is not having an impact on their quality of life, so quality of life is MASSIVE,"

"… plan an IPC, if that's what they feel is going to be beneficial because quality of life is the most important side of things for these often palliative patients. Its brilliant that we're doing that more now, I think coming in and doing chest drains and aspirations just increases the risk of infection and affects the experience of quality of life of the patient. "

Again, the underlying theme here is the matter of fact that most patients undergoing pleural procedures are bracketed within a high mortality and the priorities of the practitioner must be adjusted.

From both the scoping review and practitioner set of interviews, assessment of quality of life is paramount to the efficacy of pleural procedures and undoubtedly will form a key element in the next stage in the process of determining the core outcome set.

Theme 8. Symptom clinical resolution

Quality of life was a significantly bold theme throughout the practitioner interviews. However, it did not supersede the theme of overall improvement of patient symptoms. This encompasses some of the themes gaged from patient interviews, such as shortness of breath and pain and discomfort.

Though practitioners were open minded in their responses, a common theme was that the majority of practitioners emphasised the importance of patient symptoms in relation to pleural procedures. The underlying importance of improvement of patient symptoms first and foremost was hard to escape throughout the set, with most practitioners offering it as their most highly ranked outcome.

Practitioner #5 – Consultant Respiratory Physician

"I see, what do you feel the most significant primary outcome measure is before the procedure is started for patient?"

"I'd say categorically, resolution of symptoms."

"Do you think this changes once the procedure is completed?"

"No, the resolution of the patient's symptoms is indispensable. Anything you attain from the procedure after this fact is extra, for example for diagnostic purposes."

- *Practitioner #6 Consultant Respiratory Physician*

"Erm no I don't. I still think the primary outcome to assess the quality and efficacy of a chest drain is to ensure symptoms are under control. I feel as if once this is done other measures can be thought about. I mean there may be a perfect way of measuring how good a pleural procedure is, but the most important way in doing this is by assessing its effects on symptoms."

From the above extracts from two separate interviews with experienced consultants, the mirrored theme that is depicted is clear to see; patient symptoms are a key priority for pleural interventions with other issues to be addressed following on from this.

Looking further into the first interview quoted, a connection is made by the practitioner between two different aforementioned themes.

Practitioner #5 – Consultant Respiratory Physician

"You could make an argument there is. Like I said resolution of symptoms to affect quality of life Is paramount."

This connection suggests reasoning for the increased importance of resolution of patient symptoms. Resolution of patient symptoms can inadvertently have a positive effect on other parameters that can indicate the success or failure of a procedure, such as hospitalisation and quality of life.

There is an argument that resolution of symptoms is of paramount importance once the diagnosis has been made. This seems to be the only context in which diagnostic value may supersede overall improvement of patient symptoms, in certain circumstances.

Practitioner #2 Medical Registrar, interventional fellow

"Can you tell me from your experience, if you feel the primary outcomes between cancer and noncancer patients differ when it comes to pleural interventions on the whole?"

"Yeah, there is a big difference between the two. I think with chest drains and with all the other pleural interventions, I think, erm you're more aggressive if you're trying to prove it's a cancer if you've not proven it already. Once you have the diagnosis of cancer the outcome should only really be symptom control, and once the intervention has been made, you don't do anything extra. You just want to try and make sure the pleural effusion doesn't come back."

This general attitude towards putting the resolution of patient symptoms as a priority, seems to apply to all pleural interventions. This is depicted quite succinctly in further extracts from interviews quoted as follows.

Practitioner #2 Medical Registrar, interventional fellow

"Do you feel like the primary outcomes change depending on the intervention being carried out?"

"No, erm no I don't think there is any difference in the primary outcome between the three procedures, as long as it resolves patient symptoms."

This is an example of another experienced practitioner stating the importance in resolution of symptoms, regardless of the pleural procedure being carried out.

Practitioner #4 Consultant Intensivist

"Why?"

"Well I understand there are multiple reasons for chest drains but the main ones for the patients are the relief of symptoms, the most common and serious being dyspnoea."

"Do you feel like there is a difference in the primary outcomes when It comes to pneumothoraces compared to pleural effusions?"

"Well, in my mind again, NO, it comes down to the symptoms again for me..."

The aim of resolving patient symptoms are naturally a high priority for practitioners and must be considered in terms of potential primary outcomes. There are some underlying subthemes elicited within this, depicted in this previous quote. The repeated mention of dyspnoea in regard to resolution of patient symptoms.

Subtheme - Dyspnoea

Throughout the practitioner interview set, the mention of patient symptoms almost seemed synonymous with shortness of breath. Practitioners would make special mention of the patient's breathlessness when focusing in on the symptomatic resolution of patients.

Practitioner #3 Junior Doctor

"So, I'd say with some certainty that the degree in which the intervention is able to alleviate the patient's symptoms must rank highly as a primary outcome, whether that is pain or dyspnoea. Normally dyspnoea, as we are talking about helping the lungs do their job most of the time."

Practitioner #5 – Consultant Respiratory Physician

“Thanks Dr ***, finally I just want to wrap up by bluntly asking you to list the three most important outcomes to measure in pleural interventional trials, starting with the most significant in your opinion.”

“Erm ok. I’ll go with number one treatment of symptoms of the patient, mainly dyspnoea…”

This elicited theme indicates the importance of dyspnoea as a patient symptom for pleural interventions. Its importance to practitioners is indicated through these interviews, giving insight into the significance of shortness of breath as a marker of success of a pleural procedure. Dyspnoea is a sensation exhibited clearly by the patient’s respiratory rate and overall use of respiratory muscles and effort. Other symptoms such pain and discomfort are less easy to be detected clearly by the practitioner and more easily managed with analgesics. Dyspnoea acts as an effective instant marker on the efficacy of the pleural procedure, providing technicians with relatively instantaneous feedback.

Subtheme Clinical Parameters

Identifying resolution of symptoms can often be a difficult task. A subtheme to the resolution of symptoms involves certain parameters discussed by practitioners in their interviews, as a method in order to gage this improvement or lack thereof.

Practitioner #4 Consultant Intensivist

“Fair, and finally and overall what do you think are the most important outcomes to be measured in pleural clinical trials?”

“Resolution of clinical symptoms, including oxygenation, respiratory rate, respiratory effort, ease of ventilation, radiological evidence of improvement and finally biological parameters for example CRP, liver function tests.”

Here we see an intensivist state the importance of measurable clinical parameters, as a measure of improved or worsening clinical symptoms. This provides an objective instant measure of how effective the procedure is at achieving its aim, which as discussed, is often largely based on the comfort of the patient.

The semi structured interviews allowed me to be able to explore themes in regard to pleural interventions, and probe at more discreet issues. From thematically analysing via methods set out by (Braun and Clarke 2006), both cohorts of interviews with patients and practitioners, a balance of themes have been elicited and categorised.

A procedure will always have at least two people involved at separate ends of the spectrum. The patient and the technician; both with contrasting thoughts and feelings in regard to the practicality of the intervention. This was depicted in some of the themes that are uniquely elicited from either patient or practitioner cohorts of interviews. Nevertheless, the safety and treatment of the patient should always be at the forefront of any practitioners' mind. This key ethical element ensured there were also themes elicited that were common to both cohorts alike, termed 'bridging outcomes' in the diagram designed below. Figure 3 provides a visual representation of major themes depicted from the analysis of interviews, in a Venn diagram like structure with themes at the centre significant to both groups of interviews.

These themes from both cohorts will form the key structure of the next step in determining the core outcome set for pleural interventions. Interviewing patients of all categories from non-cancer to cancer, pre and post of varying procedures, contributes towards my aims of developing an outcome set with as much patient involvement as possible. The analysis of patient interview transcripts has more of an impact than simple patient surveys; analysis of interviews to help form and structure future surveys, ensures the voice of relevant patients is integrated into the design of further steps to come. This would be in the form of the planned patient aspect of the Delphi process.

Although I was able to complete the task of the semi-structured interviews within the allotted time, I felt the constraint of resources available to me, inflicted some drawbacks and bias into the process. Interviewer bias is a recognised phenomenon which can corrupt qualitative data in various ways. This can be introduced from simple factors such as the language and attitude of the interviewer towards the process, ensuring a balance of interest and concern is struck whilst remaining detached to ensure the validity and reliability of the data. The literature suggests these acquired qualities can up to 6 weeks to master and advocate for inexperienced interviewers to be supervised until they are more assured with the process. (Salazar 1990) (Chenail 2011) I was unable to complete such a lengthy training schedule and attended tutorials over a two week prior to the semi-structured interviews as a complete novice. Moreover, I was unable to be supervised through any of my interviews in the initial stages. I feel some direct feedback in the initial stages of this process would have ironed out any mistakes to support the quality of the attained data. To address this, I was able to review the first couple of interviews with my supervisor through audio play back. I was given advice on potentially employing a more conversational tone, and this was role played along with further discussion.

The literature suggests that face to face interviews are the most effective way of attaining the most information from participants for the benefit of researchers. (Chenail 2011) 3 out of the 8 patient interviews were completed via the telephone due to the limited time and resources available, potentially affecting the quality of the overall data as a whole. However, there is an advantage of visual anonymity for inexperienced interviewers, reducing the likelihood of interviewer behavioural

bias. (Salazar 1990) This is a rare occurrence where the limited resources of the masters ironically may have potentially aided the quality of the data collected in this stage of the study.

I felt completing the interviews myself was an extremely informative process for my own development and I certainly achieved a deeper understanding of the impact pleural procedures had for patients and practitioners. Nevertheless, its unavoidable to not assess the negative impact my inexperience may have had on the process. The lack of any other interviewers being used for the process meant the reliability of the data collected could not be assessed by observing for inter-interviewer consistency.

There is another important study design flaw that must be discussed in regard to this stage of the project pertaining to patient interviews which undoubtedly can be seen as producing an element of researcher bias. The interviews were completed whilst I was completing a four-month respiratory placement; this was beneficial for the identification of potential patients to recruit for the study, including for the interviews. Moreover, this was particularly helpful in identifying patients for pre-procedure interviews, as I was able to gage their suitability. There was an obvious conflict of interest here with the patients on the ward I was caring for, being considered to be part of the empirical work of the project. To counteract this, I made the team of doctors I was working with aware of any potential patients being approached by the research nurse acting as gatekeeper. I made an effort to not be involved in their care as much as this was feasibly possible.

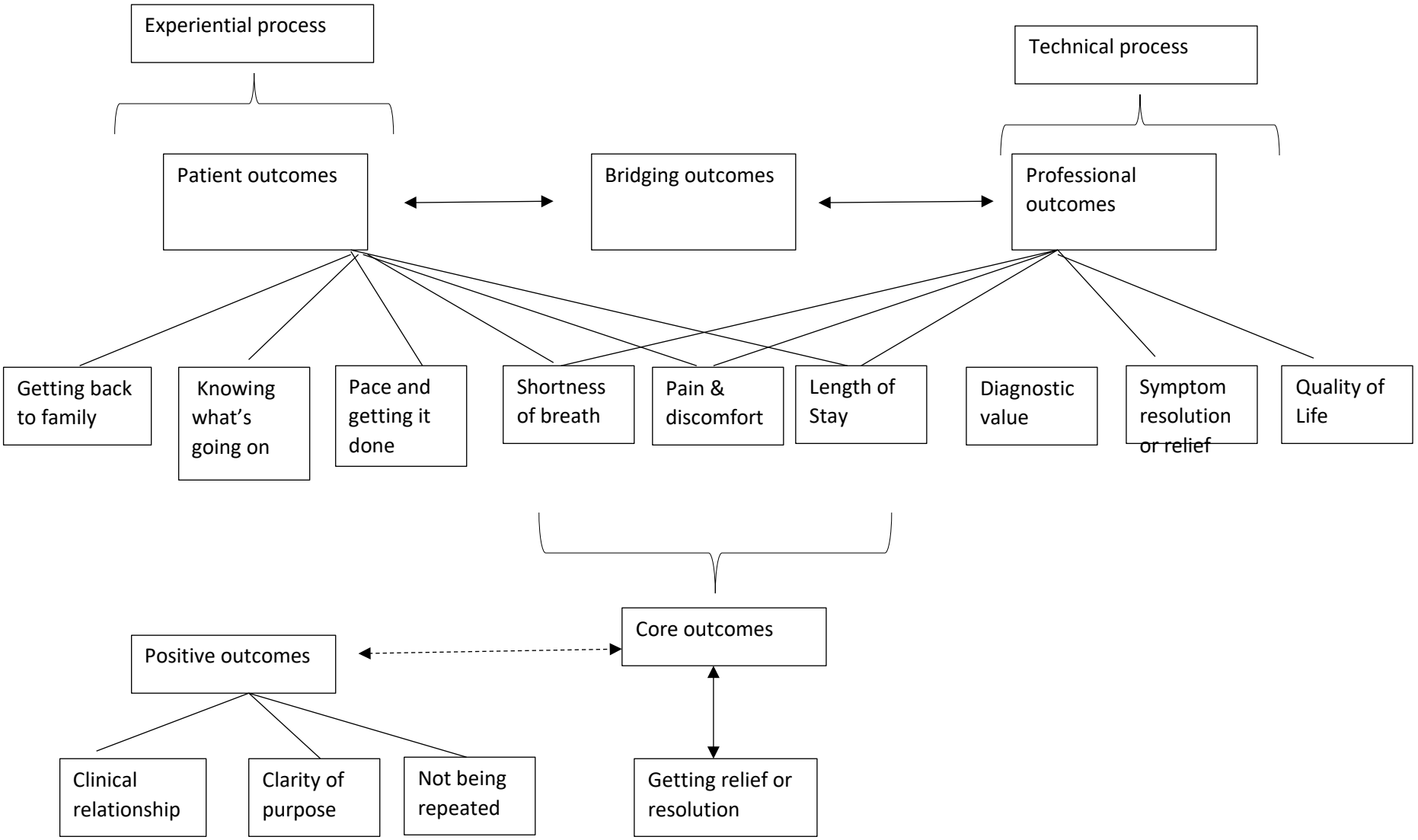
Moreover, although the research nurses working for the health-board were of great assistance they were not always available to carry out the role of gatekeeper due to commitments to other duties. This meant that in some cases I had to approach patients myself, as well as complete the interviews and the analysis to follow. This ultimately can unfortunately be deemed to be evidence of researcher bias and observer expectancy effect within the process.

Kirkham et al. 2017 set out a standard 11 step standard for COS development which will be discussed further. They state the relevant stakeholders that should be consulted in the development of new core outcome sets and included those within industry and clinical trialists who would be completing further efficacy trials within the area of clinical interest. Due to the limitations of the resources available to me, I was unable to organise semi-structured interviews with this domain of professionals who would have been able to provide a unique perspective on the applicability of a core outcome set for future research. (Kirkham et al. 2017) In an ideal situation I would have liked to have consulted a representative of a company involved in the manufacturing of new pleural interventional hardware, preferably the IPC (Indwelling pleural catheter). This is an important domain of stakeholder to engage with, as it propagates the distribution and increases the likelihood of general uptake of the core outcome set developed. It can raise awareness and add interest into further research to be completed to refine and re-evaluate the core outcome set, in the hope it continues to hold value. (Geng et al. 2022)

Finally, another limitation, which is discussed in the context of the Delphi study later, is the geographical limitations of the patient cohort and predominant practitioners interviewed in this part of the study. Patients that were involved in this part of the study were local to the hospital I was working in. This limitation in accessing a wider patient cohort, ultimately restricted the scope of this stage of the study, reducing the reliability of the data collected. Ideally, I would have liked to have had access to a national database of patient suffering with pleural disease to draw from. This was not possible in the time frame allocated for this part of the study and logistically would have not been feasible with my clinical commitments.

The next stage, Delphi process, will include a 2-stage process, involving further practitioners and patients. It will entail a questionnaire survey with a list of outcomes elicited from both scoping review and thematic analysis of semi structured interviews, in order to determine a consensus on core outcomes sets.

Figure 3 Mapping themes and interrelationships: coalescence rather than dissonance



Chapter Four

Results

Introduction

The focus of this study was to seek and establish the principal outcomes that were both valid to clinicians and significant to patients, in pleural interventional trials. In order to achieve this aim, I embarked on methods as elicited by the COMET initiative, in order to identify particular outcomes of relevance to the involved stakeholders; including sub-categories of patients, and clinicians and technicians involved in pleural procedures, of various grades and standings. (Williamson and Clarke 2012)

Background

The heterogeneity of core outcomes amongst clinical specialities has long obstructed the quality of meta-analysis of effectiveness trials (Williamson et al. 2012). This has been depicted in the ORBIT study eliciting significant outcome reporting bias, with 55% of studies failing to exhibit result data in primary outcomes. (Kirkham et al. 2010).

There is a greater onus on researchers to understand this as an issue and drive towards the use of homogenous outcome sets in order for the value of research to be greatly enhanced. The use of core outcome sets in particular clinical fields allows a) reduced heterogeneity between studies b) reduced outcome reporting bias and c) increases the likelihood of the most important outcomes being considered (Braun and Clarke 2006).

The drive towards the generic use of intelligible core outcome sets has largely been founded by the COMET (Core Outcome Measures in Effectiveness Trials) initiative, bringing together researchers

dedicated in 'the development and application of agreed standardised sets of outcomes.' (Williamson and Clarke 2012) They facilitate a database of COSs (Core Outcome Sets) for all clinical fields for researchers to identify and apply to their area of research, in order to achieve the ultimate goal of all effectiveness trials using the standardised core outcome sets. (Gargon et al. 2014) The organisation has also carried out research into methods of developing new COSs; eliciting and detailing reliable methodology in which researchers are able to apply in order to contribute to the efforts of the movement. (Gargon et al. 2014) These include semi-structured interviews and the Delphi process, techniques adopted in this project to achieve the aims and objectives as set out in the research proposal. COSs have been successfully developed in various areas for research medicine including Rheumatology, Surgery and Mental Health. (Tugwell et al. 2008) (MacLennan et al. 2015) (Keeley et al. 2016)

The scoping review of the literature of the clinical area of interest, pleural intervention, revealed a lack of consensus on the outcomes reported on and measured in efficacy trials. In a 2016 Cochrane meta-analysis of pleural interventions for malignant pleural effusions found secondary outcomes, such as side effects, quality of life and patient satisfaction, were inconsistently reported. Patients' expectations and preferences had not been taken into consideration with largely non-holistic outcomes pandered to by researchers and clinicians. (Clive et al. 2016) It is important to evaluate the priorities of patients when researchers explore outcomes to be measured.

Methods

The methodology implemented through this process will be based on the approach opted repeatedly in the literature; a combined method of qualitative research and a modified Delphi survey, preceded by a scoping of the literature. (Keeley et al. 2016) The researcher made every effort to adhere to the minimum standards as set out by Kirkham et al. 2017. This details an 11-point minimum standard within three domains of Scope specification, Stakeholders involved and Consensus process. (Kirkham et al. 2017) Referencing the 11 points on this published standard I was able to meet 10 of these points. The one point of standard the researcher had barriers meeting was engagement with clinical trialists or personnel in the relevant industry.

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Study Design

The identification of a consensus of the most important outcomes was split into two distinct phases. Phase 1 involved the generation of the list of potential outcome measures that were to be considered and which would enter phase 2.

Phase 1: Generation and refinement of a 'long-list' of relevant outcome measures

Phase 1 of the study was split into two stages, as I recruited two different methods in order to elicit a long list.

The first stage involved a *scoping* review of the available literature on pleural interventions. The specific use of this format of a literature review, was intended to allow me to be able to develop a sufficient understanding of the key outcome measures being used by researchers, whilst not allowing the qualities of evidence synthesised by studies to limit their review. This iterative and fluid method of review, described by Arksey and O'Malley 2005, allowed a broader understanding with sufficient depth into the reported outcomes for pleural interventional trials.

A search of the literature via four health science, social and welfare databases was made. Using the PICO framework, a search strategy was formulated, with a total of 765 studies being identified from the last 5 years. Citations were imported into the software programme EndNote, through which data sifting and studies were excluded. First duplicates were removed, and studies excluded due to irrelevant titles. Studies involving complex cardiothoracic surgery, GI surgery and lymphatic resection were excluded. Relevant abstracts were compiled and selected to be read and analysed in full detail, including references.

In total 29 studies were read in full and analysed, for 15 to be excluded and 14 to be selected for their relevance to the research aims and objectives.

Data and information were extracted from each piece of literature to populate an extensive table, including aims, raw data, outcome measures used in each study and a short analysis summary.

My comparative analysis focused on the various outcomes used and the methods in which they were measured and reported. (Levac et al. 2010) Outcome measures were collated into frequency tables to ascertain the most and least popular outcome measures amongst researchers.

As previously stated, there were some integral errors made in the design of the scoping study. These are discussed in the previous relevant chapter. The flaws in the design of the scoping review pertaining to the time constraint of the last five years significantly and negatively affected the inclusion of key literature. This retracts from the scoping review itself, but by definition has a direct impact on the reliability and validity of the Delphi process that draws from the results of this. Regardless of the fact that I followed a reliable structure for the process, the Delphi itself depended on an eclectic long list of potential outcome measures to decipher from. The scoping review as a method of literature research was chosen to accommodate exactly this; a literature review which would provide an inclusive list of outcome measures to equip the Delphi process with the best chance of determining the core outcome set, with reduced probability of important outcomes being missed. By applying a stringent and needless time constraint on the inclusion criteria of the studies incorporated into the scoping review directly impeded this. On reflection, it is difficult to pinpoint why this key error in judgement was made. Contributing factors included a combination of inexperience on my part in relation to the design of a scoping review along with the inexperience and unfamiliarity of my academic supervisor with the timeline and progression of key literature within the field of pleural disease and its management.

The second stage of phase 1 was the incorporation of relevant stakeholders through semi-structured interviews. Qualitative research is an inductive paradigm that helps researchers explore and understand what is important for different stakeholders from their own perspective. (Keeley et al. 2016) Semi-structured interviews are one of the more common methods in qualitative research and were used in this study. (Keeley et al. 2016) As aforementioned semi-structured interviews remain a validated method as per COMET, in order to facilitate the new production of COSs. (Williamson and Clarke 2016)

Health care professionals working in the secondary healthcare sector across the health board, who are directly involved in the delivery and aftercare of pleural interventions, were purposively samples. (Miles & Huberman 1994) This included established respiratory consultants, intensive care consultants, respiratory care nurses, junior doctors and palliative care teams. This cohort of

interviewees were invited to participate through a gatekeeper, providing each person with a Participant Information Sheet (PIS) and Consent form (APPENDIX 1). Each practitioner was asked a similar scheme of questions with room for discussion. Ultimately, they were all probed on their perspective on the most important outcome measures for pleural interventional trials.

The patient perspective was extremely important to this study. A purposive cohort of subcategorised patients were carefully selected; Non-cancer and Cancer, Pre and Post procedure, with also a conscious effort to include patients having received or receiving an intervention for pneumothorax. Patients were approached via a gatekeeper, whilst in hospital or contacted once discharged. A time, method and place were organised once patients had chance to review a PIS and signed a consent form. Patients pre-procedure had to carefully be selected to ensure their symptoms were mild enough to be able to engage in a short conversation, and to be able to have the capacity to consent to do so. All patients had a similar line of questioning, primarily being asked about what they felt was the most important aspect, to them, in regard to the procedure. 'Postprocedure' patients were asked if what they felt was most significant to them, had changed, from before and after the procedure.

The semi-structured interviews provided a depth to the empirical work, which in theory, should have positively added to the process of defining a core outcome set. I most definitely benefited from completing the semi-structured interviews in terms of my own learning and development. My training through one on one tutorials and seminars centred around, planning the general approach, the principles of purposive sampling, defining the deductive technique, the viable risk of interviewer bias and methods to counteract this, such as the development of an interview protocol. As fruitful as my training was, in terms of the principles of this type of qualitative research, I felt I was able to gain more from reflecting on interviews and on how they went after they were concluded. Although ultimately beneficial for my own development as a researcher, the fact that I was continuing to learn through the process was a sign of my own limitations in carrying out the interviews. On reflecting on some of the procedural flaws I was cognisant of the negative effect my lack of experience had on the process as a whole.

Unfortunately, my own limitations and the paucity of my training due to the time constraints were not the only recognised weaknesses of the semi-structured interviews. Completing the interviews, myself, as the principal researcher, introduced a higher risk of interviewer bias. Being integrated into the respiratory department whilst arranging interviews with patients was beneficial logistically. However, actively caring for patients being considered for the empirical work, exponentially

increased the risk of introducing interviewer bias and procedural bias. The recruitment of a gatekeeper to approach patients was helpful in counteracting this conflict of interest, but unfortunately due to other commitments, this was not consistently implemented.

The breadth of the participants not surpassing practitioners and patients was another limitation based on the 11-step standard as outlined by Kirkham et al. 2017. It can be argued, assuming a cohort of interview participants involving only patients and practitioners would encompass all relevant stakeholders, was short sighted and negligent. In hindsight, making an effort to approach members of industry would have provided the data attained from the interviews with an added dynamic; addressing the purpose of developing a core outcome set in this particular clinical field more holistically. In essence a core outcome set, as previously described, benefits clinical practice of the future by focusing the efforts of researchers carrying out interventional trials. By failing to even attempt the incorporation of this subset of stakeholder is a significant limitation to the quality of data the main empirical work is based on and I understand the defective tone it sets for the project as a whole. On a more positive note, I feel as if I have learnt from this, and appreciate the action I could have taken to ensure this oversight could have been avoided. As is a recurring theme, in hindsight, I should have made more use of my clinical supervisor in enabling myself access to potential contacts in industry. With Indwelling pleural catheters being a rising trend as a novel pleural intervention, this could have been an ideal place to investigate opportunities to incorporate a wider breadth of relevant stakeholders to this stage of the project. In future, when designing research projects, I will ensure to prioritise the incorporation of as many relevant subsets of stakeholders as possible. If this approach is adapted, it inevitably positively supplements the data harvested out of the research process and depicts an inclusive and thorough quality to the project as a whole.

I did employ a more inclusive approach with the variation of type of patients and practitioners interviewed. However due to the constraints of resources available to me I wasn't able to arrange interviews with patients and practitioners outside the catchment area of my NHS trust. In hindsight more effort could have been made to arrange telephone interviews with patients from a wider geographical area. In terms of practitioners, this notion was attempted but unfortunately, I wasn't able to secure engagement from practitioners from outside my health board for interviews. This effort however was not in complete vain, as inviting practitioners from outside my health-board for interviews for the project raised awareness for potential engagement with the Delphi process, the ultimate stage of empirical work of the project.

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The semi structured interviews were supposed to provide another dynamic insight into what the most important outcomes were to key relevant stakeholders, in conjunction with the preceding literature review. On review of the limitations of the semi-structured interviews, there are a number of aspects to consider in terms of their consequences for the reliability of the results attained from the Delphi process they contributed to.

It can be argued, the variable quality of the interviews due to my lack of experience and training, brings the qualitative data attained into disrepute. Firstly, there is uncertainty as to whether I was able to extract the true feelings and opinions of the participants with my interview technique. The inductive style of interview relies on analysis of a free and open narrative provided by participants. (Ranney et al. 2015) Without this, the thematic analysis of the transcripts becomes defective, and the themes elicited would not be reliable as a representation of the thoughts of the participants on the most important outcome measures. This would directly affect the quality of the Delphi process, hindering it instead of supplementing it with a true dynamic insight.

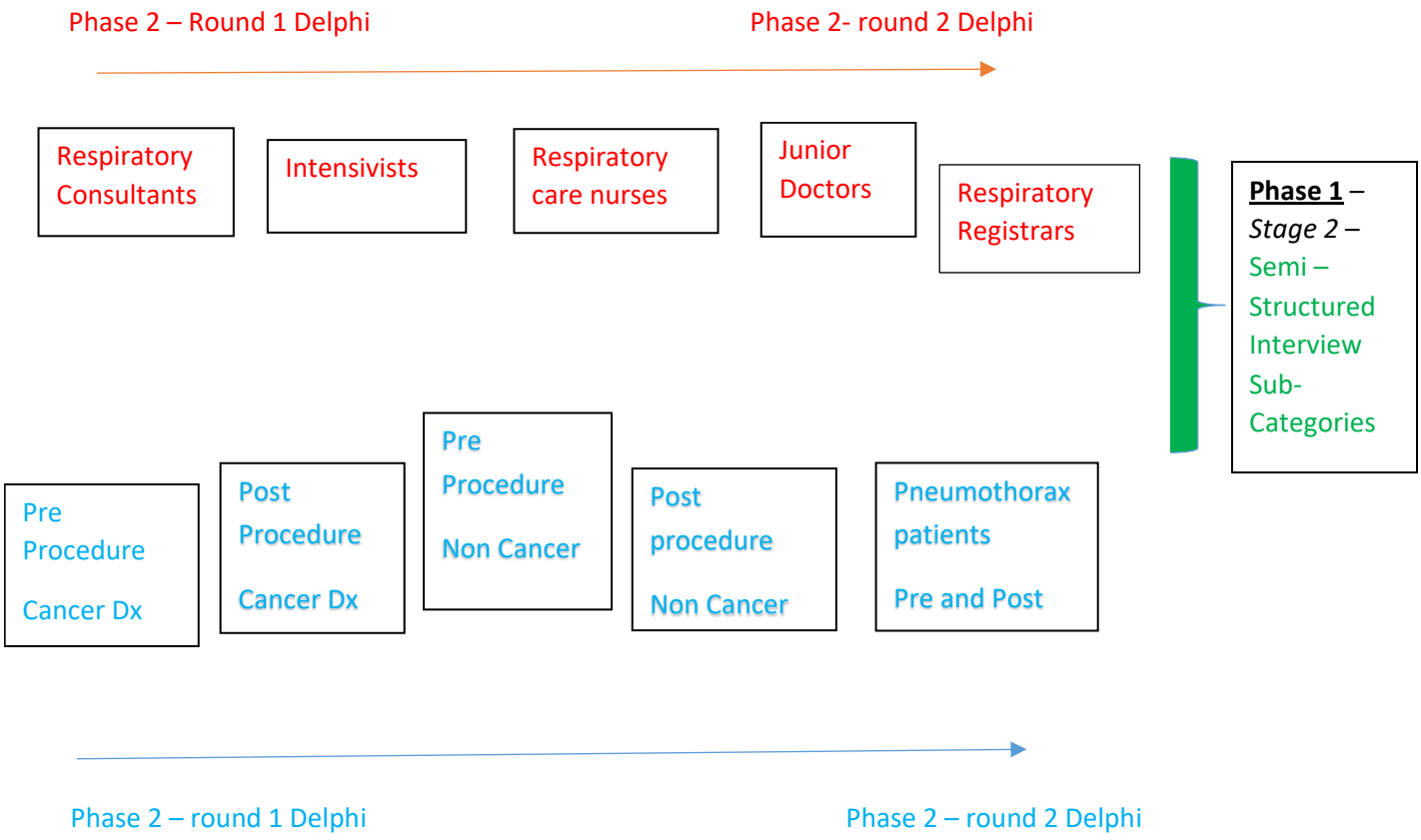
Similarly, the lack of outreach when consulting relevant stakeholders, particularly the negligence of industry and failing to engage with patients from a wider geographical area, retracts from the added insight the interviews aimed to provide for the Delphi process itself.

Moreover, the increased risk of interviewer and procedural bias in the logistical arrangement of interviews, specifically with the conflict of interest in interviews scheduled with patients and inconsistencies of the role of the gatekeeper, negatively affects the reliability of the data attained from the interviews. This in turn, unfortunately, retracts from the inferences and conclusions made from the Delphi process itself, as the stepwise progression to the Delphi from the themes elicited from the transcripts cannot be ignored. The product of the semi-structured interviews was intended to allow the Delphi process to be as comprehensive as possible. Unfortunately, if these building blocks for the Delphi process are flawed, it by definition limits the ultimate process that defined the core outcome set. When I refer to the building blocks for the Delphi process, I am also referring to the scoping review.

It is with a sense of candour that I must acknowledge the confounding effect that the limitations of both the scoping review and semi-structured interview stage of the project, undeniably had on the reliability of the results of the Delphi process. Although the structure and outline of the project was robust, I feel, key errors and discrepancies within the integral design of the study along its course,

cumulatively knocked the potential of the reliability and confidence in the core outcome set determined by the ultimate stage of the study.

Figure 4 – Delphi Procedure



All interviews were recorded on an encrypted Dictaphone and transcribed verbatim into transcripts. Transcripts were thematically analysed according to principles set out by (Braun and Clarke 2005) by my academic supervisor and I. Themes and sub-themes were identified, and outcome measures extracted to enter the next stage of the consensus building process.

Once a 'long-list' had been developed, from both stages of phase 1, this was once again reviewed and refined. Duplicates and outcome measures that were deemed to be too similar were deleted or

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condensed into single potential outcome measures. Other inviable outcome measures were also removed. This was done with the help of four independent reviewers, with experience in the clinical field. Outcomes were combined only if this was deemed to be unanimous amongst the independent reviewers. Similarly, outcomes were only omitted from the 'long-list' if they received a unanimous vote to be removed. This was done with a face to face discussion amongst four senior practitioners available to participate in the research. It is important to note the purpose of the discussion with the four independent reviewers was not to decide on outcome measures but to further refine the process. The progress made in this discussion was also made available to my academic supervisor, with decisions only being made on a unanimous basis. This step ensured the streamlined nature of the process, reducing the risk of potential researcher bias if I completed this myself unsupervised.

The stage of the project, involving four independent reviewers, was carried out based on its frequency of incorporation in the literature as a keystone step in previous development of core outcome set trials. Watson et al. 2020 in the development of a core outcome set for oral health services for dependent older adults is an example of this, using a face to face discussion with independent reviewers to condense and prioritise a long list of outcome measures to enter a final Delphi process. Rose et el. 2017, used a similar consensus meeting prior to the Delphi process using a nominal group technique to facilitate group brainstorming to achieve the final list before the Delphi process. (Rose et al. 2017) Unfortunately, I was unable to organise a meeting where all four of the independent reviewers were available for a group meeting. This was time consuming and I felt I did not gain as much from their input as I would have done in a face to face meeting with all four volunteers, as opposed to approaching them independently as I did. Criterion for the independent reviewers were senior medical practitioners, either respiratory consultants and intensivists, with significant experience in the delivery of pleural interventions, that would not partake in either the semi-structured interviews or Delphi process. This was key to reduce the risk of researcher bias, where a reviewer would be heavily involved in two influential aspects of the study, with the power to potentially skew the entire process.

The aims of the meetings with the reviewers was to allow for the outcome measures gleaned from the scoping review and semi-structured interviews to be reviewed for their eligibility to enter the Delphi process. Some of the objectives were mundane such as the removal of obvious duplicates, and the reviewers and academic supervisors were involved with this to ensure this was done at no risk of researcher bias. More input was required on the discussion of outcome measures which could potentially be coalesced into one outcome measure or on deciding whether outcomes were succinct and defined enough to exist as their own entity. An example of this was the discussion

surrounding whether 'pain' and 'shortness of breath' were distinct enough to be set aside from 'symptom resolution'. Similarly, another question posed was whether 'sleep deprivation' could be covered within symptom resolution. In hindsight, I should have taken this opportunity with senior clinicians, to discuss the design of my study including the scoping review and my semi-structured interviews, for feedback on my work so far. Unfortunately, I had a limited assorted time for each meeting, and was quite unaware of the potential flaws of my study design at the time. It was naïve of me to not take more advantage of this opportunity to double check the method of how I had collated a long list of outcomes for them to review.

Phase 2: Delphi Consensus Process

Drawing evidence from the two stages of phase one, a 'long list' was entered into the Delphi process. A questionnaire was designed on survey monkey, containing the 'long list' of outcome measures – 9 in total. A single questionnaire was designed for both practitioners and patients to complete (Figure 5). Information and instructions were provided with both medical jargon and layperson language, for both groups of recipients to understand and follow as they saw fit. Practitioners and patients were invited to fill out the questionnaire at their own convenience with an associated PIS, for this stage of the study.

Practitioners were sent an email invitation via a gatekeeper, with attached PIS (Appendix 1) and weblink to the designed survey. In order to strive for a generic consensus, respiratory consultants, advanced nurse practitioners and trainees were invited from across Wales. Access to these practitioners was granted through the network of chest specialists, already in use for the distribution of news and information across Wales, organised by Professor of Chest medicine Kier Lewis of Swansea University.

I managed to secure funding to attend the British Thoracic Society (BTS) Winter Meeting, discussing the project with prominent figures in the pleural community, requesting their consent to be involved in the Delphi process. This took place at the QEII Centre in London on the 5th December 2018.

Practitioners were also invited in person, through a gatekeeper. I also reached out to centres of respiratory excellence of Bristol and Oxford for interest in participation, including some of the pleural leads for the UK. This was to follow on from conversations I had with presenters from the

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BTS winter conference who had provided me with contact email addresses to further discuss my project. I ensured they were aware of the timeline of my project and kindly requested for their participation in the Delphi process. Unfortunately, I wasn't able to secure their involvement and was signposted to some of their proposals for further work to be done in the realms of patient related outcome measures for pleural disease. Nevertheless, from the conversations, I was able to glean that the development of a core outcome set was an important aspect of research that needed more attention, with a particular focus on patient involvement. Although I was unable to secure their involvement into the study, I felt that my efforts in trying to address this particular issue within research was validated by their interest and words of encouragement.

Patients were invited in person, through a gatekeeper, to participate at multiple opportunities in hospital such as pleural clinic and on the respiratory ward. Patients were also invited to participate through email if this was deemed appropriate, with associated web link to questionnaire.

The Delphi procedure involved two interrelated stages; with results from stage 1 informing and refining the Delphi process for stage 2, if consensus had not been reached in the first stage.

At present there isn't a consensus on the optimal number of participants required to form a Delphi panel for Core Outcome Set development. (Sinha et al. 2012) Based on review of previous successful studies submitted to COMET and discussions with my supervisors, we hypothesised that a minimum of 15 practitioners and 15 patients for each stage would form a sample size sufficiently able to achieve consensus. Two different cohorts of both patients and practitioners were recruited for the two phases. The aim was for the numbers in each category to remain congruent. The final total of participants was 78. This minimum number of participants in the Delphi process was a very crude estimate. In hindsight, further statistical work up to calculate the number of participants required to sensitively detect differences in the 9-point Likert scale would have been more appropriate. This is something I could have been able to organise through the involvement of a statistician from Bangor university and regret not actioning. (Rose et al. 2017)

All participants were asked to grade outcomes ascertained from initial interviews and scoping review. Grades were scored out of 10 respectively, 1-3 = of limited importance,

4-6 = important outcome and 7-9 = critical outcome. This scale that was used is recommended by the GRADE working group 2013, and I followed the advice provided by the group in how to interpret the scoring. (Schunemann et al. 2013) Inclusion criteria for outcomes to be considered for COS status were defined as 70% or more of respondents scoring the outcome measure between 7-9 and fewer than 30% scoring it as 1-3. Reciprocally, consensus for exclusion of an outcome was defined

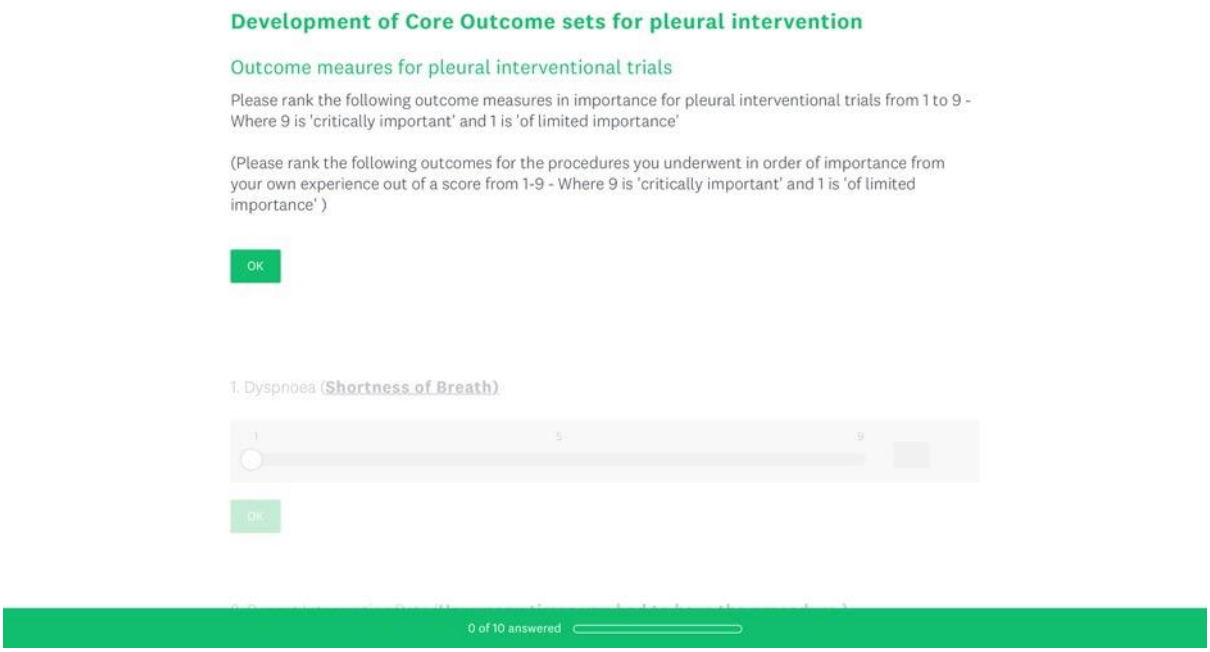
as 70% of participants scoring it as a 1-3 or fewer than 30% scoring it 7-9. All other combination of scores were considered to indicate no consensus. (Shcunemann et al. 2013)

Outcomes that gained sufficient points in round one carried into round two, and a personalised summary was sent to each participant at the end of each round. Participants were able to select 'unable to score' and were provided with a free text box at the end of the questionnaire to include outcomes that they felt should be included that may have been missed. This box was also provided to allow participants to discuss if they felt outcome measures hadn't been worded correctly.

The questionnaire results from the first round underwent a basic analysis, with the construction of a results table, including averages and percentage scores at either 'Critically Important' or 'Not Important', along with the suggestions made by participants. I felt as if a second round with new participants would be beneficial in ascertaining a consensus, as planned.

For each round, reminder emails were sent where appropriate to encourage participants to engage and a deadline of 4 weeks was implemented.

Figure 5 – Sample Questionnaire provided



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Above is a screen shot from the questionnaire provided. Due to formatting issues I was not able to provide a full copy as requested. However, I reactivated the survey link and have inserted the URL below for review in full.

https://www.surveymonkey.com/r/TZLQWP9

Questionnaires were completed in person by the use of a secured tablet device or online via email link. The questionnaire itself involved a self-selectable draggable pointer on a bar scale, ranging from 1-9 for each outcome measure included.

Data Analysis

Data was analysed from each round separately and cumulatively. Within each Delphi stage, every outcome's group mean, median and interquartile range was calculated. In the first round, using the inclusion/exclusion criteria, outcomes deemed to be insignificant were aptly removed from the second round. The second stage Delphi was subject to the identical inclusion/exclusion criterium as the first round.

Suggested outcome measures by participants in round one, were evaluated for inclusion in to the second round, pertaining to their relevancy to the aims of the study. Each suggestion was reviewed; comparing the suggestion to the evidence gleaned from literature review and thematic analysis for potential relevance.

Results Delphi Round 1

Table 6 All participants (n=47)

Outcome	Mean Delphi Score	Median Delphi Score (IQR)	Respondents scoring 7-9 'Critically Important' %	Respondents scoring 1-3 'Not Important' %
Dyspnoea	8	8.5 [7-9]	88%	0 %
Repeat Intervention Rate	5.3	5.5 [4-7]	41%	18%

Hospitalisation days	5.4	5 [4-8]	38%	23%
Pain and Discomfort	7.2	8 [6-9]	70%	3%
QOL	8.3	9 [8-9]	94%	3%
Patient Info Provided	4.6	4.5 [2-7]	26%	33%
Time Taken	3.6	3.5 [1-5]	20%	53%
Symptom Resolution	8	8 [8-9]	91%	0%
Diagnostic Value	6	7 [4-8]	52%	21%

Table 7 Practitioners (n=27)

Outcome	Mean Delphi Score	Median Delphi Score [IQR]	Respondents scoring 7-9 'critically important' %	Respondents scoring 1-3 'not important' %
Dyspnoea	7.6	7.5 [7-9]	77 %	0%
Repeat Intervention Rate	6.1	7 [5-7]	50%	11%
Hospitalisation Days	6.2	6.5 [5-8]	44%	11%

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Pain and Discomfort	7	7.5 [5-9]	61%	0%
QOL	8.4	9 [8-9]	100%	0%
Patient Info Provided	6	6 [5-7]	33%	6%
Time Taken	5	4.5 [3-7]	30%	28%
Symptom Resolution	8	8 [8-9]	94%	0%
Diagnostic Value	7.2	7.5 [7-9]	83%	11%

Table 8 Patients (n=20)

Outcome	Mean Delphi Score	Median Delphi Score [IQR]	Respondents scoring 7-9 'critically important' %	Respondents scoring 1-3 'not important' %
Dyspnoea	8.4	9 [8-9]	100%	0%
Repeat Intervention Rate	4.6	4 [4-5.5]	25%	31%
Hospitalisation Days	4.6	4 [2-7]	31%	38%
Pain and Discomfort	7.5	9 [7-9]	81%	6.3%

QOL	8.2	9 [8.5-9]	88%	6.3%
Patient Info Provided	3.1	1.5 [1-4]	18.8%	63%
Time Taken	2.1	1 [1-3]	6.3%	75%
Symptom Resolution	8	8.5 [7-9]	88%	0%
Diagnostic Value	4.5	4 [2.5-6]	25%	31%

The results from stage 1 of the Delphi are show in Table 6,7 and 8 respectively above. Results are sectioned into a cumulative table of 'ALL', 'Practitioners' and 'Patients'. A total of 47 participants completed the first round of the Delphi questionnaire with, 27 practitioners and 20 patients. From the cumulative table, 4 outcome measures qualified according to the criteria, as consensus validated core outcomes. These included 'Dyspnoea', 'Pain and Discomfort', 'Quality of Life', and 'Symptom Resolution'. In the same fashion, outcomes 'Patient Information Provided' and 'Time taken' were suitably excluded as potential core outcome sets. Other outcomes remained in the balance under the status of 'consensus not achieved'. This however qualified them into the second round of the Delphi.

Interestingly, a discrepancy between the consensus status of outcomes was identified between practitioners and patients. Analysis of data collected from practitioners using the same inclusion criteria, identified a different set of outcomes to be considered as core to the issue of pleural interventional trials. The four outcomes within the subset of practitioners included 'Dyspnoea', 'Quality of Life', 'Symptom Resolution', and finally 'Diagnostic Value'. Unlike in the cumulative data, 'Pain and Discomfort' fell 9% short of the qualifying criteria amongst practitioners, being replaced by 'Diagnostic Value'. Consensus for core outcomes deduced from patient data mirrored the overall

analysis, with ‘Dyspnoea’, ‘Pain and Discomfort’, ‘Quality of Life’, and ‘Symptom Resolution’ elicited as the most important outcomes to pleural interventions.

In regard to the free text box, 3 suggestions were repeatedly made by participants as potential outcomes that were being missed. These included, ‘Complication Rate’, ‘Cost to Health economy’, and ‘Rate of adverse incidents’.

Upon initial review, it was tempting to group ‘complication rates’ and ‘rate of adverse incidents’ into one issue to be reconsidered. However, it could be argued they are slightly different, as simple complications such as failure of pleurodesis would not count as an ‘adverse incident’.

Complication rates of pleural interventions were naturally an issue raised through semi-structured interviews with patients, prior to having the procedure. However, greater emphasis was on the level of information provided by the practitioner rather than the complications themselves.

Complication rates were however a more prominent feature through the scoping literature review. Complication rates were rarely used as primary outcomes but often occupied the list of secondary outcomes used by efficacy trials. A point that was identified was that ‘Complication rates’ were often trumped by the outcome ‘Repeat Intervention Rate’. This may be due to the encompassing nature of ‘Repeat intervention rate’ of both simple complications and failure of initial drain to achieve pleurodesis. With ‘Repeat intervention rate’ already being present on the questionnaire, reaching a status of no consensus and to be carried forward into the second round of Delphi, it felt more appropriate to ensure ‘Rate of Adverse Incidents’ was aptly included.

On the issue of ‘Cost to health economy’, I made the error of not incorporating this into the second round of Delphi. The issues of cost and financial aspects of the procedure wasn’t something brought up by a single practitioner in semi structured interviews carried out, in relation to pleural interventions. The issue of cost-benefit of pleural intervention was a feature of the scoping review, as any intervention is assessed for its cost-utility before being implemented into practice.

One of the direct measurements of cost utility of an intervention is by the calculation of quality of life or quality adjusted survival. With ‘Quality of Life’ being an outcome reaching the threshold to be carried over to the second round, ‘Cost to Health Economy’ I felt was being addressed indirectly.

Quality adjusted survival is an outcome which is favoured and recommended for cost effectiveness analysis as it allows for an easier comparison against other studies, and therefore informing choices for distribution of funds across healthcare and grounds for certain interventions to be implemented. (Anell and Norinder 2000) The effectiveness of quality adjusted survival as an outcome measure for cost effectiveness analysis can only be taken advantage of if it is a ubiquitous outcome measure taken up by researchers when performing clinical trials. The ongoing issue of heterogeneity of outcome measures used in efficacy research not only plagues the applicability of evidence synthesised from meta-analysis, but also directly impacts the progression and implementation of healthcare based on cost effectiveness analysis. To combat this, more general methods of carrying out cost effectiveness analysis have been utilised, such as cost utility analysis and the less preferred method of cost-benefit analysis. (Anell and Norinder 2000)

Cost effectiveness analysis allows the comparison of the effect on health outcomes of various interventions along with the overall cost, indicating which intervention is the most fiscally responsible to implement. This simple definition of cost effectiveness analysis can be misleading as its application can be relatively complex. For example, if a treatment option increases the life years, but these are deemed to be poor quality of life years gained, there is the added caveat of the cost of rehabilitation and ongoing care that needs to be accounted for. (Garber and Phelps 1999) Conversely, often, many treatments lead to benefits beyond survival in years and overall health status; for example, healthier workers are able to contribute more to society or preventing the early demise of a parent can mean they are able to provide better upbringing for their children. These are intricacies within cost effectiveness analysis that cannot be underestimated. It can be argued that it is due responsibility of researchers to remain cognisant of the significance of cost effectiveness analysis, to the implementation of novel interventions and treatments when designing efficacy trials, as we move towards an increasingly fiscally conscious healthcare system. (Jamison et al. 2006)

Other common outcome measures that have been favoured in cost effective analysis, which I should have considered, were number of pain or symptom free days and number of successful diagnosis. Although outcome measures such as symptom resolution and quality of life were included in the Delphi section of the study, in hindsight, I should have made more of an effort to include units of measures which could more easily be incorporated into a cost effectiveness analysis framework. Nevertheless, on reflection, I have importantly understood the significance of this, and the role cost effectiveness analysis plays in the bridge between, success of novel interventions within a research setting, to physical and routine implementation into a healthcare system.

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Results Delphi Round 2

Table 9 All participants (n=31)

Outcome	Mean Delphi Score	Median Delphi Score [IQR]	Respondents scoring 7-9 'Critically Important' %	Respondents scoring 1-3 'Not Important '%
Dyspnoea	7.6	8 [7-9]	84%	15%
Repeat Intervention Rate	5.2	5 [4-6]	15%	15%
Hospitalisation Days	5.8	6 [4-7]	36.4%	6.1%
Pain and Discomfort	7	7 [6-8]	75%	3%
QOL	8.3	8 [8-9]	97%	0%
Symptom Resolution	7.8	8 [7-9]	88%	0%
Diagnostic Value	5.7	6 [4-7]	45%	15%

Rate of Adverse Incidents	5.1	5 [3-7]	39%	31%

Table 10 Practitioners (n=16)

Outcome	Mean Delphi Score	Median Delphi Score [IQR]	Respondents scoring 7-9 'critically important' %	Respondents scoring 1-3 'not important' %
Dyspnoea	7.2	7 [6.5-8]	76%	0%
Repeat Intervention Rate	5.8	6 [5-6.75]	23.5%	0%
Hospitalisation Days	5	5 [4-6]	17.7%	11.8%
Pain and Discomfort	6.4	7 [5.5-7]	65%	5.9%
QOL	8.3	8 [8-9]	100%	0%

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Symptom Resolution	7.4	7 [6.5-8]	76%	0%
Diagnostic Value	7.3	7.5 [7-8]	88%	0
Rate of Adverse Incidents	3.8	3 [2-4]	0%	65%

Table 11 – Patients (n=15)

Outcome	Mean Delphi Score	Median Delphi Score [IQR]	Respondents scoring 7-9 'critically important' %	Respondents scoring 1-3 'not important' %
Dyspnoea	8	8 [7.25-9]	100%	0%
Repeat Intervention Rate	4.6	4 .5 [3-5.75]	6.3%	31.3%
Hospitalisation Days	6.7	7 [6-8]	56.3%	0%
Pain and Discomfort	7.4	7.5 [7-8]	88%	0 %
QOL	8.3	8.5 [8-9]	94%	0%
Symptom Resolution	8.3	8 [8-9]	100%	0%
Diagnostic Value	4	4 [3-5]	0%	31%

Rate of Adverse Incidents	6.4	6 [4-7]	57%	0%

The results from round 2 of the Delphi process are depicted in Table 9, 10 and 11 respectively. A total of 31 participants, with 15 patients and 16 practitioners, successfully engaging in the second stage of this process.

The outcome measures from round 2 of the Delphi that emerge as the core outcome set; Dyspnoea', 'Pain and Discomfort', 'Quality of Life', and 'Symptom Resolution'. These particular outcomes qualify as the defined core outcome set as per the pre-set criteria. As detailed previously this criterion was devised based on the scoring system described by the GRADE working group and previous pioneering work completed by Schunemann et al. 2013 in the development of core outcome sets for various specialties. This qualifying criterion was to be a significant method used in the literature in the generic deduction of core outcome sets of multiple clinical fields. (Gargon et al. 2017)

In attaining the results of the Delphi process, this concludes the empirical work of the thesis. The aims of the project have been addressed through an all-inclusive process; iterative and explorational at stages with an element of rigid structure in other more advanced parts of the study. This is depicted in the decision to carry out a second round of the Delphi process; with the decision being of an iterative nature whilst the Delphi process itself remaining consistent to ensure reliability.

Following on from this, a discussion, including a review of the results, potential or lack thereof, to enhance clinical research in this particular field of medicine, limitations of the study and advice on further research was planned. I also aimed to disseminate the findings from the empirical work through the appropriate channels, with particular focus on consolidating the Core Outcome Set Database (COMET). This would, in theory, address the problematic issue of the heterogeneity of outcome measures that plagues researchers and the meta-analysis of various studies. Attempting to address this issue within the field of pleural interventions has been the overarching aim. The preliminary phases of the study highlighted the presence of this problem. Although I appreciate there have been key systematic errors through the steps in this study, attempting to resolve this

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obstacle to evidence synthesis from research with a multi-faceted and structured approach, I have gained a deeper understanding of the issue heterogeneity of outcome measures poses and why this has become a focus for researchers across a wide range of medical specialties.

Chapter Five

Discussion

5.1 Introduction

Pleural interventions, like other fields of medicine have undergone advancements, and as a result have become more accessible. (McElnay and Lim 2016) With developments and the ubiquitous use of pleural ultrasound, pleural interventions are carried out at a higher rate by a wider variety of clinicians. (McElnay and Lim 2016)

Naturally, with this there is scope for the development of new techniques and interventions and their incorporation into standard practice. An effective example of this that has been discussed is the increasing use of the indwelling pleural catheter (IPC), for patients with recurrent pleural collections. (Chalhoub et al. 2018)

For newer interventions to be incorporated into standard medical practice, evidence gleaned from a plethora of appropriate studies must be meta-analysed in a systematic fashion (Hillebrand and Cardinale 2010). A significant barrier for this to be carried out effectively is the ongoing heterogeneity in reported outcomes within the same medical fields/specialties, driven by a variety of reasons. (Kirkham et al. 2010) An agreed method to overcome this has been to develop a consensus of core outcome measures for all interventional efficacy trials in all clinical disciplines. (Kirkham et al. 2018) The field of pleural interventions is also susceptible to this phenomenon.

I planned to address this issue in the field of pleural interventions. This was done using the guidance provided by initiatives and organisations conceived in the plight of resolving this problem. (Gargon et al. 2014) Moreover, there seemed to be a new school of thought when it came to outcome measures pertaining to pleural interventions, with the literature moving towards a more patient centred model. This was opposed to more traditional outcome measures such as repeat intervention rate and hospitalisation days. (Psallidas et al. 2017) The increasing variety in potential outcome measures was also something that had to be addressed.

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5.2 Discussion

I intended to develop the project 'Core Outcome Sets' (COS) for pleural interventions, with the structure of the thesis outlined in detail in chapter one. Chapter two was an iterative scoping review for me to be able to gage the literature in terms of the significance of selected outcome measures and their relevance to the identifiable stakeholders. Chapter 3 formed the basis of the empirical work, separated into two distinct stages. Initially, thematical analysis using the framework elicited by (Braun and Clark 2006) of semi structured interviews with a variety of stakeholders including patients pre and post pleural intervention. The crux of the semi-structured interviews would be for the participants to convey what they felt was the most important aspect in relation to pleural procedures. Through the thematic analysis of the transcripts, the aim was to identify a long list of potential outcome measures for the next stage, a 2 step Delphi process.

A list of potential outcome measures gleaned from the scoping review and subsequent semi structured interviews were then entered into a Delphi process with clinicians and patients alike. This was an iterative process through the two stages and was accommodated via an interactive survey that could be completed in person, via an electronic tablet, or via email link. The Delphi process involved the scoring of each potential core outcome as per the grading system established by the GRADE working group (Guyatt et al.2011) This scoring system is significant to the literature of the development of COSs in other specialities and allowed the interpretation of the scores compiled in the results to ascertain the outcomes qualifying as core. (Schunemann et al. 2013).

The core outcomes being identified through two stages of the Delphi process, following the outline of the thesis were, Dyspnoea', 'Pain and Discomfort', 'Quality of Life', and 'Symptom Resolution'.

The results of the Delphi process were assorted into practitioners, patients and cumulative tables, allowing the significance of each outcome to both sets of stakeholders to be compared and contrasted. This also allowed the identification of outcomes which had failed to score with either practitioners or patients. Overall exclusion analysis was enacted on the cumulative results table to elicit the core outcome sets.

Interestingly the four outcomes that qualified as core, were unanimous to both practitioners and patients, however the scores were not identical. The median scores given by patients for the core outcome sets were generally higher than the practitioners. In the first round this could be attributed to the higher number of patients undertaking the Delphi process, but this remains a constant

through the second round where the total participants of patients are higher. This suggests that the four outcome sets are patient friendly outcome measures, which directly addresses one of the initial aims of the study.

As exemplified by (Tugwell et al. 2007), the incorporation of patient input at every step of the process was high on the agenda; ensuring patients perspectives were healthily depicted. I was encouraged by the fact that the end product potentially reflected this.

Providing patients with information before any procedure has naturally become part of contemporary medicine, with the aims for the patient to arrive to an informed decision in regard to their health. (Kadam 2017) (Hall et al. 2012) Through the thematic analysis of semi-structured interviews with patients and practitioners, a highlighted theme had been the responsibility of practitioners to be observant in providing patients with accurate information in regard to the procedure. This was both identified in interviews pre and post procedure indicating its importance as an underlying theme.

Although considered to be a pillar-stone of procedural medical practice, unfortunately informed consent often falls short of the idealistic scenario, due to a number of variables. This can be due to the nature of patient comprehension and the inability to take on information in the short term to arrive at an informed decision, amongst other factors such as busy clinical work schedules. (Hall et al. 2012) Ensuring patients are involved in the decision making is the way this can be improved (Leeper-Majors et al. 2003), which is reflected in part of the empirical work up of this thesis, with patients expressing a desire to be consulted through the whole process.

In the first stage of the Delphi, less than 30% of participants scored 'Patient information provided' as critically important, a score from 7-9, breaking the threshold for the exclusion criteria set out in the method. It was not entered into the second stage of the Delphi and was therefore out of the standing to emerge as a core outcome for pleural intervention.

Interestingly, 'Patient information provided' scored higher with the practitioners with a median score of 6 against the median score of 4.5 for patients. The fact that practitioners scored it just under the range of critically important reflects its relative importance to clinicians as a staple to overall medical practice. The fact that patients scored it much lower can indicate how the informed consent process can often be carried out poorly due to the aforementioned variables. (Hall et al. 2012)

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Another core outcome measure to be excluded early from the Delphi process was ‘Time Taken’ in reference to the procedure itself. Interestingly, it was the absence of participants of the Delphi scoring ‘Time Taken’ as critically important rather than being graded as ‘Not important’ as per the exclusion criteria. It is understandable for patients undergoing a painful procedure the natural reaction is for patients to request for it to be as swift as possible. This a theme that was elicited from the semi structured interviews completed but could very well be attributed to natural anxieties that all patients experience that, in good practice, should be placated by practitioners. The selection of this as a potential core outcome was justified based on the thematic analysis of the transcripts of semi structured interviews. Moreover, when looking at the literature in outcomes for thoracoscopic procedures, time of procedure and duration of drainage were independent risk factors for chronic post procedural pain. (Tong et al. 2020)

In hindsight, one of the aspects of pleural procedures that must be taken into account when discussing overall ‘time taken’ as a potential outcome, is the safety of the procedure. As a general rule in order to prevent further complications, it is advisable for pleural drains to be completed in a slow manner, specifically avoiding taking too much fluid too quickly all at once. (Held-Warmkessel et al. 2008) This directly contradicts ‘Time taken’ as a potential core outcome, as the safety of the procedure naturally takes precedent.

Reassuringly, on analysis of the Delphi, the four outcomes qualifying as core outcomes to make up the core outcome set, were a strong combination of the outcomes extracted from both practitioner and patient’s legs of the process. On further analysis of the Delphi process, a highlighted contrast identified was based on the scores of ‘Diagnostic Value’ and ‘Repeat Intervention Rate’. On the whole, these outcome measures in question received globally reduced scores in the ‘Patients’ leg of the process and a noticeably higher collection of scores with participants in the ‘Practitioners’ subset.

‘Diagnostic Value’ as an outcome measure, interestingly, if it was to be assessed purely without patient input, would qualify as a core outcome measure as per practitioners. The median scores of this outcome measure were recorded as 7.3, 7.5 by practitioners against median scores of 4 by patients. Moreover, the percentage of the practitioner cohort scoring ‘Diagnostic Value’ as critically important were as high as 88%, as opposed to as low as 0% with patients.

The process of reaching a diagnosis can be interpreted in many ways and has numerous important implications. It can be viewed as an investigative process with multiple puzzle pieces, a method of

classifying an assortment of signs and symptoms, or an integral label assigned to a disease process to aid understanding and management of disease. (Balogh et al. 2015) Jutel in 2009 described it as a "pre-existing set of categories agreed upon by the medical profession to designate a specific condition". (Jutel 2009)

As depicted by the empirical work from this study, the diagnostic value to a procedure is of high importance to practitioners. The significance of this can be interpreted simply as practitioners underlying desire to complete their job. A more complex analysis lies in what an accurate diagnosis can represent; a true understanding of a patient's health condition by the clinicians in charge of their care, and therein a higher probability of the best possible health outcome. (Holmboe and Durning 2014) It is possible to hypothesise that practitioners have a better understanding of this notion and therefore this is reflected in the scoring of diagnostic value as a core outcome set as compared with the patient cohort of participants in the Delphi process. Pleural effusions are quite a common clinical finding; however, the underlying cause and potential diagnosis behind them can often be taxing to identify. (Huo et al. 2019) This added complexity of making a diagnosis in the case of an incongruently common clinical finding, can be argued, is another reason the practitioners scored the outcome measure of 'Diagnostic value' so highly.

The fact that the patient cohort scored the same outcome measure comparatively poorly, is a sign of a much wider and well documented issue of common health literacy amongst patients. It is common for patients, especially in an emergency situation, to be negligent in the details of their diagnosis and emergency treatment plans. (Yadav et al 2019). This ties into the discussion of the responsibility of the clinician to ensure the information provided for the patient is tailored and presented in such a way, that patients are involved in the decision-making process, however challenging this may be. (Yadav et al.2019)

On further analysis of the results from the Delphi process, namely the second round, the outcome measure 'Rate of Adverse Events' was entered following the iterative nature of the process. This was done following the suggestions made in the optional free text box in the first round of the Delphi and making appropriate amendments. After careful deliberation it was decided that 'Rate of Adverse Events' would be the sole addition to the selection of outcome measures as discussed in the previous chapter. The overall median score for this outcome measure was a mean of 5.1, with a median score of 5. On investigating the scores given by each subset of the Delphi process however, a noticeable gulf is recorded between the numbers. In the 'Practitioner' leg of the second round of

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the Delphi, ‘Rate of Adverse Events’ received a median score of 3, with almost 70% of participants scoring it as ‘not important’. On the other hand, Patients were generous in the respect that this outcome measure received a median score of 6, with almost 60% of participants ranking it as ‘Critically Important’. One argument for the lack of importance instilled in the rate of adverse events by practitioners can be reflected in the disparity of the scores for another potential outcome measure included in both rounds of the Delphi. This was the outcome measure of ‘Repeat intervention rate’ which saw practitioners heavily outscore it as opposed to the patient subset. With Practitioners, ‘Repeat intervention rate’ scored a median value of up to 7 against a median of as low as 4 with the Patient subset. The percentage of participants scoring this outcome measure as critically important was also notably higher in the Practitioner legs of the Delphi; as high as 50% against as low as 6.3% in the Patient sub-group. Repeat intervention rate has been an outcome measure which has been cited regularly in the literature to compare the efficacy of pleural interventions, in terms of the success of pleurodesis. (Davies et al. 2012) However ‘Repeat Intervention rate’ also encompasses two of the most common complications or ‘Adverse Events’ of blind thoracentesis, which are procedure failure and pneumothorax. (Havelock et al. 2010) A failed procedure will require a repeat procedure most of the time unless contraindicated, explaining the relatively higher importance reflected in the scores for repeat intervention rate in the practitioner group. It can be hypothesised that there is a connection between the two outcome measures, in particular with the practitioners, as when ‘Rate of Adverse Events’ was an option in the second round, the score for ‘Repeat Intervention rate went slightly down.

As a related issue it is important to mention the phenomenon of ‘ex-vacuo’ pneumothorax. This is the presence of pneumothorax once a pleural effusion is drained due to the presence of a ‘trapped lung’. This can often persist and is a poor prognostic sign. (Ponrartana et al. 2005) There has been some dispute over the ideal management of post procedural pneumothoraces in this context, with the predominant school of thought being that they shouldn’t be routinely treated with a repeat procedure. However, patients have reported symptomatic benefit from their treatment. (Havelock et al. 2010) Nevertheless, this a potential complication that is encompassed by ‘pneumothorax’ which is, as aforementioned, encompassed by the potential core outcome of repeat intervention rate. A potential reason for the disparity of the scores between practitioners and patients for the outcome measure of ‘Rate of adverse events’, is a direct cause of the adept understanding of practitioners of the inclusive nature of the potential outcome measure of

'Repeat intervention rate'. The second argument that can be made for the disparity in the scores for 'Rate of adverse events', also pivots on the further understanding of the pleural procedures by practitioners, as generally, palliative procedures.

With malignant pleural effusion the most common indication for a pleural procedure, and with survival figures being as bleak as they are for cancers traversing the pleura, it is not surprising that best practice in most of the recent literature advocates for the early involvement of palliative medical support. Active palliation of this population group is appropriate as no intervention has been recorded to improve survival in this population. (Shieh et al. 2019) Timely activation of palliative pathways in these patients with the appropriate support is necessary along with the definitive acute management of symptomatic malignant pleural effusions. In fact, the treatment of malignant pleural effusions, either pleurodesis following drainage or IPC, can be seen as a form of symptomatic palliation, as the centred aims of these procedures is comfort for the patient. (Fortin and Tremblay 2015) The knowledge of the underlying palliative approach to pleural procedures by practitioners, can potentially be a reason for why this particular subset of participants of the Delphi were more inclined to opt for potential outcome measures that focused on symptomatic management than 'Rate of Adverse events'.

The study design, empirical work and analysis leading to the selection of the four outcomes sets in this project, was an inclusive and iterative process. The study design allowed for an inclusive review of the literature with the scoping review. This has become an increasingly favourable method of evidence synthesis and been established in a wide range of disciplines. One of the criticisms of constructing an array of evidence via a scoping review in this manner has often been the variability in their conduct. (Pham et al. 2014) This is because the alternative method of a systematic review is generally a more robust and systematic analysis of a fewer studies. (Aromotaris 2014) A distinction between a scoping review and a systematic review can be based on the purpose of each. Scoping reviews can be used to map out the available evidence on a much broader scale, instead of being limited to a specific research question. (Arksey and O'Malley 2005) This was ideal for the breadth of aims set out in the study design pertaining to the scoping review. These included to map out the primary and secondary outcomes measured in pleural intervention clinical trials, looking at how they were measured and to identify any inconsistencies, evaluating common themes. Primary and Secondary outcomes were also to be reviewed in light of appropriate stakeholders and to finally illicit any gaps in the literature. This wide array of aims required a review of a large and diverse body of literature, which would have been extremely challenging through the narrow framework of a systematic review. (Higgins and Green 2011)

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It can be argued however, that producing a long list of potential outcomes from a systematic review could potentially provide a more focused list of outcome measures that have been considered important to measure in the past. This can sometimes mean important stakeholders are disregarded and the all-encompassing nature of a scoping review combats this. (Keeley et al. 2016) This also defeats the purpose of producing a long list that can be entered into a modified Delphi process, which could potentially reveal a new potential outcome which has been overlooked. (Keeley et al. 2016)

The framework of thematic analysis as set out by Braun and Clarke 2006, was utilised to analyse qualitative data as part of the preliminary stages in the empirical work of this project. It has become increasingly recognised and utilised as a tool by researchers both familiar and unfamiliar with qualitative research. (Lorelli et al. 2017) The limitations in regard to this type of analysis, stems from the flexibility of the framework its often conducted in. This variability can sometimes lead to inconsistency and a reduced confidence in the themes derived from the analysis. (Holloway and Todres 2003)

In a very similar way to the use of a scoping review, its disadvantage of a lack of structure can be viewed as an integral strength to the method; as the variable approach of a thematic analysis can be tailored to the needs of a particular study. (Cassell 2012) Braun and Clarke 2006 described thematic analysis as a useful way to investigate the perspectives of multiple research participants, eliciting common themes and discrepancies; this happened to be the exact aim and purpose for the incorporation of thematic analysis in this study.

The lack of rigorous structure also allows thematic analysis to be accessible to researchers less familiar with qualitative research, such as in the case of this project. (Braun and Clarke 2006) Despite its limitations, Thematic analysis has been established as a useful instrument in the complex paradigm of qualitative research. This is because there are multiple documented methods of ensuring the evidence synthesised from thematic analysis remains credible and dependable.

Credibility can be described as the congruence of the participants views. (Tobin and Begley 2004) A number of methods have been described to ensure credibility such as prolonged engagement and observation, with debriefing to provide an external review on the synthesis of evidence. (Lincoln and Guba 1985) This reflects the approach taken adopted in this study. The participants undergoing the semi structured interviews, particularly the patient subgroup, were interviewed at multiple stages in relation to the procedure, indicating prolonged engagement and observation. A debrief of

the analysis from the thematic analysis was carried out by the supervisor overlooking the study, ensuring an external review confirmed the themes elicited from the analysis was accurate, reproducible and credible as possible.

Tobin and Begley 2004 describe methods in which researchers are able to achieve dependability. This can be done by ensuring the research method is clearly documented. I made an effort to ensure that this was the case with the use of verbatim transcripts, in the synthesis of themes elicited by the analysis. The quotes from the transcripts and interviews were carefully labelled to portray the views of both practitioners and patients, colour coded appropriately, detailing at which point in relation to the procedure, the patients in particular, were being interviewed; pre or post.

I have confidence in the process of the thematic analysis carried out on the raw data I collected, mainly due to the fact this was a completely supervised process with my academic supervisor who is experienced with this. Unfortunately, I have less confidence in the reliability of the raw data itself due to the aforementioned limitations with this aspect of the study. These included obstacles such as; limited personal preparation and training for the interviews, limited time and resources in terms of supervision and personnel to arrange interviews in a systematic bias avoiding manner, lack of outreach of the interviews, in regard to the type of stakeholders approached and geographical location of interviewees. The experience of interviewing for research purposes was novel to me, and I did not truly appreciate the cumulative negative impact these limitations would have had on my qualitative data at the time. Its only in hindsight that I have been able to reflect on the key errors made, some of which I should have had more control over. Examples of this include aforementioned efforts I should have made in regard to approaching members of industry involved in pleural interventional trials, with a whole array of companies and I may have been able to organise informative telephone interviews with.

A significant limitation to the semi-structured interviews involved the procedural obstacles to arranging interviews with patients whilst actually working in the respiratory unit. This introduced a high risk of researcher bias, from my part, as previously discussed. This was heightened due to the fact research nurses were not always available to act as gatekeepers in approaching patients. On initial reflection, I was under the impression this was an unavoidable flaw to the process and something I had to accept due to the constraints of time and resources to my masters. On further debrief following the initial submission of my project, my presence within the department, which introduced a significant amount of bias to the process, could potentially have been avoided with better planning. In hindsight, the semi-structured interviews did not necessarily need to be done

following the scoping review, as in fact, both these stages of the study were mutually exclusive. I may have had more difficulty recruiting appropriate patients for interview, but the onus would have largely been on the acting gatekeeper to approach patients. The process to recruit enough patients may have taken longer but this would have been at less risk of any researcher or procedural bias. Completing the scoping review before the interviews was slightly beneficial to me, personally, becoming more knowledgeable in regard to the outcome measures to be expected, as I was then familiar to outcomes commonly to have been prioritised by studies in the past. However, on balance, the heavy of risk of bias I subjected the process to by arranging the later stages of the empirical work whilst integrated to the department, was more harmful than beneficial to the project. Once I had designed the study, embarking on the interviews initially or simultaneously with the scoping review at the beginning of my allotted time for the project, I would have been able to potentially avoid this limitation.

On a more positive note, my study may potentially have features that can be seen as strengths. Four outcome measures were produced through a consensus process that, in principle, followed the guidelines of COMET and the GRADE working group. (Williams and Clarke 2016) (Guyatt et al. 2008) Each of the core outcome set qualified to be one, solely through the Delphi process, achieving consensus status with the scoring system outlined. This is something that can be quite difficult to achieve, despite a modified Delphi with other core outcome set development studies relying on a post study face to face discussion. (Rowe et al. 2019) Another positive of the study lays in the wide variety of participants both in the empirical work up of the study and the final modified Delphi process; an eclectic mix of practitioners at all levels, from Regional specialists to Junior doctors and Advanced nurse practitioners. The input from such a varied cohort of practitioners, along the strong engagement throughout the process by patients, gives the four outcome measures portrayed to be a core outcome set some validity. The engagement of the patient cohort with the project, and their willingness to participate at the worst of times for the benefit of research was commendable. Personally, I can't take too much credit for this, as a lot was asked of the patient cohort, especially through the semi-structured interviews. I ensured I maximised this good intention from the patient participants, by matching their enthusiasm with determination to make their experience as pleasant as possible.

It can be argued the number of outcomes making up the core outcome set, can be considered quite high. Having a core outcome set with too many outcomes can defeat the purpose of having a COS as

it becomes difficult for studies to accommodate a long list, with reduced research uptake. However, when compared to other COS development studies four seems to be a palatable number of outcomes. Knaapen et al. 2019, in their research protocol for an ambitious international Delphi survey pertaining to appendicitis in children, aimed to have a maximum number of 10 outcomes to make up a core set. This is paired with a contingency plan that if the number does come up to over 10, a method to regulate this would be brought into action. (Knaapen et al. 2019) This in comparison to the four outcomes elicited by this study, Nevertheless, more work could potentially be done to further streamline the four outcomes down to three, but with the strong consensus each of the outcomes achieved through this process, it would be difficult for any one of them to be discarded.

Apart from the limitations mentioned in regard to the method of the initial stages of the study, there are other limitations pertaining to the modified Delphi process that should be discussed. A recognised limitation in participant selection for the Delphi, like the participants for the interview, was the geographical location and spread of patients. Most of the patients engaging with the process and participating with the Delphi process were from the catchment area of the district general hospital I worked in. This can present as a problem due to the risk of generalisability of the core outcome set. Ideally I would have liked to access patient networks across the country. This would have been demanding for me and also for elderly dependent patients, to be able to carry this out in a safe and ethical manner. (DuGoff et al. 2018) On reflection, patient engagement with the process relied on the rapport established face to face. In most cases, in relation to the online Delphi, most patients only participated if there had been a face to face discussion pre-empting this.

Although the geographical spread of patients was limited, steps were taken to counteract this. The scoping review completed in the initial steps of the thesis enrolled the use of international studies in the work up and evidence synthesis. Another method of widening the horizon, was the industrious use of already established networks in the pleural community across Wales to help disseminate the Delphi process. Reaching out to specialist centres across the UK and approaching key members in the pleural community in person at the Winter British Thoracic Society Conference, aided awareness of the study amongst targeted individuals. This helped the development and progress of the study as well as ensuring a larger geographical area was covered in terms of reliability in the core outcome sets elicited by the process. It is important to note however, I failed

to recruit engagement from any of the specialist centres in Bristol and Oxford but did manage to get input from certain practitioner cohorts in Cardiff and other areas of Wales.

76 participants were invited into the first round of the study including both practitioners and patients. In the first round 47 participants in total were included and actively responded completely. This showed a 61 % engagement rate including both practitioners and patients. The second round of the Delphi had 70 participants invited with 31 participants responding, giving an attrition rate of 35%. This is a mild attrition rate when being compared to the literature, falling at a very acceptable level when being compared to the numbers depicted by multiple COS developments. (Mckenna 1994) This is most definitely not a reflection of a poor study, despite a fall in engagement between rounds. Nevertheless, a larger sample size with lower attrition rates would have been more ideal.

The engagement rate of participants for the second round of the Delphi was quite poor at 44%. It can be argued that the individuals that responded in the surveys were considerably more interested in the project than not, especially in the second round. This draws in an element of researcher bias, with the potential for participants, namely practitioners, to be able to exert their bias preference on the process, simply by participating fully. There is also the possibility that those who did participate, were an accurate collective representation of the cohort in relation to the Delphi process and the course it took.

A contrast to other COS development studies noted, is the absence of the dependent 'consensus meeting'. (Rowe et al. 2019) This can be seen as a strength of the study as the four outcomes elicited were deemed as core as per the qualifying criteria of the Delphi process. A meeting such as this where decisions are to be made on the data collected, have the potential to strike researcher bias through the deliberation based on the strong preferences of said participants.

A similar meeting took place in this study with four independent reviewers, but rather than making definitive decisions on outcome measures, this was a meeting to steer the study forwards. Naturally, following a scoping review mapping a wide amount of evidence, along with semi structured interviews with patients, this produced a long list of outcomes. The independent review meeting ensured that every outcome measure put forward onto the rounds of the Delphi process was a viable and sensible option. No decisions were made in regard to the long list of outcome measures without there being a unanimous vote. Nevertheless, a meeting, even at this early stage, theoretically could have exposed the process to researcher bias.

With the increased uptake of COS development projects, Kirkham et al. 2017 completed an interesting project, in the development of a set of minimum standards COS development studies should aim to meet. These standards were divided into 3 domains, with 11 recommendations altogether. The methodology through which these recommendations were constructed mirror the increasingly established process of steps taken in the majority of COS development studies; a long list being developed by relevant stakeholders, undergoing a modified Delphi process with two stages, utilising the scoring system as set out by the GRADE working group. This standards development project involved an eclectic mix of over 250 expert participants, culminating in a consensus discussion on each point qualifying as a key minimum standard for studies to explore. (Kirkham et al.2017)

The first four items to be identified were the setting the COS would be used in, the health condition involved, the population and potential interventions. This was the first domain of the scoping review.

The subsequent domain, Stakeholders, includes elements that I was able to address partially, with the involvement of healthcare individuals and pertinent patients. A limitation, in regard to this, was the lack of direct discussion with clinical trialists, who would potentially be carrying the interventional prospective studies, the core outcomes developed, would augment in the future. I did however attend relevant conferences prior to the launch of this study, in order to help raise awareness of the project and made an effort to recruit a specialist panel for the Delphi survey. As aforementioned, failing to engage with clinical trialists and members of industry, retracted from the strength of the study, both in the missing data this could have potentially bolstered the project with and the lacklustre tone it sets with peers reviewing the study.

The final domain, Consensus Process, depicted by Kirkham et al. 2017, included influence of both patients and practitioners on the long list, a definitive scoring method, criteria for an element of alteration through the process and absence of ambiguity in the selected outcome measures entered into the Delphi. An attempt was made to manage this by maintaining an inclusive outlook on engagement from the inception of the project. The scoring system as set out by the GRADE working group was established early as the chosen method of governance. The modified two round Delphi allowed a stage for consideration of suggestions made by participants, with careful deliberation to consider inserting, including or dropping outcomes. Avoiding ambiguous and non-discrete language was a key focus of the independent review meeting, ensuring the long list of outcomes entering into the Delphi process were articulate, succinct and absent of noise.

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Through this assessment, against minimum standards of COS developments, an effort has been made to address the principle domains.

COS development has accelerated over the past few years with hundreds of studies currently in the preliminary stages. (COMET 2019). This increased awareness and drive towards the common goal of, overall, reducing the phenomenon of outcome reporting bias, has been recognised by Cochrane Handbook of Systematic Reviews of Interventions. (Higgins et al. 2019) This bodes well for the uptake of COS by those responsible for the construction of interventional trials of the future. The impact of the development of core outcome sets can only truly be beneficial to the research community, with the uptake of COS. I understand the importance of ensuring the dissemination of the results of this study through the appropriate channels is important to try and facilitate this within pleural intervention. This would be through the submission of this work to conferences and meetings relevant to thoracic medicine, as well as peer reviewed journals. This study is also registered and posted on the COMET website, residing in the registry for core outcome sets for clinical trials. The study is available on the COMET website for reference. It has been posted on the website along with other COS development projects in the available database. This would allow researchers going forward to be able to review the core outcome sets elicited in this study and consider their inclusion for any prospective future pleural interventional studies. Adding to the studies available is exactly what the COMET initiative intends; for researchers to accumulate a database of core outcome sets for various clinical fields in an attempt to resolve the issue of heterogeneity of outcomes in interventional trials.

5.3 Reflection

Scoping reviews have both benefits and pitfalls as a form of literature review. The breadth of the scoping review was daunting at first, but I really benefited from the framework as set out by Arksey and O'Malley. (Arksey and O'Malley 2005) Ensuring a methodical approach was adopted when data extracting, meant the evidence synthesis aspect of the review was easier. The extracting of data in a table format was time consuming but essential for an end product. The most rewarding aspect of the scoping review was becoming more knowledgeable in the particular field of pleural medicine. I failed to appreciate how unfamiliar with the topic area I was. Through a combination of naivety and a flawed methodology, I unfortunately subjected an integral aspect of the study to irretrievable damage. I was unaware of this at the time and have to take responsibility for the limitations it caused my study overall, as the scoping review formed the grounding for the more advanced empirical work. Applying a 5-year time frame to the literature search retracted from the main

advantage of the inclusive nature of a scoping review, and meant key literature was missed from a thorough review. Bizarrely, being blissfully unaware of this at the time however, meant I was able to complete the scoping review with purpose, becoming more familiar with the principles of performing a literature review. I feel this experience has taught me important lessons on designing and planning a literature review, and just how significant this is to achieve the end goal, as is the focus and resolve to complete the review itself.

Completing this scoping review for the study has equipped me with skills that will benefit me in future research projects, teaching and clinical practice. Moreover, learning from the mistakes made in the scoping review will allow me to avoid similar pitfalls in the future. Above else, completing a scoping review with the framework as a guide, I have picked up valuable experience in both, how such a literature review can be helpful, and how when done incorrectly, it can hinder the productivity and purpose of it. As aforementioned, if I had the opportunity to have another attempt at this stage of the study, I would have done a few things differently. Instead of using the process of completing the scoping review to learn about the history of research pertaining to pleural intervention and medicine, I should have completed a personal exploratory review prior to this. This would not have to have conformed to any set standard but would have given me the opportunity to become more familiar with key literature, reducing the likelihood of it being absent from the scoping review. Regardless of this, the miscalculation of not involving my clinical supervisors earlier in this stage of the study cost the reliability of the scoping review significantly. In hindsight, I was overconfident in the search strategy and was possibly hyper fixated on following the structure of the scoping review, rather than considering the options and fail safes available to me to ensure I was heading down the right track. This was depicted in how regularly I was interacting with my academic supervisor on the structure of the search and steps following on from this, rather than focusing on the quality and significance of the studies I ended up reviewing. The anxiety of not having completed a scoping review before, may partially explain the needless addition of a 5-year time constraint on the design of the review, as it provided a more robust structure to the iterative process, making the task seem more achievable.

Qualitative research is fast becoming a staple in the development of core outcome sets in multiple clinical fields. (Keeley et al. 2016) Overall, the semi structured interviews were enjoyable to complete. The most difficult aspect of the interviews with practitioners was finding availability. Patient interviews were slightly more variable. The decision to include patients that were pre-procedure in the work up of the study was an important one. This gave the interviews an additional dimension to complete the patient perspective. This was done in a fashion to ensure patient

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treatment was not delayed and done with appropriate consent to ensure the patient was comfortable enough to complete the short interview.

In hindsight, I would have been more selective with the pre-procedure patients as often patients would be so determined to be helpful and contribute to the study that they would become slightly negligent of their own acute condition. The write up of the thematic analysis was something that was also quite time consuming, but the verbatim transcripts were an important aspect of the process. I had initially expected the Delphi process to the most labour-intensive aspect of the study; however, completing the empirical qualitative research work was the most time consuming altogether.

Overall, I was satisfied with how the Delphi process was completed, although the key elements making up the raw materials of the process were significantly flawed. There most definitely seemed to be a theme brewing with the first round completed, which was confirmed with the second round. It was satisfying in the sense that a 3rd round was not required, and the fact that the process did not depend on a consensus establishing meeting at the ultimate stage. Attrition rates with both practitioners and patients was to be expected but remained disheartening. Nevertheless, the body of data achieved was deemed to be enough to address the aims and goals of the study.

5.4 Recommendations

Policy

The nature of the study means that policy in health and practice would not be directly affected by this study. Overall, health policy makers should become more engaged with COS developments, as they could be potential stakeholders in certain clinical fields.

Research

This study directly indicates recommendations for research. A central purpose for the study was to advise future pleural interventional trials on a core outcome set to incorporate into the list of outcomes measured as a minimum.

In relation to the study itself, it can be argued that a larger scale study would be beneficial. This study pertaining to core outcome sets in pleural interventional trial should be done with the aim to

achieve a more variable geographical area in terms of patients. There could be potential for the number of outcomes in the set to be reduced down to three with a larger more powerful study.

There are recognisable limitations which have been discussed in regard to the main bodies of the project, which hinder its reliability and potential as a research practice defining study. Nevertheless, there is most definitely a requirement for further work to be done, to more successfully achieve the aims and objectives of this project. The unchallenged uptake of this flawed project on the COMET website database, indicates the gap in the literature pertaining to a core outcome set in pleural interventional trials. It is an ever-evolving fold of respiratory medicine due to its relatively young establishment as a separate specialty of medicine and deserves for its novel interventions to be assessed in a comprehensive and efficacious manner. Although I may not have tackled this research need in the most competent manner, I hope I have raised awareness by contributing to the COMET database with the findings of my study. I most certainly have developed my personal knowledge of research and paradoxically gained valuable experience from the key errors in judgement made through the development and completion of this project. On balance, I have developed personally as a researcher more than I have contributed to the body of reliable research in this clinical field, but I recognise that this is an achievement in itself. As well as becoming more learned in recognising the aspects of study design that provide it with strengths and weaknesses, I feel the initial submission and feedback on my work has allowed me to reflect and improve on my writing skills. My inexperience in academic writing caused me to be negligent of the impact my writing style could have on the impression of me as a researcher. I am more cognisant of how this contributes to my identity as an author and am grateful this has been something that has been brought to my attention so early in my medical writing career.

Further work must also be done to assess and quantify the uptake of the core outcome set elicited by this project. As aforementioned, the impact of studies such as this is marginalised if researchers are negligent to issues addressed pertaining to outcome reporting bias. COS development studies provide a solution to a well-recognised problem; monitoring and assessing their uptake and refining the process are pertinent steps for researchers to make in the near future.

Practice

Due to the nature of the study, no immediate practice recommendations can be made.

In an ideal world, the results of the study would be taken up by pleural interventional trials of the future. Considering the issues surrounding the reliability of the work up of this study, makes this an unlikely possibility. My hope would be that a more comprehensive study would be completed, adopting the principles and structure used in this project on a wider scale, with my study contributing to further research in a productive manner. Interventional trials of the future would be able to draw from such progress in research centred on a developed core outcome set, resulting in consistent primary and secondary outcome measures held, possibly including some of the outcomes deemed as a core, by this study. By virtue of further work to elicit a core outcome set in this medical field, would allow these future trials to be meta-analysed due to the reduced heterogeneity in outcome reporting. This improved meta-analysis, in theory, would positively affect future practice and allow the efforts of researchers to have a greater impact.

5.5 Conclusion

In conclusion, I believe I have contributed in some fashion in my attempt to define a core outcome set for pleural interventions, providing a structured COS development study in a subset of a clinical field that has yet to establish a set of outcome measures. This study has the potential to instigate further, more comprehensive work on the aims and objectives of this project, leading to a much-needed core outcome set diffusing ubiquitously into clinical trials of the future. This will be done through raising awareness through the appropriate channels for this research need and future researchers avoiding the pitfalls affecting the reliability of the results of this study. (Gargon et al. 2017)

The heterogeneity of outcome measures used in clinical interventional trials have been a thorn in the efforts of researchers to review, compare and contrast data for too long now. The variability of outcome measures thwarts the possibility of systematic reviews being able to synthesise reliable evidence and therefore answer the question they set out to advise on. (Clarke and Williamson 2016) The work done in developing this COS in the pleural field, is another stand in the fight against this research waste caused by outcome reporting bias (Williamson et al. 2020). Though researchers are putting in resources behind the development of new COSs, the onus is on clinical trialist and systematic reviewers to ensure they make more responsible decisions when drawing up study protocols, to include core outcome measures that have been developed. (Saldanha et al. 2020)

In relation to pleural interventions, there are novel methods and techniques being trialled continuously, which could benefit from the uptake of a core outcome set. An example of this is the

Mercer et al. 2020 randomised controlled trial of the use of a ballooned intercostal drain. The gap in the literature has not been occupied by my project due to the weaknesses discussed, and ongoing advancements in the pleural interventional field justifies for further work to be done to build stronger evidence of a core outcome set.

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Appendices

Appendix 1 – Study Resources

Participant Information Sheet (English Version)

Title of Project

Development of Core Outcome Sets for Clinical Trials in Pleural Intervention.

Background

We are conducting a study to investigate the outcomes that are important for researchers, clinicians and patients alike when it comes to pleural interventions. This could be an intervention such as an insertion of a chest drain for therapeutic relief, or an aspiration of fluid with a needle to confirm a diagnosis.

Pleural interventions are quite common medical procedures and can be instrumental in the work up of a variety of conditions. However, when measuring how effective they can be for example, in clinical trials, there is a discrepancy as to what the most important things to measure are.

This study is part of a growing recognition that insufficient attention has been paid to the outcomes measured in pleural clinical trials. These issues can be addressed through the development and use of an agreed standardised collection of outcomes, known as a core outcome set, which should be measured and reported, as a minimum, in all trials specific to pleural intervention trials.

In developing these core outcome sets we will be interviewing between 10 and 20 people, including both healthcare professionals and patients, to help inform the study.

Benefits and Risks

You will be able to contribute in developing consensus and help answer an important question causing difficulty in allowing best evidenced practice to be upheld.

There aren't any serious risks to contend and the interviewee holds every right to terminate the interview at any point.

What do I need to do?

If you are happy to participate, we'll arrange a time and a date for the interview when convenient to yourself. The interview will take approximately 45 minutes to 1 hour complete.

Questions will be asked pertaining to what the participant feels is the most important aspect of having a pleural intervention. Answers will be recorded on a secured Dictaphone, which is password protected.

Participation in this process will not at all affect any ongoing care or treatment.

Sensitive issues pertaining to diagnosis will not be explored, with attention being focused on the procedure itself.

Confidentiality

1. We will not discuss the interview with any of your colleagues and anything you say will remain confidential. Only the research team will have access to the full transcripts data and the original voice recording will be destroyed immediately after transcription. Information will be held on a secure computer within BCUHB. This will be held for five years and then destroyed, which is standard practice. Information collected may be used to support other research in the future, and may be shared anonymously with other researchers.

Withdrawal

You can withdraw from the study at any time without affecting your rights. Data collected up to any point you decide to stop, will be deleted if requested to do so. You can stop the interview at any time. You do not need to give a reason if you change your mind about participating. and will be made anonymous at the point of transcription and then deleted.

Who is organising and funding this study?

This study is being conducted collaboratively by researchers from Bangor University and Betsi Cadwaladr University Health Board (BCUHB).

What will happen to the results of this study?

The results will be used to help us to better understand the way in which pleural interventional trials should be conducted. This will contribute in producing a paper to report on the consensus achieved in what the most important outcomes to be measured in pleural interventional trials are.

Who has reviewed this study?

The research project has been scrutinised by an independent group of people, called a Research Ethics Committee. This is to ensure that your interests are protected and the study is conducted according to the highest ethical standards. This study has been reviewed and given favourable opinion by the School of Health Sciences Ethics Committee at Bangor University. In accordance with standard

practice, the insurance arrangements for the study are provided by the Sponsor, who is Professor Chris Burton, Head of the School of Health Sciences at Bangor University (01248) 382556.

Complaints

If you have a concern about any aspect of the study, you should ask to speak to Professor Paul Brocklehurst, who will answer your questions (using the contact details that are provided above). If you remain unhappy and wish to make a formal complaint, you can do this by contacting Professor Chris Burton, Head of the School of Healthcare Sciences at Bangor University (01248) 382556 c.burton@bangor.ac.uk .

Further information and contact details

Specific information about this research study can be obtained from Professor Paul Brocklehurst (contact details are at the top of the page).

Participant Information Sheet (English Version)

Title of Project

Development of Core Outcome Sets for Clinical Trials in Pleural Intervention.

Background

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Pleural interventions are quite common medical procedures and can be instrumental in the work up of a variety of conditions. However, when measuring how effective they can be for example, in clinical trials, there is a discrepancy as to what the most important things to measure are.

This study is part of a growing recognition that insufficient attention has been paid to the outcomes measured in pleural clinical trials. These issues can be addressed through the development and use of an agreed standardised collection of outcomes, known as a core outcome set, which should be measured and reported, as a minimum, in all trials specific to pleural intervention.

In developing these core outcome sets we will be interviewing between 10 and 20 people, including both healthcare professionals and patients, to help inform the study.

Benefits and Risks

You will be able to contribute in developing consensus and help answer an important question causing difficulty in allowing best evidenced practice to be upheld.

There aren't any serious risks to contend and you holds every right to change your mind about participating at any stage.

What do I need to do?

If you are happy to participate, we will need you to complete a simple questionnaire. The questionnaire will ask you to order certain outcome elements using the GRADE criteria. Grades will be out of 10 respectively 1-3 = outcome of limited importance, 46 = important outcome and 7-9= critical outcomes.

Participation in this process will not at all affect any ongoing care or treatment.

Sensitive issues pertaining to diagnosis will not be explored, with attention being focused on the procedure itself.

Confidentiality

We will not discuss the results of the questionnaire with any of your colleagues and anything you say will remain confidential. Only the research team will have access to the data. Information will be held on a secure computer within BCUHB. This will be held for five years and then destroyed, which is standard practice.

Information collected may be used to support other research in the future, and may be shared anonymously with other researchers.

Withdrawal

You can withdraw from the study at any time without affecting your rights. Data collected up to any point you decide to stop, will be deleted if requested to do so.

Who is organising and funding this study?

This study is being conducted collaboratively by researchers from Bangor University and Betsi Cadwaladr University Health Board (BCUHB).

What will happen to the results of this study?

The results will be used to help us in the process of developing a consensus as to what the core outcomes pertaining to pleural interventional trials should be.

The results will be used to help us to better understand the way in which pleural interventional trials should be conducted. This will contribute in producing a paper to report on the consensus achieved in what the most important outcomes to be measured in pleural interventional trials are.

Who has reviewed this study?

The research project has been scrutinised by an independent group of people, called a Research Ethics Committee. This is to ensure that your interests are protected and the study is conducted according to the highest ethical standards. This study has been reviewed and given favourable opinion by the School of Health Sciences Ethics Committee at Bangor University. In accordance with standard practice, the insurance arrangements for the study are provided by the Sponsor, who is Professor Chris Burton, Head of the School of Health Sciences at Bangor University (01248) 382556.

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Further information and contact details

Specific information about this research study can be obtained from Professor Paul Brocklehurst (contact details are at the top of the page).

Centre: Betsi Cadwaladr University Health Board & Bangor University

Study Number: Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Development of Core Outcome Sets for Pleural Interventional Trials Name

of Researcher: Dr Zain Habib

Please initial box

2. I confirm that I have read the information sheet dated 13/10/2018 (v1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐

4. I agree to the interviews being recorded and written out in full; ☐

5. I agree that anonymised quotes may be published; ☐

6. I understand that relevant data collected during the study, may be looked at by individuals from Bangor University and BCUHB where it is relevant to my taking part in this research; ☐

7. I understand that the information collected may be used to support other research in the future, and may be shared anonymously with other researchers. ☐

8. I agree to take part in the above study. ☐

Name of Participant	Date	Signature	
Name of Person consent	Date	Signature taking	

Interview protocol for Patients

1.	Acknowledgement that the participant has had the opportunity to read through the information sheet.
2.	Tell me about the procedure you're having done?
3.	Tell me about your symptoms?
4.	Did you have any concerns, fears or expectations prior to the procedure? / after the procedure?
5.	Tell me about the conversation you had with the doctor before the procedure?
6.	What was the most important aspect of the procedure prior to it being attempted?
7.	What was the most important aspect of the procedure after it had been attempted?
8.	What was the most important aspect of the procedure to your family and friends as a whole?
9.	Would you have this procedure done again? What would stop you from having it done again?
10.	Is there anything you'd like to comment on in regards to what we have discussed?

Interview protocol for Practitioners

1.	Acknowledgement that the participant has had the opportunity to read through the information sheet.
2.	Tell me about you experience with pleural interventions?
3.	What do you feel like is the most important aspect to the primary outcome for the patient before the pleural procedure is attempted?
4.	What do you feel like is the most important aspect to the primary outcome for the patient after the pleural procedure has been attempted?
5.	Do you feel like there is a difference in the primary outcomes for the patient depending on the indication for the procedure? For example, pneumothorax vs pleural effusion?
6.	Do you think the primary outcomes change depending on the intervention being carried out?
7.	Do you think there is a difference in the primary outcomes to be measured in pleural interventional trials between cancer and non-cancer patients?
8.	What do you think are the most important outcomes to be measured in pleural clinical trials?