DOCTOR OF PHILOSOPHY

Development and application of linked pharmacometric-pharmacoeconomic analyses in clinical drug development

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Development and application of linked pharmacometric-pharmacoeconomic analyses in clinical drug development

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Contents

Declaration and Consent

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.

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.

Thesis Summary

Linked pharmacometric-pharmacoeconomic modelling (also known as pharmacokinetic-pharmacodynamic-pharmacoeconomic - PKPDPE - modelling) has emerged as a potential means of facilitating early economic evaluations to enhance decision making during drug development. The methodology proposes that PKPD models, developed from early phase trials, are used to generate inputs to pharmacoeconomic models via simulation. There are few published applications of this methodology and these have typically focussed on late, or post-marketing, decision problems such as early prediction of cost effectiveness, regimen selection and phase 3 go/no-go decisions. The aim of this thesis was to widen the scope of linked pharmacometric-pharmacoeconomic modelling by demonstrating novel applications of this methodology from the early to late stages of drug development.

A case study of urate-lowering therapies for the treatment of hyperuricemia in gout patients was chosen for developing and demonstrating the application of the methodology. Pharmacokinetic models for several urate-lowering therapies were obtained from the literature and a semi-mechanistic multi-compartment pharmacodynamic model was developed in collaboration with pharmacometricians at Pfizer. The first application of the pharmacometric model is a study into the potential implications for drug safety of adherence patterns characterised by repeated drug holidays. A pharmacoeconomic model is subsequently developed which uses the pharmacometric model outputs, serum uric acid concentrations, as inputs to predict clinically relevant outcomes and costs. The linked set of models were used to study the impact of imperfect medication adherence on treatment effectiveness and subsequently, cost effectiveness, in a study that could potentially be relevant from both an industry and reimbursement authority perspective.

Further applications of the linked pharmacometric-pharmacoeconomic model were examined, which included informing early phase candidate selection and phase 3 trial design decisions. The early phase application considers the decision of whether to invest in early drug development based on the valuation of hypothetical pharmacological profiles in terms of their predicted maximum reimbursement prices. This could serve to guide candidate selection for progression into clinical phases. The application in trial design uses a pharmacometric based clinical trial simulation and a pharmacoeconomic pricing model to compare trial designs in terms of return on investment. This combines the drug pricing perspectives of both the pharmaceutical company, setting minimum prices needed to obtain an adequate return on investment, and the reimbursement authority, setting cost effectiveness thresholds which imply a maximum price for a given benefit.

This thesis has gone beyond previous work in this area, which primarily focussed on early estimates of cost-effectiveness or estimates of the impact of protocol deviations in clinical trials, to applications in early development decisions and clinical trial design incorporating value of information methods. It concludes with a discussion of how the iterative application of this methodology within a Model-Informed Drug Discovery and Development framework may enhance drug development efficiency and communication of product value to external decision-makers.

Acknowledgements

I am extremely grateful to Professor Dyfrig Hughes for having been an excellent PhD supervisor; allowing me the freedom to pursue my own ideas and ways of working whilst making sure I stayed on course. I would also like to thank Dr Steven Lane at the University of Liverpool for his input and encouragement. I am indebted to Dr Scott Marshall and Dr Elena Soto at Pfizer for giving up so much of their time and sharing their extensive knowledge of drug development. Their contribution has greatly enhanced what I have been able to achieve during this PhD studentship. It has also provided me with invaluable insights into drug development within the pharmaceutical industry that would not have been possible otherwise. I am grateful to them also, along with rest of the pharmacometrics group in Sandwich, for making me welcome during an internship in the final year of my PhD studentship.

Thesis Publications

Chapters 2 – 4 have already been published in academic journals and are provided as references below and the complete publications are contained in the Appendix of this thesis. At the time of writing, Chapter 5 has been submitted to an academic journal.

Chapter 2

Hill-McManus, D., Soto, E., Marshall, S., Lane, S., & Hughes, D. A. (2018). Impact of non-adherence on the safety and efficacy of uric acid-lowering therapies in the treatment of gout. British Journal of Clinical Pharmacology, 84(1), 142–152.

Chapter 3

Hill-McManus, D., Marshall, S., Soto, E., Lane, S., & Hughes, D. A. (2018). Impact of non-adherence and flare resolution on the cost effectiveness of treatments for gout: Application of a linked pharmacometric/pharmacoeconomic model. Value in Health, 21(12), 1373–1381.

Chapter 4

Hill-McManus, D., Marshall, S., Soto, E., & Hughes, D. A. (2019). Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout. Clinical Pharmacology & Therapeutics, 106(3), 652–660.

List of Abbreviations

ALL	Allopurinol
AUC	Area Under the Concentration Curve
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CrCl	Creatinine Clearance
CTS	Clinical Trial Simulation
CV	Coefficient of Variation
EMA	European Medicines Agency
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Partial Perfect Information
FBX	Febuxostat
FDA	Food and Drug Administration
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
IIV	Inter-Individual Variability
IND	Investigational New Drug
LES	Lesinurad
MBDD	Model Based Drug Development
MEMS	Medication Event Monitoring System
MID3	Model Informed Drug Discovery and Development
MRP	Maximum Reimbursement Price
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
NPV	Net Present Value
OECD	Organisation for Economic Co-operation and Development
PD	Pharmacodynamic
PK	Pharmacokinetic
PKPD	Pharmacokinetic-Pharmacodynamic
PKPDPE	Pharmacokinetic-Pharmacodynamic-Pharmacoeconomic
PRMA	Pricing, Reimbursement and Market Access
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
QSP	Quantitative Systems Pharmacology
RCT	Randomised Controlled Trial
ROI	Return on Investment
sUA	Serum Uric Acid
UA	Uric Acid
ULT	Urate Lowering Therapy
uUA	Urinary Uric Acid
VBP	Value-Based Price
VoI	Value of Information
XOi	Xanthine Oxidase Inhibitor

Chapter 1

Introduction

1. Drug Discovery and Development

The provision of medicines (the medicinal form of drugs), is an essential function of health care systems. Drug discovery and development is the process by which chemical or biological entities with potential therapeutic properties are identified and subsequently brought through successive phases of testing to measure their safety and efficacy (Lipsky and Sharp, 2001). This typically results from a combined effort by academia, governments and the pharmaceutical industry. The process is notoriously labour intensive, time consuming and costly, and this is often reflected in the high prices health care providers are charged by the pharmaceutical industry to access new medicines. Very few entities that show potential in the drug discovery phase are eventually approved for use in patients (Dimasi, Grabowski and Hansen, 2016). This high, and increasing, rate of failure and cost of drug development is hampering the search for new medicines and can result in medicines being unaffordable for many patients or health care systems (Dickson and Gagnon, 2004; Paul *et al.*, 2010).

1.1. Drug Discovery

The typical process of drug discovery and development is outlined in Figure 1.1, reproduced based on Hughes et al. (Hughes *et al.*, 2011). A drug discovery effort may be initiated following basic research identifying a drug target, such as a protein or pathway whose activation or inhibition may have a disease-modifying effect. Hit discovery will typically involve a screening phase during which a large number of compounds are tested for a desired interaction with the target. Hits in the screening phase may be reduced further following additional testing for potency of target interaction and the extent to which they display 'drug-like' properties. The most promising hits are progressed to optimisation which aims to modify their structures so as to maintain efficacy whilst optimising 'drug-like' properties (such as desirable physicochemical properties) and enhancing the likely safety profile. Typically a screening phase may include tens of thousands of compounds, whereas the number progressing to pre-clinical drug development may number in the hundreds.

Figure 1.1. Basic elements of drug discovery

1.2. Drug Development

For promising compounds or biologics identified during drug discovery, drug development (Figure 1.2) begins with a pre-clinical phase involving further assays and testing in cell cultures and animal models. Candidates showing toxicity in animal models are likely to be terminated. The preclinical results are submitted to regulatory authorities (e.g. Investigational New Drug (IND) application to the US Food and Drug Administration or a clinical trial application to the European Medicines Agency) which, if approved, allows for the transition to testing in human trials.

The first in human trials are known as phase 1, although sometimes 'exploratory' very low dose phase 0 trials may be performed prior to phase 1 (Norman, 2016). The objective of phase 1 is to evaluate the safety of the drug candidate in humans. Initial studies involve the administration of a single dose followed by ascending dose and multiple dose studies. These trials will identify the maximum tolerated dose before unacceptable side effects occur, as well as characterise the drug's pharmacokinetics and potentially pharmacodynamics as well. These studies are conducted in healthy volunteers and each may typically recruit between 20 and 80 subjects.

Following phase 1 studies which focus on safety endpoints, phase 2 seeks to establish the efficacy of the candidate drug in diseased patients while still maintaining acceptable safety. Phase 2 trials are typically larger, recruiting in the region of 100 to 300 subjects. Phase 2 may be further divided into an initial stage 2a, involving fewer subjects, a variety of dosing or dose regimens and intensive pharmacokinetic monitoring. The following stage, phase 2b, then recruits larger numbers of patients and may assess a larger number of doses and are known as 'dose finding' studies. Phase 2 studies are often conducted in comparison to placebo.

The principle objective of phase 3 clinical trials is to confirm the therapeutic effect of a new compound and assess the risk to benefit ratio in order to gain regulatory approval (Bourin, 2017). In order to obtain greater evidence of the long term benefits and risks of the drug, these trials recruit much larger numbers of patients and follow-up over a longer duration, this may involve many thousands of patients over many years depending on the treatment and type of health condition. The evidence gained in this phase also underpins the health technology assessments required by many reimbursement authorities. The most common phase 3 trial design involves a study in parallel groups with the patients randomly divided into two groups which by definition receive the active treatment, or placebo/active comparator, throughout the trial period. For a given compound in development, phase 3 is likely to require two or more trials which may also investigate more than one dosage of the study drug.

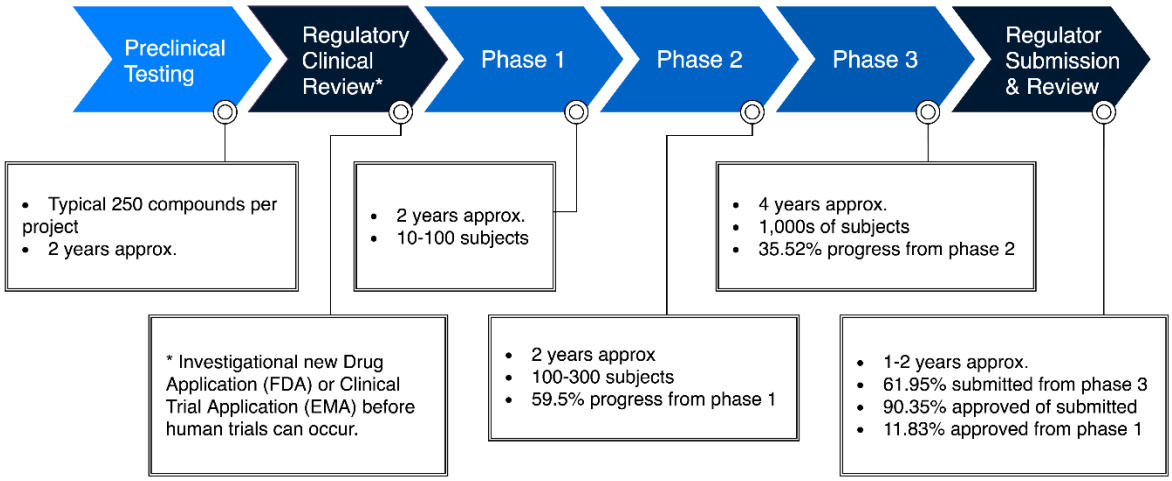


Figure 1.2. Principal stages of drug development

1.3. Regulatory Approval

The majority of new drugs developed by the pharmaceutical industry are submitted for regulatory approval first to either the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) (Van Norman, 2016). In 2017 the US and the combined European states represented the largest markets in terms of sales revenues followed by China and Japan. Before a pharmaceutical product can be marketed in either Europe or the US it must first receive regulatory approval (also known as marketing authorisation). The evidence generated throughout the development process is synthesised and submitted to the regulatory authority who will grant the marketing authorisation if the evidence is sufficient to demonstrate that the drug is safe and efficacious. It typically takes approximately one year for the regulator to review the evidence and for a final decision to be reached. The level of evidence required by a submission will depend on the drug and the target disease or indication, but will normally need to include at least one phase 3 trial to have been completed. However, in some cases regulatory approval has been obtained without evidence from phase 3 studies (Downing *et al.*, 2014).

Even after a new drug has secured marketing authorisation, there may be need for further trials to understand the drug's use in different populations or for monitoring of longer term safety. These are known as phase 4 trials and those that have been mandated to occur by a medicines regulator are additionally known as post-marketing studies. Unlike studies during drug development, phase 4 takes place once the drug is in routine use and can therefore evaluate the real-world effectiveness, as opposed to efficacy in clinical trials (Suvarna, 2010).

1.4. Failure in Drug Development

Drug development is notoriously risky, with only roughly 10% of those drugs that enter clinical development eventually going on to receive regulatory approval. A substantial fraction of candidate compounds are terminated in phase 1 (60%), followed by a slightly lower failure rate at phase 2 (36%) and a final 60% that undergo phase 3 but are not submitted for regulatory approval. Of those compounds that are submitted for regulatory approval, 90% have historically been successful. These phase transition probabilities were estimated in a study which surveyed a sample of medium to large pharmaceutical companies and included small molecule chemical entities and biologics (Dimasi, Grabowski and Hansen, 2016).

The cost of bringing a single medicine to market is undoubtedly high but difficult to quantify. A widely cited estimate of the total pre-approval cost, accounting for the additional cost of failures for every success, is $2,558 million (in 2013 US dollars) (Dimasi, Grabowski and Hansen, 2016). This figure has proven controversial and is likely an overestimate, others have derived lower figures such as a recent study of cancer drugs reporting the median cost of development of a single drug (in 2017 US dollars) to be $648 million (range, $157.3 million to $1950.8) (Prasad and Mailankody, 2017). Development costs are weighted toward later phases, since later phases typically involve larger and longer lasting clinical trials. Phase 3 costs are in the region of 4 times more expensive than phase 2 and 10 times those of phase 1. Therefore, it is desirable to fail development candidates at the earliest stage possible before having incurred large costs – hence the mantra “fail fast, fail cheap”.

The number of medicines receiving regulatory approval in the US, often where first approvals are granted, has been relatively stable over recent decades, with 2018 achieving a record high of 43 new approvals (Mullard, 2019). Despite this, however, the trend in drug development has been one of increasing cost and time taken to achieve approval. Over the space of roughly a decade phase 2 clinical trial average duration has increased by 7 months and phase 3 by 6 months (Martin, Hutchens and Hawkins, 2017). It has also been estimated that the overall cost per approved medicine increased in the order of 2.5 times between 1997 and 2008 (Dimasi, Grabowski and Hansen, 2016). An important factor in explaining the increase in development costs is the increasing likelihood of failure during development.

The productivity of pharmaceutical research and development (R&D), or the return on investment (ROI), fell to relatively low levels between the 1990s and 2008. Since around 2012, however, there have been signs of productivity increasing (Schulze *et al.*, 2014; Smietana *et al.*, 2015), although recent data for the largest pharmaceutical companies do not support this trend (Deloitte: Centre for Health Solutions, 2018). All else being equal, the rising cost and duration of drug development, which reduces

the duration of market exclusivity post regulatory approval, will reduce the return on investment (ROI) of pharmaceutical R&D. This has the potential to result in higher drug prices, justified by the pharmaceutical industry in terms of rising R&D costs, and could eventually act to reduce the incentive to invest in future research. If price increases become necessary to sustain R&D investment, and if increasingly budget constrained reimbursement authorities increasingly refuse to accept high prices, then the existing model of drug development may begin to break down. A response to these challenges has included making best use of mathematical modelling methods in order to identify candidate compounds likely to fail as early as possible and to optimise treatment and trial designs to reduce development cost. This discipline known as Model Informed Drug Development and Discovery is described in the next section.

2. Model Informed Drug Discovery and Development (MID3)

The high, and increasing, cost and rate of failure in drug development has incentivised the pharmaceutical industry to develop and apply a range of mathematical modelling tools to support development decisions. The intention is that modelling may allow problems that could halt development being identified sooner and before large investment of time and resources have already been committed. If small improvements in the likelihood of selecting the optimal compound, identifying the optimal trial design or predicting potential safety issues can be achieved, the resulting increase in efficiency could be substantial.

2.1. History of MID3

The term 'model-based drug development (MBDD)' was used by the FDA in 2004 and encompassed 'pharmaco-statistical models of drug efficacy and safety' with the aim of 'improving drug development knowledge management and development decisions' (Food and Drug Administration, 2004). This was followed up by Lalonde et al. in 2007 in a study that aimed to further define this concept and collate the various tools that are used across the drug development process to support decision making (Lalonde *et al.*, 2007). Six core components of MBDD were identified, as shown in Figure 1.3. These components of MBDD included 1) pharmacokinetic-pharmacodynamic models and disease models; 2) meta-analytic models potentially including competitor compounds; 3) models of trial design and execution; 4) statistical data analytic model; 5) decision analytic models; and 6) trial performance metrics.

MBDD includes activities that have long been routine at certain stages in drug development, such as the use of PKPD models, but that which weren't part of any overarching framework of modelling methods that could support decision making across the lifecycle of development candidates in a consistent and coherent way. More recent work has been undertaken to update what constitutes MBDD and to outline how it can be implemented with greater consistency across drug development projects within the pharmaceutical industry. With an expansion in the potential scope of MBDD and the concept that decisions are 'informed' rather than 'based' on model outputs the term Model Informed Drug Discovery and Development (MID3) is now used (Marshall *et al.*, 2016). This is defined as 'quantitative framework for prediction and extrapolation, centred on knowledge and inference generated from integrated models of compound, mechanism and disease level data and aimed at improving the quality, efficiency and cost effectiveness of decision making'.

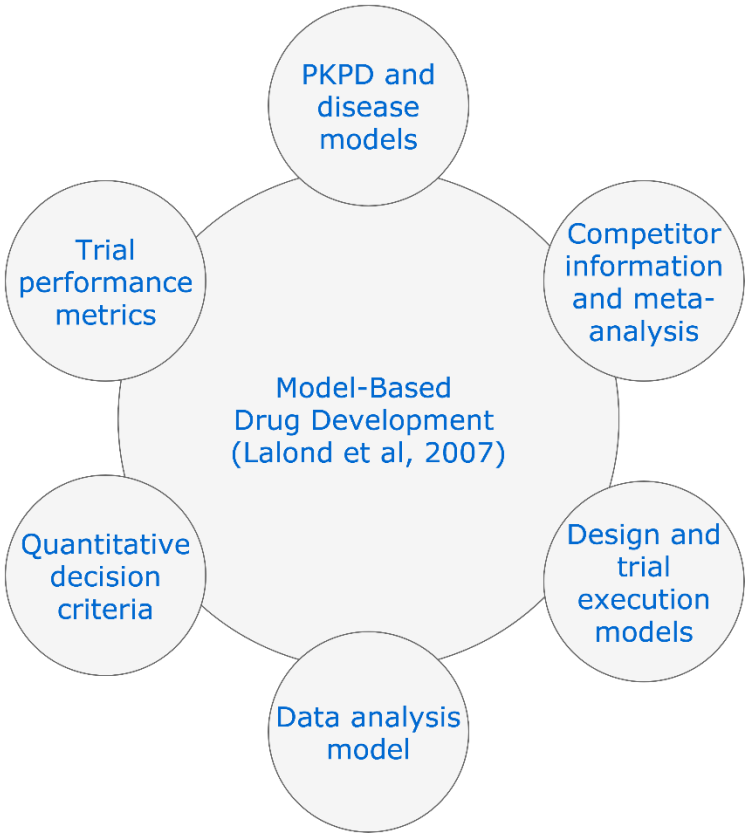


Figure 1.3. Model-Based Drug Development (Lalonde *et al.*, 2007)

The objective of this work was to encourage the move of MID3 from dissociated ad-hoc exercises occurring in isolation to an integrated framework, planned according to the knowledge gaps and in compliance with good practice standards. Seven themes were identified within which R&D questions typically arise, these are reproduced in Table 1.1. These themes span the development cycle from early modelling to evaluate the extent of unmet need and commercial viability of a disease area to designing late phase trials to support regulatory submissions. Related to the R&D themes are five broad quantitative approaches organised according to the degree to which models are mechanistic.

MID3 R&D Themes:

1. Medical need/commercial viability

R&D questions related to the understanding of medical need and areas of potential differentiation from the standard of care for a particular disease/indication. These can inform the likelihood of a particular compound achieving the important aspects of a product profile at each development stage.

2. Efficacy

R&D questions related to the characterization the dose-exposure–response relationship for important efficacy outcomes.

3. Safety/tolerability

R&D questions related to the characterization the dose-exposure–response relationship for important safety/tolerability outcomes.

4. Pharmacokinetics

R&D questions related to the characterization and extrapolation of the pharmacokinetic properties of a drug across species and patient populations, the general expected impact of a progressive disease state, intrinsic (e.g., age, organ impairment), or extrinsic factors (e.g., co-administered drugs), influence of formulation, or administration method on drug exposure, etc.

5. Risk/benefit

R&D questions related to the definition and quantification of the relative trade-offs between important efficacy and safety outcomes in order to determine optimal dose regimens that are sufficiently effective and safe.

6. Clinical viability

R&D questions related to the assessment of potential development programs for a particular indication, considering options with respect to populations, subpopulations, inclusion/exclusion criteria, etc.

7. Study design

R&D questions related to the optimum design of the subsequent studies, balancing the cost and time of the current study vs anticipated future risk given the predicted confidence in achieving the required product profile.

MID3 Quantitative Approaches:

1. Empirical dose/time analysis

Data-driven statistical models that integrate pharmacodynamics (PD) data across doses (or average exposures) and/or time. These are established using empirical functions models with no or limited assumptions related to underlying pathology, physiology, or pharmacology.

2. Empirical Pharmacokinetics and Pharmacodynamics (PKPD)

Standard PKPD modelling where models are established based on available data. General PK and PD principles are utilized in model development.

3. Model Based Meta-Analysis

Estimation of underlying efficacy and/or safety effects through combination of direct or indirect treatment comparisons of summary statistics taking into account the impact of treatment, patient population, and trial characteristics. This type of analysis can help to estimate the probability that a drug is superior to its competitors in the same drug class or across drug classes. Use for the assessment of the comparative risk benefit of compounds of interest.

4. Semi-mechanistic PKPD

PK/PD modelling where models are established based on ‘‘known mechanistic understanding’’ of biology and pharmacology. Most often this will utilize data from different sources (e.g., separate clinical and preclinical studies with different endpoints). Knowledge from one data source will be used to add mechanistic understanding in the interpretation of another data source. Although the model structure and some parameters are derived based on mechanistic understanding, the model is fitted to available data.

5. Systems pharmacology modelling and Physiologically Based PK

Physiologically based or multiscale models that are established based on wide variety of data sources. ‘‘Parameters’’ from these data are extracted via separate analyses and combined together in a mechanistic framework. Multiscale models link target to outcome via modelling that scales from target level interaction to cellular and whole body processes utilizing the understanding of the biology, physiology, PK, pharmacology, and pathology.

Table 1.1. Model Informed Drug Development and Discovery (MID3) research themes and quantitative approaches (Marshall *et al.*, 2016)

2.2. Pharmacometrics

The discipline of pharmacometrics has been defined as 'the science of developing and applying mathematical and statistical methods to characterise, understand, and predict a drug's pharmacokinetic, pharmacodynamic, and biomarker-outcomes behaviour' (Ette and Williams, 2007). Pharmacometrics principally consists of the sub-disciplines of pharmacokinetics (PK) and pharmacodynamics (PD). PK is concerned with 'what the body does to the drug' in terms of its absorption, distribution, metabolism and excretion, or ADME. PD is then concerned with 'what the drug does to the body' in terms of the mechanisms of drug action and understanding the relationship between drug concentration and effect.

PK analysis can be undertaken according to two approaches, a 'non-compartmental' or 'compartmental' approach. Non-compartmental analysis (NCA) imposes no structural assumptions regarding the underlying drug kinetics and does not attempt to explicitly model the concentration-time curve. Many pharmacokinetic parameters can be estimated in this way, including: area under the concentration curve (AUC), rate of drug clearance, mean residence time (MRT), volume of distribution and bioavailability. Explicit modelling of the concentration time curve, such as in Figure 1.4, very often utilises a compartmental modelling approach. Compartmental models are crudely mechanistic in that different compartment are assumed to represent different body tissues or fluid types acting as separate drug reservoirs. A more mechanistic approach to PK modelling and simulation in which model compartments and parameters are intended to explicitly represent physiological entities, such as organs or tissues, or processes are known as physiologically based pharmacokinetic (PBPK) models (Jones and Rowland-Yeo, 2013).

The structures of the two most common compartmental PK models are shown in Figure 1.5. The choice between a one- or two- compartment structure is motivated by observation of the elimination phase of drug disposition. One compartment models may be appropriate when the elimination phase can be modelled using a mono-exponential function, whereas bi-exponential elimination would require a two-compartment model. The modelling approach also depends on the route of drug administration, the examples given in Figures 1.4 and 1.5 are consistent with an orally administered drug since they include an absorption phase and k_a rate parameter to quantify the rate at which the drug enters the central compartment after being ingested. The simulated concentration time curve in Figure 1.4 assumed first-order elimination whereby the elimination rate is proportional to the concentration, however, other types of elimination may be observed (Mould and Upton, 2013).

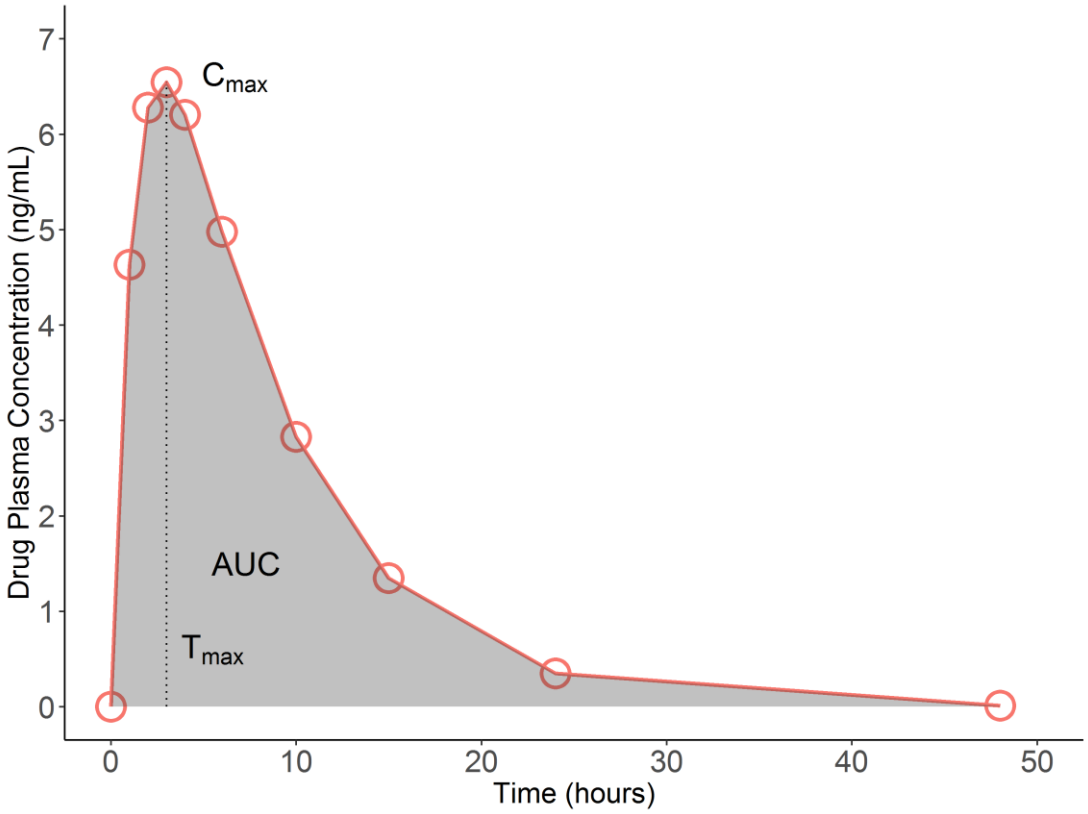


Figure 1.4. Simulated concentration time curve from a one-compartment pharmacokinetic model

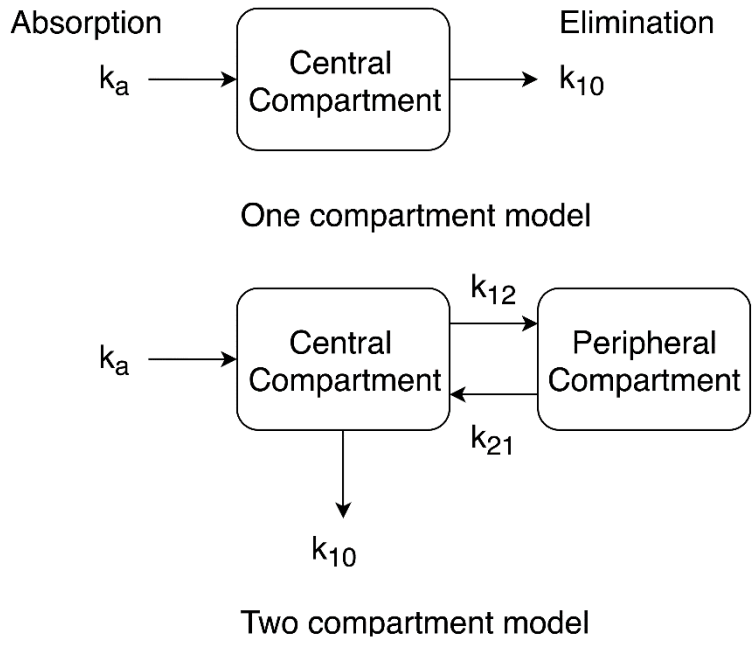


Figure 1.5. One compartment and two compartment pharmacokinetic models (k_{12} = elimination rate constant of drug from central compartment to peripheral compartment; k_{21} = elimination rate constant of drug from peripheral compartment to central compartment)

Analysis of PK data from multiple subjects can be done using a naïve pooled approach or by explicitly modelling the between subject variability, known as population PK, with the addition of fixed and random effects parameters in PK models. Population PK enables the analysis of data where sampling was sparse and quantification of the impact of subject specific covariates (such as age, weight or renal function) on the time course of drug concentration. Estimating the parameters of individual or population PK models can be challenging and specialist software packages are required, NONMEM being the current industry standard (Beal *et al.*, 2013). Population PK modelling has been used to identify appropriate dosing regimens, to identify variability that might contribute to lack of efficacy or predispose patients to adverse events and to extrapolate into different patient populations or different therapeutic areas (Upton and Mould, 2014).

As an example, the rate of change of drug plasma concentration using a one-compartment PK model for oral administration with first order absorption and elimination takes the form of the differential equation 1 (Gabrielsson and Weiner, 2016). This equation can be integrated to give equation 2 describing the time course of drug plasma concentration. The parameters of this PK model are the absorption rate constant (k_a), the elimination rate constant (k_{10}) and the volume of distribution (V_d). Equation 2 is non-linear in these parameters and, when analysing data from multiple subjects as for population PK, there may be both fixed and random effects associated with the parameters (Bonate, 2011).

$$\frac{dC(t)}{dt} = \frac{Dk_a}{V_d}\exp(-k_a t) - k_{10}C(t) \quad (1)$$

$$C(t) = \frac{Dk_a}{V_d(k_a - k_{10})}[\exp(-k_{10}t) - \exp(-k_a t)] \quad (2)$$

The aim of pharmacodynamics (PD) in humans is to describe the relationship between drug concentration and the time course of the effect of the drug, which may be a therapeutic effect or harmful adverse effects. Unlike PK, the possible PD endpoints are more variable and could include effects on biomarkers such as blood glucose or enzyme levels, or could use clinical outcomes such as the occurrence of an adverse event. The most commonly used PD drug models were developed based on models of drug-receptor binding. In the situation where drug response is mediated by a receptor, and assuming conditions of dynamic equilibrium between drug, receptor and drug-receptor complex, the drug effect (E) can be shown to be described by equation 3. This PD model is known as a sigmoid E_{max} concentration effect equation, where E_{max} is the maximum achievable effect, EC_{50} is the drug concentration producing 50% of the maximum effect, n is known as the Hill coefficient and C is the drug concentration. Drugs may also act to reduce or inhibit a response, in which case equation 3 becomes a sigmoid I_{max} model with parameters I_{max} and IC_{50}. In the situation where the Hill coefficient

is assumed or estimated to be 1, the simplified model is referred to as an E_{max} concentration effect equation.

$$E = \frac{E_{max} C^n}{EC_{50}{}^n + C^n} \quad (3)$$

These concentration effect models described above can be applied in different ways depending on whether or not the effect can be assumed to occur without delay, and whether or not the effect of the drug is the same as the pharmacodynamic endpoint of interest (Upton and Mould, 2014). This gives rises to categories of approaches known as direct effect, effect compartment, indirect response and transit models. The example given in Figure 1.6 is of an indirect response model using a stimulatory E_{max} drug PD model applied to the rate constant governing the production of the pharmacodynamic effect of interest, often a biomarker. The net effect/biomarker is the balance between the rate of production and rate of removal and following a change in drug concentration there will be a time delay before a new steady-state of effect/biomarker is achieved. Figure 1.6 is also an example of an integrated PKPD model that provides a framework for modelling the time course of drug effect following drug administration.

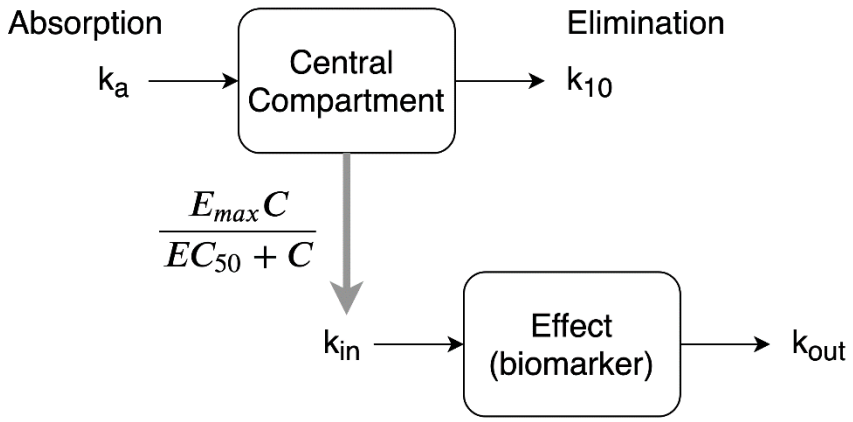


Figure 1.6. One compartment PK model and an indirect effect PD drug model acting to stimulating the production of an effect/biomarker

3. Drug Pricing and Pharmacoeconomics

A successful drug development exercise resulting in a new drug being granted marketing authorisation from a medicines regulator means that it can then legally be provided to patients. It does not, however, guarantee that this will occur. Different jurisdictions across the globe maintain different drug formularies, but almost all are restricted to some extent (Barnieh *et al.*, 2014). In almost all jurisdictions, a reimbursement authority will review the case for adding a new medicine to their formulary which often includes consideration of the effectiveness of the medicine and its price. A common approach includes the use of expert committees for decision making with explicit consideration of the cost of the new drug and often a formal approach to assess cost effectiveness.

The objective of the pharmaceutical industry is to develop medicines that will gain marketing authorisation, reimbursement and provide an acceptable return on investment (ROI). Once a medicine has obtained regulatory approval and is ready for marketing, the resulting revenues depend on many factors including the duration of market exclusivity, the size of the patient population, the share of the market in the situation where there are alternative treatments, the medicine's price and whether or not reimbursement authorities will accept this price. Prices are set by a pharmaceutical company with consideration of reimbursement authorities' perspectives and their willingness to pay for the clinical benefits expected from the new medicine, as well as the companies own costs and ROI requirements (Gregson *et al.*, 2005). This section reviews the processes reimbursement authorities use for making decisions regarding reimbursement of new medicines following regulatory approval.

3.1. Medicine Pricing Summary

Many countries, notably not the Unities States, typically have some level of universal health care provision and a majority of health care financed publicly via taxation or national insurance. Publicly funded health care providers are under pressure to prevent a rapid increase in their costs, including that of medicines. The result is that the providers' drug formularies are restricted and decisions have to be made as to which medicines are reimbursed and for whom. A review of publicly funded health care provision in 34 OECD countries describes many similarities between the reimbursement decision making processes within respective reimbursement authorities (Barnieh *et al.*, 2014). Differences include the initiator of the process of considering a medication having obtained regulatory approval for reimbursement, this may be the manufacturer, the government or patients. Some systems allow for price negotiation to take place during the decision making process, while others do not and make a recommendation/decision on the basis of the proposed drug price.

The systematic evaluation of the properties and effects of a medicine with a view to informing decision making is known as health technology assessment (HTA). A typical HTA to inform a reimbursement decision uses an expert committee that reviews the clinical evidence of effectiveness of a new medication and also its cost. Historically, Japan and the United States have been the exceptions which typically reimbursed nearly all medications without additional consideration of effectiveness and cost following regulatory approval. Recently, however, Japan has established a body responsible for undertaking such evaluations and in the United States, reimbursement decision makers are increasingly considering additional evidence on the cost and effectiveness of new medicines (Pizzi, 2016). A majority of jurisdictions do consider the cost and many also consider evidence in terms of cost effectiveness with either mandatory or recommended use of the QALY (quality adjusted life year) as the measure of effectiveness. The evaluation of costs and QALYs in the reimbursement decision making process can be challenging and require the use of evidence synthesis and economic evaluation. The next section provides an overview of pharmacoeconomics, the discipline concerned with making a comparison of the value of pharmaceutical products.

3.2. Pharmacoeconomics

Pharmacoeconomics is concerned with the comparison between alternative medicines in terms of their cost and health impacts. The process of conducting the analysis of alternative courses of action in terms of both their costs and consequences is known as economic evaluation. As described previously, many payers across different jurisdictions make use of economic evaluation to support their reimbursement decisions. The appropriate method of quantifying health impacts and performing an economic evaluation depends on the underlying economic theoretical framework. All approaches aim to facilitate decision making in order to maximise the well-being of society, but differ in terms of whether health should be valued against other types of goods and in whether individual preferences are accounted for.

The ‘welfarist’ approach, derived from welfare economics, assumes that i) individuals gain utility from the consumption of goods and services; ii) individuals are the best judge of their own welfare and act in order to maximise their utility; and iii) that societal welfare is the sum of individual utilities. The aim may be considered the maximisation of societal welfare with reference to a societal budget constraint (Buchanan and Wordsworth, 2015). Individual utility is defined according to an individual’s willingness to pay for marginal improvements in health, and is therefore a function of individual income and preferences. Health benefits are thus monetised and may be summed over all individuals in society and compared with the societal costs associated required to deliver these health benefits. This process is referred to as cost-benefit analysis (CBA).

The ‘extra-welfarist’ approach departs from standard welfare economics by replacing utility with health as the primary outcome of interest for evaluation. The aim is then generally considered to be to maximise health outcomes in a resource-constrained health care system. It is assumed that health has the same effect on all individuals, thus overriding individual preferences, current level of health and other differences including income (Gyrd-hansen, 2005). The analysis of the incremental health benefit and incremental cost under this approach is known as cost-effectiveness analysis (CEA). While CBA may be considered to have a stronger theoretical foundation it is challenging to implement in practice and for this reason, as well as others including equity concerns, CEA has become the domination approach in the evaluation of health care interventions. Cost utility analysis is a subset of cost effectiveness analysis in which the outcome is measured using quality adjusted life years (QALYs).

QALYs are a composite outcome measure combining quality of life and length of life into a single measure (Torrance, 1986). It was developed in order to facilitate comparisons across different disease areas and interventions. It is calculated by combining weights for the quality of life of being in different health states (i.e. perfect health = 1; death = 0) with the length of time spent in each health state, to obtain an overall measure of length of life weighted by quality of life. There are a variety of different instruments which can be used to determine the quality of life weights (or utility value). The EuroQol 5 Dimension (EQ-5D-3L) (EuroQol Research Foundation 2018, 2018), for example, is a health questionnaire consisting of questions on 5 domains of health. All combinations of responses define 243 possible states and each can be converted to a utility by apply health domain preference weights obtained from surveying the general population.

As well as impacting on the health of patients, alternative choices regarding medication use has the potential to impact on health care spending, either directly via medication price differences or indirectly via changing the levels of use of related health care resources. Economic evaluations generally attempt to capture all the cost implications of alternative decisions that are relevant from the perspective of the health care funding organisation. In the United Kingdom, for example, this organisation is the National Health Service.

When performing an economic evaluation of a newly approved medication, it is the pivotal phase 3 randomised controlled trials (RCT) that provide the highest quality of evidence. However, there are many reasons why RCT data may not be sufficient to estimate the outcomes that are of interest to the decision maker. These include 1) the need to extrapolate beyond the duration of the trial to a time horizon more appropriate to the decision; 2) the need link surrogate to clinical outcomes, if surrogate end points were used in the trial; 3) the need generalise the trial results to a different patient population in which the medications will be used in practice; and 4) the need to make a comparison

to a treatment not included in the RCTs. The solution is to use a decision analytic model comprised of components designed to address these issues. For example, the treatment benefit may be synthesis from multiple sources via network meta-analysis or a disease progression model may be used to link surrogate and clinical outcomes.

3.3. Types of Pharmacoeconomic Model

We refer to a simulation model framework used to extrapolate and generalise based on clinical trials data, and to predict the costs and health benefits of a drug, as a pharmacoeconomic model. The main structural choices that have to be made when developing a pharmacoeconomic model relate to the way in which patients and time are represented (Brennan, Chick and Davies, 2006). This decision is likely to be primarily based on the natural history of the specific health condition and the way that this is modified by the medication options. A high level overview of the most common types of pharmacoeconomic modelling approaches is given in Figure 1.7. In situations where the potential downstream consequences of alternative choices of medication are not too numerous and a relatively short time horizon is appropriate, common in the treatment of acute conditions, then a simple decision tree model structure may be appropriate (Stahl, 2008).

If the time horizon is relatively long and the risks of certain events occurring changes over time, such as for a progressive chronic condition, this can rapidly become unmanageable using a decision tree structure. An alternative and very popular model structure, well suited to modelling chronic conditions, is the discrete time semi-Markov cohort model. The health condition must be described using a finite set of discrete states such that a patient may only ever occupy one state at a time. Where it is appropriate to allow transitions between defined health states, these occur over fixed time intervals known as Markov cycles. The transition probabilities need not remain constant and are typically estimated based on survival data from RCTs. Quality of life (utilities) and costs must be assigned to the health states and these will accrued by the patients that reside in that state per Markov cycle. The model is evolved over many cycles up until the decision time horizon, with costs and QALYs discounted and summed across health states weighted by the numbers of patients occupying each state over time. A diagram showing a simple Markov model structure is given in Figure 1.8.

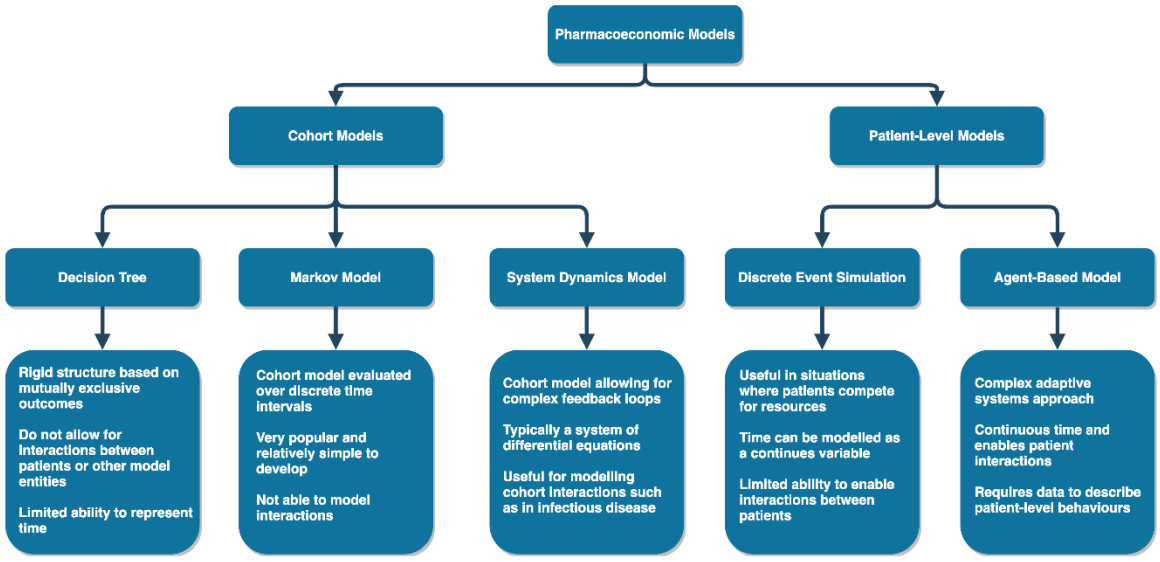


Figure 1.7. Common types of pharmacoeconomic models (Based on (Stahl, 2008; Goeree and Diaby, 2013))

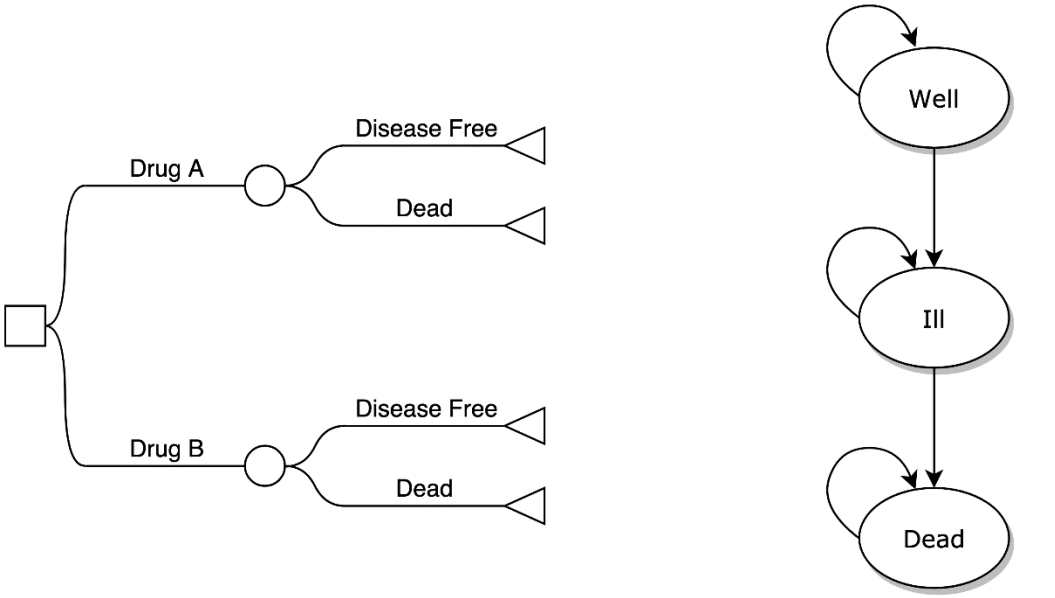


Figure 1.8. Diagrams depicting the two most prevalent pharmacoeconomic modelling approaches

Other less commonly applied pharmacoeconomic model structures include system dynamics models, discrete event simulations and agent-based models. Systems dynamics models represent the system under study as a system of differential equations, this type of model is also used in the compartmental PK models described previously. A discrete event simulation models events occurring over time to

individual patients, where event times may be continuous. The model must cycle through the events in order while updating the attributes of patients within the system. This is well suited to modelling the interaction of patients with resources, such as a hospital bed or a unit of doctor's time. Finally, agent based models adopt an approach that focusses on the micro-level interactions of model agents (such as patients) and allows the macro-level behaviour of the system to emerge through simulating a large number of interaction agents.

3.4. Cost Effectiveness Metrics

The results of pharmacoeconomic modelling may be used to inform decisions regarding the most cost effective medication option, for example, whether a new drug should be adopted over the current standard of care. Decision rules are applied that relate the differences in costs between medication options to the differences in health benefit (Briggs, Claxton and Sculpher, 2006). If one option is expected to result in greater health benefit and to cost less, a situation known as dominance, then this option is cost effective. If, however, as is more commonly the case, one option delivers greater benefits but at higher cost then it may be cost effective depending on the decision makers 'willingness to pay' to obtain greater benefits. The willingness to pay threshold, also known as cost effectiveness threshold, is commonly used in decision rules in pharmacoeconomics and can represent either the value of a unit of health to society or the opportunity cost of displaced alternative medications (Vallejo-Torres *et al.*, 2016).

The incremental cost per unit of health benefit (usually one QALY), known as the incremental cost effectiveness ratio (ICER) as given in equation 4, can be compared with the decision maker's cost effectiveness threshold. Medication options with an expected ICER below the decision maker's threshold are considered cost effective and would be reimbursed. An alternative to the ICER is the net monetary benefit, equation 5, where λ is the cost effectiveness threshold. Where a comparison of medication A and B produces a positive NMB, treatment B would be deemed cost effective.

$$ICER = \frac{cost_B - cost_A}{Utility_B - utility_A} \quad (4)$$

$$Incremental\ NMB = \lambda(utility_B - utility_A) - (cost_B - cost_A) \quad (5)$$

3.5. Sensitivity Analysis

One of the main reasons for using a pharmacoeconomic model, that explicitly links the inputs to a decision problem to the expected outcomes of the possible decisions, is that it enables the impact on these outcomes of uncertainty in model inputs to be quantified. This allows a measure, not only of the best decision in terms of expected outcomes, but also of the probability that the preferred decision

will in fact, not be the best decision once uncertainty on model inputs is resolved. It is common in economic evaluations to implement probabilistic sensitivity analysis (PSA), whereby probability distributions are assigned to all uncertain input parameters. These distributions may be obtainable from the data used to estimate the parameter or it may be necessary to assign distributions using assumptions or expert elicitation. Uncertainty in the model outputs can then be simulated by repeatedly generating new sets of inputs parameters and using the model to generate the corresponding outputs. In pharmacoeconomics, where outcomes are typically the incremental costs and QALYs of alternative medication options, the results of PSA can be presented on the cost effectiveness plane as shown in Figure 1.9.

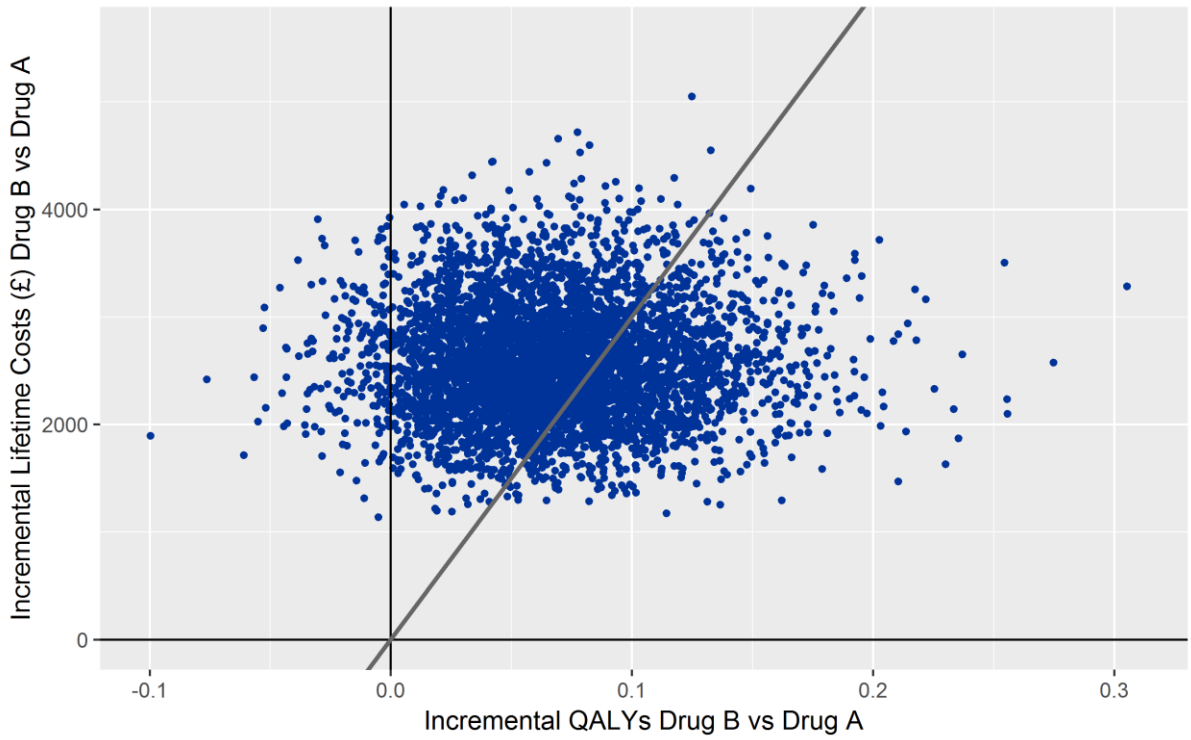


Figure 1.9. The cost effectiveness plane showing the range of possible results obtained via probabilistic sensitivity analysis

3.6. Value of Information

The Expected Value of Perfect Information (EVPI) estimates the value of obtaining perfect information regarding all model inputs, and as such quantifies the cost of uncertainty (Wilson, 2015). It is a function of both the probability of making a decision that is not optimal and the cost associated with the non-optimal decisions. The standard approach to calculating EVPI for a health economic decision problem using a pharmacoeconomic model is to use the PSA results and equation 6, where NMB(j,θ) is the monetary benefit for the j^{th} treatment decision for a given set of input parameters θ. The first term is, therefore, the expectation of the monetary benefit if always able to make the choice j that maximises

the NMB for any parameter set θ, and the second is the payoff for the decision made based on the monetary benefit averaged over all parameter sets.

$$EVPI = E_{\theta} max_j NMB(j, \theta) - max_j E_{\theta} NMB(j, \theta) \quad (6)$$

EVPI can be restricted to perfect information for specific input parameters or groups of parameters, known as partial EVPI. The partial EVPI value for an input parameter reveals the sensitivity of the decision to the uncertainty about that input parameter (Brennan *et al.*, 2007). The partial EVPI for parameter(s) of interest has typically been calculated using a 2-level nested Monte Carlo approach. This requires sampling values of the input parameter(s) of interest in an outer loop and then to sample values from the joint conditional distribution of the remaining parameters and run the model in an inner loop. For complex models, this process can become prohibitively computationally intensive. It is only relatively recently that alternative and less computationally demanding methods of calculating partial EVPI have become available (Strong, Oakley and Brennan, 2014).

4. Medication Adherence

Medication adherence can broadly be defined as 'the extent to which patients take medications as prescribed by their health care providers' (Osterberg and Blaschke, 2005). It is a major contributor to the therapeutic failure of medicines across all disease areas. This is not only true of the routine use of medications in clinical practice, but also applies to patients within later phase clinical trials (Vrijens *et al.*, 2008). Although medication adherence is not the focus of this thesis, it does feature to some extent in each of the four chapters. This section provides an introduction to the relevant topics from the field of medication adherence research, including the terminology used to describe adherence, the methods which exist to measure adherence and what is known about adherence in routine use and in clinical trials.

4.1. Terminology

Medication adherence is a complex behaviour which spans multiple research areas, and as such a large number of overlapping terminology developed to describe its various components. An international research consortium funded by the European commission (Vrijens *et al.*, 2012) published a study in 2012 that aimed to synthesise the various approaches to studying adherence and present a new taxonomy for future research on medication adherence. Throughout this thesis medication adherence is discussed in terms that are consistent with this taxonomy.

Medication adherence is the process by which patients take their medications as prescribed and is composed of three phases. These phases are the time preceding treatment **initiation**; the time between the patients' first and last dose (**implementation**); and the time following cessation or **discontinuation** of treatment. Both initiation and discontinuation are discrete events that are straightforward to describe quantitatively as time-to-event variables from an origin such as when a prescription was given. Between initiation and discontinuation is the implementation phase that encompasses the degree to which a patient's dose taking matches the prescribed regimen while nominally adhering. Imperfect medication implementation can vary to a degree that is effectively infinite, and is therefore challenging to summarise using a small number of variables. Some summary statistics used to describe implementation include the overall proportion of doses taken, the number of drug holidays (missed doses) or the longest inter-dose interval. An overview of the medication adherence process is given in Figure 1.10.

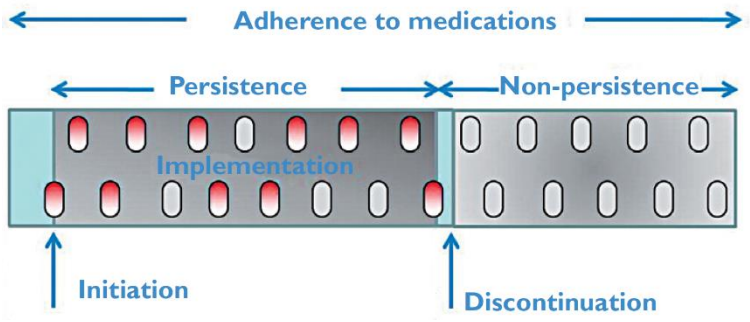


Figure 1.10. Overview of the components of drug adherence from Vrijens et al., 2012, 'A new taxonomy for describing and defining adherence to medications'

4.2. Measurement

Direct electronic monitoring methods provide a means of adherence monitoring that collects reliable data at the level of individual doses (Osterberg and Blaschke, 2005). These include electronic detection of package entry, pills containing sensors activated on ingestion and photographic recording of dose events. The Medication Event Monitoring System (MEMS) (Vrijens *et al.*, 2005) is one such package detection system that has been widely used. MEMS uses an electronic monitor fitted to the lid of pill containers that records the date and time of each bottle opening. This provides data on whether and when individual doses were taken and is, therefore, ideally suited to monitoring the implementation phase of drug adherence, but would be an excessively labour intensive and costly way of tracking initiation and discontinuation. Disadvantages include it relatively high cost and that bottle opens do not guarantee doses are administered.

Alternatives to direct electronic observation of dose events include patient self-report, the use of electronic databases for prescription claims or refill history and patients' unused pill counts (Lam and Fresco, 2015). Electronic prescription databases are accurate but don't capture dose taking at the day-to-day level and can't pinpoint the timing of initiation or discontinuation. Pill counts are also reliable but similarly lack granularity, while self-reports typically result in overestimates of the level of adherence (El Alili *et al.*, 2016). Self-reports and electronic databases are the most common methods used for measuring adherence in the literature (Pednekar *et al.*, 2019).

4.3. Adherence in Clinical Trials

Early phase trials, such as phase 1 first-in-human and phase 2a studies, are likely to be conducted in well controlled clinical settings, in which dose taking is observed by clinicians, which should ensure perfect adherence to the study drug (Czobor and Skolnick, 2011). Later phase studies, however, will generally move to take place in an outpatient setting in which trial participants are required to take responsibility for their own dose taking, resulting in a decline in drug adherence. It is expected that as

adherence declines in later phases of development that the efficacy, or outcomes, observed in each phase will diminish as a consequence. The outcome that would be observed under conditions of perfect adherence is known as 'method-effectiveness' while that which would be seen with the suboptimal adherence typical to routine use of marketing drugs is known as 'use-effectiveness'. The expected decline in efficacy/effectiveness in each phase of development and post-approval is shown in Figure 1.11. Participation in clinical trials enhances overall medication adherence, based on pharmacy refill data (Van Onzenoort *et al.*, 2011), and consequently there is likely to be a final fall in adherence when a drug is marketed.

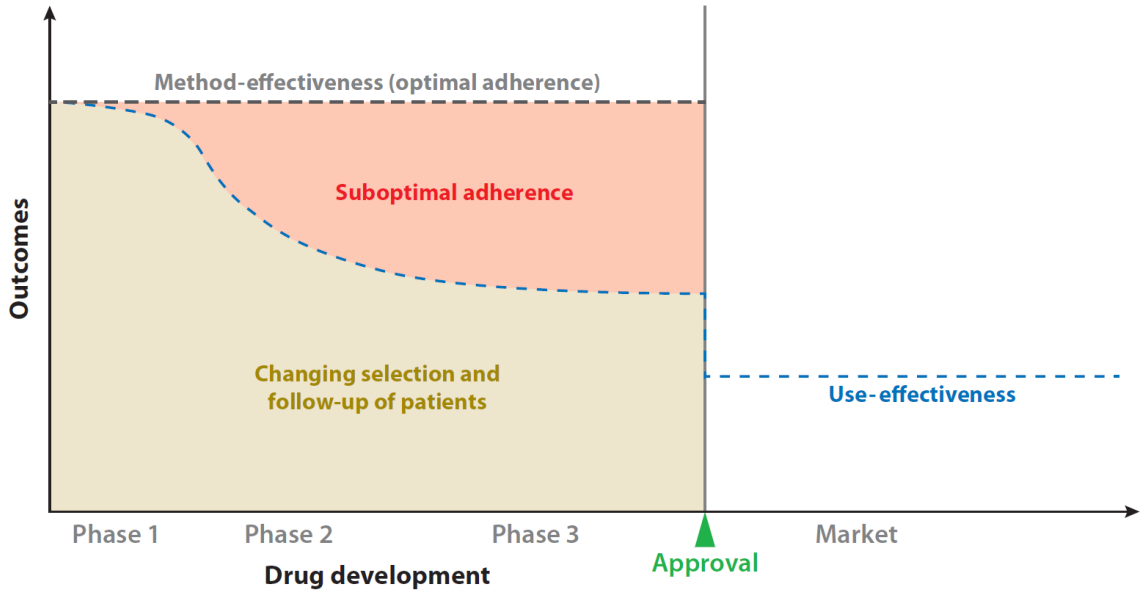


Figure 1.11. Expected decline in adherence and treatment outcome during drug development and beyond reproduced from Blaschke et al., 2012, 'Adherence to Medications: Insights Arising from Studies on the Unreliable Link between Prescribed and Actual Drug Dosing Histories'

Blaschke et al. (Blaschke *et al.*, 2012) presented data on the time course of medication adherence in a cohort of 16,907 patients enrolled in 95 clinical studies which used MEMS to measure adherence. This showed a continuous decline in the number of patients adhering to their medication both in terms of the number who discontinue completely and those who continue to dose correctly. As an example, by day 100, 20% of the participants had discontinued their treatment and of those who would later resume 12% did not take their medication on that day. The results of this study have been reproduced in Figure 1.12.

The potential impact of imperfect adherence in clinical drug development includes an increased probability of type 2 errors, underestimation of efficacy, underestimation of adverse event risks (Breckenridge *et al.*, 2017) and confounding cost effectiveness studies upon which decision regarding pricing and reimbursement may be based (Hughes *et al.*, 2001). In the presence of imperfect drug

adherence, retaining a desired statistical power would require increased sample sizes (Mallayasamy *et al.*, 2018) thus adding to the development costs. It can also have an impact on the development and utility of pharmacokinetic and pharmacodynamic models routinely used to inform a multitude of drug development decisions (Vrijens and Goetghebeur, 1999).

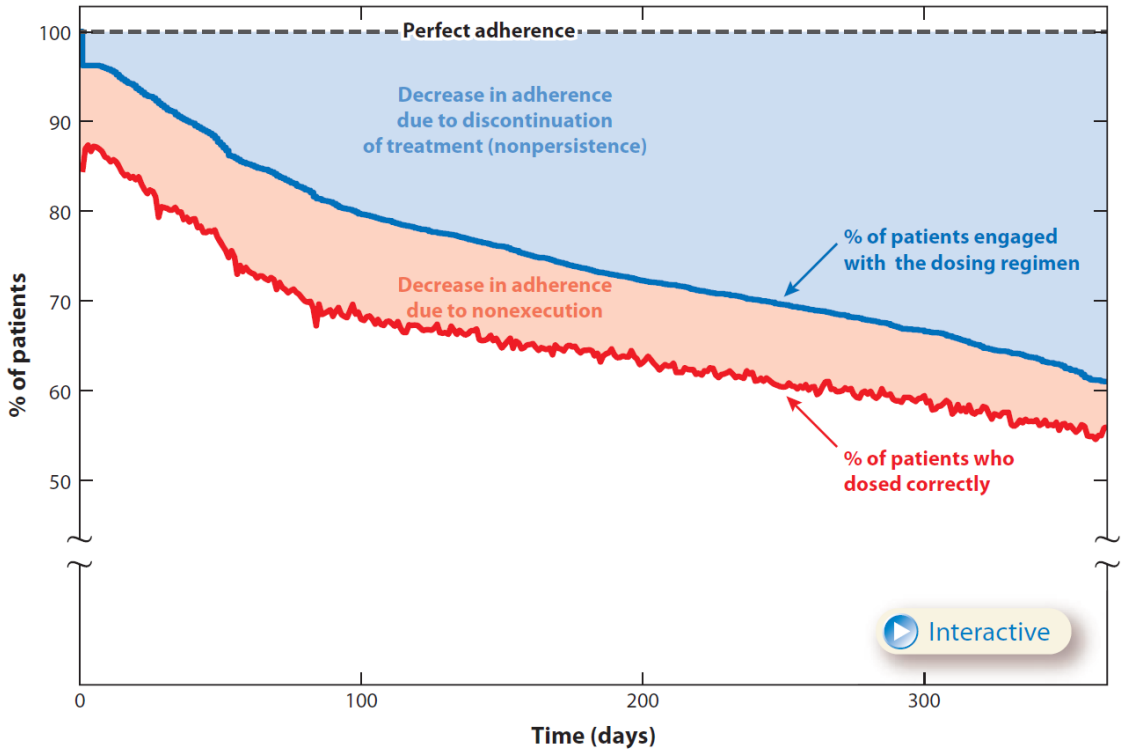


Figure 1.12. Kaplan Meier plots of drug persistence and correct dosing taken from Blaschke et al., 2012, 'Adherence to Medications: Insights Arising from Studies on the Unreliable Link between Prescribed and Actual Drug Dosing Histories'

4.4. Adherence in Routine Use

To study adherence in the routine use of medications in whole populations, the most scalable solution has proved to be pharmacy prescription claims databases. Studies analysing prescription claims databases provide crude measures of adherence, but can provide estimates from large patient populations. In 167,907 patients in the United States, in the 12 months following first prescription the proportion of days with drug supply based on collected prescriptions (proportion of days covered) was between 35 and 72% across 6 different chronic medication classes (Yeaw *et al.*, 2009). Another similar study classed patients as adherent to their medication if, during the year following first collected prescription, they collected enough medication to cover 80% of more of days. Analysing data from 706,032 patients with at least one of seven medical conditions the proportion of patients classed as adhering ranged from 37 to 68% (Briesacher *et al.*, 2008). Measures of adherence from prescription

claims databases provide an upper bound on patient adherence, since not all doses collected are necessarily taken.

In addition to increasing the likelihood of therapeutic failure, imperfect adherence of marketed drugs may have further negative consequences including; inappropriate dose escalation (Heaney and Lindsay, 2013), allowing the emergence of drug resistant pathogens (Vrijens and Urquhart, 2005), hazardous rebound/first-dose effects (Urquhart, 1998) and misdiagnosis. All of these have the potential to reduce the benefit or cause harm to patients and increase costs on the health care system.

4.5. Drug Forgiveness

When a patient ceases to take their medication, whether temporarily or permanently, the therapeutic effect of the drug will diminish over time. The rate at which this occurs will depend on the drug, the formulation and the disease. This post-dose duration of drug action determines the extent to which the drug may remain effective when dose implementation is erratic and is known as 'forgiveness' (Urquhart, 1995). The probability of therapeutic success under conditions of perfect adherence can be compared with that under real-world imperfect adherence conditions to define the drug's relative forgiveness (Assawasuwannakit, Braund and Duffull, 2015). A consideration of relative forgiveness could inform decision making during drug development, since those candidates with greater forgiveness can be expected to maintain a greater therapeutic effect in later phase and post-marketing studies in which adherence is likely to decline.

Another aspect of therapy that can also have an impact on the ability of a drug to maintain a therapeutic effect under conditions of imperfect adherence is the dosing regimen. Studies comparing the overall proportion of doses taken under different regimens find superior adherence to once-daily versus more frequently dosing intervals (Claxton, Cramer and Pierce, 2001). However, the shorter dose interval of high frequency regimens has been found to mitigate against this difference to some extent. Since the same relative drop in drug plasma concertation in a twice-daily regimen requires 2-3 consecutive missed doses for a single missed dose in a once-daily regimen it is not straightforward to conclude that once-daily regimens are always superior in terms of adherence (Tousset *et al.*, 2007).

5. Pharmacology of Urate-Lowering Therapies

The chapters of this thesis have used urate-lowering therapies for the treatment of hyperuricemia in gout patients as the case study in which to demonstrate applications of the linked pharmacometric pharmacoeconomic methodology. Each chapter will introduce the relevant treatment options and describe important aspects of their pharmacology. However, it is useful to have an overview of the pharmacology of the three urate-lowering therapies that will be the focus of subsequent chapters and this is provided below.

5.1. Allopurinol

Allopurinol has long been the first-line urate lowering therapy for the treatment of hyperuricemia in gout patients. It was first approved by the FDA in 1966 for the treatment of gout. It is approved for once daily dosing up to 800 mg in the US and 900 mg in Europe; guidelines also recommend titration up to these maximum dosages until treatment target is achieved (D. Khanna *et al.*, 2012; Hui *et al.*, 2017). Despite this, 300 mg/day is commonly prescribed and is one that has most frequently been used in clinical trials of more recently developed urate-lowering agents (Kydd *et al.*, 2014).

Allopurinol is rapidly absorbed following oral administration and has a bioavailability of approximately 80%. Peak allopurinol plasma concentrations of approximately 2 mg/L are achieved at about 1.5 hours following an oral dose of 300 mg. Allopurinol is rapidly and extensively metabolised to oxypurinol, the active metabolite that is responsible for the majority of the urate lowering effects (Day *et al.*, 2007). The binding to plasma proteins of both allopurinol and oxypurinol is negligible.

Allopurinol is an analogue of hypoxanthine and oxypurinol is an analogue of xanthine. The typical half-life for allopurinol is 1.2 hours and for oxypurinol it is 23 hours. The small fraction of allopurinol not converted to oxypurinol is renally excreted. The primary route of elimination of oxypurinol is also by renal excretion, and therefore, the clearance of oxypurinol is decreased in patients with renal impairment (Day *et al.*, 2007). There are several transporters involved in the reabsorption of oxypurinol after it's filtration at the glomerulus. Some of these are the targets of uricosuric agents, which results in an increase in the renal clearance of oxypurinol thus reducing its urate lowering effects.

Both allopurinol and oxypurinol lower serum concentrations of uric acid by inhibiting xanthine oxidase, the enzyme responsible for catalysing the conversion of hypoxanthine to xanthine and xanthine to uric acid. The most significant safety concern relating to allopurinol is the rare but serious allopurinol hypersensitivity syndrome (Dalbeth, Merriman and Stamp, 2016).

5.2. Febuxostat

Febuxostat is another xanthine oxidase inhibitor that received regulatory approval in Europe in 2008, in the US in 2009 and in Japan in 2011. The recommended daily dosages are 40 mg or 80 mg in the US or up to 120 mg in Europe (Sattui and Gaffo, 2016). Unlike allopurinol, febuxostat is not a purine analogue.

Febuxostat is rapidly absorbed after oral administration and reaches maximum plasma concentrations after about 1.5 hours and is highly bound to plasma proteins. It is primarily metabolised in the liver via either glucuronidation or oxidation. The metabolites and some unchanged drug are then excreted either via the gut or kidneys (Kamel *et al.*, 2017). Monitoring of liver function is recommended since possible side effects of febuxostat may include liver enzyme elevations. It is contraindicated in patients with liver disease (Dalbeth, Merriman and Stamp, 2016).

Febuxostat reduces the rate of uric acid synthesis by mixed-type competitive and uncompetitive inhibition of xanthine oxidase. In four pivotal phase 3 trials of febuxosatat 80 mg the percentage of patients achieving the primary end-point of reduction of serum uric acid to target concentrations ranged from 57% to 73%. In all cases this was determined to be superior efficacy compared to allopurinol at a daily dose of 300 mg (Tayar, Lopez-Olivo and Suarez-Almazor, 2012).

Due to concerns regarding the cardiovascular safety of febuxostat a post-marketing study was conducted to determine whether febuxostat was noninferior to allopurinol with regard to major cardiovascular events in patients with gout and cardiovascular disease (White *et al.*, 2018). This study found that all-cause mortality and cardiovascular mortality were higher for febuxostat than for allopurinol.

5.3. Lesinurad

Lesinurad is a selective uric acid reabsorption inhibitor that inhibits urate transporter 1 (URAT1). This transporter, located in the renal proximal tubule, is one of those responsible for the reabsorption of uric acid after filtration at the glomerulus. This serves to stimulate the renal excretion of uric acid and lower serum uric acid concentrations. It has marketing authorisation for use in combination with a xanthine oxidase inhibitor, in patients who are not treated successfully on a xanthine oxidase inhibitor alone (Keenan and Schlesinger, 2016).

A 200 mg dose of lesinurad reaches a maximum plasma concentration after around 1-4 hours following administration. Once absorbed, lesinurad is extensively bound to plasma proteins. It is metabolised predominantly by CYP2C9 enzymes before being excreted via the kidney and the gut. In urine, approximately 30% of the dose of lesinurad is present in an unmetabolized form. Lesinurad's

elimination half-life is approximately 5 h. No dosage adjustments are required in patients with mild or moderate hepatic impairment. It has potential to reduce the efficacy of concomitant medications that are CYP3A substrates (Hoy, 2016).

A dose dependant increase in renal adverse events was observed in clinical trials of lesinurad. This is likely to be due to uric acid crystalluria, made more likely due to the increase in urinary uric acid concentration induced by lesinurad (Sanchez-Nino et al., 2017). For example, in data pooled from the three phase 3 studies, over 2-fold increases from baseline in serum creatinine levels were observed in 1.8%, 6.7% and 0% for the 200 mg, 400 mg and placebo plus xanthine oxidase inhibitor groups respectively (Hoy, 2016). A second safety signal observed in clinical trials was from cardiovascular events; the percentage of patients experiencing major cardiovascular events within the first year was 34% higher with lesinurad 200 mg/day than with placebo (Sanchez-Nino *et al.*, 2017).

5.4. Other Urate-Lowering Therapies

There are many urate-lowering therapies other than those described above. These will be mentioned occasionally in the various chapters. These include uricosurics such as probenecid, benzbromarone, sulfinpyrazone; and recombinant uricases such as rasburicase and pegloticase. There are various reasons that the use of these medications is not very widespread, and this will also be described where relevant. A more detailed description of the pharmacology of these agents is, therefore, not considered necessary. Summaries can be obtained elsewhere in the published literature, e.g. (Dalbeth, Merriman and Stamp, 2016; Keenan and Schlesinger, 2016).

6. Pharmacoeconomics in Drug Development

The traditional objective of a drug development exercise is to successfully obtain regulatory approval of a new medicine for a specific patient population. However, this makes no account of the fact that following regulatory approval there is also the reimbursement hurdle to be crossed before patients can receive the medicine or the company can gain a return on its investment. It is notable that economic evaluation is not present in the literature regarding MID3. Not considering the requirements of drug reimbursement authorities during development may result in late stage termination of projects that are deemed not commercially viable only after substantial resources have been invested, or in medicines gaining regulatory approval only to prove unmarketable at a commercially viable price or failing to gain substantive market share.

6.1. Early Economic Evaluations

Despite the fact reimbursement is not traditionally integration within drug development or MID3, early economic evaluation is not new. Ijzerman et al. (Ijzerman *et al.*, 2017) provide a recent review of the field of early health technology assessment that dates back to at least the mid-90s. The definition of early HTA used is 'all methods used to inform industry and other stakeholders about the potential value of new medical products in development, including methods to quantify and manage uncertainty'. This review found 22 studies published between 2013 and 2016 that discussed, proposed, or applied early HTA as defined above. While the overall objective of such exercises is to identify commercial failures as early as possible, various approaches were identified depending on the decision and development stage. The five main reasons (Hartz and John, 2008) that early economic evaluation have been performed are to:

1. **Inform strategic R&D decisions**: synthesis of evidence throughout the development processes to predict economic outcomes for existing candidate compounds early and reduce the risk in R&D decisions.
2. **Perform preclinical market assessments**: combine information on disease natural history, target population, epidemiological factors and existing interventions to assess the economic potential for successful drug development efforts in this area.
3. **Inform portfolio decisions**: study economic potential of candidate compounds over an entire development portfolio to inform go/no-go decisions, improve allocative efficiency and reduce R&D spending.
4. **Support clinical trial design**: Study the impact of design choices such as number of subjects, comparator arms, trial endpoints, and inclusion/exclusion criteria on the subsequent economic analyses. Also to evaluate the impact of uncertainty and those parameters most influential to subsequent estimates of cost effectiveness.
5. **Inform market access and pricing strategies**: Estimation of potential prices acceptable to reimbursement authorities or market placement in terms of patient population and indication.

In some cases, such as in informing market access and pricing strategies, early economic models may be designed as closely as possible to reflect the reimbursement authorities' approach to valuing new medicines. However, other applications of early economic modelling may take a different approach to the typical HTA in support of reimbursement more consistent with a valuation of development candidates from the pharmaceutical perspective. The major challenge to early economic modelling is uncertainty regarding a drug's potential efficacy and safety prior to large scale phase 3 trials being

conducted (Hartz and John, 2008). This results from the small samples used in phase 1 and 2 trials, the short follow-up periods and medication taking settings that are likely to differ substantially from both routing use and phase 3 settings.

6.2. Linked Pharmacometric and Pharmacoeconomic Modelling

Linked pharmacometric and pharmacoeconomic modelling (also known as pharmacokinetic-pharmacodynamic-pharmacoeconomic - PKPDPE - modelling) has emerged as a potential means of reducing the limitation of small trials and facilitating early economic evaluations (Hughes and Walley, 2001; Poland and Wada, 2001; Pink, Lane and Hughes, 2012). This makes use of the potential of pharmacometric models to describe dose response relationships while accounting for individual covariates, and to extrapolate and simulate untested medication use scenarios. The methodology proposes that PKPD models, developed from early phase trials, are used to generate inputs to pharmacoeconomic models via simulation.

Experience of pharmacometrics in pharmacoeconomic evaluation is limited and the notable examples of this methodology are reviewed below. The potential applications of PKPDPE include (Swift *et al.*, 2018):

1. Providing early indications of cost-effectiveness before large-scale trial data become available;
2. Directing future research based on the cost of reducing uncertainty;
3. Providing early indications of cost-effectiveness for specific subgroups, dosing schedules or protocol deviations (e.g. impact of non-adherence on cost-effectiveness);
4. Informing strategic research and development along with pricing decisions;
5. Estimating the cost-effectiveness of complex pharmaceutical interventions (such as pharmacogenetic testing).

Poland & Wada (2001) (Poland and Wada, 2001) were amongst the first to publish an application of this methodology. They linked a drug-disease model to an economic model in order to compare dosing strategies of an HIV protease inhibitor in the presence of imperfect drug adherence. This described a real-world case study at phase 2 and included models for medication adherence, PK, PD and economics used to forecast net present value (NPV) under alternative dosing strategies. At a similar time, Hughes & Walley (Hughes and Walley, 2001) published a study examining how the results of clinical trial simulations may be used to provide inputs to economic models, enabling economic consequences to be considered at phase 2.

Pink et al. (Pink, Lane and Hughes, 2012) tested the concept of a linked PKPDPE modelling by comparing the results of a trial based economic evaluation with those obtained via a PKPD model

driven CTS. This found that both methods provided similar results in terms of the likely decision based on cost effectiveness, however, they note this will be more challenging in examples that are borderline cost effective. Pink et al. (Pink *et al.*, 2014) applied PKPDPE to estimate the effectiveness of pharmacogenetics-guided warfarin, for which no trials had been conducted, and then to compared this to alternative anticoagulants and estimated cost effectiveness.

Van Hasselt et al. (Van Hasselt *et al.*, 2015) developed an integrated simulation framework consisting of models for disease progression/clinical outcome, adverse events, treatment dropout, quality of life and cost effectiveness. The case study was of eribulin for the treatment of castration-resistant prostate cancer and the model was applied to assess the cost effectiveness of alternative dosing regimens, treatment protocols and patient characteristics.

Slejko et al. (Slejko *et al.*, 2016) present an early economic model based on a hypothetical compound in drug development. The limitations of predicting efficacy associated with early development is addressed with the application of a model-based meta-analysis. Most recently, Kamal et al. (Kamal *et al.*, 2017) demonstrate the application of linked PKPD, epidemiology and health economic models in estimating the benefits and cost effectiveness of oseltamivir to contain an influenza pandemic. Their work does not adopt a drug development perspective but could potentially be applied to compounds undergoing development.

7. Thesis Aim and Objectives

The principal aim of this thesis is to develop, and to demonstrate the value of, linked pharmacometric and pharmacoeconomic modelling in clinical drug development. In particular, the objectives are to:

- Develop novel applications: to begin to define the limits for the utility of this approach in terms of the drug development timeline or in the types of decision problems it could be used to inform.
- Identify limitations: As well as demonstrating the value of this methodology, this thesis aims to provide a greater understanding of the limitations and assumptions that are likely to be required.
- Promote uptake: by expanding the existing library of applications it will showcase the potential value of linking these two disciplines in order to promote their uptake by the pharmaceutical industry.

These objectives will be achieved through the application of the linked pharmacometric and pharmacoeconomic methodology to a case study which includes many of the challenges commonly encountered during drug development. The case study is of urate-lowering therapies for the

treatment of hyperuricemia in gout patients and was selected, and developed, in collaboration with scientists within global pharmacometrics at Pfizer Ltd. This group have a longstanding interest this discipline and have made substantial contributions to the development of MID3 (Marshall *et al.*, 2016).

Chapter 2 develops a PKPD model for the chosen case study of urate-lowering therapies (ULTs) for the treatment of hyperuricemia in gout patients. Pharmacokinetic models for two ULTs, febuxostat and lesinurad, were reconstructed from literature sources. A pharmacodynamic model structure was obtained through the collaboration with the pharmacometrics group at Pfizer Ltd. Estimation of the parameters of this model required structural modifications and data from several published sources. The functionality of this model, in particular the semi-mechanistic indirect response pharmacodynamic model, was demonstrated by simulating the time course of serum uric acid (sUA) concentration and urinary uric acid (uUA) under conditions of imperfect medication adherence. The results were used to study the potential for hazardous first dose effects resulting from partial adherence.

Chapter 3 presents the development of a pharmacoeconomic model comparing alternative ULTs in gout patients and the application of linking this to the PKPD model. The pharmacoeconomic model predicts the long term cost and QALY impacts of moving patients into lower sUA concentration subgroups. The PKPD model was also extended to include an additional ULT, allopurinol. The linked PKPDPE model was then applied to simulate cost effectiveness results for lesinurad dual-therapies versus monotherapies under conditions of varying drug adherence. This chapter is potentially relevant from the pharmaceutical industry perspective moving into phase 3, or from the perspective of the reimbursement authority interested in cost effectiveness under more realistic adherence patterns.

While Chapter 3 applies linked PKPDPE to a late stage decision problem, Chapter 4 applies the same models but to inform early decision making, when selecting which compounds to take forward into clinical development. The aim was to estimate the value in selecting compounds more forgiving to missed doses by explicitly acknowledging that drug adherence is likely to fall in later phase trials. The value of hypothetical compounds, with modifications to either the rate of systemic clearance or potency, is estimated in terms of their ability to reduce sUA and maximum reimbursement price following a health technology assessment.

Finally, Chapter 4 applies the PKPDPE model to the problem of designing a phase 3 trial. The PKPD model was embedded within a clinical trial simulation that also includes recruitment and adherence components. Simulated trial results were then used as inputs to the pharmacoeconomic model that estimates the maximum reimbursement price for a given cost effectiveness threshold, such that

pricing is linked to the trial outcomes. Probabilistic sensitivity analyses and an efficient method of estimating parameter level value of information were implemented to quantify the impact of uncertainty in specific input parameters on the decision between trial design options.

Chapter 2

Impact of Non-Adherence on the Safety and Efficacy of Uric Acid-Lowering Therapies in the Treatment of Gout

1. Summary

Dual-urate lowering therapy (ULT) with xanthine oxidase inhibitor and uricosuric medications is a treatment option for severe gout. Uricosurics can cause hyperuricosuria, a risk factor for nephrolithiasis and acute uric acid nephropathy. The aims of this study were to simulate the relation between suboptimal drug adherence and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving mono and dual-ULTs.

The impact of poor medication adherence was studied using 2-compartment PK models based on published evidence and a semi-mechanistic, 4-compartment pharmacodynamic (PD) model. The PKPD model was used to simulate mono and dual-ULT in gout patients with either under-excretion (lowered clearance) or overproduction of uric acid, with suboptimal adherence modelled as either a single drug holiday of increasing duration or doses taken at random.

Simulation results showed a surge in urinary uric acid occurring when dosing is restarted following missed doses. For under-excreters taking a 20 day drug holiday, the addition of 200 mg (or 400 mg) lesinurad to 80 mg febuxostat increased the percentage of patients experiencing hyperuricosuria form 0% to 1.4% (or 3.1%). In overproducers, restarting ULTs following drug holidays of more than 5 days leads to over 60% of patients experiencing hyperuricosuria.

Sub-optimal medication adherence may compromise safety and efficacy of mono and dual-ULTs, especially in patients with gout resulting from an overproduction of uric acid. Clinicians and pharmacists should consider counselling patients with respect to the risks associated with partial adherence, and offer interventions to improve adherence or tailor treatments, where appropriate.

2. Introduction

Gout is a painful and disabling chronic disease which has proven difficult to treat and affects a large and increasing number of people (Dalbeth, Merriman and Stamp, 2016). Long term treatment with urate lowering therapies (ULTs) aims to reduce serum uric acid (sUA) concentrations to below the point of saturation (approximately 7 mg dL^{-1} (420 µmol L^{-1})). When treatment with a xanthine oxidase inhibitor (XOi) alone is unsuccessful, a uricosuric can be used in combination (Richette *et al.*, 2017). Historically, the use of uricosurics for long-term therapy has been limited due to possible hepatotoxicity (benzbromarone) and drug-drug interactions (probenecid). However, the uric acid transporter-1 (URAT-1) inhibitor lesinurad has recently gained regulatory approved and is intended for long-term therapy in combination with an XOi (such as allopurinol or febuxostat) (Miner *et al.*, 2016).

As they increase the renal excretion of uric acid, uricosurics such as lesinurad, can cause hyperuricosuria (urinary excretion of uric acid ≥800 mg day^{-1} in men; ≥750 mg day^{-1} in women) (Pak *et al.*, 2002). High levels of urinary uric acid (uUA) can cause kidney damage which may be acute, such as stone formation (nephrolithiasis) (Bluestone, Klinenberg and Lee, 1980) and intrarenal obstruction (acute urate nephropathy), or chronic as in chronic (or gouty) nephropathy. Acute kidney injury can occur when uric acid concentrations in renal tubules reach supersaturation, which also depends on urine pH (Maalouf *et al.*, 2004; Hahn *et al.*, 2017). Chronic nephropathy is thought to result from long-term hyperuricosuria which may be below supersaturation concentrations. The existence of chronic nephropathy remains controversial (Moe, 2010), but is supported by animal models and some epidemiological studies (Bellomo, 2013). The harmful effects of uric acid on the kidney are a possible explanation of the association, in recent clinical trials, between lesinurad and an increase in the rate of raised serum creatinine and, for higher doses, with serious renal adverse events (EMA, 2015).

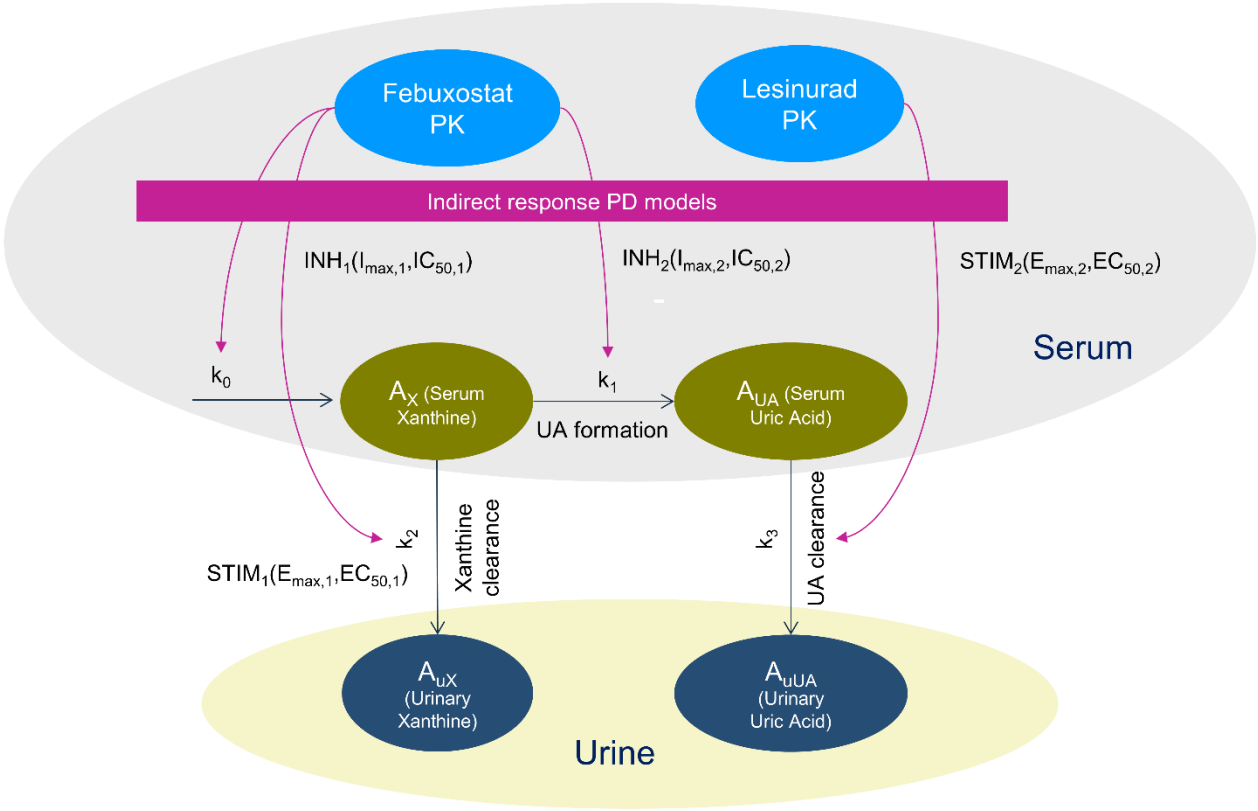
Adherence to ULT is known to be amongst the lowest of any chronic disease treatment (Briesacher *et al.*, 2008; De Vera *et al.*, 2014), with 70% of patients having a drug holiday of at least 60 days over 6 years. Poor adherence to allopurinol monotherapy is associated with lower treatment success rates (Halpern, Mody, *et al.*, 2009). While dual-therapy increased response rates compared with monotherapy in clinical trials (Dalbeth *et al.*, 2015; Bardin *et al.*, 2017; Saag *et al.*, 2017), interruption in dosing (drug holiday) could result in high peaks in uUA concentration when treatment is restarted. Sub-optimal implementation of the dosing regimen (e.g. late doses, skipping a dose, or drug holidays) (Vrijens *et al.*, 2012), may therefore increase the risk of renal adverse events caused by uric acid nephropathy.

This study aims to simulate the relation between poor implementation of dosing and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving mono- and dual-ULT.

3. Methods

3.1. Strategy

A semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) model, based on previous research on the systems pharmacology of the purine metabolic pathway (Dua *et al.*, 2014), was developed to capture the pharmacology of ULTs (Figure 2.1). The system was comprised of four compartments utilising a zero order production rate (k_0) governing the formation of xanthine and first order production rates characterising its biotransformation to uric acid (k_1) and the elimination of xanthine (k_2) and uric acid (k_3) into the urine. These in turn were parameterised in terms of volumes and clearance terms.



$$\frac{dA_X}{dt} = k_0 INH_1 - k_1 INH_2 A_X - k_2 STIM_1 A_X \quad (7)$$

$$\frac{dA_{UA}}{dt} = k_1 INH_2 A_X - k_3 STIM_2 A_{UA} \quad (8)$$

$$\frac{dA_{uX}}{dt} = k_2 STIM_1 A_X \quad (9)$$

$$\frac{dA_{uUA}}{dt} = k_3 STIM_2 A_{UA} \quad (10)$$

$$INH_1 = \frac{IC_{50,1}}{IC_{50,1} + C_F(t)} \quad (11)$$

$$INH_2 = \frac{IC_{50,2}}{IC_{50,2} + C_F(t)} \quad (12)$$

$$STIM_1 = 1 + \frac{E_{max,1} C_F(t)}{EC_{50,1} + C_F(t)} \quad (13)$$

$$STIM_2 = 1 + \frac{E_{max,2} C_L(t)}{EC_{50,2} + C_L(t)} \quad (14)$$

Figure 2.1. Diagrammatic and mathematical representations of the pharmacodynamics of dual-urate lowering therapies. k_0, k_1, k_2 and k_3 are the rate parameters for the production of xanthine, xanthine to uric acid conversion, removal of xanthine to urine and removal of uric acid to urine, respectively. INH_1, INH_2, $STIM_1$ and $STIM_2$ are the pharmacodynamic model drug functions. A_X and A_{UA} are the total time-varying amounts of xanthine and uric acid in serum, respectively.

The PD model characterises the time course of sUA, uUA, xanthine and urinary xanthine. Two inhibitory indirect response (turnover) models were used to account for the effect of multiple doses of febuxostat on k_0 and k_1 (Gabrielsson and Weiner, 2016). A stimulatory indirect response (Sharma and Jusko, 1998) equation acting on the k_2 rate parameter was incorporated to model the increased xanthine renal clearance associated with febuxostat (Khosravan *et al.*, 2006). The clearance of uric acid upon multiple doses of lesinurad was modelled using a stimulatory indirect response equation acting on the k_3 rate parameter.

The system and drug PD model parameter estimates were obtained from literature and other publicly available sources. As described below some parameters values were taken directly from the literature while others were estimated using non-linear mixed effects models and clinical trials data**.** The parameters required to characterise the pharmacodynamic model are given in Table 2.1.

Model	Name*	Source	Parameter estimates		BSV (SD^2)#	
System PD Parameter	BX (mg)	Estimated	θ_1	8.94	-	NE
	VX (dl)	Estimated	θ_2	333	-	NE
	CLX (dl/h)	Literature	θ_3	10.57	-	NE
	BUA (mg)	Estimated	θ_4	703	-	NE
	VUA (dl)	Estimated	θ_5	154	-	NE
	CLUA (dl/h)	Literature	θ_6	4.11	-	NE
Febuxostat PD Parameter	$E_{max,1}$	Assumed	θ_7	3	-	NE
	$EC_{50,1}$	Assumed	θ_8	0.001	-	NE
	$I_{max,1}$	Assumed	θ_9	1	-	NE
	$IC_{50,1}$	Estimated	θ_{10}	0.1320	η_3	0.2
	$I_{max,2}$	Assumed	θ_{11}	1	-	NE
	$IC_{50,2}$	Estimated	θ_{12}	0.00113	η_3	0.2
Lesinurad PD Parameter[a]	E_0	Literature	θ_{13}	6.77	-	NE
	E_{max}^D	Literature	θ_{14}	-2.55	η_4	0.346
	b_{crcl}	Literature	θ_{15}	0.564	-	NE
	EC_{50}^D	Literature	θ_{16}	0.0974	-	NE

Table 2.1. PD parameters for febuxostat and lesinurad - literature and statistical estimates combined

*BX: Baseline amount of xanthine; VX: Volume of xanthine distribution; CLX: Renal clearance of xanthine; BUA: Baseline amount of uric acid; VUA: Volume of uric acid distribution; CLUA: Renal clearance of uric acid; $E_{max,1}$ and $EC_{50,1}$: parameters of $STIM_1$ acting on k_2; $I_{max,1}$ and $IC_{50,1}$: parameters of INH_1 acting on k_0; $I_{max,2}$ and $IC_{50,2}$: parameters of INH_2 acting on k_1; E_0, E_{max}^D, b_{crcl} and EC_{50}^D: literature values used to derive parameters of $STIM_2$ acting on k_3

#BSV: Between subject variability; SD: Standard deviation; NE: Not estimated; Error model used: $\theta_i = \theta_u \exp(\eta_i)$

[a]Lesinurad: Parameters of the direct Emax model used to derive the corresponding parameters of the indirect response model.

3.2. Pharmacokinetics

Two-compartment models with first order absorption for febuxostat and lesinurad obtained from the literature (Center for Drug Evaluation and Research., 2008, 2014) were used to simulate typical and individual subject level drug plasma concentration time courses. The PK parameters, covariate effects and associated between subject variability are reproduced in Table 2.2.

Parameter	Febuxostat		Lesinurad	
	Estimate	BSV (CV%)	Estimate	BSV (CV%)
CL/F_0 (dl h^{-1})[a]	49.3	18.3	69.9	63.4
b_CRCL	0.142	NA	0.322	NA
b_WT	0.155	NA	-	NA
Vc/F_0 (dl)[b]	322	NE	241	12.2
b_WT	-	NA	0.511	NA
Vp/F (dl)	222	NE	83	20.5
Q/F (dl h^{-1})	55.7	NE	4.48	NE
Ka (h^{-1})	13.7	176	0.69	121.7
Tlag (h)	0.23	NE	0.233	38.9

Table 2.2. PK parameters for lesinurad and febuxostat

[a]Febuxostat: CL/F = CL/F_0 + b_CRCL*CRCL + b_WT*WT; Lesinurad: CL/F = CL/F_0 * (CRCL/87)^b_CRCL

[b]Lesinurad: VC/F = VC/F_0 * (WT/70)^b_WT

CL/F: Apparent clearance; Vc/F: Volume of the central compartment; Vp/F: Volume of the peripheral compartment; Q/F: Inter-compartmental clearance rate; Ka: First-order absorption; Tlag: Absorption time-lag; BSV: between-subject variability; CV%: Percentage coefficient of variation; NE: Not estimated; NA: Not applicable

3.3. Pharmacodynamics

i) Parameters obtained from literature

The mean rates of renal clearance of uric acid and xanthine (CLUA and CLX) in healthy volunteers, along with the between-subject variability, were obtained using summary data from a phase I dose-escalation study of 154 healthy volunteers receiving febuxostat (TAP Pharmaceutical Products Inc., 2004). The reported average clearance in each group and standard deviations were used to obtain a weighted average estimate of population typical value and the between subject variability.

This trial also found that the rate of xanthine renal clearance in subjects taking febuxostat, even at doses as low as 10 mg per day, increased 3- to 5-fold from baseline. This may result from saturation of active transport processes responsible for the reabsorption of xanthine from renal tubules (Khosravan *et al.*, 2006). A step function was assumed using a stimulatory E_{max} drug function, eq. 13 in Figure 2.1, with an $EC_{50,1}$ of 0.001 mg dl^{-1} (a low concentration associated with the 10mg dose) and $E_{max,1}$ of 3.

A previous PD model of lesinurad used a direct effect E_{max} model to relate steady-state average plasma concentration of lesinurad to the individuals' sUA concentration (Center for Drug Evaluation and Research., 2014). The parameters of the indirect model ($E_{max,2}$, $EC_{50,2}$) were derived from those given in the published direct model (E^D_{max} and EC^D_{50}) using the steady state equations (Gabrielsson and Weiner, 2016). The published model includes a covariate effect of creatinine clearance on the

maximum reduction in uric acid, E^D_{max}. The stimulatory model drug function $STIM_2$ is given by eq. 14 in Figure 2.1, while the equations used to derive $E_{max,2}$ and $EC_{50,2}$ are given below.

$$E_{max,2} = \frac{E_0}{E_0 - (E^D_{max}\left(\frac{CrCl}{87}\right)^{b_{crcl}})} - 1 \quad (15)$$

$$EC_{50,2} = \frac{E_{max,2}\, EC^D_{50}}{E_0/(E_0 - \left(\frac{E^D_{max}}{2}\right)) - 1} - EC^D_{50} \quad (16)$$

CrCl is the individual's creatinine clearance rate and E_0 is the baseline sUA concentration of trial participants used to derive the direct E_{max} model parameters.

ii) Estimated using statistical modelling

All other parameters were estimated using non-linear mixed effects modelling and febuxostat Phase I trial summary data on daily area under the plasma concentration curve (AUC) and 24-hour urinary excretion of xanthine and uric acid (TAP Pharmaceutical Products Inc., 2004). This was conditional on the clearance estimates and drug PD function parameters obtained directly from the literature in the previous section. A NONMEM dataset was created using the AUC and urinary data and the trial dosing schedule. Each value was an average across all individuals within a dose group and has, therefore, been replicated according to the number of subjects within the group in order to weight by sample size.

The PKPD modelling was conducted using NONMEM 7.3 and the ADVAN6 routine for solving differential equations. The PD model was coded using the differential equations (eqs. 7-10 in Figure 2.1) where equations 9 and 10 correspond directly to published data on 24-hour urinary excretion (TAP Pharmaceutical Products Inc., 2004). However, additional sUA and serum xanthine accumulation compartments were added to compute the area under the concentration curve at 24 hour intervals. Parameter estimation used the first order algorithm and different initial parameter estimates were tested. No random effects were included on system parameters estimated in NONMEM since the data points do not come from individual subjects. The inhibitory model drug functions INH_1 and INH_2 are given by equations 11 and 12 respectively in Figure 2.1.

In order to simplify the modelling procedure and make use of all available evidence the statistical modelling was performed in two stages. The first stage used a published PKPD model of febuxostat that used an indirect inhibitory response model applied to a zero order rate of uric acid production (Center for Drug Evaluation and Research., 2008). Rewriting uric acid production in the differential equations in our model as zero order the literature parameter estimate of 0.0239 mg dl^{-1} was assumed for $IC_{50,2}$ and the remaining parameters were then estimated. In the second stage, the uric acid

production was returned to being first order, such that it is a function of changing xanthine levels, and a new parameter estimate was made of $IC_{50,2}$ with all other parameters fixed.

3.4. Gout Patient Simulation Model

We assumed that the febuxostat pharmacodynamic parameters estimated for healthy volunteers could be applied to gout patients with hyperuricemia. However, systems parameters have been adjusted to be representative of a patient population. A typical patient sUA concentration was assumed to be 8.83 mg dl^{-1} (525 μmol L^{-1}; standard deviation of 1.53 mg dl^{-1}) as this was the pre-treatment sUA concentration for patients in the CRYSTAL trial which compared febuxostat with lesinurad (Ardea Biosciences., 2015). We considered two phenotypes, overproducers and under-excreters of uric acid (Pittman and Bross, 1999; Choi, Mount and Reginato, 2005), and modified the healthy subject system parameters accordingly. For overproducers, the amount of xanthine was scaled up and for under-excreters the clearance of uric acid was scaled down in proportion to the sUA concentration (Table 2.3). This assumes the same volumes of distribution of xanthine and uric acid for patients as for healthy subjects.

Parameter	Healthy subject	Gout patient	
		Under-excreter	Overproducer
sUA (mg dl^{-1})	-	LN(8.83,1.53)	LN(8.83,1.53)
BX (mg)	θ_1	θ_1	θ_1*(BUA/θ_4)
VX (dl)	θ_2	θ_2	θ_2
CLX (dl h^{-1})	θ_3	θ_3	θ_3
BUA (mg)	θ_4	θ_5*sUA	θ_5*sUA
VUA (dl)	θ_5	θ_5	θ_5
CLUA (dl h^{-1})	θ_6	θ_6*(θ_4/BUA)	θ_6

Table 2.3. Individual system parameters for healthy subject and gout patients

The model was used to simulate treatment with 120 days ULT in a hypothetical cohort of 1,000 patients with baseline characteristics corresponding to the CRYSTAL trial. The cohort was all male (95% were male in CRYSTAL) and baseline sUA, weight and age were assumed to be lognormally distributed with mean and standard deviations taken from CRYSTAL (study 304) (Food and Drug Administration, 2015a). CrCl, calculated using the Cockcroft-Gault equation (Cockcroft and Gault, 1976), overestimated the distribution of the trial participants. All estimates were reduced by 15 ml min^{-1} and estimates below 30 ml min^{-1} were excluded to obtain a better representation of the trial population CrCl. Variability of drug effects in INH_1 and INH_2 could not be estimated and the IC_{50} parameters were assumed to vary according to η_3 with a coefficient of variation of 20%. Steady state was assumed following 30 days of simulated treatment and only the latter 60 days was used to derive results.

The outcomes of interest were the simulated time course of sUA and uUA concentrations, from which we estimated the proportion of patients responding (sUA below ≤5 mg dl^{-1} (300 µmol L^{-1}) on day 120) and the proportion of patients experiencing hyperuricosuria (uUA ≥800 mg day^{-1} on any day). The normal range of 24-hour volume of urine is 0.5-1 ml kg^{-1} hr^{-1}, but is likely to be lower in the elderly (Parsons *et al.*, 2007; Tissot *et al.*, 2008). On this basis a representative daily urine output for a 99 kg male of 15 dl has been assumed for the purpose of estimating uUA concentrations. The soluble limit for uric acid is highly sensitive to urine pH, being much greater in alkaline than in acidic urine. For a given uUA concentration the pH at which saturation would occur was estimated by fitting a linear model to literature data (Mehta and Goldfarb, 2012) to obtain: saturation pH = 6.36 – 40.96/[uUA].

3.5. Modelling Adherence

The impact of poor adherence was studied for four different ULT options, namely febuxostat 80 mg monotherapy and lesinurad 400 mg monotherapy, and febuxostat 80 mg combined with either lesinurad 200 mg or 400 mg. All are once daily regimens and it was assumed that doses are taken at the same time each day. Two types of poor adherence were considered, the first being a single drug holiday of increasing duration, from 1 to 20 days to assess the impact on uUA burden of restarting treatment following increasing lengths of drug holiday. The second assessed the impact of poor implementation on response rates and peaks in uUA by simulating doses taken completely at random, with a probability ranging from 1 to 0.1. For all dual-ULTs missed doses included both drugs being missed simultaneously. A total of 30 simulations were conducted for each adherence scenario, which used random samples of the model parameter between subject variability, and the results were averaged over the range of simulation results.

4. Results

The combined set of pharmacodynamics (PD) parameters and corresponding between subject variabilities (BSV) which were derived or estimated from the literature are presented in Table 2.1. Goodness of fit plots and visual predictive checks for the nonlinear mixed effects modelling are presented in Figures 2.2 – 2.6.

With perfect adherence, uUA concentrations are maintained at low levels under the combined action of febuxostat 80 mg and lesinurad 200 mg (see plots for a typical patient in Figures 2.7 and 2.8). During a simulated drug holiday of 8 days, urinary concentrations increase as sUA concentrations return towards baseline. After dosing is restarted, peaks in uUA concentrations occur, for the typical under-excreter the peak reached 39 mg dl^{-1} (2.3 mmol L^{-1}) which exceeds the typical average concentration for a healthy person (30 mg dl^{-1} or 1.8 mmol L^{-1}). For the typical overproducer, the peak uUA concentration was 85 mg dl^{-1} (5.1 mmol L^{-1}) which exceeds the threshold for typical average uUA concentration of an individual with hyperuricosuria (53 mg dl^{-1} or 3.2 mmol L^{-1}). For the typical under-excreter, uUA concentrations after restarting treatment following an 8 day drug holiday could become supersaturated if the urinary pH was towards the acidic end of the normal range (pH < 5.3; normal range 4.5-8.0). For the typical overproducer, peak uUA concentrations after restarting treatment are more likely to reach supersaturation at closer to the mid-point of the normal range at approximately 5.9.

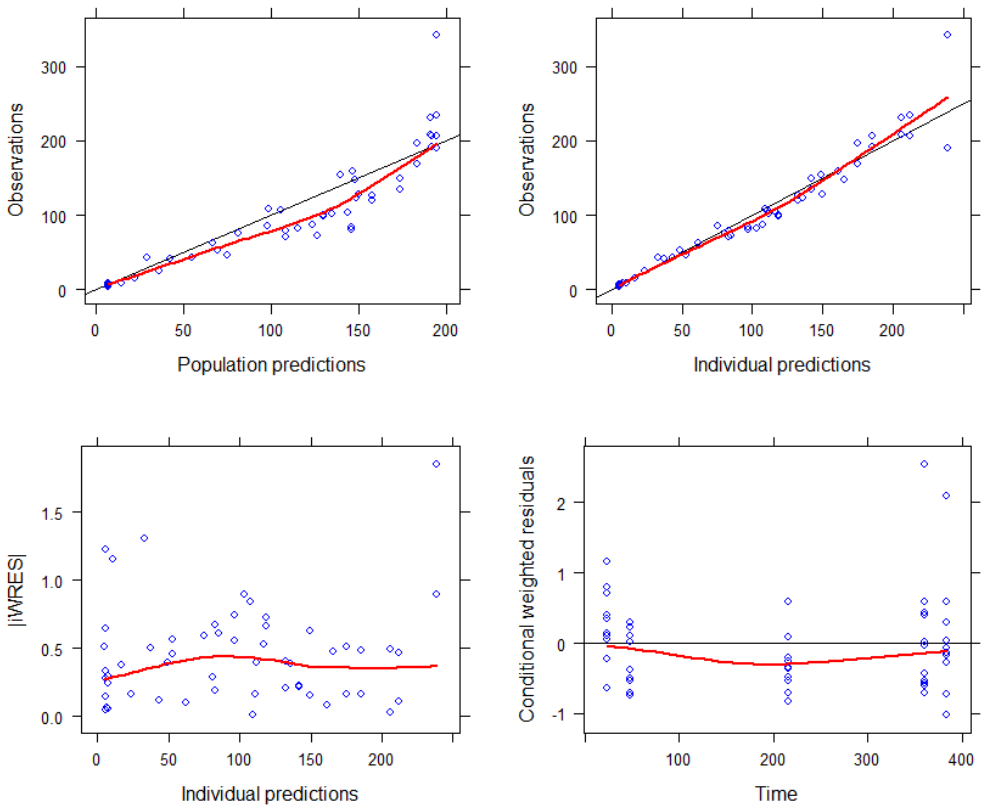


Figure 2.2. Goodness of fit plot for 24-hour amount of xanthine removed to urine compartment

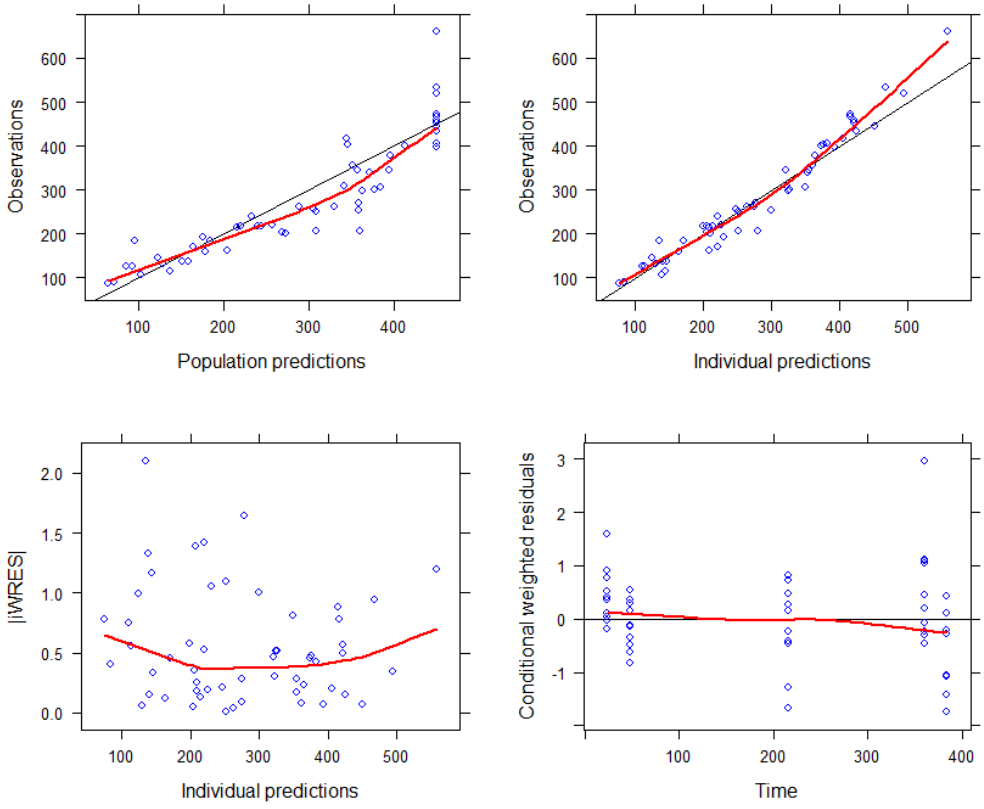


Figure 2.3. Goodness of fit plot for 24-hour amount of uric acid removed to urine compartment

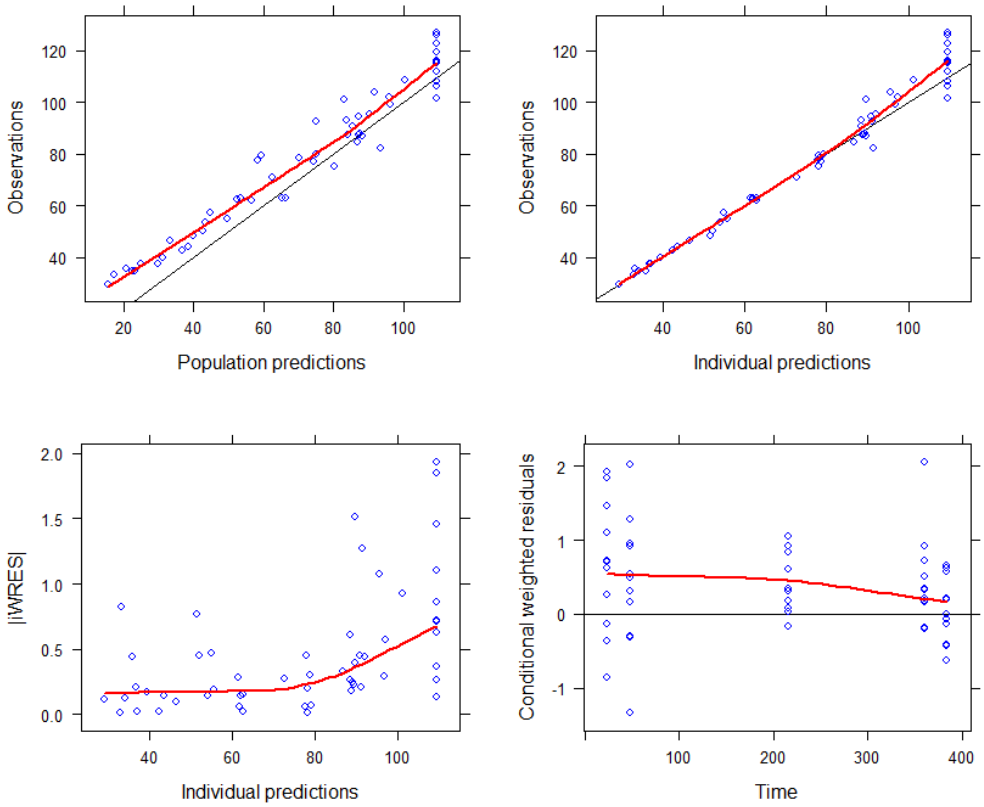


Figure 2.4. Goodness of fit plot for 24-hour serum uric acid concentration AUC compartment

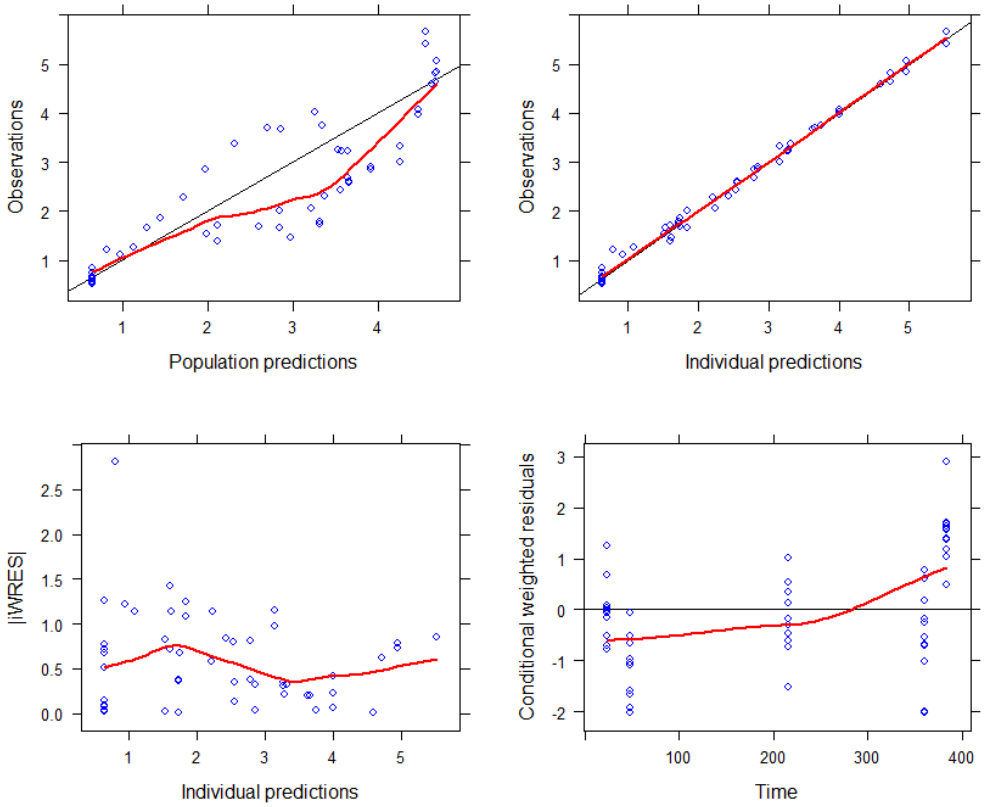


Figure 2.5. Goodness of fit plot for 24-hour serum xanthine concentration AUC compartment

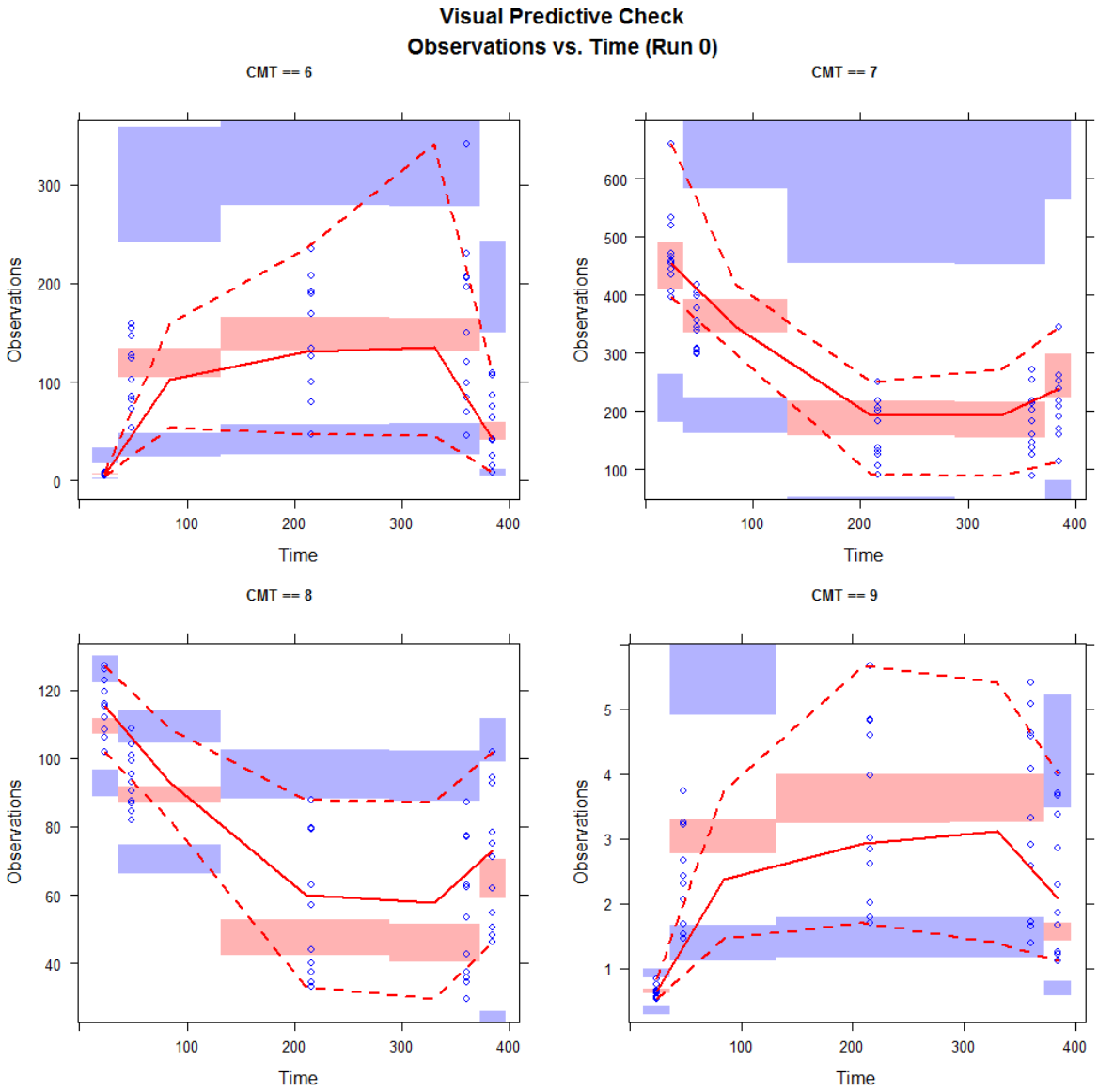


Figure 2.6 Visual predictive checks (observations vs time) for febuxostat model fitted to phase 1 data

CMT==6: Urinary xanthine compartment; CMT==7: Urinary uric acid compartment; CMT==8: Serum uric acid collection compartment; CMT=9: Serum xanthine collection compartment

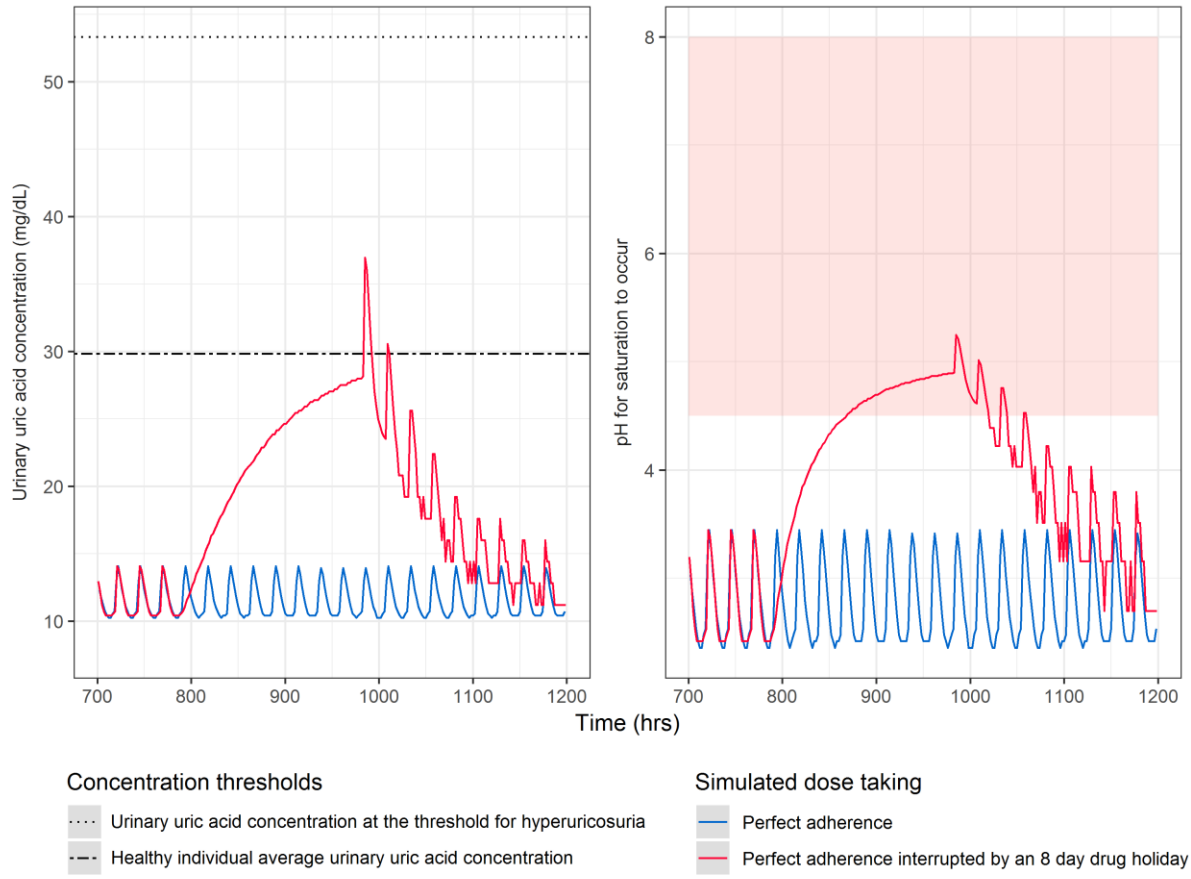


Figure 2.7. Simulated urinary uric acid (uUA) concentration and estimated pH for uric acid supersaturation in a gout patient with hyperuricemia due to a reduced rate of uric acid clearance assuming a daily volume of urine of 15 dl. The simulated uUA concentration over time (left-hand panel) and the estimated pH at which this concentration would become supersaturated (right-hand panel). Imperfect adherence is modelled as an 8-day drug holiday (beginning on day 33). The red shaded area represents the normal range for urine pH. ULTs used in simulations were febuxostat 80 mg and lesinurad 200 mg, both once daily.

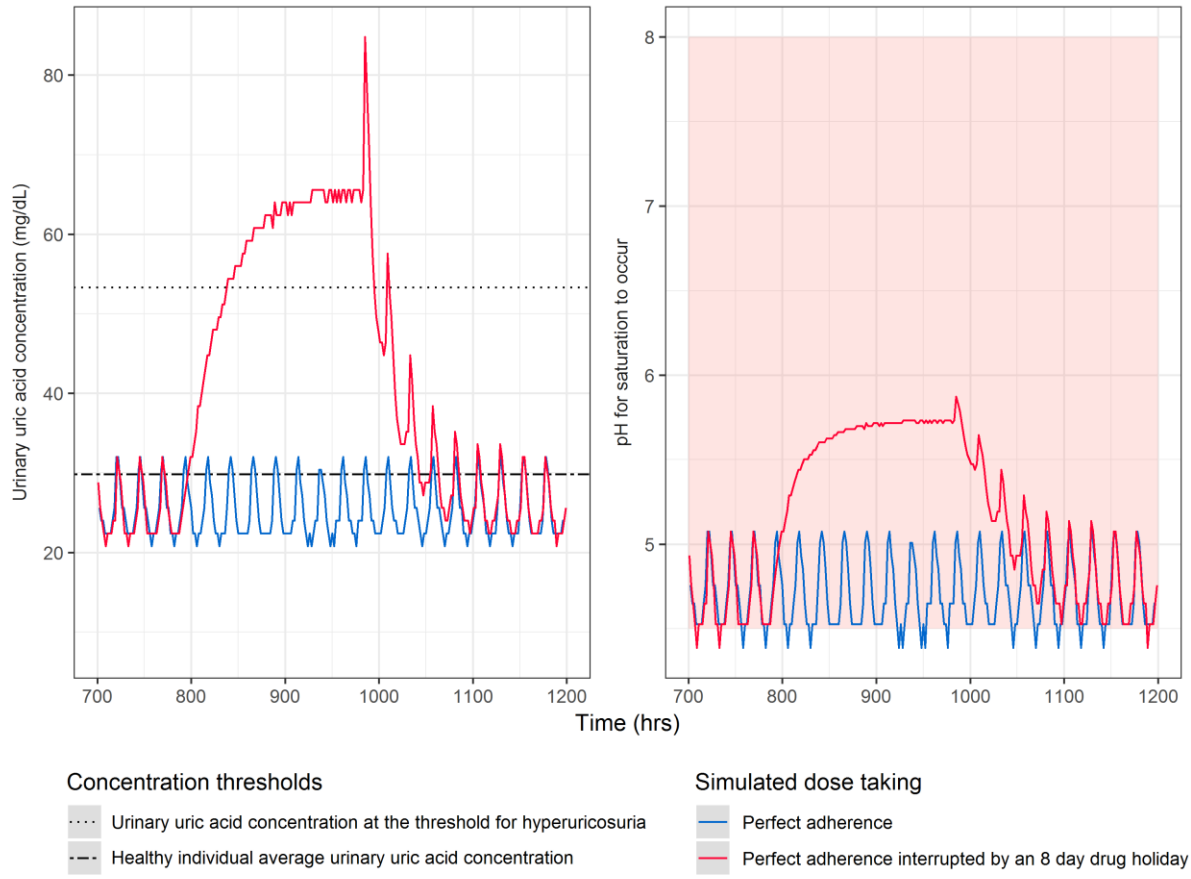


Figure 2.8. Simulated urinary uric acid (uUA) concentration and estimated pH for uric acid supersaturation in a gout patient with hyperuricemia due to an overproduction of xanthine assuming a daily volume of urine of 15 dl. The simulated uUA concentration over time (left-hand panel) and the estimated pH at which this concentration would become supersaturated (right-hand panel). Imperfect adherence is modelled as an 8-day drug holiday (beginning on day 33). The red shaded area represents the normal range for urine pH. ULTs used in simulations were febuxostat 80 mg and lesinurad 200 mg, both once daily.

Across the population, increasing the length of a drug holiday increases the proportion of patients whose daily amount of uric acid excreted exceeds the threshold for hyperuricosuria upon restarting treatment (Figure 2.9). The proportion of patients with hyperuricosuria increases with increasing doses of lesinurad and is greatest for lesinurad 400 mg monotherapy. For under-excreters taking a 20 day drug holiday, the addition of 200 mg (or 400 mg) lesinurad to 80 mg febuxostat increased the percentage of patients experiencing hyperuricosuria form 0% to 1.4% (or 3.1%). In overproducers, restarting ULTs following drug holidays of more than 5 days leads to over 60% of patients experiencing hyperuricosuria. In both patient groups, one- or two-day drug holidays are well tolerated compared to longer holidays with only moderate increases in the rates of hyperuricosuria.

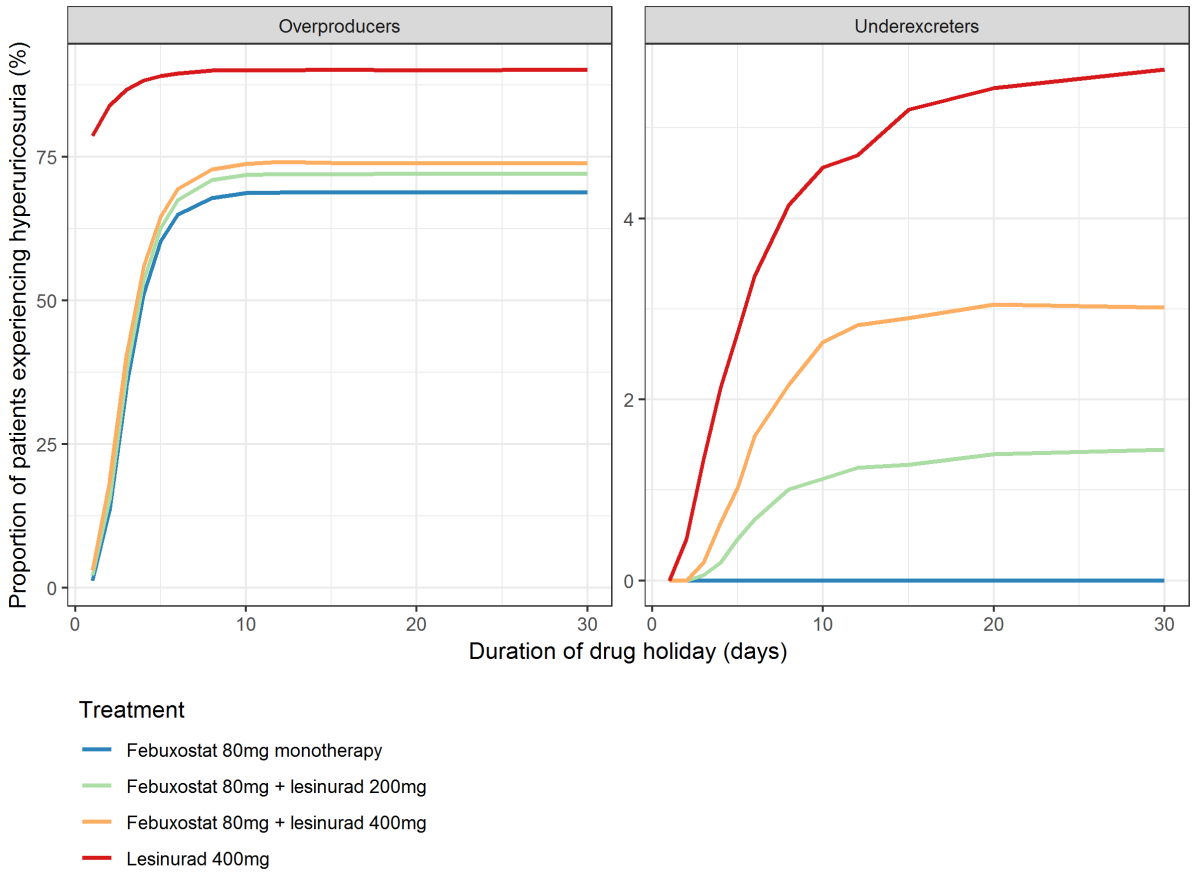


Figure 2.9. These figures show the proportion of simulated patients who experience a daily urinary uric acid output sufficiently high to be classed as hyperuricosuria, for four different urate-lowering therapies and a range of drug holiday durations. All patient simulations consisted of perfect dose taking interrupted once by a drug holiday of duration given on the x-axis in each plot.

With perfect adherence, the proportion of patients treated to target (sUA ≤5 mg dL^{-1} (≤300 µmol L^{-1}) on day 120) is greater than was observed in the CRYSTAL trial (Figure 2.10). However, success rates fall rapidly as an increasing proportion of doses are missed at random. For daily doses of febuxostat 80 mg, febuxostat 80mg with lesinurad 200 mg, febuxostat 80 mg with lesinurad 400 mg and lesinurad 400 mg monotherapy, the success rates at 100% of doses taken in under-excreters are 87.2%, 94.5%, 96.0% and 15.4%, respectively. At 50% of doses taken at random, these success rates fall to 27.2%, 42.6%, 47.3% and 7.4%, respectively. The corresponding plots for overproducers is shown in Figure 2.11.

Increasing the proportion of doses missed at random results in higher rates of hyperuricosuria due to randomly occurring drug holidays, especially in the presence of a uricosuric (Figure 2.10). The baseline daily uUA excreted in under-excreters is below healthy baseline levels and none of the simulated cohort showed hyperuricosuria in the absence of ULT. For dual-ULT with a uricosuric, however, randomly occurring drug holidays resulted in increasing rates of hyperuricosuria. For example at 30%

of doses taken, for febuxostat 80 mg with lesinurad 200 mg, febuxostat 80 mg with lesinurad 400 mg and lesinurad 400 mg monotherapy the rates of hyperuricosuria are 1.3%, 3.2% and 4.9%, respectively.

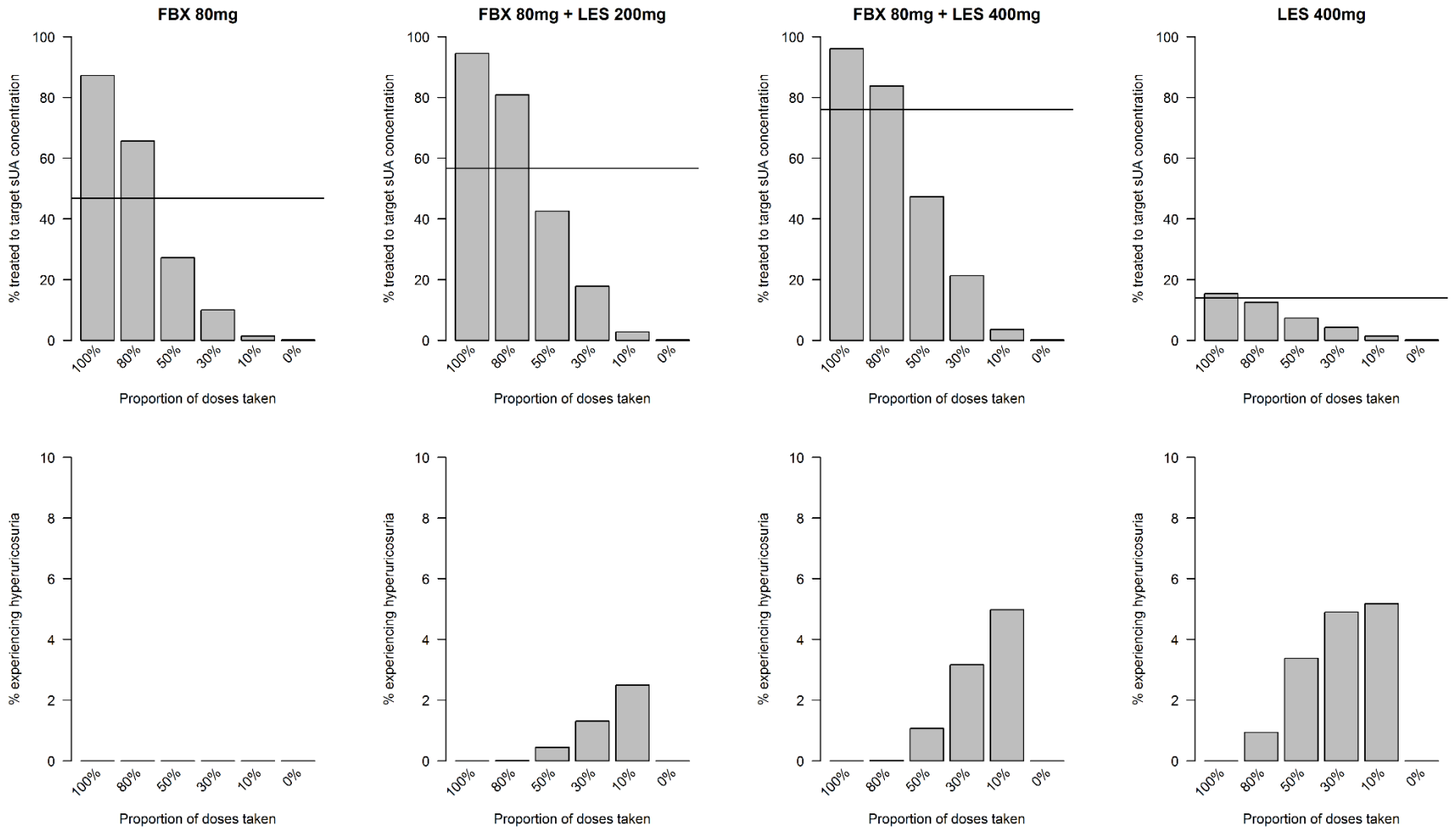


Figure 2.10. Treatment success rates (top row) and the proportion of patients experiencing one-day hyperuricosuria during two months of urate lowering therapy (ULT) (bottom row). Horizontal lines provide the reference response rates for this treatment arm from the CRYSTAL trial comparing febuxostat and lesinurad and study 303 for lesinurad 400 mg monotherapy. Results are for under-excreters of uric acid only. FBX: Febuxostat; LES: Lesinurad.

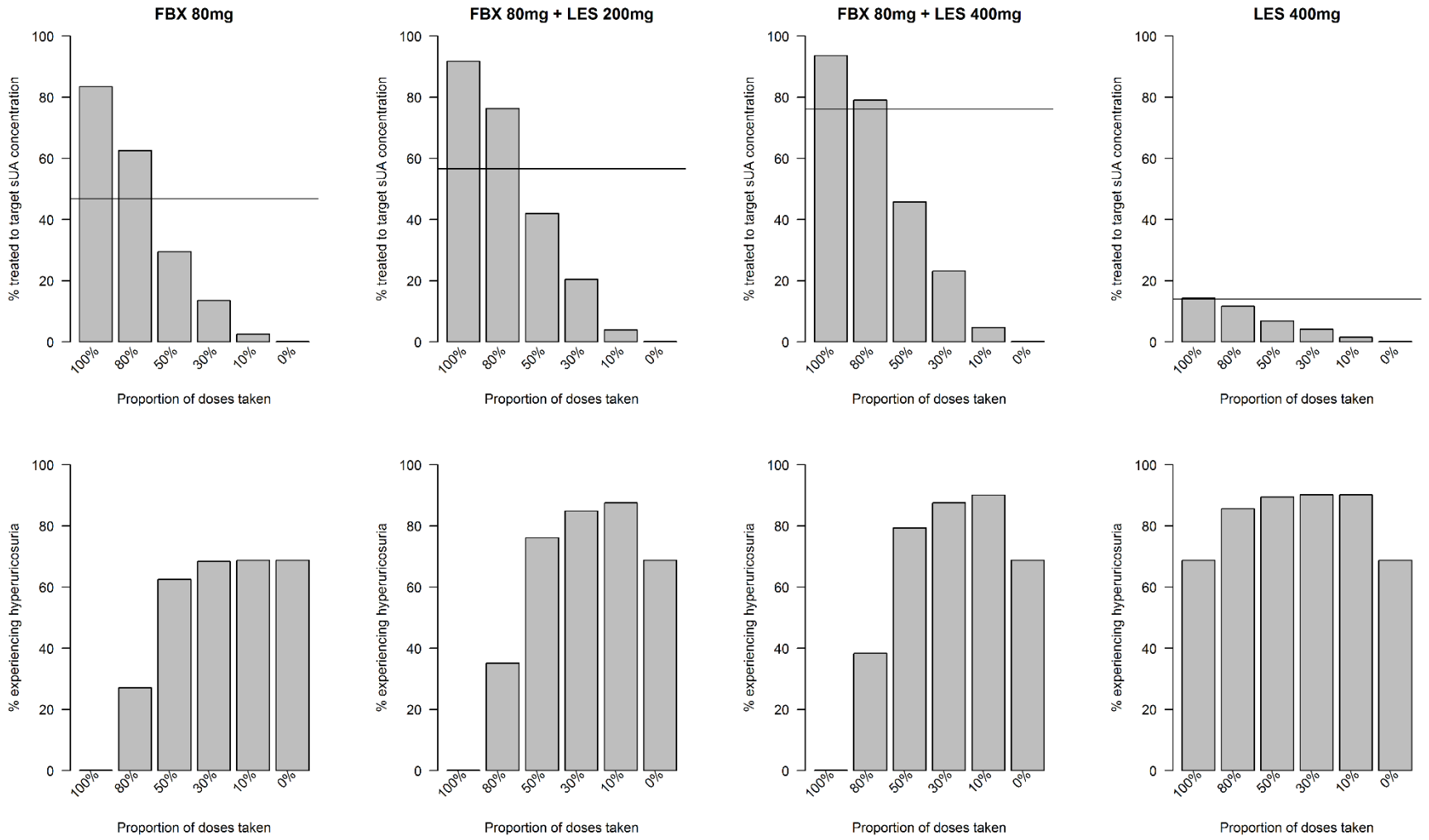


Figure 2.11. Treatment success rates (top row) and the proportion of patients experiencing one-day hyperuricosuria during two months of urate lowering therapy (ULT) (bottom row). Horizontal lines provide the reference response rates for this treatment arm from the CRYSTAL trial comparing febuxostat and lesinurad and study 303 for lesinurad 400 mg monotherapy. Results are for overproducers of uric acid only. FBX: Febuxostat; LES: Lesinurad.

5. Discussion

The use of uricosurics, either as monotherapy or in combination with an XOi, results in transient increases in uUA concentrations when dosing is restarted after a drug holiday. As a result, supersaturation of uric acid in urine can occur at pH values within the normal expected range and therefore precipitation of uric acid in the renal tubules is more likely to occur during routine clinical practice. This effect is likely to be greater following a drug holiday from dual-ULTs, than when starting treatment for the first time where, as per the regulatory approval of lesinurad, patients must already have been taking an XOi. Specifically, our simulations indicate that peak uUA concentrations reach the threshold for supersaturation at a urinary pH of 5.3 for under-excreters and of 5.9 for overproducers, so that crystal formation may occur for a urinary pH at or below this level.

Increasing the length of a drug holiday increased the proportion of patients whose daily amount of uric acid excreted exceeded the threshold for hyperuricosuria. The increase was more rapid for patients with over production, suggesting poorer drug forgiveness in this population. Treatment outcomes deteriorated rapidly as an increasing proportion of doses were missed at random. For under-excreters taking febuxostat 80 mg with lesinurad 200 mg, treatment to target rates fell by more than 50% when adherence reduced from 100% to 50%.

Approximately 90% of gout patients have hyperuricemia caused by the renal under-excretion of uric acid (Choi, Mount and Reginato, 2005). In these cases, unless sUA concentrations are very high, or urinary volume is also lowered, uUA concentrations are likely to be lower than healthy subjects. However, in simulations of drug holidays, after restarting dual-ULT under-excreters had uUA concentrations raised to above the baseline levels for healthy subjects and a small proportion exceeded the threshold for hyperuricosuria. For these patients to be at an increased risk of kidney damage would likely require either a very low urinary output volume or a low urine pH (though still within the typical pH range). Urine pH is itself a primary predictor of nephrolithiasis, since the solubility of uric acid is very sensitive to small changes in pH (Mehta and Goldfarb, 2012).

Genetic disorders or a high-purine diet can be the cause of an overproduction of uric acid in the remaining 10% of gout patients (Doherty, 2009). Hyperuricosuria is a defining feature of uric acid overproduction (Pittman and Bross, 1999), putting these patients at an increased risk of kidney injury without treatment. Our simulations suggest that in the case of very good medication adherence (≥80% doses taken), dual-ULT would result in sustained reductions in sUA concentrations and also, therefore, uUA excreted. Regular drug holidays, however, would result in episodes in which uUA output was raised above its already high baseline. For this reason uricosurics may not be appropriate for patients

with hyperuricemia due to uric acid overproduction (D. Khanna *et al.*, 2012), but no cautions are made in the label for lesinurad (Food and Drug Administration, 2015b).

To our knowledge this is the first study of the relationship between medication adherence and the efficacy and safety of dual-ULT therapy for the treatment of gout. This is especially timely given the recent approval of lesinurad for use in combination with an XOi in patients who have not responded on an XOi alone (Center for Drug Evaluation and Research., 2015). Our analysis benefits from having used a semi-mechanistic PD model which provides a level of complexity capable of capturing the non-steady state system dynamics. The effects of treatments have been investigated in two distinct patient subgroups; the cause of hyperuricemia being either an overproduction or under-excretion of uric acid. When comparing our simulation results with the findings from clinical trials, all of our perfect adherence simulations produced higher treatment success rates than was reported in trials. Mathematical models such as this could be used to anticipate the problems resulting from sub-optimal adherence, and to potentially help identify the properties of more forgiving uricosurics.

The main limitation of this study was our reliance on different sources of data from different populations. This limited our ability to fully quantify the variability and co-dependencies, nonetheless, we consider the model to be representative of existing dual-ULTs. We assumed that non-renal clearance of uric acid, which is responsible for around a third of total excretion (Ichida *et al.*, 2012), was negligible. Nevertheless, the contribution of non-renal clearance relative to renal clearance will be less in scenarios where a uricosuric is taken. Finally, the analysis has focussed on the XOi febuxostat, but allopurinol is by far the most commonly prescribed ULT. However, we have no reason to believe that these findings do not extend to other XOis (allopurinol) and uricosurics (probenecid and benzbromarone).

With currently available ULTs, a large proportion of patients do not achieve sustained reductions in sUA to below saturation concentrations. The potential reasons for treatment failure include poor implementation (adherence) to treatment, under-dosing, variation in treatment response and the underlying cause of hyperuricemia (Stamp *et al.*, 2014). Persistence to ULTs is known to be amongst the lowest of any chronic disease treatment (Briesacher *et al.*, 2008; De Vera *et al.*, 2014) and studies provide evidence for both long (Harrold *et al.*, 2010) and short (de Klerk *et al.*, 2003) drug holidays. This study shows that renal safety may also be compromised by sub-optimal medication adherence and highlights the need to improve adherence and adapt treatments to poorly adherent populations. This could include instructions on drug labelling (Levy, Zamacona and Jusko, 2000), indicating a number of doses which can be missed based on the forgiveness of the drug to missed doses (Assawasuwannakit, Braund and Duffull, 2015). Such measures may improve the safety profile of

future uricosurics, which for lesinurad may have influenced reimbursement decisions (National Institute for Health and Care Excellence, 2016c).

If gout patients adhere well to dual-ULT then it appears to offer a means of further reducing sUA concentrations with a negligible increase in urinary uric acid output. However, regular drug holidays, which are commonplace amongst gout patients using ULTs, result in much lower rates of long term treatment success and increased rates of hyperuricosuria when treatment is restarted. This has the potential to increase the risk of kidney damage in all patients, but especially those with hyperuricemia due to overproduction of uric acid. Further research is needed into the impact of adherence patterns on treatment success rates and kidney safety in order to better understand how dual-ULT could be optimally used in the treatment of hyperuricemia in patients with gout. However, at present counselling patients with respect to the risks associated with poor adherence should be advised.

Preface to Chapter 3

The previous chapter has presented a pharmacometric model for two urate-lowering therapies, febuxostat and lesinurad, developed using published data sources. This model is semi-mechanistic to the extent that it is capable of simulating the time course of the biomarker serum uric acid under conditions of imperfect medication adherence. A natural application of a linked pharmacometric-pharmacoeconomic model is to study the impact of imperfect medication adherence on modelled economic outcomes, such as cost effectiveness. This may be of interest from both a pharmaceutical industry and regulatory perspective, since a decline in mediation adherence may be anticipated in the transition from phase 2 to phase 3 trials and from phase 3 into routine medication usage.

The following chapter is primarily concerned with the development of the pharmacoeconomic model that can use simulated serum uric acid concentrations as inputs to drive a reduction in gout flares and subsequent impacts on quality of life. This has, to a large extent, replicated the approach that was taken in the manufacturer of lesinurad submission to the UK reimbursement authority. As such, we can compare the economic outcomes simulated in this chapter with those presented in the original manufacturer submission. It was also necessary to extend the pharmacometric model to include an additional urate-lowering therapy, namely allopurinol.

This first application of the linked pharmacometric-pharmacoeconomic models was to simulate treatment effectiveness and subsequent cost effectiveness for three medication adherence scenarios and a range of different dual- and mono-therapy treatment options. This provides an estimate of how cost effective alternative treatment options may be under the hypothetical scenario of perfect medication adherence and how rapidly cost effectiveness ratios increase with decreasing levels of adherence

Chapter 3

Impact of Non-adherence and Flare Resolution on the Cost Effectiveness of Treatments for Gout: Application of a Linked Pharmacometric/Pharmacoeconomic Model

1. Summary

Dual urate-lowering therapy (ULT) with lesinurad in combination with either allopurinol or febuxostat is an option for gout patients unsuccessfully treated on either monotherapy. Treatment failure is often a result of poor medication adherence. Imperfect adherence in clinical trials may lead to biased estimates of treatment effect and confound the results of cost effectiveness analyses. This study aims to estimate the impact of varying medication adherence on the cost effectiveness of lesinurad dual therapy; and estimate the value-based price of lesinurad at which the incremental cost effectiveness ratio (ICER) is equal to £20,000 per quality-adjusted life-year (QALY).

Treatment effect was simulated using published pharmacokinetic-pharmacodynamic (PKPD) models and scenarios representing adherence in clinical trials, routine practice and perfect use. The subsequent cost and health impacts, over the lifetime of a patient cohort, were estimated using a bespoke pharmacoeconomic model.

The base case ICERs comparing lesinurad dual-ULT with monotherapy ranged from £39,184 to £78,350 per QALY gained using allopurinol and £31,901 to £124,212 per QALY using febuxostat, depending on the assumed medication adherence. Results assuming perfect medication adherence imply a per-quarter value-based price of lesinurad of £45.14 when used in dual-ULT compared with allopurinol alone and £57.75 compared with febuxostat alone, falling to £25.41 and £3.49 respectively in simulations of worsening medication adherence. The estimated value-based prices of lesinurad only exceeded that which has been proposed in the United Kingdom when assuming both perfect drug adherence and the eradication of gout flares in sustained treatment responders.

2. Introduction

Gout is a painful and disabling condition and one that is relatively common in developed countries (Kuo, Grainge, Zhang, *et al.*, 2015). When the concentration of uric acid in serum exceeds the saturation point (hyperuricemia) it may crystallise in peripheral joints and surrounding tissues which can lead to gout symptoms. Treatment guidelines recommend that serum uric acid (sUA) be reduced to below a target of either 5 or 6 mg/dL (300 or 360 µmol/L) (Hui *et al.*, 2017), to allow for the dissolution of monosodium urate crystals from affected joints (Shoji, Yamanaka and Kamatani, 2004). As well as preventing the progression to more severe disease (e.g. tophaceous gout) and, albeit controversially, reducing the potential of cardiovascular and renal comorbidities, long term treatment reduces and may eventually eliminate the painful flares that characterise gout (Pascual and Sivera, 2007).

The mainstay of therapy is the xanthine oxidase inhibitor (XOi) allopurinol; however, a large proportion of patients are not treated successfully (Kydd *et al.*, 2014). Treatment failure has been postulated to result from suboptimal dosing or non-adherence, or a combination of both over the long (often symptom-free) treatment period (Stamp *et al.*, 2014). Medication adherence is known to be especially poor for urate-lowering therapies (ULTs) (Scheepers *et al.*, 2018; Yin *et al.*, 2018) and, if not recognised and managed appropriately, can result in unnecessary switching to more expensive ULTs such as febuxostat or combined XOi therapy with a uricosuric, such as lesinurad.

Medication adherence can be decomposed into three distinct phases; 1) the initiation of treatment, 2) the degree to which a patient's dose taking matches the prescribed regimen while nominally adhering (implementation) and 3) the discontinuation of treatment (persistence) (Vrijens *et al.*, 2012). Persistence can often be accounted for in the analysis of clinical trials and, while implementation can be recorded using electronic pill dispensers (El Alili *et al.*, 2016), this is seldom done in clinical trials. Imperfect implementation may lead to biased estimates of treatment effect (Breckenridge *et al.*, 2017) and confound the results of cost effectiveness analyses.

Key influences on the decisions not to recommend lesinurad, or febuxostat as first-line treatment in the United Kingdom (UK) were the uncertainties in their effects on acute flares and their lack of cost effectiveness as estimated using economic modelling (National Institute for Health and Care Excellence, 2008, 2016a, 2017b). However, an important limitation of conventional economic models is their limited capacity to account for the impact of poor implementation (i.e. missed or delayed doses) on health outcomes and costs. Pharmacokinetic-pharmacodynamic (PKPD) models together describe the relationship between doses taken and the observed drug effects, via the time course of drug concentration. By specifying variable dose implementation as an input function, this offers a

method for predicting the influence of non-adherence on the clinical effectiveness and cost effectiveness of drug treatments (Hughes *et al.,* 2007).

This study aims to estimate the impact of varying dose implementation and persistence on the cost effectiveness of the uricosuric lesinurad as an add-on treatment in patients non-responsive on either allopurinol or febuxostat alone.

3. Methods

The PKPD model of lesinurad and febuxostat, developed in Chapter 2, was extended to include allopurinol and used to simulate the time course of sUA concentration among patients with differing adherence to the dosing regimen. A bespoke pharmacoeconomic (PE) model was developed, with reference to previous economic evaluations of ULTs (Beard *et al.*, 2014; National Institute for Health and Care Excellence, 2016c), and linked to the PKPD model to estimate the costs and quality-adjusted life-years (QALYs) accrued over patients' lifetimes for different treatment and adherence scenarios. All PKPD simulations were performed using NONMEM 7.3 (Beal *et al.*, 2013).

3.1. ULT Pharmacokinetic-Pharmacodynamic Model

The lesinurad and febuxostat PKPD model was used without modification. A separate study presenting PKPD modelling of allopurinol (Wright *et al.*, 2015) was used to obtain the PK relationships and associated parameter estimates which were also used without modification. However, since a direct-effect sigmoid E_{max} PD model had been used to relate sUA concentrations to oxipurinol (allopurinol's active metabolite) plasma concentrations, a semi-mechanistic indirect-response model (Gabrielsson and Weiner, 2016) was derived from the estimated parameters. This allows for the expected delay between the PK and PD of XOis and is better suited to modelling patterns of imperfect adherence.

3.2. Patient Population

A cohort of 500 gout patients was created for simulations based on the population characteristics of the recently completed CLEAR 1 clinical trial of lesinurad (Food and Drug Administration, 2015a). Individual age and weight, which account for some of the variability in PKPD model parameters, were sampled at random from log-normal distributions using CLEAR 1 mean body weight of 110 kg (SD = 23) and age of 52 (SD = 11). Creatinine clearance (CrCl), a covariate in the PK models, was estimated using the Cockcroft-Gault equation (Cockcroft and Gault, 1976). The resulting distribution was reduced by 15 mL/min and estimates below 30 mL/min were excluded (as per protocol criteria) in order to adjust for the underlying degree of renal impairment and obtain an approximation of the broad CrCl categories available for the CLEAR 1 trial population (Saag *et al.*, 2017). In accordance with gout epidemiology, patients were also assigned to have gout resulting from either an overproduction or under-excretion of uric acid in the ratio of 1:9 (Pittman and Bross, 1999; Choi, Mount and Reginato, 2005).

3.3. PKPD Simulation Modelling

The PKPD model was used to generate twelve sUA concentration distributions from the patient cohort using four ULT options and three models of medication adherence. These twelve distributions then provide the treatment effectiveness inputs in subsequent pharmacoeconomic modelling. We have considered two scenarios for first-line ULT; these being gout patients eligible for ULT being either prescribed once daily allopurinol 300 mg or once daily febuxostat 80 mg. This is the recommended dose of febuxostat (National Institute for Health and Care Excellence, 2008), and 300 mg is the most commonly used dose of allopurinol (Sarawate *et al.*, 2006). If a patient did not achieve a reduction to the 6 mg/dL (360 µmol/L) target on a monotherapy, then dual therapy was used as second-line with lesinurad 200 mg once daily.

The first method of modelling adherence (Adherence model 1) represents the hypothetical best-case scenario in which all patients persist with treatment and implement perfectly. The second and third adherence models are broadly intended to represent a phase 3 clinical trials setting and routine practice, respectively. With the second adherence model (Adherence model 2), treatment persistence was based on discontinuation observed in lesinurad pivotal trials (National Institute for Health and Care Excellence, 2016c), and patients implemented doses randomly according to a probability that was sampled from a beta(2.4,0.6) distribution, such that the population average was 80% of doses with standard deviation of 20%. The third adherence model (Adherence model 3) also used treatment persistence from lesinurad pivotal trials (National Institute for Health and Care Excellence, 2016c) and dose implementation sampled from a beta(2.6,2.6) distribution, such that the population average was 50% of doses with standard deviation of 20%.

For each ULT option and adherence model, treatment in each patient was simulated for 120 days, with the initial 30 days used only to achieve steady-state on first-line monotherapy. On day 30, those patients in the dual-ULT simulation scenarios whose sUA concentration was above 6 mg/dL (360 µmol/L) had lesinurad as second-line added to their daily dosing schedule. Days 30 - 60 were then used to establish those patients newly switched to dual therapy at steady state. The final days from 60 – 120, for all four ULT options, provided the treatment effects that drive the pharmacoeconomic model, including the distribution across sUA concentration categories on day 120 as well as the proportion of days each patient was below 6 mg/dL (360 µmol/L). The sUA concentrations were collapsed onto four categories: <6, 6 to <8, 8 to <10 and ≥10 mg/dL (<360, 360 to <476, 476 to <595 and ≥595 µmol/L) which provide the distribution across sUA sub-states in the pharmacoeconomic model and are static throughout pharmacoeconomic model simulations (Figure 3.1).

3.4. Pharmacoeconomic Model

Overview

Consistent with previous economic evaluations of gout treatments (Beard *et al.*, 2014; National Institute for Health and Care Excellence, 2016c), we used a Markov state-transition model to estimate lifetime costs and QALYs in a cohort of patients eligible for ULT. Whilst treatment was simulated for individual patients in the PKPD model, the economic model used a cohort approach. The model adopts the perspective of the National Health Service in the UK, has a cycle length of 3 months, and a lifetime (50 year) time horizon. Costs and QALYs were both discounted at a rate of 3.5% per annum (National Institute for Health and Care Excellence, 2013b). The economic model was implemented in R version 3.4.3 (R Foundation for Statistical Computing, 2017).

Treatments and Transitions

The Markov model consisted of 6 main health states which included 4 possible ULT options, no treatment and an absorbing dead state. Within each of the 5 treatment options, patients were distributed between the four sUA concentration sub-states, such that there was a total of 21 model states. The distribution across the sUA concentration sub-states for each treatment depended on the level of dose implementation and was generated using the PKPD model (Figure 2.1).

In each pharmacoeconomic simulation, all patients are initially allocated to a single ULT option, where they remain unless they discontinue (non-persistence). A proportion of patients on monotherapy could, therefore, transition to the no-ULT health state and a proportion of those on a dual therapy could transition to either the no-ULT state or to the XOi monotherapy health state if only discontinuing the uricosuric component. It was assumed that no patients will discontinue a XOi while continuing to take lesinurad as it is not licensed as a monotherapy (Food and Drug Administration, 2015b). The patients transitioning to either no-ULT or a monotherapy (Figure 3.1) were redistributed according to the sUA concentration distribution of this new treatment. Per-cycle treatment discontinuation probabilities, summarised in Table 3.1, were calculated using the results of clinical trials of febuxostat (Becker *et al.*, 2009) and lesinurad (National Institute for Health and Care Excellence, 2017a). After every cycle, a proportion of patients transitioned to the death state according to all-cause mortality probabilities derived from life tables for England and Wales in 2015 (The Office for National Statistics, 2015).

Treatment dropout	Mean	Standard Deviation	Distribution	Source
From allopurinol to				
No treatment, 0-3m	11.90%		Beta	
No treatment, 4-6m	8.88%		Beta	FACT and APEX trials
No treatment, 7-9m	5.24%	Assumed 20% of	Beta	
No treatment, 10-12m	5.24%	mean	Beta	
No treatment, 13-24m	4.35%		Beta	EXCEL trial
No treatment, >24m	2.80%		Beta	
Febuxostat	NA	-	-	Not allowed
From febuxostat to				
No treatment, 0-3m	17.40%		Beta	
No treatment, 4-6m	13.90%		Beta	FACT and APEX trials
No treatment, 7-9m	7.53%	Assumed 20% of	Beta	
No treatment, 10-12m	7.53%	mean	Beta	
No treatment, 13-24m	3.26%		Beta	EXCEL trial
No treatment, >24m	1.75%		Beta	
Allopurinol	NA	-	-	Not allowed
From lesinurad + allopurinol to				
No treatment, 0-3m	7.02%		Beta	
No treatment, 4-6m	7.02%		Beta	
No treatment, 7-9m	2.98%	Assumed 20% of	Beta	CLEAR 1 and CLEAR 2
No treatment, 10-12m	2.98%	mean	Beta	trials
No treatment, >12m	1.40%		Beta	
Allopurinol	1.52%		Beta	
From lesinurad + febuxostat to				
No treatment	See above		Beta	Assumed as for
febuxostat	1.52%	20% of mean	Beta	lesinurad + allopurinol

Table 3.1. Quarterly treatment discontinuation probabilities

Gout Flares

Gout sufferers experience acute episodes of intense pain and inflammation known as flares whose frequency is directly proportional to sUA concentration (Halpern, Fuldeore, *et al.*, 2009). Clinical trials of newer ULTs have not demonstrated a reduction in the frequency of gout flares when compared with allopurinol; economic evaluations have instead relied on observational data to estimate the reduction in flares resulting from reduced sUA concentrations.

In the base case analysis, we modelled the frequency of gout flares within sUA concentration sub-states using the results of a cross-sectional survey in which 172 out of 620 participants provided both a most recent sUA measurement and a number of flares in the previous 12 months (P. Khanna *et al.*, 2012). This was used to derive quarterly flare frequency distributions across five categories (1-2, 3, 4-5 and ≥6 flares per annum) for each sUA concertation sub-state assuming a constant rate of occurrence. The data on annual flare frequency by sUA concertation sub-state is presented in Table 3.2. This survey data, however, reporting a single sUA measurement, may not be representative

of patients who maintain low sUA concentrations. In order to assess the potential quality of life and cost implications of a trial being able to demonstrate clear benefits in sustained responders and therefore not relying solely of survey data, we developed a second, alternative, model of flare reduction. This assumed that gout patients who sustain a sUA concentration of <6 mg/dL (360 µmol/L) on >80% of days will become flare-free after 2 years, while the survey data flare rate distributions are applied to all other patients. This is broadly in line with a study that found 86% of patients whose average sUA concentration was below 6 mg/dL (360 µmol/L) had no recurrent gouty attacks during the 2-year follow-up (Shoji, Yamanaka and Kamatani, 2004; Shiozawa *et al.*, 2017).

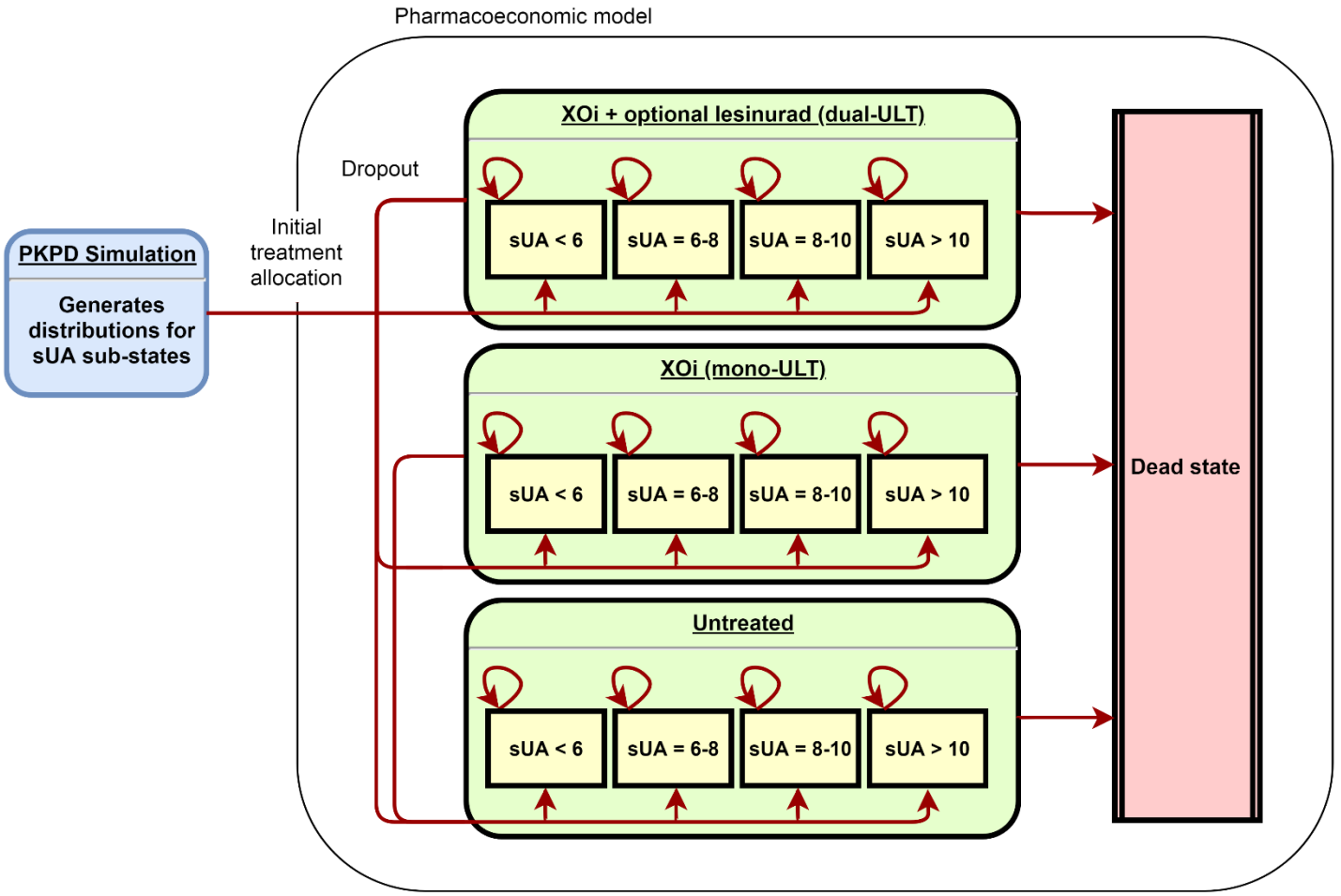


Figure 3.1. Illustration of the structure of the pharmacoeconomic model showing patient subgroup transitions and the sUA distributions set by PKPD simulations. In this example, the model estimates the lifetime costs and QALY gains resulting from all patients being initially allocated to an XOi (allopurinol or febuxostat) with optional lesinurad dual-ULT. This process is repeated using three adherence models and four initial ULT allocations in order to compare treatments options.

sUA Category and Flare Rate	Mean	Number	Distribution	Source
sUA < 6 mg/dL (360 µmol/L)				
0 flares	37%	N = 23	Dirichlet (23,28,4,5,2)	Khanna et al, 2012, Tophi and frequent gout flares are associated with impairments to quality of life, productivity and increased healthcare resource use: Results from a cross-sectional survey
1-2 flares	45%	N = 28		
3 flares	6%	N = 4		
4-5 flares	8%	N = 5		
>6 flares	3%	N = 2		
sUA 6 to <8 mg/dL (360 to <476 µmol/L)				
0 flares	8%	N = 6	Dirichlet (6,30,18,15,6)	
1-2 flares	40%	N = 30		
3 flares	24%	N = 18		
4-5 flares	20%	N = 15		
>6 flares	8%	N = 6		
sUA 8 to <10 mg/dL (476 to <595 µmol/L)				
0 flares	17%	N = 6	Dirichlet (6,9,4,9,7)	
1-2 flares	26%	N = 9		
3 flares	11%	N = 4		
4-5 flares	26%	N = 9		
>6 flares	20%	N = 7		
sUA ≥10 mg/dL (≥595 µmol/L)				
0 flares	As for sUA 8 to <10 mg/dL above			
1-2 flares				
3 flares				
4-5 flares				
>6 flares				

Table 3.2. Distribution of annual frequency of flares by sUA level

The initiation of ULT is known to initially result in an increase in the risk of experiencing gout flares (Shoji, Yamanaka and Kamatani, 2004) that is proportional to the extent of sUA reduction (Becker *et al.*, 2008; Beard *et al.*, 2014). This was modelled by fitting a linear model to data on the mean number of flares during the first 3 months of treatment and treatment response rate, for four different ULTs (Beard *et al.*, 2014). The predicted number of flares for a zero response rate and for a response rate following treatment were used to calculate a multiplier that is then used to increase the baseline number of quarterly flares. This multiplier was applied to every flare frequency category in the first model cycle only.

Costs

The daily cost of lesinurad 200 mg was assumed to be £0.93 (National Institute for Health and Care Excellence, 2016a), allopurinol 300 mg £0.03, and febuxostat 80 mg £0.87 (Joint Formulary Committee, 2018). We assumed that for all patients, gout flare prophylaxis was provided by 0.5 mg daily colchicine for the full 6 months as recommended (Hui *et al.*, 2017). This would require 200 tablets at a cost of £28.56 and it was assumed that unused doses would be discarded.

The average cost of treating a flare was assumed to be £43.78 (2016 prices) and the proportion of flares requiring treatment to be 26.7% (National Institute for Health and Care Excellence, 2016c). The National Institute for Health and Care Excellence (NICE) recommends quarterly monitoring of sUA concentration and renal function during the first year of ULT and annually thereafter. The estimated average cost of a treatment monitoring visit for lesinurad (£153.07) was assumed for all treatments. Although monitoring may vary between treatments, e.g. liver function tests with febuxostat and urinary uric acid tests with lesinurad (D. Khanna *et al.*, 2012), in the absence of data on the frequency of such testing no difference in overall cost was assumed. A summary of cost inputs is provided in Table 3.3.

Model Cost Input	Mean	Standard Deviation	Distribution	Source
Daily Drug Costs				
Allopurinol 300 mg	£0.030	Assumed 20% of mean	Gamma	British National Formulary
Febuxostat 80g	£0.870		Gamma	
Lesinurad 200 mg	£0.930		Gamma	Lesinurad STA report
Colchicine 0.5 mg	£28.56	NA	NA	British National Formulary
Patient Monitoring Cost				
Monitoring per visit	£153.07	Assumed 20% of mean	Gamma	Lesinurad STA
Monitoring frequency	Quarterly 1-year then annual			BSR guidelines
Cost of Treating Flares				
Gout flare requiring treatment (GFRT)	26.72%	NA	NA	Lesinurad STA
Cost of Treating Flares	£43.76	Assumed 20% of mean	Gamma	

Table 3.3. Daily drug costs, patient monitoring cost and cost of treating flares

Health State Utilities

A literature review and a range of trial derived health state utility values are presented in recent reports submitted to NICE as part of the reappraisal of lesinurad in the UK (National Institute for Health and Care Excellence, 2016b). As in these published reports, we adopt a base case that uses the mean SF-6D scores in CLEAR 1 and CLEAR 2 clinical trials (Bardin *et al.*, 2017; Saag *et al.*, 2017) stratified by flare frequency (Table 3.4). These annual health state utilities, stratified according to flare frequency, were used to calculate an average decrement of 0.043 utilities per flare. This was used to reduce the utility of those experiencing flares from the reference health state utility of 0.768 for gout patients experiencing no flares over 12 months. We did not model any impact of sUA concentration on mortality, on the basis of a lack of substantiated evidence of such an association (Li *et al.*, 2017).

Annual number of flares	Health State Utility	Standard Deviation*	Distribution	Source
0	0.768	0.0154	Beta	NICE et al. (2016) Committee papers 2
1-2	0.751	0.0150		
3	0.729	0.0146		
4-5	0.729	0.0146		
6+	0.701	0.0140		

Table 3.4. Health state utilities by frequency of gout flares

*Assumed to be 2% of the mean utility estimate

3.5. Sensitivity Analyses

A total of 500 iterations of the PKPD model were conducted, each simulating 120 days of treatment in 500 patients. Each iteration produced a sUA concentration distribution that provided inputs to 10 pharmacoeconomic model simulations, resulting in a total of 5,000 simulations. The incremental costs and QALYs were derived for each treatment comparison and can be averaged over all simulations or presented as individual outputs on the cost effectiveness plane.

4. Results

4.1. PKPD Model Results

The results of PKPD simulations (Table 3.5) suggest that febuxostat 80 mg could be nearly 100% effective in patients who adhere perfectly to their dosing regimen, and only a small minority of patients would be eligible for dual-ULT with lesinurad. For allopurinol 300 mg, even with perfect adherence, only 57% of patients were estimated to achieve the sUA concentration target of <6 mg/dL (<360 µmol/L), but this is increased to 83% with the addition of lesinurad. As expected, the proportion of patients achieving target concentrations fell with worsening adherence across all treatments, while the proportion eligible for dual-ULT rose. The rank of treatments by response rate remained constant across the three adherence scenarios. Sub-optimal adherence has a larger impact on sustained response (<6 mg/dL on >80% of days) than the single time point response (day 120).

Figure 3.2 provides a comparison between the results of pivotal clinical trials and the simulated response rates. Treatment response is defined as sUA <5 mg/dL (<300 µmol/L), as <6 mg/dL (<360 µmol/L) was unavailable for all treatments, and the simulated results have been adjusted to account for treatment discontinuation at 6 months in the corresponding trial arm to provide a more appropriate comparison. While our simulated results are broadly in line with the results from pivotal trials, the differences may be difficult to interpret owing to the many factors relating to trial conduct that have not been accounted for in the PKPD modelling.

4.2. Economic Model Results

Table 3.6 presents the means of simulated total costs and QALYs accrued over the lifetime of the patient cohort, with allopurinol 300 mg as first-line and lesinurad add-on as second-line ULT. Under the base case method of calculating flare frequency and with perfect medication adherence (adherence model 1), the incremental cost effectiveness ratio (ICER) of allopurinol with optional lesinurad dual-ULT compared with allopurinol alone was £39,184 per QALY gained. This is considerably higher than the £20,000 per QALY threshold of cost effectiveness used in the UK. The ICER increased to £47,848 and £78,350 per QALY gained in adherence models 2 and 3, in which patients discontinue treatment over time and have implementation rates of 80% and 50%, respectively. The ICERs were lowered using the alternative flare frequency methodology to £19,019, £31,803 and £77,903 per QALY gained across the three adherence models 1 to 3, respectively.

Patients not eligible for first line treatment with allopurinol may be prescribed febuxostat and, if not adequately controlled, may subsequently be offered dual-ULT with lesinurad. In both perfect adherence scenarios (Table 3.7), the ICER of febuxostat with optional lesinurad dual-ULT compared

with febuxostat alone was £31,901 and £15,376 per QALY gained in the base case and alternative flare frequency models, respectively. The simulations suggest it would be more cost effective to provide lesinurad to non-responders on febuxostat than on allopurinol monotherapy, assuming perfect adherence. However, under adherence models 2 and 3, it appears lesinurad is more cost effective with allopurinol than febuxostat.

The complete distributions of simulated incremental QALY and incremental cost results are presented in Figure 3.3, for lesinurad (+ optional febuxostat) versus febuxostat alone, and Figure 3.4, for lesinurad (+ optional allopurinol) versus allopurinol alone. Figures 3.5 and 3.6 are the equivalent plots but using the alternative flare frequency methodology. These figures provide a visual representation of the probability that each type of dual-ULT is cost effective when compared with the corresponding monotherapy using a cost effectiveness threshold of £20,000 per QALY. Each point is one of the 5,000 simulations and those falling below and to the right of the red line, which defines the cost effectiveness threshold, would be deemed cost effective.

Urate lowering therapy option*	Percentage of subjects in sUA category (mg/dl) at day 120[#]				% < 6 mg/dl on ≥80% of days	% Receiving lesinurad
	<6	6 to <8	8 to <10	≥10		
100% dose implementation						
Allopurinol 300mg (ALL)	57	40	3	0	56.6	NA
ALL + optional lesinurad 200mg	83	17	0	0	83.0	43.7
Febuxostat 80mg (FBX)	97	3	0	0	97.3	NA
FBX + optional lesinurad 200mg	99	1	0	0	99.3	2.6
80% dose implementation						
Allopurinol 300mg (ALL)	41	49	10	0	35.7	NA
ALL + optional lesinurad 200mg	63	33	5	0	52.5	59.6
Febuxostat 80mg (FBX)	81	15	4	0	71.3	NA
FBX + optional lesinurad 200mg	84	14	3	0	74.6	18.4
50% dose implementation						
Allopurinol 300mg (ALL)	19	53	24	3	12.7	NA
ALL + optional lesinurad 200mg	36	46	16	2	21.0	80.1
Febuxostat 80mg (FBX)	49	36	14	1	25.1	NA
FBX + optional lesinurad 200mg	53	34	12	1	30.2	49.5
No Treatment	0	21	57	22	0	NA

Table 3.5. Distribution of patients across sUA concentration categories following ULT with varying levels of dose implementation using 500 PKPD simulations
*Allopurinol 300 mg once daily; febuxostat 80 mg once daily; lesinurad 200 mg once daily
[#]6 mg/dL = 360 µmol/L; 8 mg/dL = 476 µmol/L; 10 mg/dL = 595 µmol/L

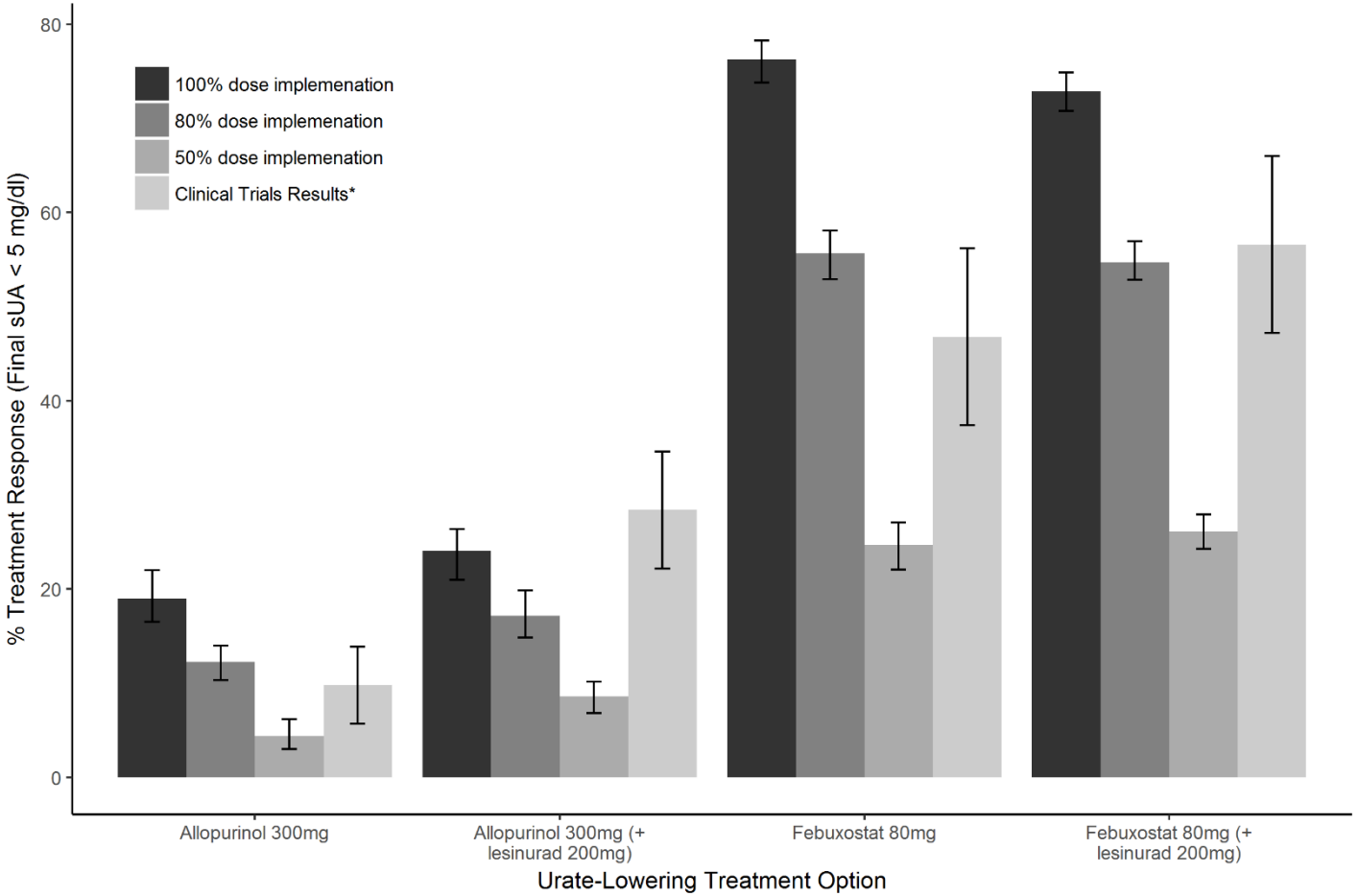


Figure 3.2. Simulated treatment response rates for three adherence models and the treatment response in the corresponding treatment arm in clinical trials. The threshold for treatment response has been defined as 5 mg/dl (300 µmol/L). Clinical trials results are at 6 months and assume non-responder imputation for patients who discontinued. Discontinuation rates were also applied to simulated results assuming equal probability of discontinuation amongst responders and non-responders. Confidence intervals on PKPD simulations account for patient heterogeneity and parameter random effects, but not uncertainty in parameters estimates or within individual residual variability.

* Allopurinol 300 mg and allopurinol 300 mg + lesinurad 200 mg response rate is 9.8% and 28.4% respectively from CLEAR 1 and CLEAR 2 trials; Febuxostat 80mg and febuxostat 80 mg + lesinurad 200 mg response rate is 46.8% and 56.6% respectively from the CRYSTAL trial.

ULT Treatment Option	Lifetime Cost	Lifetime QALYs	Δ Cost vs ALL	Δ QALYs vs ALL	ICER vs ALL
Base case flare frequency methodology					
Adherence model 1					
Allopurinol 300 mg (ALL)	£3,757	13.36	-	-	-
ALL + optional lesinurad 200 mg	£6,352	13.42	£2,594	0.066	£39,184
Adherence Model 2					
Allopurinol 300 mg (ALL)	£2,246	13.22	-	-	-
ALL + optional lesinurad 200 mg	£4,068	13.26	£1,822	0.038	£47,848
Adherence Model 3					
Allopurinol 300 mg (ALL)	£2,277	13.19	-	-	-
ALL + optional lesinurad 200 mg	£4,796	13.22	£2,519	0.032	£78,350
Alternative flare frequency methodology					
Adherence model 1					
Allopurinol 300 mg (ALL)	£3,614	13.49	-	-	-
ALL + optional lesinurad 200 mg	£6,139	13.63	£2,525	0.133	£19,019
Adherence Model 2					
Allopurinol 300 mg (ALL)	£2,221	13.24	-	-	-
ALL + optional lesinurad 200 mg	£4,024	13.30	£1,804	0.057	£31,803
Adherence Model 3					
Allopurinol 300 mg (ALL)	£2,277	13.19	-	-	-
ALL + optional lesinurad 200 mg	£4,784	13.23	£2,507	0.032	£77,903

Table 3.6. Economic model results in patients with allopurinol 300 mg monotherapy as first line treatment and add-on lesinurad 200 mg in non-responders as second line treatment. The ICER was calculated as the difference in lifetime costs divided by the difference in lifetime QALYs. Costs and effects were discounted at 3.5%; ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life-years; adherence model 1: perfect adherence to dosing regimen; adherence model 2: treatment discontinuation and 80% average implementation; adherence model 3: treatment discontinuation and 50% average implementation

ULT Treatment Option	Lifetime Cost	Lifetime QALYs	Δ Cost vs FBX	Δ QALYs vs FBX	ICER vs FBX
Base case flare frequency methodology					
Adherence model 1					
Febuxostat 80 mg (FBX)	£9,157	13.46	-	-	-
FBX + optional lesinurad 200 mg	£9,311	13.46	£154	0.005	£31,901
Adherence Model 2					
Febuxostat 80 mg (FBX)	£5,094	13.28	-	-	-
FBX + optional lesinurad 200 mg	£5,803	13.29	£709	0.010	£74,136
Adherence Model 3					
Febuxostat 80 mg (FBX)	£5,122	13.23	-	-	-
FBX + optional lesinurad 200 mg	£7,015	13.25	£1,893	0.015	£124,212
Alternative flare frequency methodology					
Adherence model 1					
Febuxostat 80 mg (FBX)	£8,884	13.70	-	-	-
FBX + optional lesinurad 200 mg	£9,034	13.71	£149	0.010	£15,376
Adherence Model 2					
Febuxostat 80 mg (FBX)	£5,024	13.34	-	-	-
FBX + optional lesinurad 200 mg	£5,724	13.36	£700	0.017	£40,078
Adherence Model 3					
Febuxostat 80 mg (FBX)	£5,151	13.23	-	-	-
FBX + optional lesinurad 200 mg	£7,031	13.25	£1,880	0.022	£86,870

Table 3.7. Economic model results in patients with febuxostat 80 mg monotherapy as first line treatment and add-on lesinurad 200 mg in non-responders as second line treatment. The ICER was calculated as the difference in lifetime costs divided by the difference in lifetime QALYs. Costs and effects were discounted at 3.5%; ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life-years; adherence model 1: perfect adherence to dosing regimen; adherence model 2: treatment discontinuation and 80% average implementation; adherence model 3: treatment discontinuation and 50% average implementation

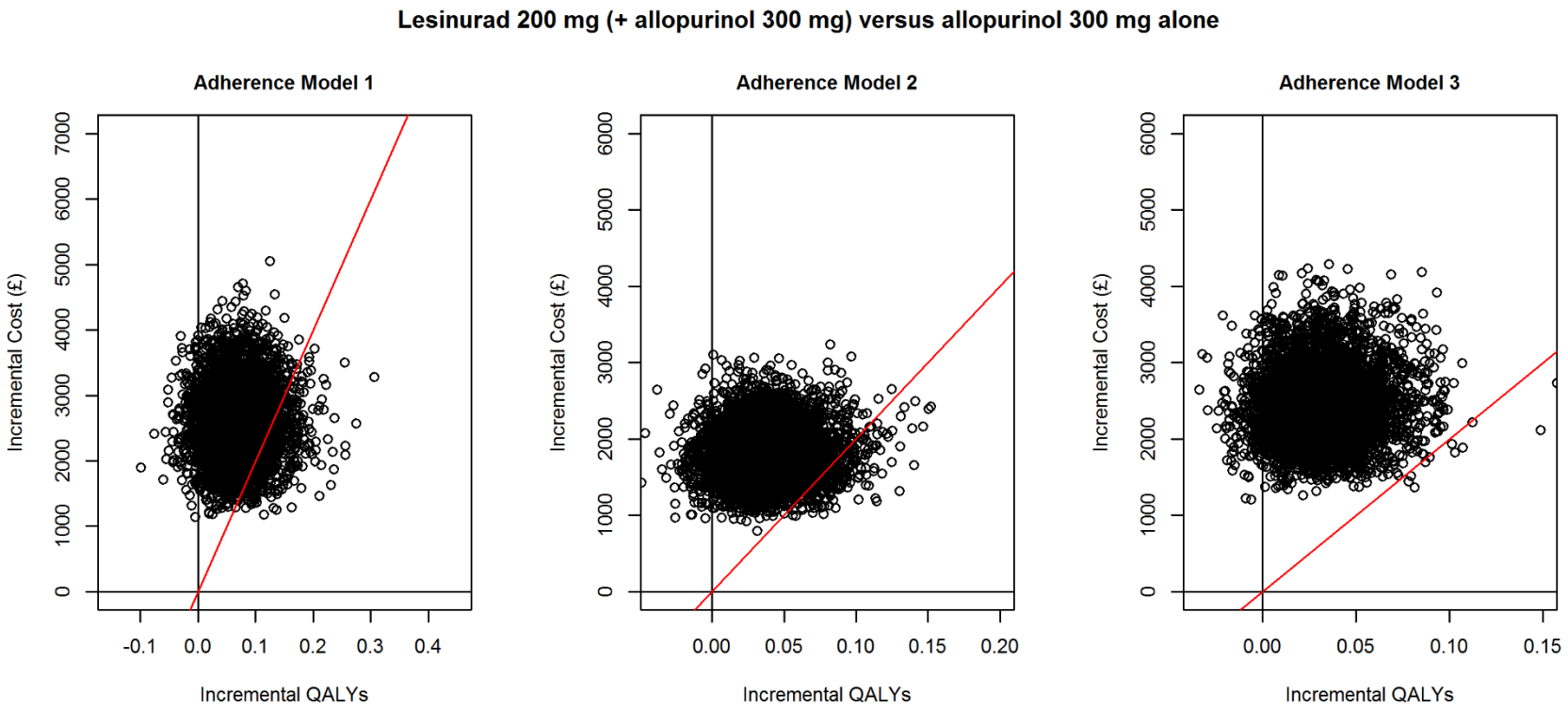


Figure 3.3. Base case probabilistic sensitivity analysis results. Cost-effectiveness plane showing the incremental costs and QALYs when comparing lesinurad 200 mg and optional allopurinol 300 mg with allopurinol 300 mg alone. Results generated from 500 pharmacometric and 5,000 pharmacoeconomic model simulations. The red line shows the willingness to pay threshold of £20,000.

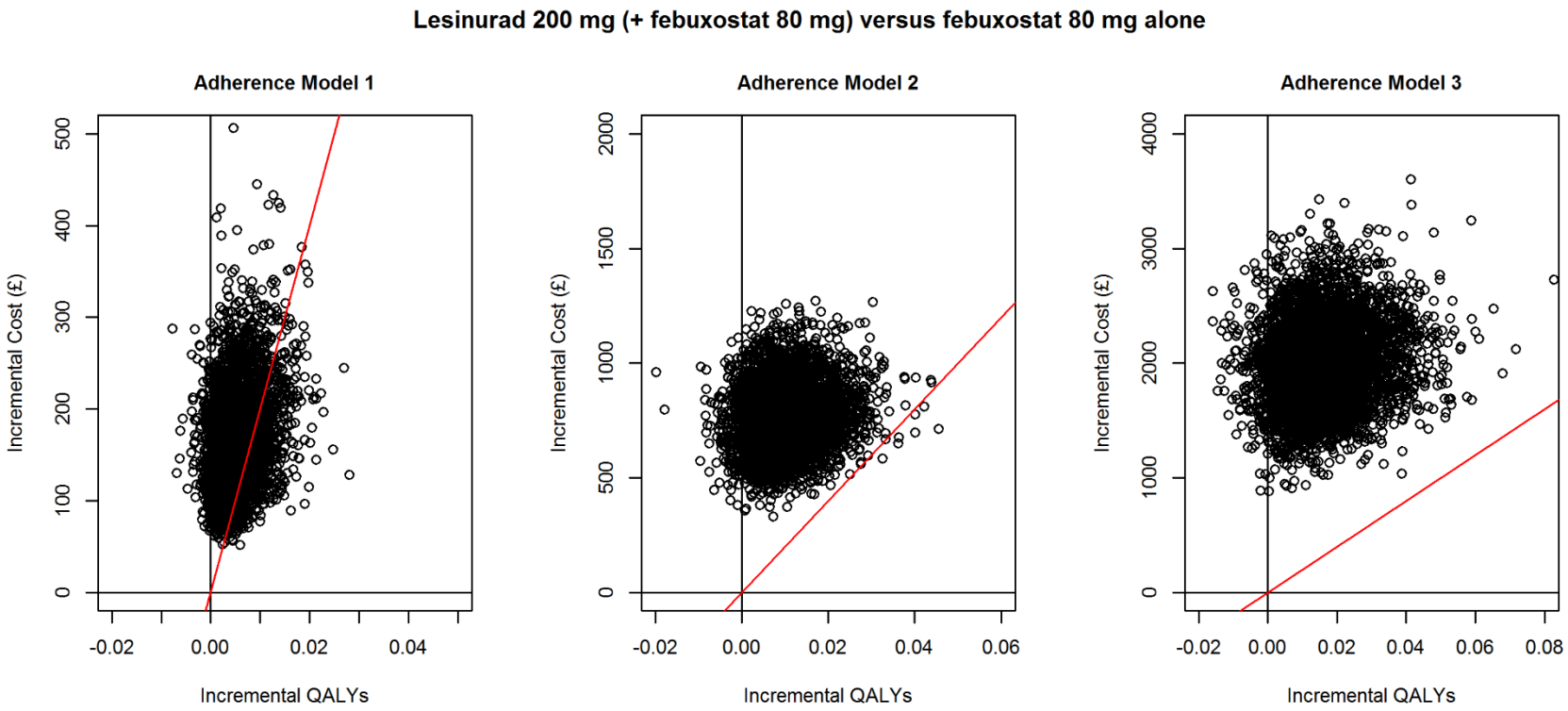


Figure 3.4. Base case probabilistic sensitivity analysis results. Cost-effectiveness plane showing the incremental costs and QALYs when comparing lesinurad 200 mg and optional febuxostat 300 mg with febuxostat 300 mg alone. Results generated from 500 pharmacometric and 5,000 pharmacoeconomic model simulations. The red line shows the willingness to pay threshold of £20,000.

Alternative flare frequency methodology probabilistic sensitivity analysis results.

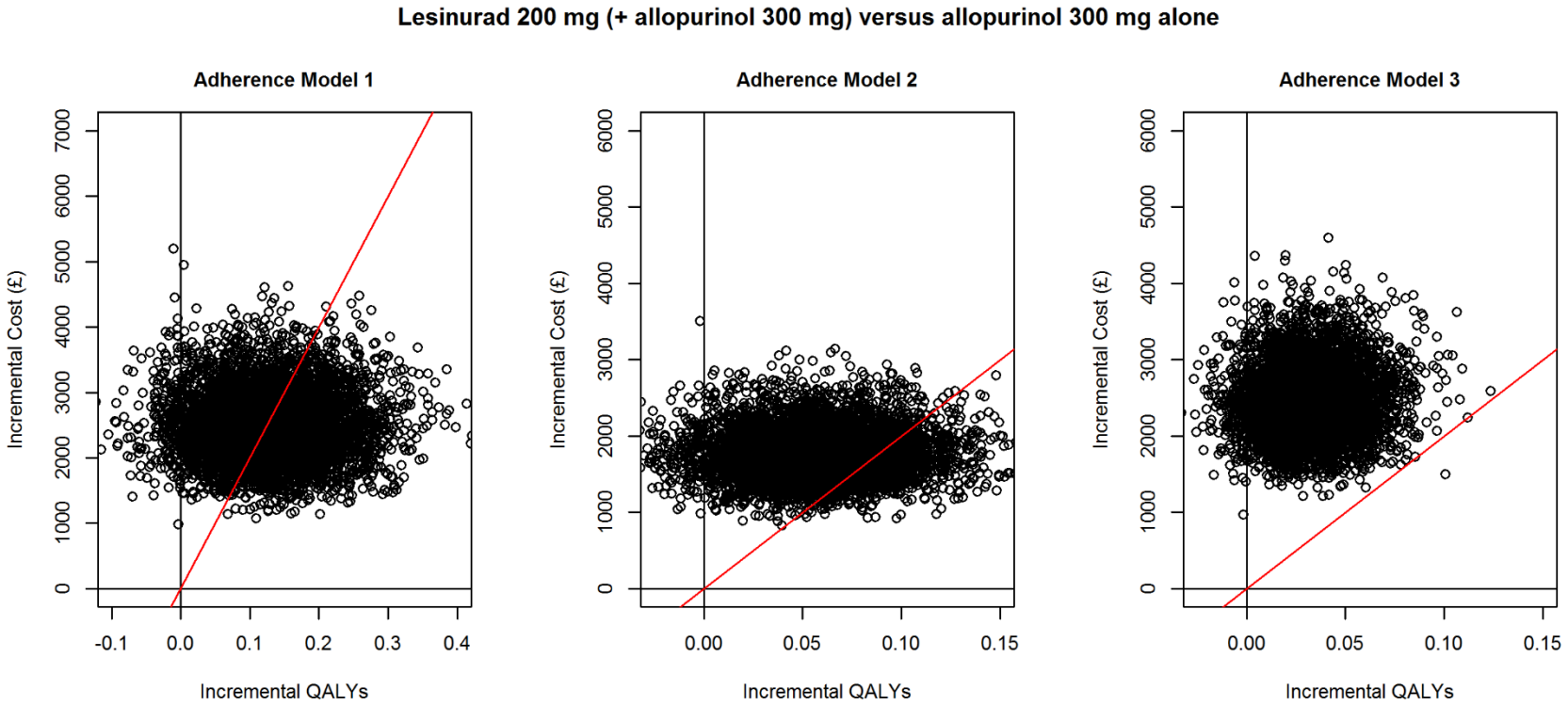


Figure 3.5. Alternative flare frequency methodology probabilistic sensitivity analysis results. Cost-effectiveness plane showing the incremental costs and QALYs when comparing lesinurad 200 mg and optional allopurinol 300 mg with allopurinol 300 mg alone. Results generated from 500 pharmacometric and 5,000 pharmacoeconomic model simulations. The red line shows the willingness to pay threshold of £20,000.

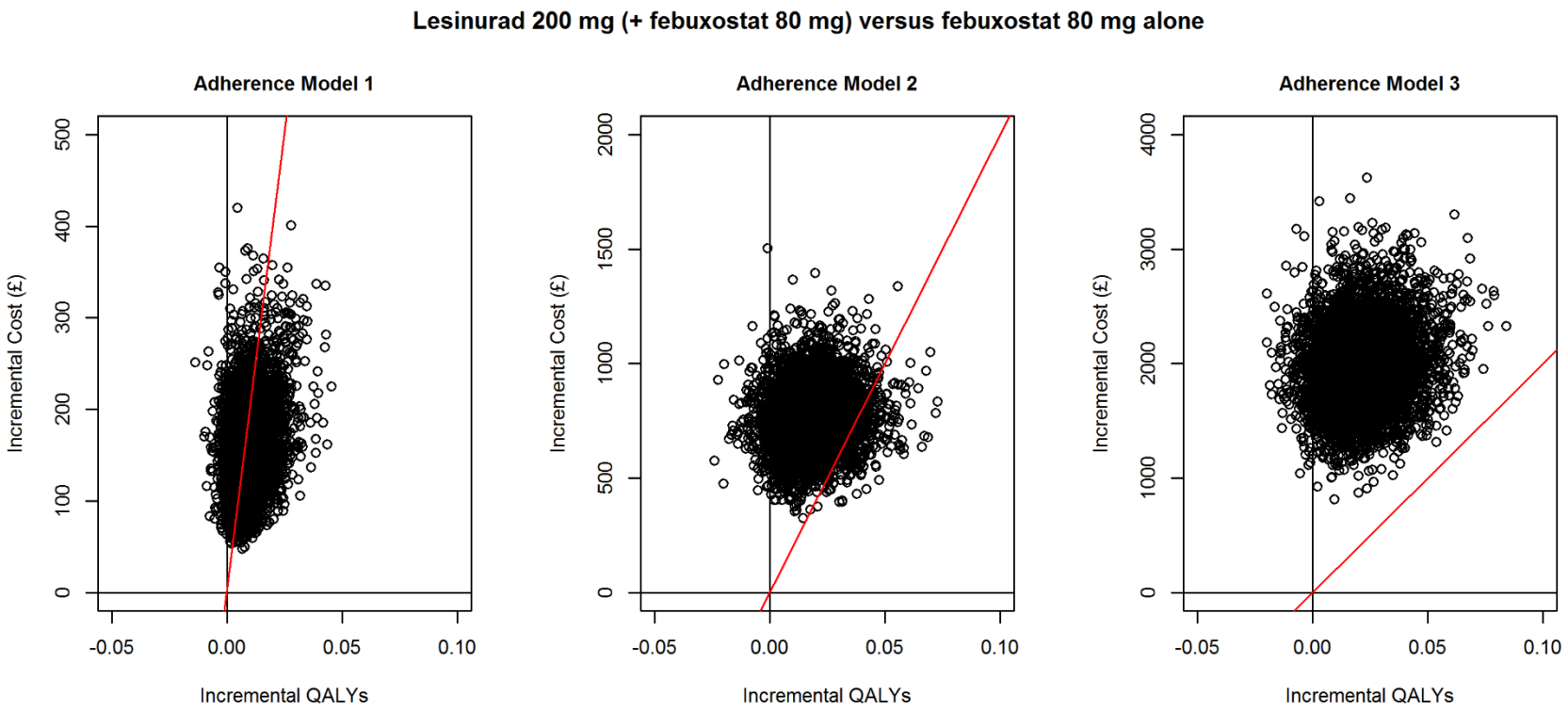


Figure 3.6. Alternative flare frequency methodology probabilistic sensitivity analysis results. Cost-effectiveness plane showing the incremental costs and QALYs when comparing lesinurad 200 mg and optional febuxostat 300 mg with febuxostat 300 mg alone. Results generated from 500 pharmacometric and 5,000 pharmacoeconomic model simulations. The red line shows the willingness to pay threshold of £20,000.

4.3. Value-Based Price

For each probabilistic economic simulation we calculated the price of lesinurad at which the ICER comparing dual-ULT to allopurinol or febuxostat monotherapy is equal to the £20,000 per QALY threshold (value-based price). The resulting distributions of prices are plotted in Figure 3.7 along with a line indicating the price of lesinurad originally proposed for the UK market (National Institute for Health and Care Excellence, 2016c). Using the base case methodology for flare frequency, very few value-based prices of lesinurad are more than, or equal to, the price originally proposed for the UK market, regardless of the adherence model which was assumed. The simulations resulting in the highest proportion of value-based prices greater than, or equal, to the proposed price used the alternative flare frequency methodology and required adherence models 1 (53% versus allopurinol and 61% versus febuxostat). In scenarios of imperfect adherence the value-based prices of lesinurad often fall below zero. This is primarily due to dual-ULT being associated with lower rates of treatment discontinuation (an assumption we used based on clinical trial data), therefore, accruing higher costs from the XOi component of dual-therapy.

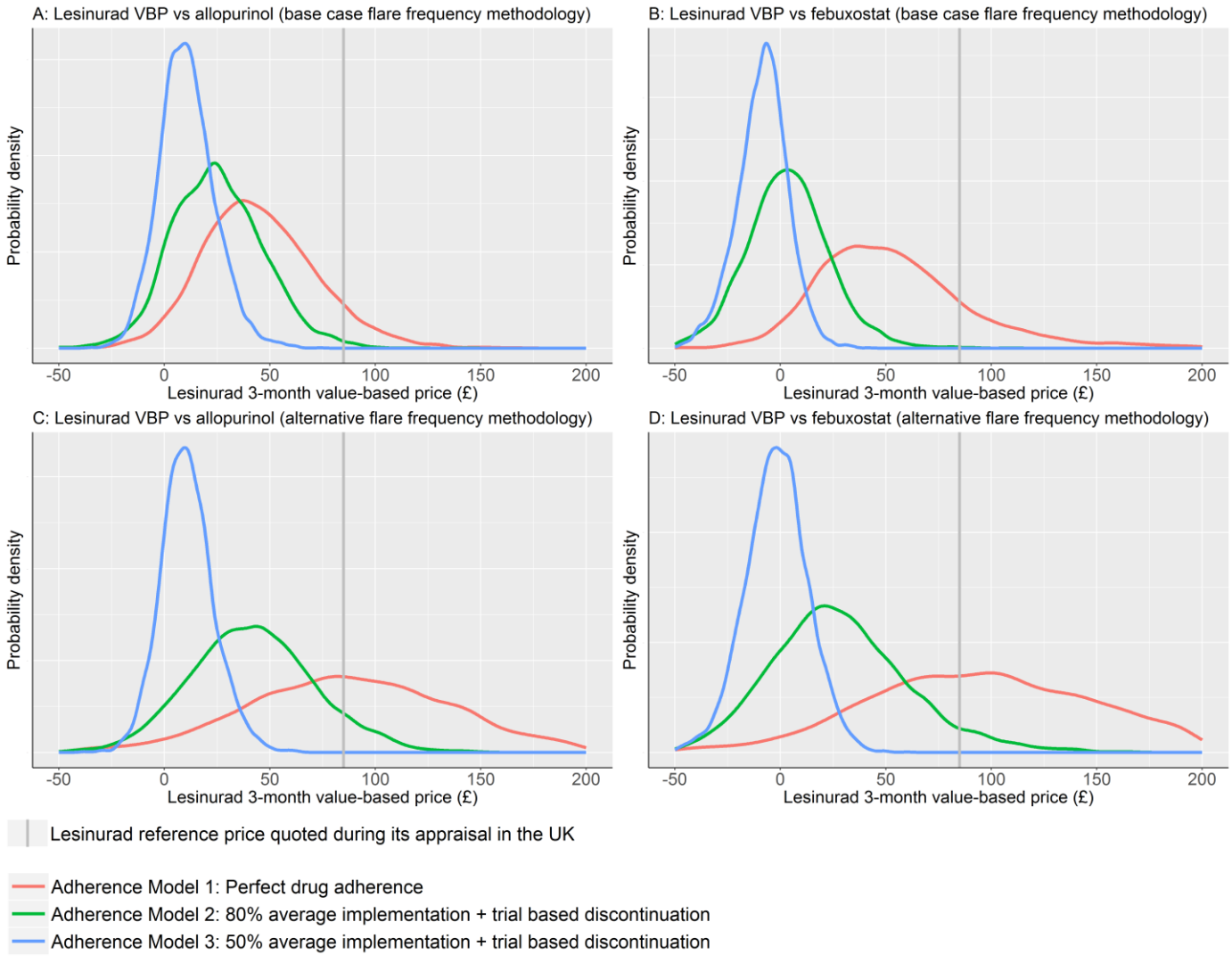


Figure 3.7. The value-based price of lesinurad as part of dual-ULT in combination with either febuxostat or allopurinol in patients not responding to either monotherapy alone. The value-based price distributions are obtained using the results of 5,000 probabilistic economic model simulations. Value-based price is defined as the price of lesinurad at which the modelled incremental cost per QALY comparing dual-ULT to mono-ULT is equal to the £20,000 threshold. The vertical line indicates the price of lesinurad quoted during its appraisal in the UK.

5. Discussion

This was a study of the effectiveness and cost effectiveness of lesinurad as a second-line ULT following first-line treatment with either allopurinol 300 mg or febuxostat 80 mg, adopting an approach to cost effectiveness that is consistent with a UK NICE appraisal (National Institute for Health and Care Excellence., 2009). A population PKPD model used to simulate mono and dual-ULTs showed that while treatment could be highly effective at reducing sUA concentrations to below target, response rates rapidly fell as adherence was reduced by allowing treatment discontinuation and reducing dose implementation from an average of 100% down to 50%. Using the price of lesinurad originally proposed for the UK market, there was only one scenario in which the ICER of dual therapy with lesinurad compared with allopurinol or febuxostat monotherapies was below the higher end of the cost effectiveness threshold of £30,000 per QALY. This was using treatment effectiveness simulated using perfect drug adherence and a pharmacoeconomic model which used the alternative flare frequency methodology in which sustained responders become flare-free. By calculating the value-based price at a threshold of £20,000 per QALY, we have shown the extent to which the pricing of a uricosuric for second-line ULT depends on drug adherence.

Our results broadly agree with the results of previous economic evaluations of lesinurad. Based on the manufacturer's evidence and independent review, a NICE appraisal committee considered the most plausible ICER for lesinurad plus allopurinol compared with allopurinol alone to be at least £62,298 per QALY gained (National Institute for Health and Care Excellence, 2017b). Our base-case estimates range from £39,184 to £78,350 depending on the level of medication adherence assumed.

Linked PKPD and pharmacoeconomic modelling provide a means of studying the implications of drug pharmacology and adherence on the economic potential of new medicines (Pink, Lane and Hughes, 2012). These methods can reveal the best-case economic value of new treatments in the case of perfect drug adherence and estimate the rate at which this changes with worsening persistence or dose implementation. The linkage of these two disciplines is increasingly being implemented in order to study a variety of issues in drug development (Pink, Lane and Hughes, 2012; Hoogendoorn *et al.*, 2014; Pink *et al.*, 2014; Van Hasselt *et al.*, 2015; Slejko *et al.*, 2016; Kamal *et al.*, 2017). However, we are not aware of any studies that have estimated the impact of changing levels of drug adherence on modelled economic outcomes. Since treatment discontinuation and imperfect dose implementation are both a feature of latter stage clinical trials and routine practice use of medicines, understanding how this may affect cost effectiveness could be of use to both manufacturers and health care providers.

While PKPD simulation allows rapid analysis of previously untested treatment scenarios, it may not always provide a substitute for clinical trials. The mixture of data sources informing the models, possible model misspecification, simplifying assumptions and differences in time or in the patient population can all result in predictions that differ from what would be observed in a trial setting (Holford, Ma and Ploeger, 2010). Furthermore, we have assumed that within the data from which the PKPD models were constructed patients adhered to their dosing regimen. This may not be the case and could result in biased model results (Vrijens, Gross and Urquhart, 2005). The adherence patterns we assumed were not based on real-world evidence of adherence to ULTs due to an absence of studies that disentangle persistence from implementation. The possible treatment strategies for gout are more nuanced than was considered in this study. Guidelines recommend that allopurinol is used as first line but that it should be initiated at a low dose (e.g. 100 mg) before being titrated up to 900 mg per day or until response is achieved. Similarly, febuxostat could also be initiated at 40 mg and titrated up to a possible 120 mg. The economic evaluation did not consider the potential adverse drug reactions; allopurinol is known to cause rare hypersensitivity reactions, there are possible cardiovascular complications associated with febuxostat, and lesinurad is associated with renal complications that the results of Chapter 2 indicate may be exacerbated by poor medication adherence.

Gout remains a condition that is typically poorly managed, even in a clinical trials setting with newer ULTs. For health care payers our results provide an indication of the extent to which poor adherence to ULTs erodes the cost effectiveness of these medicines when translating from clinical trials to routine practice. Development of ULTs with greater drug forgiveness (Assawasuwannakit, Braund and Duffull, 2015) would to some extent mitigate the effects of poor implementation and result in greater effectiveness relative to existing treatments. Pharmaceutical companies conducting future clinical trials of novel ULTs should be mindful that achieving sUA endpoints alone, without also showing reductions in gout flares, is not likely to provide an attractive value-based price. This is due, in part, to uncertainty in the rate and scale of reductions in gout flares following a reduction in sUA and the weak evidence base linking sUA to other potential health outcomes, such as cardiovascular diseases. Designing clinical trials to demonstrate the eradication of gout in sustained responders, which is expected in most patients (Shoji, Yamanaka and Kamatani, 2004), is likely to increase the potential value-based price of new ULTs. An alternative approach could be a sub-study designed to bridge the evidence gap between sUA concentration and flares. For example, Jutkowitz et al. (Jutkowitz *et al.*, 2017) have estimated the potential value of conducting various 1-year studies.

This study has found that medication adherence has a significant influence on the potential cost effectiveness of second-line dual-ULT with lesinurad compared with either allopurinol or febuxostat

alone. However, although treatment effect is enhanced under perfect medication adherence, dual-ULT is not expected to be cost effective relative to either monotherapies at a threshold of £20,000 per QALY. The estimated value-based prices of lesinurad only exceeded that which has been proposed in the UK when assuming both perfect drug adherence and the eradication of gout flares in sustained treatment responders.

Preface to Chapter 4

Around the time that the uricosuric urate-lowering therapy lesinurad was in developed, there was significant activity in the area of gout treatment with a number of other compounds also undergoing development. Whilst there exists significant unmet need in gout, the commercial success of novel compounds is uncertain owing to the low cost of the generic allopurinol and the prevalence of poor medication adherence. Since linked pharmacometric-pharmacoeconomic models consist of a framework linking drug pharmacology to the clinical and economic outcomes which, in many jurisdictions, determine the pricing options and probability of positive reimbursement decisions, it could be used to identify the pharmacological profiles expected to be sufficiently effective to obtain a minimum commercially acceptable price.

The application in this chapter examines xanthine oxidase inhibitors and, using real world adherence data, estimates the maximum reimbursement prices that could be obtained for hypothetical drugs where reimbursement decisions are made using a cost effectiveness threshold. The pharmacology of febuxostat is taken as a starting point and adjustments are made to either the potency or the systemic clearance. These changes result in pharmacological profiles that are more forgiving to missed doses and, therefore, retain a greater level of effectiveness under conditions of imperfect dose implementation. This methodology is used to quantify the degree to which higher prices may be justifiable for drugs that have the property of increased forgiveness, which may not have been attempted previously and which may only be possible using a linked pharmacometric-pharmacoeconomic approach. This type of study could be of value in early clinical trials as the pharmacological attributes become observable for candidate compounds and very early estimates of their commercial viability can be obtained.

Chapter 4

Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Non-Adherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout

1. Summary

Linked pharmacometric and pharmacoeconomic models provide a structured approach for assessing the value of candidate drugs in development. The aim of this study was to assess the utility of such an approach for identifying the properties of xanthine oxidase inhibitors (XOi) providing improved forgiveness to non-adherence and estimate the maximum reimbursement price. The pharmacometric and pharmacoeconomic models were used to simulate the time course of serum uric acid concentrations, and estimate quality-adjusted life years and costs for the XOi febuxostat and a range of hypothetical alternatives. Compounds with reduced clearance or increased potency were more forgiving to missed doses, however, even following relatively large changes in these properties the predicted maximum reimbursement prices represented an increase of only 19% above febuxostat 80 mg. Linked pharmacometric and pharmacoeconomic modelling methods have the potential to inform early drug development by providing an early indication of pricing options in jurisdictions operating value-based pricing.

2. Introduction

Linked pharmacokinetic-pharmacodynamic-pharmacoeconomic (PKPDPE) models can provide a framework capable of testing the influence of drug pharmacology on long term clinical and economic outcomes, such as cost-effectiveness and value based pricing (Pink, Lane and Hughes, 2012; Hoogendoorn *et al.*, 2014; Slejko *et al.*, 2016). This offers distinct advantages over conventional pharmacoeconomic analyses during clinical drug development by making explicit consideration of the relation between dose taking, dose-response, health outcomes and costs. Linked PKPDPE modelling can be used to predict the likelihood of therapeutic success and quantify the implications for pricing. One application, which exploits the mechanistic properties of this approach, is in determining the influence of non-adherence on the value of treatments. This represents a natural extension to previous research in which different patterns of adherence serve as inputs to PK (Rubio, Cox and Weintraub, 1992; Hughes, 2008) and PKPD (Vrijens *et al.*, 2014; Challenger *et al.*, 2017) models, and provides a basis for estimating cost-effectiveness in preference to cost-efficacy (Swift *et al.*, 2018).

Imperfect medication adherence can limit the benefit of treatments, result in poorer outcomes for patients, and increase healthcare costs (Blaschke *et al.*, 2012). Medication adherence can be decomposed into three distinct phases; 1) the initiation of treatment, 2) the degree to which a patient's dose taking matches the prescribed regimen while nominally adhering (implementation) and 3) the discontinuation of treatment (persistence) (Vrijens *et al.*, 2012). The design of medicines which remain effective when dose implementation is erratic – a property known as 'forgiveness' (Osterberg, Urquhart and Blaschke, 2010; Assawasuwannakit, Braund and Duffull, 2016) – may improve treatment effectiveness under conditions of routine care and provide added value. Conventional PK and PD modelling can offer insights on the impact of variable dosing on clinical endpoints (Hughes and Walley, 2003; Stauffer *et al.*, 2017); however to our knowledge, there are no published methods for predicting the value of improving treatment forgiveness.

Despite the availability of effective urate-lowering therapies (ULTs) for gout, such as xanthine oxidase inhibitors (XOi) allopurinol and febuxostat, many patients fail to achieve serum uric acid target concentrations. Within clinical trials, allopurinol 300 mg/day reduced serum uric acid (sUA) concentrations to below target (6 mg/dL (360 µmol/L)) in 12% – 41% of patients (Becker *et al.*, 2005, 2009; Schumacher *et al.*, 2008; Bardin *et al.*, 2017; Saag *et al.*, 2017); and febuxostat 80 mg/day in 57% – 76% of patients (Becker *et al.*, 2005, 2009; Schumacher *et al.*, 2008). Rates of target attainment in routine practice are also low, and range from 22% (US primary care or rheumatology clinic) (Khanna *et al.*, 2016), 38% (UK primary care) (Cottrell *et al.*, 2013) to 45% (UK rheumatology) (Roddy *et al.*, 2018). A principal cause of treatment failure is non-adherence, with as few as 40% of patients being

classed as adherent (medication possession ratio > 0.8) using prescription claims data but with higher estimates obtained using other methods (Scheepers *et al.*, 2018; Yin *et al.*, 2018).

One potential way in which the next generation XOi could add value is through improved forgiveness. Of the many structurally dissimilar candidate lead compounds (Šmelcerović *et al.*, 2017), the potential for one to have such a property e.g. through reduced clearance or increased potency, could result in improved use-effectiveness (Assawasuwannakit, Braund and Duffull, 2015). More forgiving drugs that retain greater effectiveness under real world adherence would be expected to result in quality of life benefits, and potentially impact on costs, compared with existing treatments. Many jurisdictions operate a form of value-based pricing where the maximum reimbursement price is linked to the added value, in terms of both cost and health impacts, a medicine provides. A higher maximum reimbursement price makes it more likely that a pharmaceutical company would achieve a return on investment offsetting the risk of development.

This study uses real-world adherence data and PKPDPE modelling to simulate the effectiveness and determine the value of a series of hypothetical XOi. The aim was to assess the utility of using a PKPDPE model to link pharmacology to treatment effectiveness to the maximum reimbursement price in order to inform early decision making based on the predicted value that could be gained from developing a more forgiving drug.

3. Methods

3.1. Overview

In the first stage, the time course of sUA was simulated based on real-world dose taking histories and using a range of drug models, representing both real-world and hypothetical XOi. This stage was repeated a large number of times with resampling from probability distributions for patient characteristics, including baseline sUA concentration, age and weight. In the second stage the post-treatment sUA was used to predict the annual frequency of acute gout flares over the patients' remaining lifetime and to estimate the overall costs and impacts on quality-adjusted life years.

3.2. Pharmacometric and Pharmacoeconomic Models

The two compartment PK model and multi-compartment semi-mechanistic PD model developed for febuxostat in Chapter 2 was used to simulate sUA concentrations. The structure of the PD model was presented in Figure 2.1, while PK and PD model parameters were given in earlier chapters. In addition to febuxostat at approved daily doses of 80 mg and 120 mg (Joint Formulary Committee, 2018), twelve 'hypothetical' ULTs were assessed by changing the values of potency or clearance parameters for febuxostat (Table 4.1).

The rationale for the clearance, potency and dose adjustments is that i) reduced clearance prolongs residual drug concentration (and therefore extends the duration of action), but for an unbiased comparison with constant area under the concentration curve a corresponding dose reduction was made; and ii) for a given concentration with increased potency there is greater effect and we have, therefore, tested scenarios with and without dose adjustments. In reality, decisions concerning dose would be guided by a consideration both of the efficacy and the safety profiles of a candidate compound. We have not considered safety in this study.

Scenario description	ULT ID	Parameter (units)			Steady-state sUA conc. perfect adherence* (mg/dL)
		Dose (mg)	CL / half-life* (dL h^{-1} / hours)	IC_{50}# (mg/dL)	
Febuxostat 80 mg	FBX80	80	75.9 / 6.5	$1.13x10^{-3}$	3.33
Febuxostat 120 mg	FBX120	120			2.48
Hypothetical ULTs with reduced IC_{50}	A1	80	75.9 / 6.5	$9.04x10^{-4}$	2.86
	A2			$6.78x10^{-4}$	2.30
	A3			$4.52x10^{-4}$	1.60
	A4			$2.26x10^{-4}$	0.74
Hypothetical ULTs with reduced IC_{50} and dose	B1	64	75.9 / 6.5	$9.04x10^{-4}$	3.34
	B2	48		$6.78x10^{-4}$	3.37
	B3	32		$4.52x10^{-4}$	3.42
	B4	16		$2.26x10^{-4}$	3.55
Hypothetical ULTs with lower clearance and dose reduction	C1	64	60.7 / 7.7	$1.13x10^{-3}$	2.91
	C2	48	45.5 / 9.7		2.52
	C3	32	30.3 / 13.8		2.20
	C4	16	15.2 / 26.2		1.97

Table 4.1. Summary of urate-lowering therapies used in PKPD simulations

*Simulations used a reference subject of age 60, weight 100 kg, and baseline sUA of 9 mg/dL

The ULTs are xanthine oxidase inhibitors and inhibit the rate of conversion of hypoxanthine to xanthine and xanthine to uric acid. The IC_{50} given here is for the inhibition of xanthine to uric acid conversion. The IC_{50} for hypoxanthine to xanthine is assumed to scale proportionately.

The pharmacoeconomic model used a Markov state-transition structure with a 3-month time cycle to estimate costs and QALYs in a cohort of patients eligible for ULT. This pharmacoeconomic model was developed in Chapter 3, its use here is restricted to monotherapies. In summary, the approach to modelling cost effectiveness is consistent with the methods of the National Institute for Health and Care Excellence in the UK (National Institute for Health and Care Excellence., 2009), adopting a National Health Service cost perspective, a lifetime (50 year) time horizon, and costs and QALYs both discounted at a rate of 3.5% per annum (National Institute for Health and Care Excellence, 2013b). The model was implemented in R version 3.5.1 (R Foundation for Statistical Computing, 2017).

For each ULT in Table 4.1, a nominal 10,000 patients are initially allocated to treatment and distributed between four sUA sub-states (<6, 6 to <8, 8 to <10 and ≥10 mg/dL or <360, 360 to <476, 476 to <595 and >595 µmol/L) based on the results of PKPD simulations. In each model cycle, a proportion of patients discontinue treatment and are redistributed between the sUA sub-states to an untreated sUA distribution. A proportion also move to a dead state according to all-cause mortality probabilities derived from life tables for England and Wales in 2015 (The Office for National Statistics, 2015). The model conservatively assumes that the only benefit of reducing sUA concentrations is to reduce the frequency of acute gout flares. A flare frequency distribution was derived from cross-sectional survey data (P. Khanna *et al.*, 2012) across five categories; 0, 1-2, 3, 4-5 and 6+ flares per annum. Fewer gout flares then result in improved quality of life and reduced treatment costs (P. Khanna *et al.*, 2012).

3.3. Adherence Data

Adherence to ULTs was assumed from real world data on chronic treatment (119 subjects, 15,959 individual doses and follow-up between 90 and 529 days (Bovet *et al.*, 1997; Vrijens and Goetghebeur, 1999)) using electronically-recorded pill bottle cap opening times (Urquhart, 1997) (MEMS, Aardex Group). Many of the adherence patterns are characterised by an implementation phase of varying levels of adherence followed by a complete cessation of doses prior to the end of the observation period. Instances of non-adherence following the implementation phase were discarded, as discontinuation was modelled separately in the pharmacoeconomic model. The distribution of dose implementation is given in Table 4.2, while figures showing all doses taken by every subject are provided in the Appendix.

% of doses taken	N of dosing histories	% of dosing histories
0 - 10	6	5.0%
10 - 20	7	5.9%
20 - 30	5	4.2%
30 - 40	4	3.4%
40 - 50	12	10.1%
50 - 60	13	10.9%
60 - 70	20	16.8%
70 - 80	37	31.1%
80 - 90	6	5.0%
90 - 100	4	3.4%
100 - 110	3	2.5%
110 - 120	2	1.7%

Table 4.2. Levels of dose implementation in MEMS dosing histories (Individual mean number of doses taken 60.4%)

3.4. Simulation Modelling

Linked PKPDPE simulations were performed for each of the 14 ULTs. The pharmacometric stage was performed for each of the 119 real world adherence patterns ranging from 57 days to 529 days of dose implementation. Each simulation was repeated 500 times with resampling from individual random effects and from the probability distributions (based on recent clinical trial baseline data (Becker *et al.*, 2009)) assumed for subject covariates including age (log-normal), weight (log-normal) and baseline sUA concentration (normal). However, uncertainty in the parameter estimates, in the estimates of the random effects parameters and residual variability was not included in PKPD simulations.

The simulated sUA time courses were used to generate post-treatment sUA concentration distributions across four states for use in the pharmacoeconomic model. These were obtained by taking the mean of the simulated daily sUA levels for days beyond day 50 but before discontinuation. The primary measure of treatment response for a ULT, equivalent to the primary outcome measure used in many clinical trials (Becker *et al.*, 2005, 2009; Schumacher *et al.*, 2008), is the proportion of subject simulations in the < 6 mg/dL (< 360 µmol/L) state. Further alternative measures of treatment response were derived using daily sUA concentrations for all available days beyond day 50 but before discontinuation. The proportions of subject simulations which were < 6 mg/dL (< 360 µmol/L) on at least 80, 70, or 60% of days have been calculated to measure sustained response. Although not reported in clinical trials, there are more likely to be associated with a reduction in gout symptoms (Shoji, Yamanaka and Kamatani, 2004).

In each iteration of the pharmacoeconomic model, the process of collapsing sUA concentration measurements on to the four sUA states was repeated with random sampling to bootstrap and propagate PKPD variability. Other pharmacoeconomic model inputs, such as flare frequency distributions, health state utilities and discontinuation rates, were also varied according to probability distributions used to represent uncertainty regarding their true value. A total of 5,000 pharmacoeconomic models were performed for each unique ULT and adherence pattern combination.

The outputs of the pharmacoeconomic model for each ULT are the mean per patient lifetime QALYs and costs associated with gout following the initiation of treatment and the mean number of cycles of drug supplied. All hypothetical ULTs can be compared with febuxostat 80 mg or 120 mg both with an annual price of £317.72 (Joint Formulary Committee, 2018). Cost effectiveness thresholds can be used to determine whether a higher cost treatment is sufficiently effective to justify reimbursement. We have used a cost effectiveness threshold of £20,000 per QALY gained which is routinely used in the UK (McCabe, Claxton and Culyer, 2008).

Where a hypothetical ULT is more effective than febuxostat 80 mg we have estimated the maximum price at which the hypothetical ULT would be cost effective using the mean QALY and cost differences. The maximum cost effective price can be found by solving equation 1 for P_h when net monetary benefit (NMB) is equal to zero.

$$NMB = \lambda \Delta Q - \left(\Delta C_{ND} + \left(S_f * P_f - S_h * P_h\right)\right) \quad (17)$$

NMB is the net monetary benefit, λ is the cost effectiveness threshold, ΔQ is the difference in lifetime QALYs, ΔC_{ND} is the difference in non-drug costs, S_f is the number of cycles febuxostat 80/120 mg, P_f is the price of febuxostat 80/120 mg, S_h is the number of cycles of hypothetical ULT, and P_h is the price of the hypothetical ULT.

4. Results

The time courses of drug concentration in plasma and sUA concentration following single doses are presented in Figure 4.1 to illustrate the differences in pharmacokinetics and pharmacodynamics between febuxostat and hypothetical ULTs. The doses of hypothetical ULTs of group B (reduced IC_{50} and dose) and C (lower clearance and dose reduction) are reduced and consequently plasma concentrations of B4 and C4 are lower than febuxostat at 80 mg and 120 mg. A4 (reduced IC_{50}) results in the greatest reduction in sUA concentration but its effect is short lived relative to C4 with an extended half-life.

The predicted response rates for the hypothetical cohort over all PKPD model simulations are summarised in Table 4.3, where several possible measures of response have been presented. Febuxostat 80 mg and 120 mg were predicted to result in 55% and 64% of subjects with a mean sUA concentration below a 6 mg/dL (< 360 µmol/L) target respectively. The hypothetical ULTs leading to the greatest proportion of responders was C4 (extended half-life with dose reduction) and A4 (increased potency without dose reduction) both achieving < 6 mg/dL (< 360 µmol/L) in 75% of subjects. Scenarios assuming a greater potency and a reduced dose resulted in slightly lower response rates, down to 51%, relative to febuxostat 80 mg.

Average response rates (< 6 mg/dL) over all PKPD simulations by dose implementation groups, as shown in Table 4.2, are presented in Figure 4.2. There is very little differentiation between the ULTs when implementation is below 20% or above 90%, with the best-worst treatment differences being between 0.8 and 10.3 percentage points. Greater differentiation occurs between 20% and 90%, where the best-worst treatment difference ranges from 15.1 to 38.8 percentage points. A more pronounced pattern is observed for sustained treatment response, Figure 4.3, where there is no response predicted until at least 40% dose implementation. Only once implementation exceeds 70% of doses taken are high response rates (> 50%) achieved.

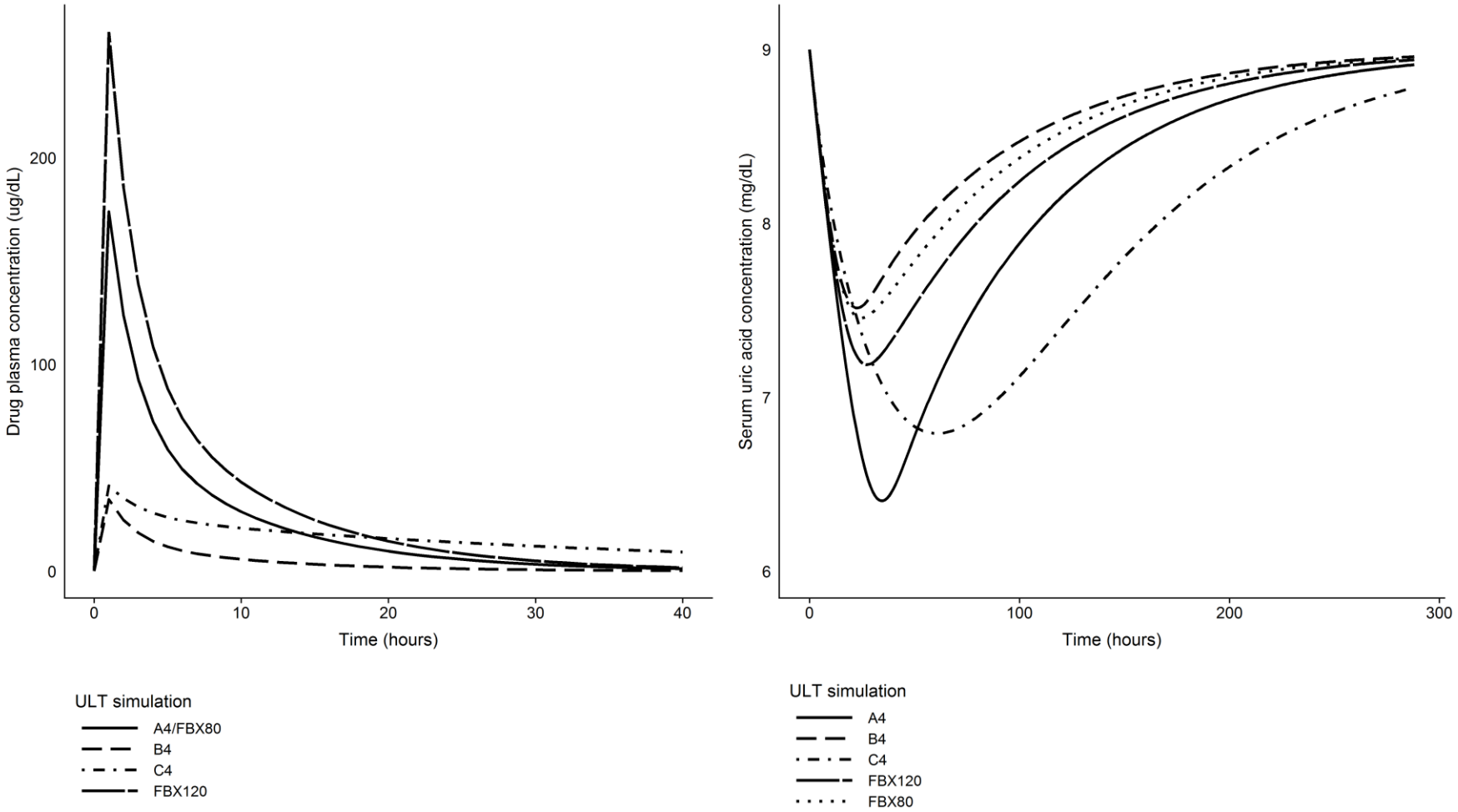


Figure 4.1. Simulated drug plasma concentration and serum uric acid time course following a single oral dose (taken at hour 12) of febuxostat 80mg or 120mg as well as 3 hypothetical ULTs (simulations used a reference subject of age 60, weight 100 kg, and baseline sUA of 9 mg/dL (< 535 µmol/L))

Urate-lowering therapy	Mean sUA conc.		% of subjects below target on >x% of days*		
	< 5 mg/dL (< 300 µmol/L)	< 6 mg/dL (< 360 µmol/L)	80% days	70% days	60% days
FBX80	35.88%	55.23%	32.02%	41.90%	52.12%
FBX120	47.06%	63.86%	37.90%	48.40%	58.87%
A1	41.79%	60.00%	35.07%	45.40%	55.71%
A2	48.92%	64.98%	38.66%	49.18%	59.80%
A3	57.12%	70.08%	42.80%	53.15%	63.69%
A4	66.02%	75.24%	47.78%	57.43%	67.87%
B1	35.56%	54.89%	31.74%	41.53%	51.68%
B2	34.97%	54.39%	31.30%	41.00%	51.11%
B3	34.04%	53.51%	30.54%	40.12%	50.10%
B4	31.86%	51.43%	28.98%	38.20%	48.08%
C1	42.31%	60.61%	36.08%	46.44%	56.76%
C2	49.49%	65.76%	40.82%	50.96%	61.38%
C3	56.77%	70.55%	46.09%	55.58%	65.83%
C4	64.04%	75.16%	52.50%	60.72%	70.24%

Table 4.3. Summary of PKPD simulations including % of subject simulations below target thresholds and the proportion of subject simulations below 6 mg/dL on at least 60, 70 or 80% of days

* For each adherence pattern and PKPD simulation the proportion of simulated days below 6 mg/dL was calculated, then the proportion of these results above 80, 70 or 60% are shown here

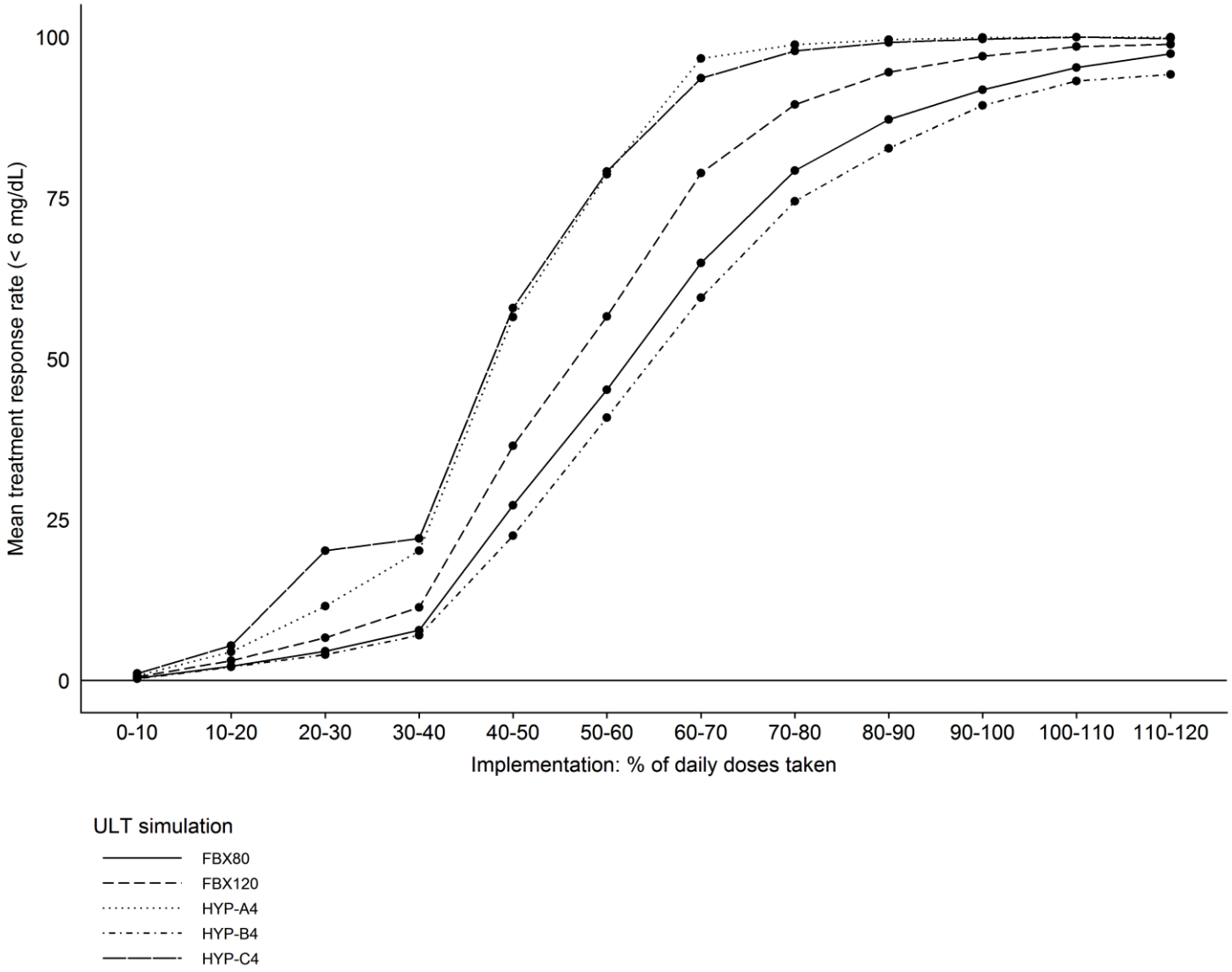


Figure 4.2. Mean treatment response rates for hypothetical ULTs compared with febuxostat 80 mg by dose implementation using response defined using mean daily sUA concentration below 6 mg/dL target (< 360 µmol/L)

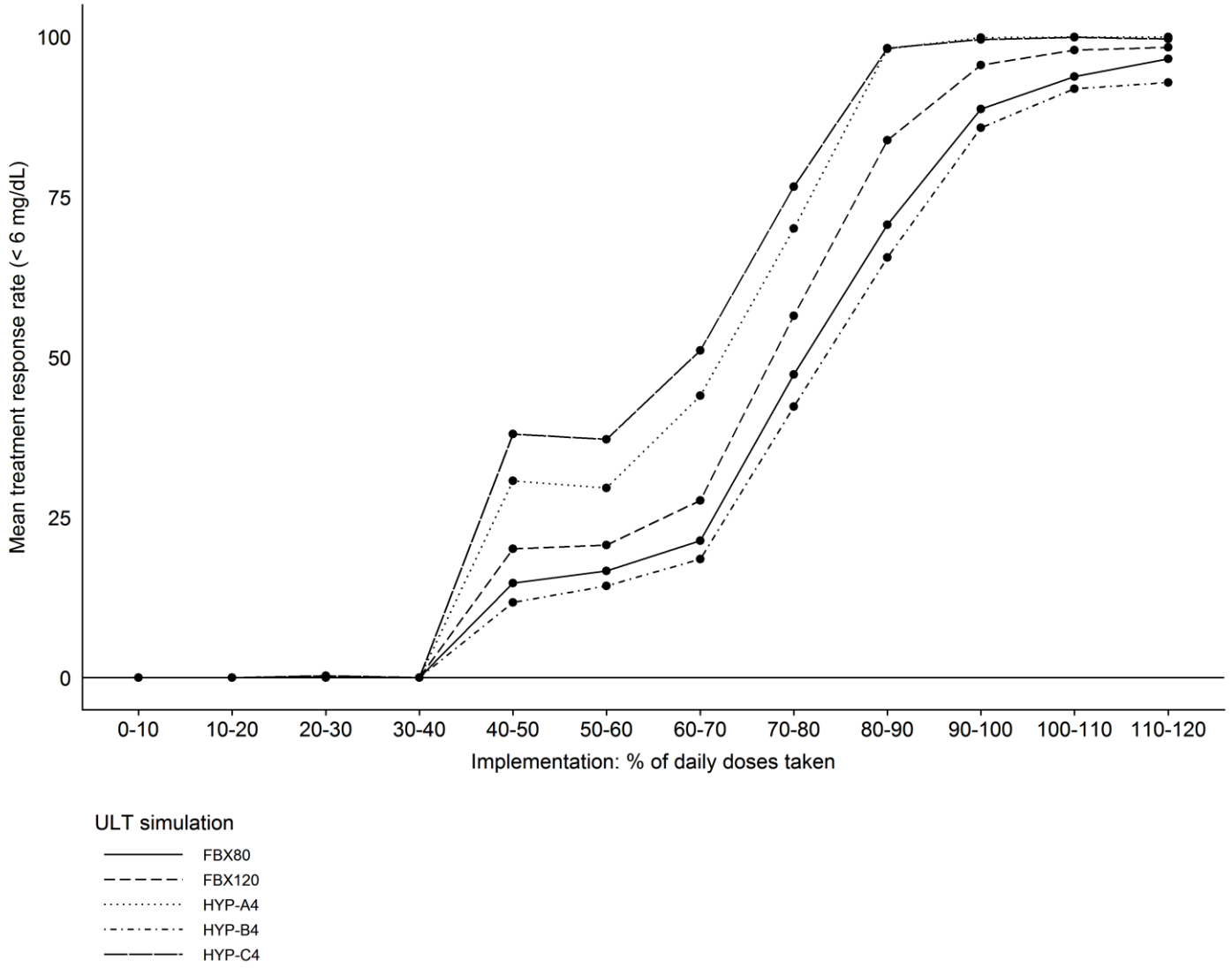


Figure 4.3. Mean treatment response rates for hypothetical ULTs compared with febuxostat 80 mg by dose implementation using response defined using proportion of subject simulations responding (< 6 mg/dL (< 360 µmol/L)) on 80% or more of days (sustained response)

Table 4.4 presents the estimated maximum reimbursement prices at which treatments are cost effective, based on differences in estimated lifetime QALYs and costs, resulting from expected changes in flare frequency. Prices are given using either febuxostat 80 mg or 120 mg as the comparator. The highest maximum reimbursement prices are achieved by A4 and C4, which are expected to be cost effective at an annual price of £376, an increase of 19% on febuxostat 80 mg at a threshold of £20,000 per QALY.

Figure 4.4 shows the relationship between the responder rate and the pricing of a hypothetical ULT versus the comparator febuxostat 80 mg. The price axis is the difference between the maximum reimbursement prices at every response rate compared with the price of febuxostat 80 mg, hence the price at the response rate of 55% is fixed at £0. The two curves plot the relationship for a £20,000 per QALY cost effectiveness threshold and a probability of 10% and 50% of being cost effective at or below this threshold. This curve provides an estimate of the maximum reimbursement price for any response rate, and indicates that with 100% response the maximum reimbursement price would be £140 above the annual cost of febuxostat 80 mg.

Urate-lowering therapy	Lifetime QALYs	Versus Febuxostat 80 mg		Versus Febuxostat 120 mg	
FBX80	13.272	-	-	-	-
FBX120	13.283	-	-	-	-
A1	13.278	331.63	+4%	306.48	-4%
A2	13.284	346.16	+9%	321.01	+1%
A3	13.291	360.92	+14%	335.77	+6%
A4	13.297	376.08	+18%	350.92	+10%
B1	13.272	316.77	0%	291.62	-8%
B2	13.271	315.22	-1%	290.07	-9%
B3	13.270	312.56	-2%	287.41	-10%
B4	13.267	306.38	-4%	281.23	-11%
C1	13.279	333.45	+5%	308.30	-3%
C2	13.285	348.54	+10%	323.39	+2%
C3	13.291	362.66	+14%	337.51	+6%
C4	13.297	376.61	+19%	351.46	+11%

Table 4.4. The maximum cost effective annual price (£) of hypothetical ULTs based on mean lifetime QALYs, costs and number of cycles of drug required in 5,000 simulations and using 119 real-world adherence patterns. The percentage change columns compare the estimated prices with that of febuxostat (80 or 120 mg) with an annual price assumed to be £317.72.

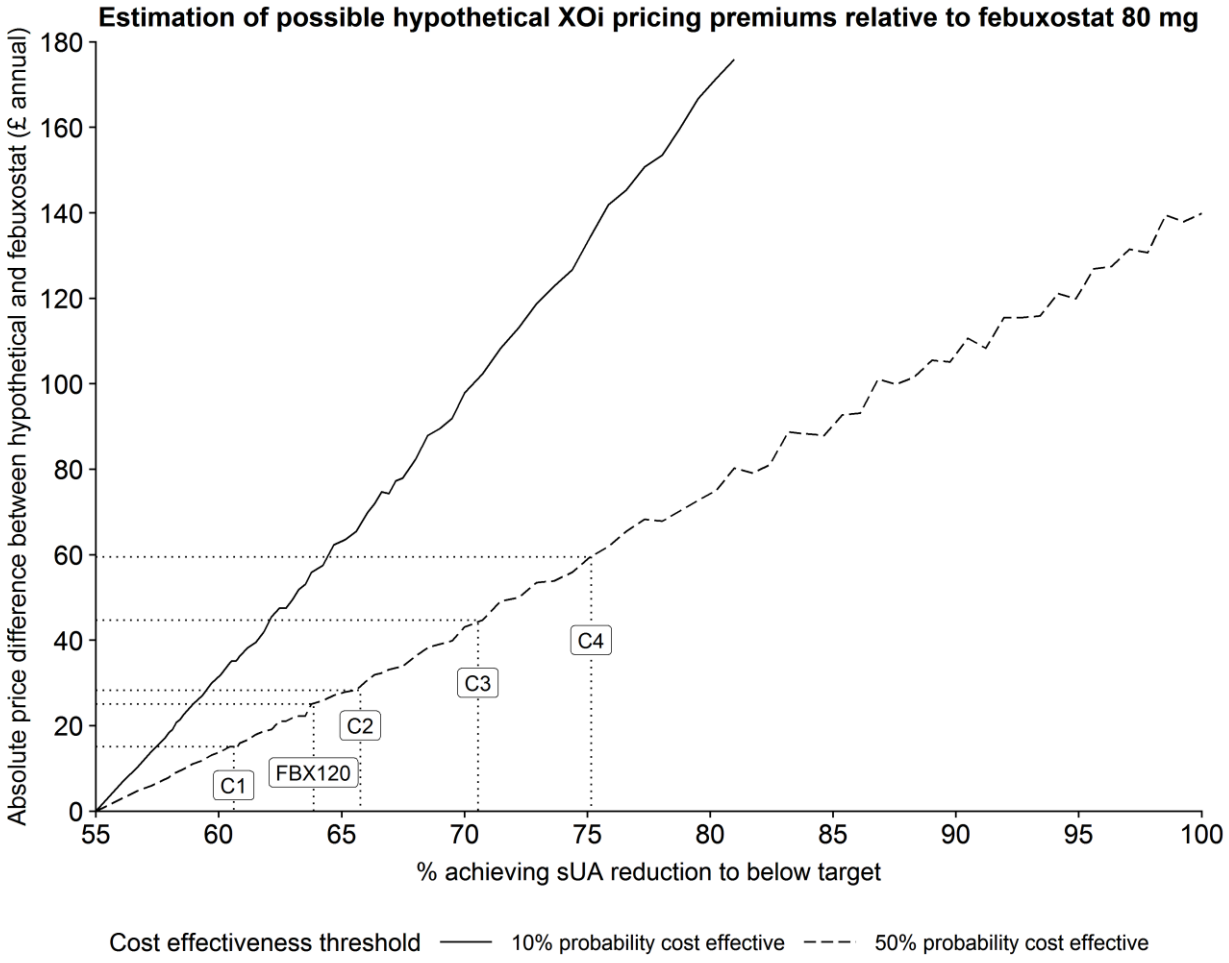


Figure 4.4. Curve of estimated pricing to achieve cost effectiveness versus febuxostat 80 mg with probability of 50% and 10% at a willingness to pay threshold of £20,000

5. Discussion

This study has demonstrated the application of linked PKPDPE models to inform drug development by estimating the maximum reimbursement price from drug pharmacology, using real-world data on medication adherence. In this case study, hypothetical XOi with reduced dose and extended duration of action were predicted to increase the proportion of treatment responders to a similar extent as those with increased potency alone. Simulations estimated a proportion of patients responding to treatment for these more 'forgiving' ULTs of between 60% and 75% compared with 55% for febuxostat 80 mg. Based on this improvement and assuming that treatment benefit is limited to a reduction in the frequency of acute gout flares, maximum reimbursement prices were estimated of between 4% and 19% above the £317.72 current annual cost of febuxostat using a cost effectiveness threshold of £20,000 per QALY gained.

The results of this study suggest that, under conditions of imperfect adherence, reduced clearance is of equal value as a target for early candidate selection as increased potency. The identification of compounds that have long half-lives, maintain oral absorption properties and potency may be challenging. However, some structurally diverse and highly potent XOi molecules have been identified and these may offer some potential lead molecules (Šmelcerović *et al.*, 2017), so further research and drug discovery endeavours could be justified. While there are alterative ULT mechanisms, such as uricosurics which lower sUA by stimulating its renal excretion, these have had limited success due to safety issues (Sanchez-Nino *et al.*, 2017). Similarly, administration of the enzyme uricase (e.g. Pegloticase) that converts uric acid into the more soluble component, allantoin, is not widely used due to occurrence of anti-drug antibodies, injection site reactions and its high cost (National Institute for Health and Care Excellence, 2013a).

The linkage of pharmacometrics with pharmacoeconomics remains relatively novel and there are few published examples, but has potential across a range of applications from early drug research and development (Slejko *et al.*, 2016); in estimating cost effectiveness in alternative subgroups and treatment protocols (Van Hasselt *et al.*, 2015); in the evaluation of complex pharmaceutical interventions such as pharmacogenetic testing (Pink *et al.*, 2014); and modelling health economics of treatments for use during pandemics (Kamal *et al.*, 2017). Pharmacometrics has been used to study issues relating to medication adherence for some time (for example (Vrijens *et al.*, 2005)). This study is the first, of which we are aware, to combine adherence, pharmacometrics and pharmacoeconomics to inform early drug design decisions. In doing so this further demonstrates the value of an interdisciplinary approach and the need to interconnect existing methods to improve efficiency in drug

development. As such, linked PKPDPE modelling may be seen as an additional component within the model informed drug development paradigm (Milligan *et al.*, 2013).

This study has advantages over conventional pharmacometric studies that do not assess the future value of compounds beyond market authorisation; and conversely, it has advantages over standard pharmacoeconomic practices which do not account for exposure response relationships. It has benefitted from a semi-mechanistic pharmacodynamic model that can account for the system dynamics resulting from intermittent dose taking. Unlike in some previous economic evaluations of ULTs (Beard *et al.*, 2014; National Institute for Health and Care Excellence, 2016c; Perez-Ruiz, Diaz-torne and Carcedo, 2016), in this study, the clinical benefits of lowering sUA concentration have been assumed to be limited to reduced frequency of flares alone. However, this is consistent with the findings of recent meta-analyses (Li *et al.*, 2017).

Limitations of this study include the assumptions which were necessary in order to develop a model structure and to obtain parameters estimates. It has been assumed that the structure of the pharmacometric and pharmacoeconomic models provide a sufficiently accurate representation of ULTs and their impacts to make predictions. The PKPD model was developed from a variety of published sources without fully accounting for the additional uncertainty this introduced. Aspects of the pharmacoeconomic modelling, such as the frequency of acute gout flares, relied on survey data obtained from a small number of patients. We have not considered the safety aspects of hypothetical XOi which would inform dose selection, and would need to be accounted for in pharmacoeconomic models in terms of the cost and health implications. The adherence data was not collected in gout patients but does contain a wide variety of adherence patterns and the overall low level of adherence is consistent with studies on the routine use of ULTs.

Many jurisdictions make use of economic evaluations as a part of the decision making process of whether to reimburse medicines having obtained market authorisation. A new medicine failing to meet the criteria for cost effectiveness may not be marketable at a commercially viable price or may struggle to capture market share because of its lack of affordability. The framework used here provides a direct link between drug pharmacology and the probability of a drug being cost-effective while explicitly accounting for realistic medication adherence. These methods have the potential to inform early drug development by providing an indication of whether drug candidates possess the properties that would result in a maximum reimbursement price that justifies their progression through the long and costly drug development process.

Preface to Chapter 5

Clinical drug development is, to an extent, an exercise in conducting studies to 'learn and confirm' in order to reduce uncertainty regarding a drug's efficacy and safety. As such, it would seem a natural application for approaches broadly termed value of information. Value of information can be used to quantify the value of reducing uncertainty by obtaining new information in key areas based on how this affects the probability of making the optimal decision using the new information. When designing a clinical trial there are many uncertain variables that may influence the trial outcomes; these include the level of medication adherence and uncertainty regarding the characterisation of the pharmacology of the study drugs.

The traditional approach sample size selection for phase 3 trials uses power calculations with inputs that include thresholds for type I and type II errors and estimates of treatment effect sizes and variances. Alternatives, such as value of information, have emerged which account for the cost associated with making errors rather than using arbitrary thresholds. Their disadvantage is often the requirement for a prior treatment effect distribution, typically centred on previous trial results. An alternative to the assumption that a new trial under different conditions in a new population will yield consistent results is to use clinical trial simulation to generate a distribution of outcomes that takes into account subject specific covariates and trial design inputs.

This next chapter examines how a linked pharmacometric-pharmacoeconomic model can provide a framework for clinical trial simulation, and for quantifying the cost of uncertainty in aspects of drug pharmacology and the medication adherence of trial subjects. The PKPD model of earlier chapters is used to simulate clinical trials using a range of sample sizes. The simulated results are valued according to the implied maximum reimbursement price and a simple model of the resulting return on investment. The cost of uncertainty on specific model parameters is estimated using accelerated methods of calculating expected value of partial perfect information.

Chapter 5

Clinical trial simulation and value of information to optimise design of clinical trials from a pharmaceutical industry perspective

1. Summary

The design of a clinical trial using value of information (VoI) methods will typically require prior distributions for trial outcomes, either based on past trials or expert opinion. However, a proposed trial may not be expected to produce data that is consistent with earlier studies. The aim of this study was to demonstrate the utility of using pharmacometric clinical trial simulation (CTS) to address key limitations of current VoI approaches to phase 3 clinical trial design using gout treatments as a case study. The methods consist of four principal stages: a CTS to predict the distribution of treatment response rates for a given sample size; a payer model that links response rate to an estimate of the maximum price a payer would be willing to pay to access the drug; a model of the pharmaceutical company return on investment linking drug prices to sales revenue; and an analysis of the sensitivity of the optimal decision to the uncertainty in model parameters using expected value of partial perfect information (EVPPI). The optimal sample size for a single trial comparing febuxostat 80 mg and allopurinol 300 mg once daily was estimated as 500 patients per arm, given assumptions regarding disease incidence and the minimum launch price. EVPPI for each uncertain model parameter indicated that uncertainty in parameters for drug adherence, rather than drug pharmacology, dominated the uncertainty regarding the optimal sample size decision. Using clinical trial simulation to generate distributions of trial outcomes removes a key limitation of value of information approaches to trial design, the requirement for prior distributions on outcomes, and EVPPI may focus efforts to reduce uncertainty to specific areas.

2. Introduction

The principal objective of phase 3 clinical trials is to confirm the therapeutic effect of a drug and assess the benefit to risk ratio in order to gain regulatory approval (Sheiner, 1997). They may also further explore the dose-response relationship or the drug's use in wider populations, in different stages of disease, or in combination with another drug (European Medicines Agency, 1998). The evidence gained in this phase forms the basis for economic evaluations and decision making regarding reimbursement (Saramago, Manca and Sutton, 2012). The design of phase 3 trials, sample size calculations in particular, has typically used power calculations with inputs including thresholds for type I and type II errors and estimates of treatment effect sizes and variances (Lachin, 1981; Bacchetti, 2010). There are well known limitation with this approach, in particular that the thresholds for type I or type II error are arbitrary and do not take into account the cost associated with making these errors (Willan and Pinto, 2005). Furthermore, the focus is on passing the regulatory hurdle even though pricing and reimbursement decisions will also be determined by the evidence that is generated in this phase and may impact on pricing options.

Alternative methods of estimating the optimal sample sizes for clinical trials from a societal or health care payer perspective have been proposed in an attempt to address the limitations of traditional power-based calculations. Most notably, this includes Bayesian approaches (Pezeshk, 2003) and those which compare the expected value of sample information with the cost of conducting the trial (Willan and Pinto, 2005). Taking a decision theoretic approach, the latter has the advantage of explicitly modelling the consequences of the possible decisions made based on data from a trial of a given design. The optimal design for a clinical trial under this methodology is defined as the point at which it becomes more costly to collect additional data than the value of the information gained from that data. However, despite the numerous methodological publications in this area, real-world applications are limited.

Value of information methods have also been adapted for trial design from the perspective of a pharmaceutical company (Willan, 2008; Breeze and Brennan, 2014). From a pharmaceutical industry perspective the value of additional data is that it leads to greater precision in estimates of treatment benefit which may increase the probability of regulatory approval and reimbursement. Payers in many jurisdictions consider the cost-effectiveness of new pharmaceuticals during the reimbursement decision making process (Barnieh *et al.*, 2014), with more effective and less costly drugs more likely to be reimbursed. If the decision making process is sufficiently transparent, applying cost effectiveness thresholds for example (McCabe, Claxton and Culyer, 2008) then , for a given level of treatment

benefit, it may be possible to set a maximum reimbursement price (MRP) that would be acceptable to the payer.

The value of information approach to trial design uses a prior distribution of the expected treatment benefit, either based on past trial outcomes (Breeze and Brennan, 2014), expert opinion (Bojke *et al.*, 2017) or an assumed minimal clinically significant difference (Bader *et al.*, 2018). This represents a major limitation since there are likely to be many reasons that a proposed trial cannot be expected to produce data that is consistent with earlier studies, such as at phase 2. These include differences in the characteristics of the patient population, differences in medication adherence (Breckenridge *et al.*, 2017), selection bias (Pereira, Horwitz and Ioannidis, 2012) and change of dose or regimen as well the addition of comparator arms. Furthermore, unless normality of treatment benefits is assumed, the calculation of the posterior may require computationally intensive Markov chain Monte Carlo (MCMC).

A possible alternative to using priors of treatment benefit based on past trials is to simulate the phase 3 trial using clinical trial simulation (CTS) (Holford, Ma and Ploeger, 2010) based on pharmacometrics models fitted to early phase data. CTS has often been used to study issues in the design of clinical trials (Ridder, 2005; Abbas *et al.*, 2008; Laouénan, Guedj and Mentré, 2013; Bajard *et al.*, 2016; Smania *et al.*, 2016), but we are not aware of any examples of a CTS being used to value trial designs based on return on investment (ROI) in which drug prices are set according to a payer's cost effectiveness threshold. The advantage of pharmacometric-based CTS is that it can account for subject-specific covariates, imperfect mediation adherence, alternative doses and regimens and can be used to simulate the comparator arm(s) of the proposed trial (Holford, Ma and Ploeger, 2010). This could, therefore, be applied to study a variety of design issues, apart from sample size, including trial inclusion/exclusion criteria, duration, drug adherence or discontinuation.

While the optimal trial design is that which maximises the expected company ROI, due to uncertainty in the inputs of a CTS model, there will be uncertainty in the model prediction of the optimal design. Using probabilistic sensitivity analysis and simulating a distribution of trial outcomes and resulting ROI, it would be possible to quantify the cost of uncertainty due to each uncertain model input parameter using the expected value of partial perfect information (EVPPI) (Strong, Oakley and Brennan, 2014). The expected value of perfect Information (EVPI) estimates the value of obtaining perfect information regarding all model inputs, and as such quantifies the cost of uncertainty (Claxton, Sculpher and Drummond, 2002). The EVPPI for an input parameter reveals the sensitivity of the decision to our uncertainty about that input parameter (Brennan *et al.*, 2007).

The aim of this study was to demonstrate the utility of using CTS to address key limitations of current value of information approaches to phase 3 clinical trial design. The objectives were to simulate a distribution of trial outcomes of treatments for gout using pharmacometrics and trial execution models, specific to the trial inclusion/exclusion criteria, doses, regimens, and expected drug adherence. Multiple trial designs were simulated of different sample sizes to derive an MRP and the company ROI accounting for disease incidence, time horizon, trial duration, market share and trial costs. Uncertainty in the optimal sample size in terms of ROI was examined using EVPPI for drug pharmacology and trial execution input parameters.

3. Methods

Despite some more recent treatment options for gout patients, such as febuxostat and lesinurad, allopurinol is still considered to be the first line treatment option (Hui *et al.*, 2017). The objective of treatment, both in clinical trials and in routine practice, is to reduce a patient's serum uric acid (sUA) concentration to below 6 mg/dL (< 360 µmol/L) which should lead to the reduction or elimination of symptoms. There were a total of 4 phase 3 trials of febuxostat versus allopurinol, including once daily doses of febuxostat between 40 and 240 mg and of once daily allopurinol between 100 and 300 mg. In every trial febuxostat was found to be superior to allopurinol in the analysis of the primary end point of a sustained (or final) reduction in sUA concentration to below 6 mg/dL (< 360 µmol/L). The present study uses febuxostat as a case study and takes the perspective of a pharmaceutical company making a decision between trial designs, potentially including a no-trial option (i.e. continued clinical development would not be economically viable). For the purpose of developing the methodology a simplified scenario was assumed consisting of a single two-arm trial comparing febuxostat 80 mg to allopurinol 300 mg in patients without renal impairment.

The method consists of four principal stages: 1) a CTS to predict the distribution of treatment response rates (sUA < 6 mg/dL (< 360 µmol/L)) for a given trial design; 2) a payer model that links a rate of treatment response to an estimate of the maximum reimbursement price (MRP) a payer would be willing to pay to reimburse the drug; 3) a model of the pharmaceutical company ROI in which future sales are estimated using drug prices set at the MRP; and 4) an analysis of the sensitivity of the optimal decision to the uncertainty in specific model parameters using expected value of partial perfect information (EVPPI). Each stage is described in order in the following sections. Sections 3.2 and 3.3 replicate a previously published approach to forecasting ROI (Breeze and Brennan, 2014).

3.1. Clinical Trial Simulation

The CTS consisted of linked pharmacokinetic (PK) and pharmacodynamic (PD) models for both allopurinol and febuxostat, as well as a trial execution model. The PK for allopurinol was described using a one-compartment model structure, whereas the PK for febuxostat was described using a two-compartment model. The pharmacodynamic model consisted of a multi-compartment, semi-mechanistic model of uric acid production and renal excretion. The drug PD models used inhibitory indirect response equation, with febuxostat having an additional stimulatory impact on the renal excretion of the uric acid precursor xanthine. Details of the model development can be found in earlier chapters.

The trial execution model includes the study design, inclusion/exclusion criteria, recruitment and drug adherence. The trial consists of two arms; one in which subjects receive 300 mg of allopurinol once daily and another for 80 mg of febuxostat once daily. Both arms are populated by sampling at random from the gout population, represented by the data given in Table 5.1. These include the subjects' baseline sUA concentration, body weight and age, which are covariates in the PKPD model. Drug adherence includes the initiation of treatment, the degree to which a patient's dose taking matches the prescribed regimen while nominally adhering (implementation) and treatment discontinuation (Vrijens *et al.*, 2012). It was assumed that all patients initiate treatment and patients who discontinue revert to their baseline sUA concentration. Implementation was modelled according to a subject specific probability of taking each dose, independent of whether any previous doses were taken. As shown in Table 5.2, the mean population dose implementation probability is assumed to 0.9 and is resampled in each simulation according to a beta distribution with coefficient of variation (CV) of 10%. Subject specific implementation probabilities were then generated from the new population mean and inter-individual variability (IIV). Discontinuation was simulated using a daily hazard, modelled as a Weibull hazard function such that the risk of discontinuation falls over time. The uncertainty in the population mean discontinuation rate was simulated using the Weibull scale parameter.

For simplicity in presenting the development of this methodology we have focussed only on sample size selection, ranging from 100 to 1000 subjects per arm. The proposed trial is of six month duration (182 days) and only subjects with a sUA concentration of more than 8 mg/dL (< 476 µmol/L) at baseline are recruited. The outputs of the CTS included two outcome measures, the first is sustained response defined as a subject's final 3 monthly sUA measures being < 6 mg/dL (< 360 µmol/L) and the second is response on the last day of the trial. The first of these was the primary endpoint in two of the pivotal febuxostat (Becker *et al.*, 2005; Schumacher *et al.*, 2008) studies and the second, in line with previous studies (Beard *et al.*, 2014; Gandhi, 2015), was used to drive the economic model and the calculation of the MRP. The sequence diagram in Figure 5.1 shows each stage of the CTS which ends with the simulated sUA concentration results being passed to the economic model.

Parameter*	Mean	Units
sUA TV[1]	8.34	mg/dL
sUA IIV (SD)[1]	2.15	mg/dL
sUA min	8	mg/dL
sUA max	NA	mg/dL
Body weight TV[2]	100	Kg
Body weight IIV (CV%)[2]	10	-
Body weight min	50	Kg
Body weight max	150	Kg
Age TV[1]	60	years
Age IIV (SD)[1]	15.1	years
Age min	40	years
Age max	95	years

Table 5.1. Trial simulation subject characteristics

*sUA: serum uric acid; TV: population typical value; IIV: inter-individual variability; SD: standard deviation; CV%: percentage coefficient of variation

[1]Sample of gout patients referred to rheumatologist in the UK (N = 434) (Roddy *et al.*, 2018)

[2]In the absence of data on the weight distribution of gout patients in the UK assumptions have been made regarding mean population weight and inter-individual variability

Parameter*	Mean	CV%	Distribution
Arm: Allopurinol 300 mg			
Discontinuation : Weibull scale (λ)	3.2×10^{-3}	10	Beta
Discontinuation: Weibull shape (ν)	0.8	-	NA
Implementation Fraction	0.9	10	Beta
Implementation IIV (CV%)	10	-	NA
Arm: Febuxostat 80 mg			
Discontinuation: Weibull scale (λ)	5×10^{-3}	10	Beta
Discontinuation: Weibull shape (ν)	0.8	-	NA
Implementation Fraction	0.9	10	Beta
Implementation IIV (CV%)	10	-	NA

Table 5.2. Trial simulation adherence model parameters

* Discontinuation has assumed a Weibull hazard function such that the hazard to discontinuation can decrease over time. The population mean parameters have been assumed to be broadly in line with the discontinuation observed in the pivotal trials of febuxostat vs allopurinol, summarised in Beard et al. (Beard *et al.*, 2014). Both the Weibull scale parameter for discontinuation and the population mean implementation fraction vary between simulations according to beta distributions with an assumed 10% CV. IIV: Inter-individual variability.

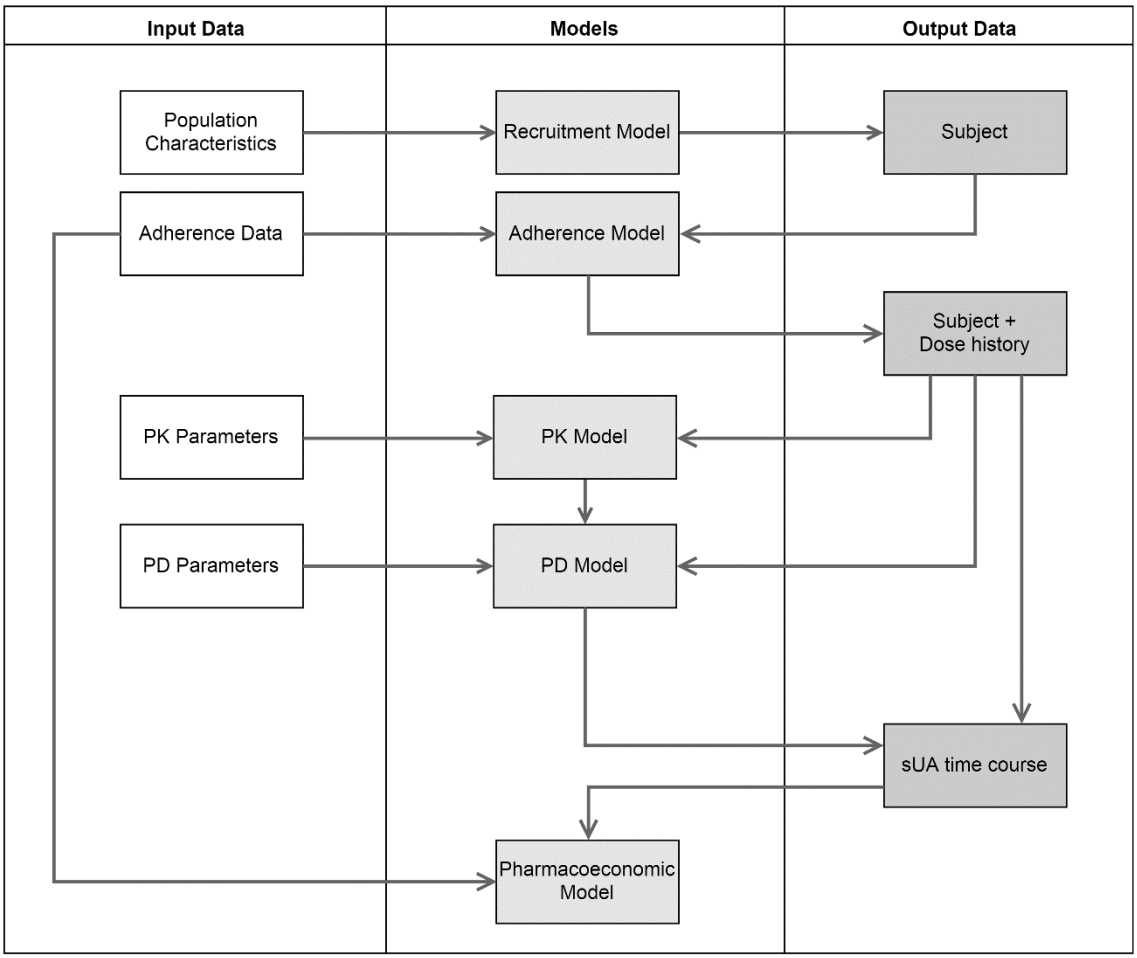


Figure 5.1. Sequence diagram showing the stages of the clinical trial simulation performed for each subject and providing inputs to the pharmacoeconomic model

3.2. Value and Pricing

For the purpose of this study we have assumed the perspective of the National Health Service in the UK, but other payers or multiple payer models could also be developed. In summary, newly approved drugs typically undergo an health technology assessment (HTA) after which they may or may not be recommended for use and reimbursement (National Institute for Health and Care Excellence, 2013b). Cost effectiveness is central to this decision and is assessed via economic evaluation that estimates the long term costs and benefits of adopting the new drug. A cost effectiveness threshold of £20,000 - £30,000 per QALY is used, and drugs are then deemed cost effective if estimated to result in a positive incremental net monetary benefit (NMB). Incremental NMB is defined as $\lambda\Delta Q - \Delta C$, where λ is the payers cost effectiveness threshold (e.g. £20,000 per QALY), ΔQ is the incremental health impacts and ΔC is the incremental cost impacts. Using the observed trial health impacts, along with non-drug cost data, it is possible to calculate the price necessary to achieve a zero NMB.

The CTS results provided inputs to the pharmacoeconomic model, developed in Chapter 3, that links sUA concentration subgroupings to acute gout flare frequency to estimate long term QALYs and costs. In summary, the economic model used a Markov state-transition structure with a 3-month time cycle, a lifetime (50 year) time horizon, discounting of costs and QALYs at a rate of 3.5% per annum (National Institute for Health and Care Excellence, 2013b), and assumed a starting cohort of untreated gout patients representative of the UK. The model predicts the impacts of two alternative payer decisions; 1) recommend febuxostat as first line therapy, or 2) reject febuxostat as first line therapy and instead continue to treat all patients with allopurinol. This case study has assumed that treatment response rates are the only economic input obtained from the trial, whereas in practice other data, such as health state utilities and resource use, may also be collected. Economic model inputs other that treatment response rates, given in earlier chapters, were not varied during simulations since reimbursement decisions are typically based on expected values (Dakin *et al.*, 2015).

The MRP from the payer perspective was calculated by rearranging the NMB formula for the price of febuxostat (P_F), when NMB is equal to zero (eq. 18). The variables on the right-hand side are outputs of the economic model and are a function of the simulated trial data X_{ij} for the i^{th} parameter set of the j^{th} trial design. λ is the cost effectiveness threshold, C_A is the mean per-patient lifetime cost on allopurinol 300 mg, including both direct drug costs and other indirect costs, C_F^{ND} is the mean per-patient lifetime cost on febuxostat 80 mg excluding febuxostat drug costs, Q_F and Q_A are the total lifetime per-patient QALYs of febuxostat 80 mg and allopurinol 300 mg respectively and t_F is the mean per-patient number of years of febuxostat 80 mg use.

$$P_{F_{ij}}^{MRP} = \frac{C_A(X_{ij}) - C_F^{ND}(X_{ij}) + \lambda(Q_F(X_{ij}) - Q_A(X_{ij}))}{t_F(X_{ij})} \quad (18)$$

3.3. Return on Investment

This method proposes a process of trial design based on maximising company ROI and has utilised an existing and straightforward approach to forecasting company ROI (Willan and Eckermann, 2012; Breeze and Brennan, 2014). The inputs required in this approach are summarised in Table 5.3. It was assumed that the price of febuxostat is set at the payer's MRP, determined based on the estimates of efficacy from the trial as described in the previous section. It was further assumed that the company has a minimum price (P_{min}) which, if above the payer's MRP, results in termination of development and zero revenue. The cost of producing and marketing a year's supply of febuxostat ($cost_{p\&m}$) was included on a per-patient basis. Total revenue was calculated for the i^{th} simulation and j^{th} trial design scenario according to the MRP less the cost of production and marketing, then multiplied by the mean number of year's supply of febuxostat per patient (t_F) and the number of new patients receiving febuxostat per year (S_F). Eq. 19 summarises the calculation of company ROI.

$$ROI_{ij} = \begin{cases} (P_{F_{ij}}^{MRP} - cost_{p\&m})t_F(X_{ij})S_F(H) - cost_{trial} & if\ P_{F_{ij}}^{MRP} \geq P_{min} \\ -cost_{trial} & if\ P_{F_{ij}}^{MRP} \geq P_{min} \end{cases} \quad (19)$$

Drawing on the work of Hoyle (Hoyle, 2011) and Willan (Willan, 2008), we predict the number of new patients receiving febuxostat per year (eq. 20) as a function of the annual disease incidence (k), the market share (s) and a depreciation factor (v). One potential time horizon (H) is the number of years of patent protection (or market exclusivity) remaining when the drug reaches the market, which we have assumed to be 10 years.

$$S_F(H) = \sum_{h=0}^{H} ksv^h \quad (20)$$

Finally the cost of the trial was decomposed into fixed and variable elements, with the latter being proportional to the number of patients recruited. The separation of trial costs is shown in eq. 21 below, where n_A and n_F are the numbers of patients recruited to the allopurinol and febuxostat trial arms respectively.

$$cost_{trial} = cost_{trial:fixed} + (n_A + n_F)cost_{trial:per-patient} \quad (21)$$

Parameter	Parameter Value*			
	Base Case	SA1	SA2	SA3
Development model inputs				
Fixed trial costs ($C_{trial:fixed}$)	£5,000,000	-	-	-
Variable/per-patient trial costs ($C_{trial:pp}$)	£2,000	-	-	-
Production and marketing costs (C_{pm}) (per patient, per annum)	£40.00	-	-	-
Minimum marketable price (P_{min}) (per patient, per annum)	£120.00	-	-	-
Payer model inputs				
Cost Effectiveness Threshold (λ)	£20,000	£50,000	£20,000	£50,000
Sales model inputs				
UK annual gout incidence (k)[#]	100,000	-	-	-
Market share (s)	40%	40%	20%	20%
Time horizon (H)	10 years	-	-	-
Drug price deflation index (v)	4%	-	-	-

Table 5.3. ROI model input values

*SA: Sensitivity analysis

[#]Estimate based on Kuo et al. (2014) (Kuo, Grainge, Mallen, *et al.*, 2015)

3.4. Expected Value of Partial Perfect Information (EVPPI)

The linked CTS and pharmacoeconomic modelling approach in this study enables the influence of specific aspects of drug pharmacology, or trial execution, on the optimal design decision to be examined. The EVPPI for parameters has typically been calculated using a 2-level nested Monte Carlo approach. For complex models, this process can become prohibitively computationally intensive. There are now alternative and less computationally demanding methods of calculating EVPPI available (Sadatsafavi *et al.*, 2013; Strong, Oakley and Brennan, 2014; Heath, Manolopoulou and Baio, 2016). We have used a non-parametric regression approach (Strong, Oakley and Brennan, 2014) to examine the influence of individual parameters that requires only the results of probabilistic sensitivity analysis (PSA). Each PSA run generated a new set of inputs from the parameter probability distributions and then implemented the CTS and pharmacoeconomic model using these inputs. In total, for each trial design, we performed 19,140 PSA runs. The modelling was implemented in R version 3.5.1 (R Foundation for Statistical Computing, 2017) on the Supercomputing Wales cluster.

4. Results

The results of the CTS are summarised in Figure 5.2. The left-hand panel presents the distribution in the simulated trial primary outcome measure, sustained response over 3 months; while the right-hand panel presents the secondary measure of final day response. Overall, the final day response rates are slightly higher than sustained response rates. The average simulated sustained response for febuxostat 80 mg once daily was approximately 57% across all trial designs, whereas it was approximately 8% for allopurinol 300 mg. The standard deviation of simulated response rates falls as the number of simulated subjects rises, however, even with 1,000 subjects per arm, considerable variability remains. This reflects the range of possible outcomes which may occur due the uncertainty in inputs parameters, such as drug pharmacology or adherence, used in the CTS.

The plots in Figure 5.3 show the predicted number of lifetime flares (bottom-left) based on the final simulated sUA concentrations, and how these relate to the resulting lifetime QALYs (bottom-right) and the estimated annual MRP of febuxostat 80 mg (top). Larger samples sizes in the CTS result in less uncertainty in the effectiveness of febuxostat 80 mg versus allopurinol 300 mg in terms of final sUA concentration, the lifetime number of flares and therefore the difference in lifetime QALYs. There is, therefore, a narrower distribution of MRPs obtained from the economic analysis, in the base case using a cost effectiveness threshold of £20,000 per QALY.

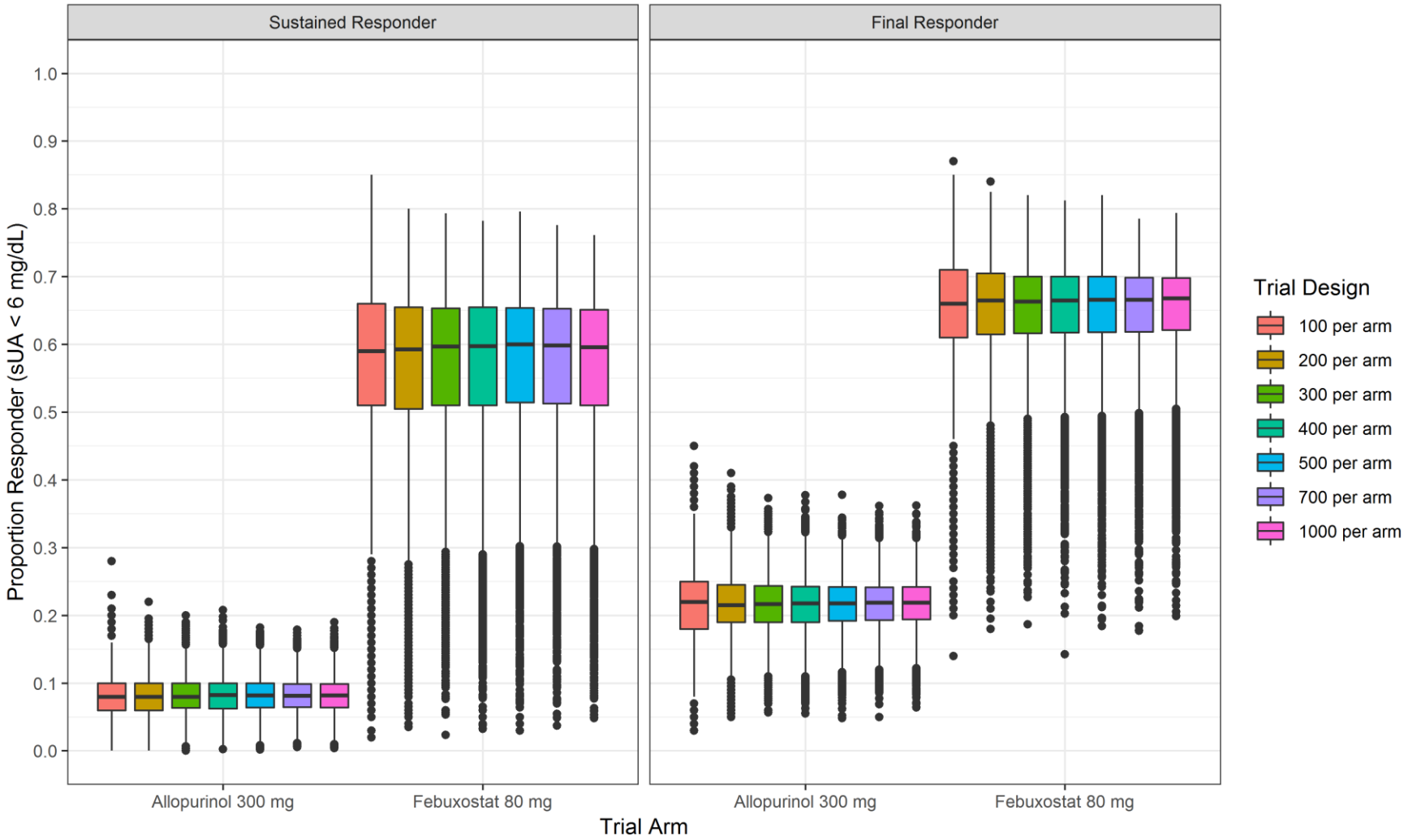


Figure 5.2. Results of the clinical trial simulation in terms of final day and sustained treatment response

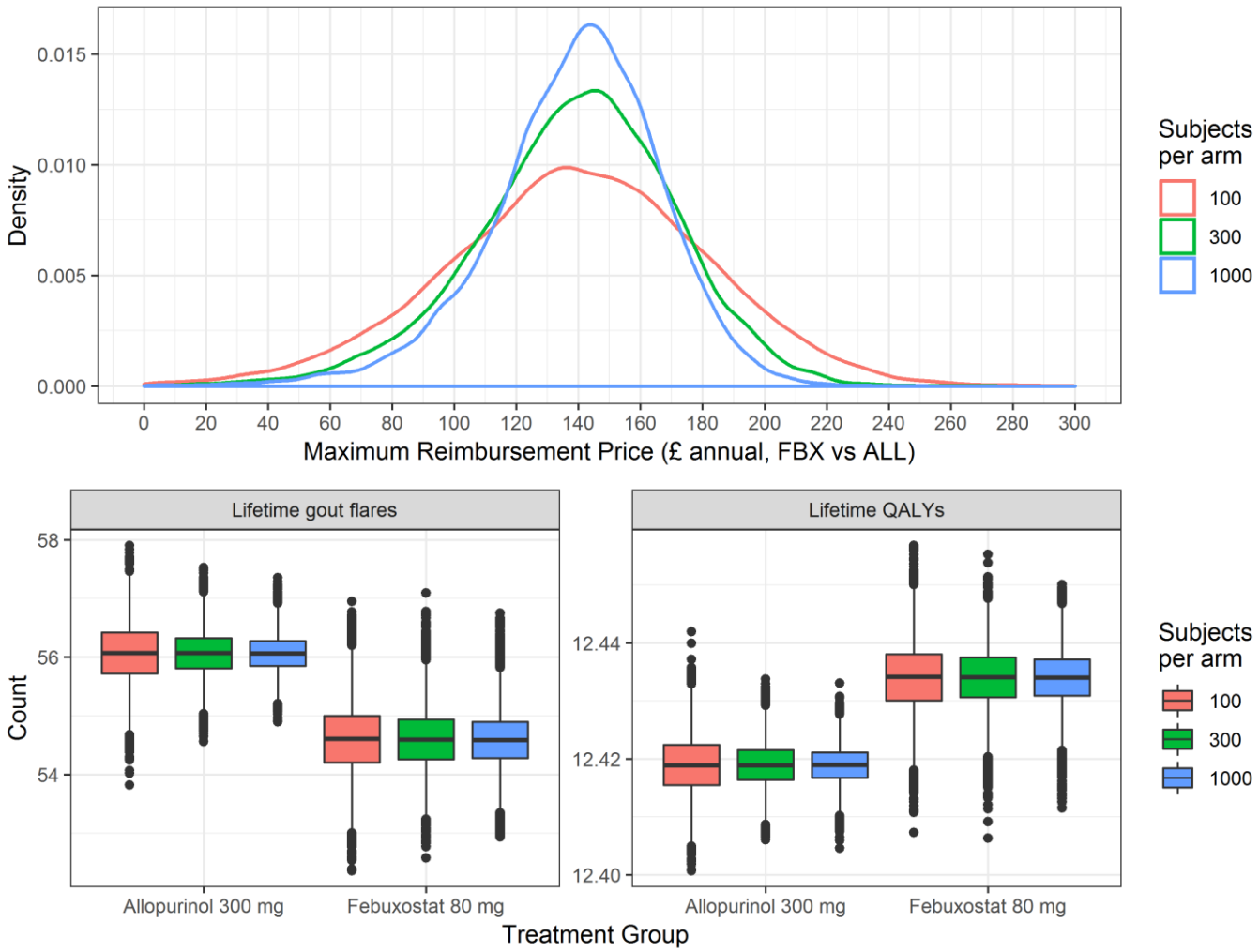


Figure 5.3. Pharmacoeconomic model results for three sample sizes: predicted number of lifetime flares (bottom-left), predicted number of lifetime QALYs (bottom-right) and the estimated annual MRP of febuxostat 80 mg (top)

The pricing, revenues and ROI results, based on CTS for each trial sample size, are summarised in Table 5.4. Overall, the mean of the MRPs are stable across designs, however, with the application of a minimum launch price of £120 per annum, MRPs below this threshold will generate zero revenues. Therefore, the predicted revenues increase in line with the number of trial subjects per arm as the distributions of predicted MRPs become narrower. The ROI results are revenues less the cost of the trial and, in this example scenario, have a maximum for the design with 500 subjects per arm. Table 5.4 also presents the probabilities that a design will result in zero revenue or in relatively high revenue, exceeding £150m. These probabilities are both greatest for the smallest trial size considered, since this design yields more variable treatment effect sizes and therefore MRPs.

The ROI is sensitive to the annual sales, the minimum launch price and the payer's cost effectiveness threshold, as is illustrated in Figure 5.4. The upper-left plot shows the ROI for the base case, assuming a fixed market share 40% and a cost effectiveness threshold of £20,000 per QALY for which the design maximising ROI is 500 subjects per arm. The remaining plots, however, assume either a higher cost effectiveness threshold or a lower fixed market share, or both. In general under these alternative assumptions, the cost of collecting additional data outweighs the benefits that data provides and the optimal design is the smallest trial with 100 subjects per arm.

The uncertainty in input parameters, trial execution and drug pharmacology, gives rise to a distribution of possible response rates and MRPs as demonstrated in figures 5.2-5.3. The impact of uncertainty on specific parameters on the optimal design decision has been quantified using the EVPPI and the results are summarised in Figure 5.5. The top three most influential parameters on the decision uncertainty are all related to drug adherence, with the top two being the population mean level of drug implementation. The discontinuation rate for febuxostat, which was assumed to be higher than for allopurinol, also makes a substantial contribution to decision uncertainty.

Trial ID	N per arm	Trial cost (£ millions)	Mean MRP* (SD)	Revenue (£ millions)	ROI (£ millions)	Probability revenue = £0	Probability revenue > £150m
1	100	5.4	139.23 (42.35)	96.62	91.22	30.8%	23.4%
2	200	5.8	139.30 (34.74)	96.97	91.17	27.4%	19.3%
3	300	6.2	139.19 (32.11)	97.88	91.68	25.3%	17.0%
4	400	6.6	139.40 (30.46)	98.60	92.00	24.0%	16.0%
5	500	7.0	139.37 (29.71)	99.30	92.30	23.0%	14.9%
6	700	7.8	139.50 (28.25)	99.88	92.08	21.9%	13.7%
7	1000	9.0	139.30 (27.46)	100.20	91.20	21.1%	13.2%

Table 5.4. Pricing and return on investment results summary for the base case (cost effectiveness threshold of £20,000 per QALY; a minimum pricing threshold for launch of £120 per annum; and market share of 40%)

*Maximum reimbursement price per annum

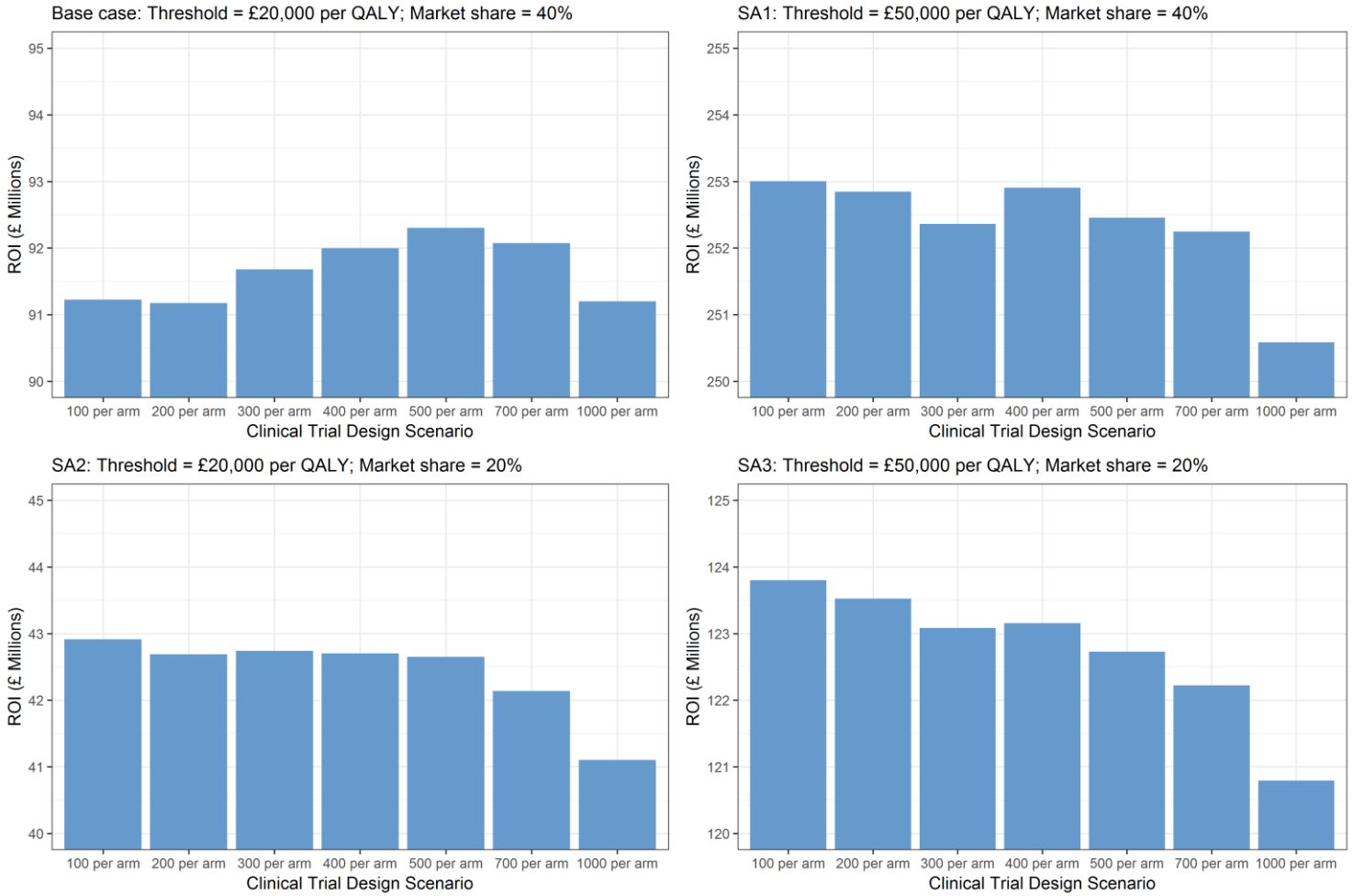


Figure 5.4. The projections of company ROI with febuxostat 80 mg prices set at the MRP and an assumed minimum launch price of £120 per annum

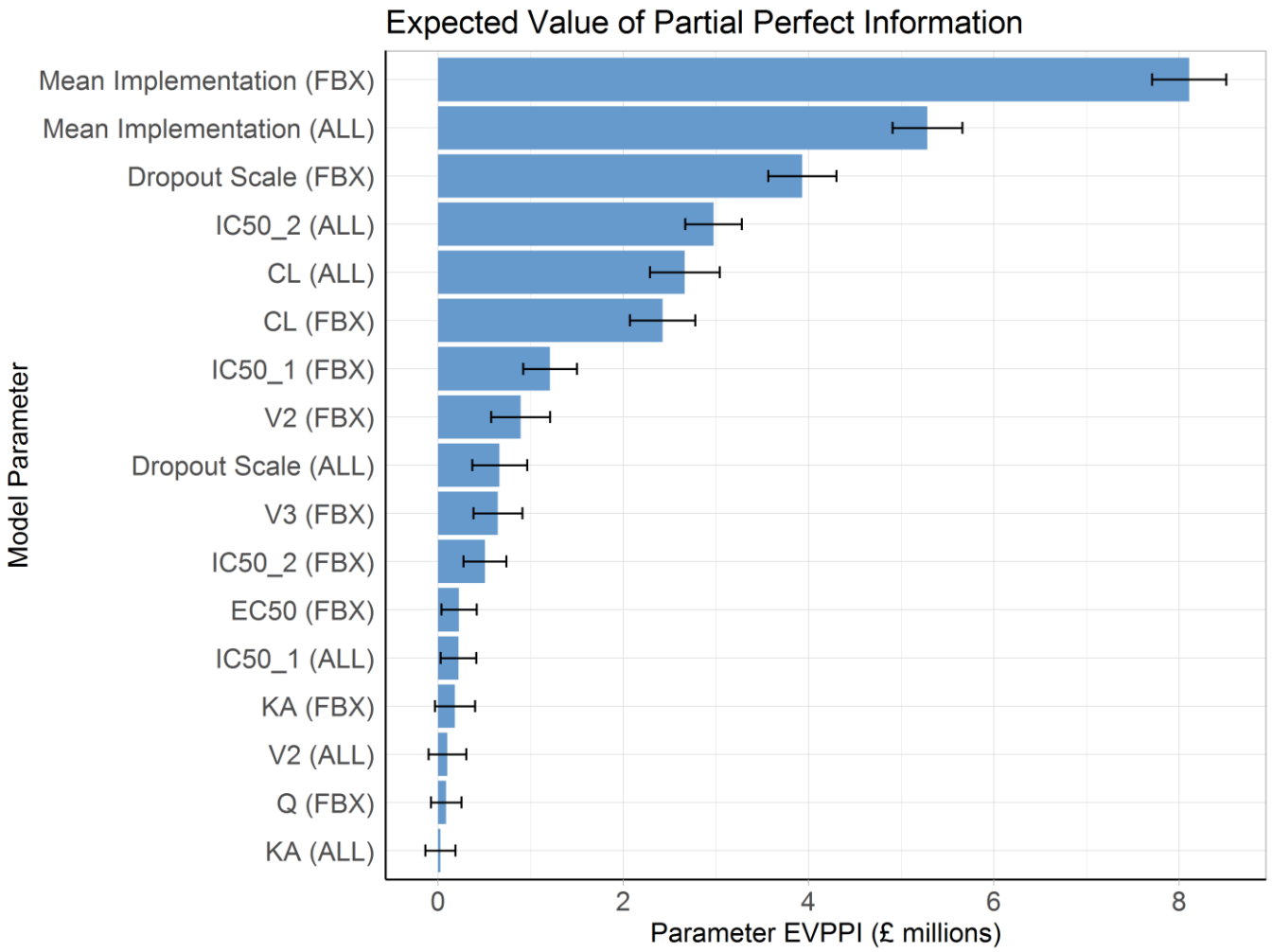


Figure 5.5. The EVPPI estimates for each of the model input parameter assumed to be uncertain

5. Discussion

This study has demonstrated an approach to sample size calculation that is based on the value of information analysis in which the optimal sample size is that which results in the greatest return on investment to the pharmaceutical company (Willan, 2008; Breeze and Brennan, 2014). However, this approach benefits from avoiding the need for priors, by simulating the posterior directly using PKPD based CTS. This provides a significant advantage as in many cases, an appropriate prior will not exist and a PKPD based CTS can provide a posterior that is adjusted for trial inclusion/exclusion criteria, duration, medication adherence and discontinuation.

We illustrated this interdisciplinary approach using a case study of a sample size decision for a single phase 3 trial of febuxostat versus allopurinol, both xanthine oxidase inhibitors for the treatment of gout. The base case scenario considered a single payer, using a cost effectiveness threshold of £20,000 per QALY as the decision rule. Assuming an annual incidence of eligible gout patients of 100,000, a fixed market share of 40%, and a minimum launch price of £120 per annum, the optimal sample size was 500 patients per arm which resulted in an ROI of £92.3 million based on UK revenues. There was uncertainty associated with the decision, and by calculating the EVPPI for each uncertain parameter it was found that uncertainty in parameters for drug adherence, not drug pharmacology, dominated the uncertainty regarding the optimal sample size decision.

CTS has typically been implemented within a model informed drug development (Marshall *et al.*, 2016) context, for example to support design decisions based on predicted performance in statistical tests in order to meet efficacy and safety objectives and obtain regulatory approval (Nixon *et al.*, 2009). Linking CTS results to an economic model designed to represent the reimbursement authorities approach to drug pricing is a natural extension that is consistent with a model informed drug development approach. Poland & Wada (Poland and Wada, 2001) presented a combined PKPD and economic model to compare alternative dose regimens, including models for non-adherence. However, although the drug price was linked to the drug's simulated efficacy and safety, it did not consider whether the drug would be reimbursed at these prices. Similarly to our findings, their study observed that treatment success was more sensitive to the uncertainty in population adherence than uncertainty in population PK parameters.

For the purpose of demonstrating the value of this interdisciplinary approach, the decision problem was simplified. In reality, there may be the need to consider the design and value of multiple phase 3 trials as was the case for febuxostat (Robinson *et al.*, 2018). There are also multiple markets to consider and, therefore, multiple reimbursement authorities with differing approaches the valuing medicines, with the additional complication that prices cannot be set in each market independently

(Gregson *et al.*, 2005). Others have adopted more realistic decision contexts by, for example, linking the market share to trial outcomes (Poland and Wada, 2001; Willan, 2008), considering multi-stage trials (Willan and Kowgier, 2008; Chen and Willan, 2013) and assuming imperfect implementation of a policy decision (Willan and Eckermann, 2010). As has been observed in previous research in this area (Breeze and Brennan, 2014), the value of information approach does not easily apply to a free market setting unless there is a means of linking pricing and sales volumes to trial outcomes.

Furthermore, this study has assumed that the proposed trial is only used to inform the estimate of treatment efficacy, implying that the treatments considered are equivalent in terms of safety. This method could be extended to include simulation of safety outcomes, into order to predict benefit-risk assessments in cases where treatments may differ in terms of safety. This also applies to other data that may be collected from a proposed trial, such as evidence regarding the utility of different health states or resource use that is typically derived from pivotal studies.

The technical challenge of performing a linked CTS and economic modelling exercise may be considered a limitation of this approach, however, much of the modelling effort already takes place within industry; PKPD models are used extensively during drug development and economic modelling is often required in order to secure reimbursement. The combined models incorporate a large number of input parameters and also require many simplifying assumptions, to which the results may be sensitive. This may be considered both a strength and a limitation, since while it reduces our confidence in the model predictions, it does provide a framework within which to understand the impact of alternative assumptions and the impact of parameter uncertainty.

Individual level CTS and economic modelling is likely to require significant computing resources to implement within a reasonable timeframe. This study used an individual level CTS with a much simpler cohort economic model. It was written in the R statistical programming language and on a computing cluster of 320 CPUs required several days to run. This does pose a potential constraint, however, other applications may not be as computationally intensive. As this case study was used primarily to illustrate the methods, some parameters and parameter uncertainty were assumed rather than estimated, and the important issue of correlation between input parameters was not considered.

Using clinical trial simulation to generate distributions of trial outcomes removes a key limitation of value of information approaches to trial design, the requirement for prior distributions on outcomes. It furthermore links the uncertainty in the drug pharmacology and trial execution model input parameters to the uncertainty in the predicted return on investment for possible trial designs, and may thus focus efforts on reducing uncertainty to specific areas. For febuxostat 80 mg versus allopurinol 300 mg the optimal sample size was found to be highly uncertain and sensitive to the size

of the market and the cost effectiveness threshold of the reimbursement authority. The EVPPI results indicated that uncertainty in the optimal sample size resulted primarily from uncertainty in the level of dose implementation and treatment discontinuation.

Chapter 6

Discussion

1. Summary

This thesis has expanded the scope of linked pharmacometric-pharmacoeconomic modelling by demonstrating novel applications of this methodology from the early to late stages of drug development. This goes beyond previous work in this area, which primarily focussed on early estimates of cost-effectiveness or estimates of the impact of protocol deviations in clinical trials, to applications in early development decisions and clinical trial design incorporating value of information methods. The dissemination of these applications through published case studies and conference presentations will, it is hoped, facilitate greater adoption of the methodology by those engaged in drug development. Collaboration with pharmacometricians in industry has helped to ensure that the selected applications are relevant to the perspectives and objectives of the pharmaceutical industry.

Three of the four chapters have applied linked pharmacometric-pharmacoeconomic modelling to inform decision making at different stages of development. These applications included i) estimation of the impact of decreasing drug adherence on modelled cost effectiveness in the transition to phase 3 or into routine use; ii) informing early candidate selection based on the value of hypothetical differences in drug pharmacology (clearance and potency) in terms of potential reimbursement pricing; and iii) sample size selection using clinical trials simulation and quantification of the aspects of pharmacology and trial execution leading to decision uncertainty.

The second chapter describes the development of a pharmacometric model that was the basis of simulations and scenario analyses in later chapters. Urate lowering therapies for the treatment of hyperuricemia in gout patients was chosen as a case study in collaboration with pharmacometricians in industry. Urate lowering therapies present some complex challenges to drug development and an absence of commercial interests allowed for unrestricted collaboration. Gout is characterised by a fairly reliable biomarker, serum uric acid (sUA), and although there is uncertainty regarding the relationship between sUA concentration and the risk of clinically relevant acute gout flares which severely impact on patients' quality of life, this biomarker has been used as a primary endpoint in pivotal phase 3 studies. A PKPD model was developed using sUA as the PD endpoint and used to simulate the time course of several biomarkers, including sUA, under conditions of imperfect medication adherence. This highlighted the potential for harm during re-initiation following a period of non-adherence in patients using a uricosuric.

The third chapter modelled the cost effectiveness of lesinurad in combination with either allopurinol or febuxostat versus these treatments as monotherapies, for different medication adherence scenarios. The results may be relevant from both an industry and reimbursement authority perspective. For industry, this study could inform decisions regarding whether to proceed into phase

3 testing, or whether adherence enhancing interventions or adherence monitoring should be implemented. From the perspective of the reimbursement authority, quantifying the expected loss of cost effectiveness resulting from a decline in adherence in routine use compared with clinical trials could inform decisions regarding whether, or under what conditions, to reimburse a drug.

The same set of models applied in Chapter 3 to a late stage development context were used in Chapter 4 to address an early development problem; the valuation of hypothetical pharmacological profiles in terms of predicted maximum reimbursement prices. This could serve to guide candidate selection for progression into clinical phases, based, in this example, on the balance between a potent compound and one that is cleared more slowly and which would, therefore, be more forgiving to missed doses if imperfect adherence is an issue in later phase studies. This method could be used in the absence of a candidate compound, to understand how potent a compound would need to be at the target in order to produce a level of effect that implies a price achievable that may justify drug discovery and development efforts. This type of analysis may be termed an early market assessment or also a type of headroom analysis (Girling *et al.*, 2015).

The third application of linked pharmacometric-pharmacoeconomic modelling in Chapter 5 demonstrated the use of a pharmacometric based clinical trial simulation and a pharmacoeconomic pricing model to compare trial designs in terms of return on investment (ROI). This combined the drug pricing perspectives of both the pharmaceutical company, setting minimum prices needed to obtain an adequate return on investment, and the reimbursement authority, setting cost effectiveness thresholds which imply a maximum price for a given benefit. In the event that the reimbursement authority maximum price is below the company minimum price, it may be optimal to terminate development, or if the expected return on investment is negative. This enables the selection of the optimal sample size based on maximising ROI and can link the uncertainty in aspects of drug pharmacology or trial conduct to uncertainty in the optimal design decision using a value of information approach.

2. Implications of this Study

2.1. Drug Development

The business model under which pharmaceutical companies have historically operated, which has provided society with medical innovation and the industry with returns on investments, is under growing pressure from increasing costs and falling revenues for new products. While the number of new drugs receiving marketing authorisation from the FDA does not appear to be declining (Mullard, 2019), there is a trend of increasing cost per new approval (Dimasi, Grabowski and Hansen, 2016) and of longer clinical development phases (Martin, Hutchens and Hawkins, 2017). Longer lasting clinical development will generally result in shorter periods of market exclusivity in which to recover the costs of drug development. As a result the prices of branded pharmaceuticals on the key US market have risen rapidly (Wineinger, Zhang and Topol, 2019), leading payers to make greater use of HTA (Pizzi, 2016), in an attempt obtain lower prices, and restrict use to fewer patients. This trend is likely to be unsustainable and may lead to falling returns on pharmaceutical R&D investment, thus reducing incentives for investment in future R&D.

The pharmaceutical industry is adapting in order to meet the challenges posed by increasing costs and falling revenue. In particular, there are trends toward leaner and more focussed drug development pipelines in fewer therapeutic areas; fewer and more consolidated research sites; increasing focus of speciality medicines and biologics over small molecules in primary care, and; increasing reliance on non-US and European markets (Gautam and Pan, 2016). Successful efforts have also been made to reduce the cost of drug development by failing development projects earlier before substantial resources have been invested (DiMasi *et al.*, 1991; DiMasi, Hansen and Grabowski, 2003; Dimasi, Grabowski and Hansen, 2016), in part through the successful application of MID3 (Marshall *et al.*, 2016). There is also a growing interest in the use of early pharmacoeconomic evaluation in order to identify commercially unviable products early and to align the clinical development outcomes with the requirements of reimbursement authorities (Ijzerman *et al.*, 2017). However, according to Miller (Miller, 2005) in 2005 the use of pharmacoeconomics in early phases of drug development was far from optimised, and in developing this thesis it is apparent that this remains true today.

Linked pharmacometric-pharmacoeconomic modelling is a method of performing early pharmacoeconomic evaluations in order to identify commercial failures before substantial resources are invested. Pharmacometrics can predict the effectiveness of compounds based on their pharmacology, or estimate the type of pharmacological profiles necessary to achieve a target level of effectiveness (Marshall *et al.*, 2016). Pharmacoeconomics provides a bridge between the pharmacodynamic/clinical endpoints used in clinical development and value that is placed on these

attributed by a reimbursement authority. This can be updated to reflect changes in the reimbursement authority's priorities or to reflect different approaches between jurisdictions. The design of development strategies and of individual studies, the size, duration and data collection, can be tailored to simultaneously meet the potentially differing requirements of regulators and reimbursement authorities. Apart from identifying and failing commercially unviable compounds early, this has the potential to avoid unnecessarily large or lengthy trials, trials that measure unnecessary endpoints and study duplication, thus reducing the cost and duration of drug development.

2.2. Iterative Pharmacoeconomic Modelling

In order to incorporate the additional objective of reimbursement within drug development, the current scope of MID3 (Marshall *et al.*, 2016) should be expanded to include early pharmacoeconomic modelling methods, in particular linked pharmacometric-pharmacoeconomic modelling. MID3 currently focusses on the application of pharmacometrics and provides a framework for the use of modelling to inform decision making across the R&D timeline that adheres to the principle of making use of all available evidence. Linked pharmacometric-pharmacoeconomic modelling could be applied iteratively, beginning with early market assessment and evolving, as studies generate new evidence, into an evaluation used to demonstrate value to prospective reimbursement authorities. Outlined below is an iterative approach to pharmacoeconomic evaluation during drug development, described in four stages, based on the work of Sculpher et al. (Sculpher, Drummond and Buxton, 1997) but adapted to the perspectives of the pharmaceutical industry.

Stage 1: Early Market Assessments

If a drug discovery effort yields compounds modifying a target in such a way as to suggest the possibility of therapeutic benefit in humans, a decision must be made whether to proceed into subsequent phases of development. Early pharmacoeconomic modelling at this stage is likely to focus on the level of unmet need that exists, given the effectiveness of competitors. This may constitute a model of the disease area, including evidence relating to the characteristics of the target patient population, disease incidence, epidemiology and natural history of the disease. Evidence regarding the current or future competitors would also be required and an understanding of the priorities of reimbursement authorities in terms of the value placed on different aspects of benefit.

Rather than predicting pricing options for specific compounds, pharmacoeconomics at this stage may instead seek to quantify the types and scale of benefits that would be required to obtain a price in a range that may justify progression. This can be compared with the properties of candidate compounds

in order to assess the likelihood of obtaining the required level of benefit. By incorporating the perspective of reimbursement authorities, the value of candidates may also be assessed according to other criteria, such as convenience, for example, in having a different route of administration to the competition. This type of analysis may suggest investment in compounds that are equivalent (non-inferior) to competitor products but may offer other advantages in terms of convenience or fewer contraindications. Brandes et al. (Brandes *et al.*, 2015) present an example of this type of analysis but for a hypothetical medical device rather than a pharmaceutical product.

Uncertainty at this early stage is considerable and through the quantification of model and parameter uncertainty, this can inform planning both future trials and pharmacoeconomic modelling. By highlighting challenges and evidence gaps in the data required by pharmacoeconomic models, future trials can be designed with a view to addressing these limitations. Thus at the point of using pharmacoeconomic evaluation in support of reimbursement, the evidence requirements and value perspective of a reimbursement authority will be well understood and accounted for. Such analyses could be the sole reason of terminating a project before entering clinical trials if it is deemed that, although a drug may be safe and effective, the economic environment is such that a positive ROI is unlikely.

Stage 2: Phase1/2

Following phase 1 there will be data to begin to characterise the human PK and potentially PD. This may be the stage that compartmental or more mechanistic PKPD models could be developed and applied to give more reliable early cost effectiveness estimates or to plan clinical trials. A decision analytic modelling approach provides an intuitive framework, a means of synthesising data, captures the impact of uncertainty, and may evolve into the economic evaluation that is used to demonstrate value/cost effectiveness at the stage of securing reimbursement and negotiating with reimbursement authorities.

At this stage the most likely use of linked pharmacometric-pharmacoeconomic modelling is in quantifying the cost of uncertainty and attributing that cost to specific parameters, groups of parameters or types of evidence. This could inform future research activities that may be useful in order to address these evidence gaps – depending on the cost of undertaking such research. In the case of ULTs, for example, there is considerable uncertainty surrounding the impact of acute flares on quality of life (Scottish Medicines Consortium, 2010), a value of information study found that a trial to measure efficacy and health utilities of gout patients would be of most value out of the options considered (Jutkowitz *et al.*, 2017). There could also be applications involving the comparison of

treatment effects in different population subgroups in an effort to balance effectiveness against the number of patients who would be eligible for treatment (Slejko *et al.*, 2016).

Stage 3: Phase 2/3

The development of a linked pharmacometric-pharmacoeconomic model at stage 2 can be a powerful tool to inform the design the pivotal studies that are likely to be central to the subsequent reimbursement process. Crucially this can be used to optimise trial design using clinical trials simulation based on maximising return of investment; which takes account of the costs of type I and II errors in place of arbitrary threshold values (Breeze and Brennan, 2014). This can also account for, or quantify the influence of, imperfect medication adherence during trials. This process simultaneously allows for the optimisation of trial design along with consideration of the go/no-go decisions, based on whether any design results in positive ROI.

With the addition of probabilistic sensitivity analyses, especially since the development of efficient value of information methods (Strong, Oakley and Brennan, 2014), the linked pharmacometric-pharmacoeconomic model can not only optimise based on trial size or duration, but also inform the data collection during a trial. Data collection should be prioritised in those areas where evidence is weakest and those that account for the largest proportion of the overall decision uncertainty. For example, this may show that the go/no-go decision or optimal design decision is most sensitive to population medication adherence (Poland and Wada, 2001); or alternatively that cost outcomes should be prioritised over effectiveness outcomes.

Stage 4: Phase 3/Post-Marketing

This includes the use of pharmacoeconomic models in support of applications for reimbursement or for pricing negotiations. It also provides a mechanism for demonstrating cost effectiveness if expanding the use of a medicine into new markets, where additional trials may not be necessary or practicable. This type of analysis could include the evaluation of complex pharmaceutical interventions such as alternative treatment sequences or pharmacogenetic-guided therapy (Pink *et al.*, 2014). This can make use of the existing models developed much earlier in development incorporating any new evidence from trials, post-marketing experience or on competitor products. These analyses may inform whether post-marketing studies are needed to address evidence gaps based on the expected value of information versus the cost of conducting a study. Other applications include providing an indication of real-world effectiveness, known as ‘use effectiveness’, which may be of value to reimbursement authorities.

2.3. Medication Adherence

All of the analytical chapters in this thesis have allowed for the fact that patients may not be perfectly adherent to their dosing regimen, except perhaps in the closely monitored settings of phase 1 and 2 trials. Medication adherence is a well-developed and active area of research, and the purpose of this thesis was not to produce novel insights in this area. Many other authors have applied pharmacometric modelling and simulation to study the impact of imperfect medication adherence, whilst using more sophisticated and realistic models of dose taking than have been implemented here. There are also examples, provided in the introduction and analytical chapters, of studies which have accounted for adherence in linked pharmacometric-pharmacoeconomic models, albeit without including the perspectives of reimbursement authorities explicitly.

The findings relating to adherence in this thesis do serve to highlight the potential for it to be an area of concern in later phases of development that can drive down effectiveness, reduce cost effectiveness and have consequences in terms of drug safety. The extent to which it will prove detrimental, however, depends both on the prevailing patters of non-adherence within the study population and the pharmacology of the candidate drug (Stauffer *et al.*, 2017). Linked pharmacometric-pharmacoeconomic modelling should be the methodology of choice here, since pharmacology and dose taking are the required inputs and it can provide outputs in terms of both effectiveness and economic consequences of non-adherence.

It would appear that it remains uncommon for phase 3 trials to make use of electronic monitoring methods, or for sponsors to implement interventions designed to encourage a high level of adherence. Thus there exists the situation in many phase 3 trials in which it can reasonably be assumed that participants are not fully adherent, while evidence suggests that adherence is likely to be superior to that of the medication in routine use (Van Onzenoort *et al.*, 2011). The ratio of benefit to risk of treatments studied is, therefore, biased to some degree owing to the unknown extent of non-adherence. What is observed may not be representative of the true efficacy or the drug, nor its real-world effectiveness. Some trials use 'pragmatic' designs, or transition into this design (Selker *et al.*, 2019), in order to provide evidence of real-world effectiveness and cost effectiveness to better inform reimbursement decisions. In the absence of a pragmatic trial design being implemented, linked pharmacometric-pharmacoeconomic modelling is one method which can be used to estimate the likely difference in cost effectiveness based on patient characteristics and adherence more representative of real-world use (Alshreef *et al.*, 2019).

2.4. Urate Lowering Therapy

This thesis has studied the development and application of linked pharmacometric and pharmacoeconomic modelling using ULTs for the treatment of gout as a case study. The primary objective was to demonstrate the value of the methodology as a general approach during drug development. However, while it can be turned to the study of many different development issues, this thesis necessarily focussed on those specific to the development of ULTs. Many of the challenges of drug development in this area are common to other chronic diseases, such as the availability of low cost generic medications, imperfect medication adherence and uncertainty regarding long term safety.

Allopurinol is the low cost generic medication that has long been the standard of care for treating hyperuricemia in gout patients. Although allopurinol is generally safe and effective, a large proportion of gout patients are not successfully treated using allopurinol alone and gout remains a prevalent disease (Kuo, Grainge, Zhang, *et al.*, 2015). Failure on allopurinol is largely due to inappropriate prescribing and poor medication adherence, rather than its inadequate ability to lower sUA (Stamp *et al.*, 2014). Hypersensitivity reactions are another drawback of allopurinol and there is a market for a second line therapy, such as febuxostat, in those who cannot tolerate allopurinol or who do not show adequate response. That febuxostat appears more effective than allopurinol in clinical trials is largely a result of the lower than recommended (Hui *et al.*, 2017) doses of allopurinol used in comparator arms. These doses, however, do reflect to a large extent the prevailing real-world use of allopurinol. More recent studies have found that the use of febuxostat is associated with a higher rate of all-cause and cardiovascular mortality (White *et al.*, 2018), which may limit the use of febuxostat even if it becomes available at lower cost.

Another treatment option for hyperuricemia in gout patients is dual-therapy combining a xanthine oxidase inhibitor with a uricosuric, such as lesinurad. Whilst dual-therapies were shown to be superior to either monotherapy option (Haber *et al.*, 2018), lesinurad was associated with an incidence of renal related adverse events (Wu *et al.*, 2018). It remains uncertain whether or not the drug itself is nephrotoxic, but it is considered more likely to be related to high concentrations of urinary uric acid (uricosuria) (Sanchez-Nino *et al.*, 2017). In Chapter 2 of this thesis, using a pharmacometric model of ULTs, it was shown how intermittent medication adherence could result in episodes of higher urinary uric acid concentrations. This suggests that the risk of nephrotoxicity may be related to imperfect patterns of dose implementation. There exists other uricosurics which may be used in combination with xanthine oxidase inhibitors, but these too have safety concerns which limit their use as long-term therapies (Dalbeth, Merriman and Stamp, 2016).

Given the limitations of the existing drug therapies for treating hyperuricemia in gout patients, it may be possible that a new treatment option could be sufficiently successful as to justify investment in drug discovery and development. A drug with differing pharmacological profiles could mitigate, to some extent, the loss of potential effectiveness resulting from imperfect dose implementation. Such a compound would retain a greater level of effectiveness in later phase trials and show greater differentiation under more pragmatic trial designs. This was studied in Chapter 4 using linked pharmacometric-pharmacoeconomic modelling to value hypothetical pharmacological profiles of more forgiving febuxostat analogues. While the results suggest that improved forgiveness alone might not be sufficient to justify the risks of drug development, it could form an important aspect of the added value provided by future medications.

3. Comparison with Previous Research

The literature around early economic modelling has evolved somewhat separately to that for MID3. A 2017 scoping review by Ijzerman et al. (Ijzerman *et al.*, 2017) provides an overview of the emerging use of early HTA in medical product development. One of the principal types of early HTA identified was 'headroom' analysis, where 'headroom determines the maximum reimbursable price of a product by using the prevailing willingness-to-pay thresholds'. It is notable that the published examples of headroom analysis have so far tended to focuss on medical devices rather than on drugs (e.g. (Vallejo-Torres *et al.*, 2008; Brandes *et al.*, 2015; Girling *et al.*, 2015; Markiewicz *et al.*, 2016)). The application of linked pharmacometric-pharmacoeconomic modelling in Chapter 4, where hypothetical improvements in treatment response rates were linked to future reimbursement prices, is similar to a headroom analysis. However, this thesis has gone further by not only expanding the approach into pharmaceuticals but estimating the pharmacological profiles necessary to obtain such response rates. This does not only have potential to inform decisions regarding whether to invest in drug discovery and development, but also to guide the search towards candidate compounds with particular properties.

There has not been a recent review of the use of early economic modelling in drug development. In 2008 Hartz & John (Hartz and John, 2008) published a review of 'methodological contributions as well as economic evaluations that used data from early phases of product development', but some notable examples have been published since then. Swift et al. (Swift *et al.*, 2018) did not set out to conduct a review, but do include many of the examples of linking pharmacometrics and pharmacoeconomics. The previous works most related to this thesis, or upon which this thesis aimed to build, include; Poland & Wada (Poland and Wada, 2001), Hughes & Walley (Hughes and Walley, 2001), Pink et al. (Pink, Lane and Hughes, 2012; Pink *et al.*, 2014), van Hasselt et al. (Van Hasselt *et al.*, 2015), Slejko et al. (Slejko *et al.*, 2016) and Kamal et al. (Kamal *et al.*, 2017). Several of these studies have addressed the issue of medication adherence. One simulated adherence patterns based on data from electronic pill bottle caps (Poland and Wada, 2001), which was varied during sensitivity analyses to show adherence as being the primary driver of uncertainty in treatment effectiveness. Another allowed for imperfect adherence during simulations by taking a simple approach (Pink *et al.*, 2014) similar to that adopted in Chapter 3 of this thesis.

Most of the previous studies were intended to inform decision making at a late stage of development (post-phase 2), including early prediction of cost effectiveness (Pink, Lane and Hughes, 2012), regimen selection (Poland and Wada, 2001) and phase 3 go/no-go decisions (Hughes and Walley, 2001). Although the findings from these studies could be relevant to the design of phase 3 trials, they did not

attempt to address trial design issues directly such as determining an optimal sample size. Other studies have been applied to problems at a post-marketing stage, such as the cost effectiveness in new indications (Van Hasselt *et al.*, 2015), of complex pharmaceutical interventions (Pink *et al.*, 2014) and of alternative treatment strategies (Kamal *et al.*, 2017). This is unsurprising since the necessary data for PKPD modelling and simulation is more likely to be available during the later stages of development. One study did consider hypothetical treatments in a similar way to Chapter 4 of this thesis (Slejko *et al.*, 2016) with the potential to inform trial inclusion/exclusion criteria and identify important treatment benefits. However, this study did not examine the pharmacology of the hypothetical treatments and how aspects of pharmacology relate to treatment response and subsequent cost effectiveness.

4. Study Strengths

4.1. Methodology

The strengths of this research include its methodological rigour and the novel contributions it has made to the discipline of MID3. The fundamental strength of the linked pharmacometric-pharmacoeconomic methodology is that it allows a reimbursement authority perspective on value in treating a population to be explicitly linked to the pharmacology of candidate compounds throughout development. It provides a Bayesian decision analytic framework enabling the synthesis of all available evidence, in which assumptions are made explicit and can be scrutinised, and where the cost of uncertainty can be quantified. This has potential to increase the efficiency of drug development by identifying and terminating potential commercial failures and tailoring development programs towards the requirements of reimbursement authorities.

This research is a rare example of an interdisciplinary approach spanning pharmacometrics, clinical pharmacology and health economics. This methodology may be readily incorporated within drug development programs, since it builds on existing pharmacometric modelling and simulation techniques, and is suited to informing a range of development decisions. As all the research chapters have been reviewed by pharmacometricians working within the pharmaceutical industry, this has helped ensure that this work is not only at a high standard of rigour but also relevant to the perspectives of the pharmaceutical industry. Whilst it did not prove possible to collaborate in an area of active drug development owing to commercial sensitivities, having input on the research from the industry perspective proved invaluable.

The pharmacodynamic model that was developed for the case study in this thesis, and that it was possible to estimate parameters of this model from published data sources, represents a key strength of this research. The model uses a semi-mechanistic indirect-response pharmacodynamic model structure that can account for the system dynamics resulting from intermittent dose taking. Its structure is as simple as possible whilst still retaining the critical aspects of the system but is sufficiently complex to enable simulation of intermittent dose taking. This pharmacodynamic model structure was obtained through collaboration with industry pharmacometricians and was based on considerable work on quantitative systems pharmacology modelling of uric acid synthesis and elimination.

4.2. Novel Contributions

This thesis was able to combine pharmacometrics based clinical trial simulation and value of information approaches in a single study. This is a novel application and one which allows a link to be

made between the uncertainty in specific aspects of drug pharmacology, or of trial conduct, and the return on investments following a trial of a specific design. This methodology may potentially be of high value during drug development for designing development programmes and optimising clinical trial design. Modelling and simulation in the areas of pharmacometrics and pharmacoeconomics, especially where there is an interest in uncertainty, can be highly computationally demanding. This research has benefitted from access to computing resources through the Supercomputing Wales programme. Without access to the computing resources this allowed, the studies in this thesis would have been on a substantially smaller scale.

This thesis has demonstrated a method of quantifying the cost of imperfect medication adherence in terms of the maximum reimbursement drug prices meeting any given cost effectiveness threshold. Furthermore, the costs can be assessed separately according to changes to discontinuation and varying levels of dose implementation. This is likely to be the first study to accomplish this. The use of linked pharmacometric-pharmacoeconomic modelling in order to compare aspects of drug pharmacology (clearance vs potency), in terms of their ability to confer forgiveness and therefore higher reimbursement prices, has also not been previously described. In the context of drug development this represents the earliest application of this methodology along the drug development timeline.

5. Study Limitations

5.1. Development Silos

A potential barrier to the integration of pharmacoeconomics within drug development decision making is the historical separation of clinical development and commercial functions, with each operating in its own so-called silo. Clinical development groups, which include pharmacometricians, have responsibilities including the design of clinical studies and decisions regarding optimal doses and regimens. The goal of clinical development has been to develop medicines to the point of marketing authorisation, following which commercial teams have taken over to manage objectives related to pricing, reimbursement and market access (PRMA). However, as has been shown in this thesis, decisions during development may impact on PRMA outcomes. Therefore, a further breaking down of such silos is required in order that drug development can work towards the joint objectives of marketing authorisation and reimbursement (Levin, 2015).

That there remains a separation between the clinical and commercial functions within the pharmaceutical industry is evidenced by the published literature. It is those in the former group who are responsible for the development and dissemination of MID3 (Milligan *et al.*, 2013; Marshall *et al.*, 2016; Dockendorf *et al.*, 2018), which has not as yet fully embraced pharmacoeconomics and commercial objectives, whereas the principle proponents of early economic modelling are those operating in the commercial space (Miller, 2005; Hartz and John, 2008; Ijzerman *et al.*, 2017). Until greater integration between clinical and commercial functions occurs, this presents a barrier to the adoption of techniques such as linked pharmacometric-pharmacoeconomic modelling, as the methodology requires the collaboration between these two disciplines or by those with training in both. There may, however, be examples of collaboration within the pharmaceutical industry that have not been published.

5.2. Retrospective Case Study

This thesis has not involved a real-world drug development project. Therefore, the applications in this thesis are all retrospective or hypothetical. Although the collaboration with industry pharmacometricians was sustained throughout the project and proved extremely valuable in providing access to expertise in drug development, industry practices and MID3 techniques including pharmacometrics, active drug development case studies were deemed too commercially sensitive to form part of this thesis. The case study in gout, however, was based upon Pfizer's experience of previously having been active in developing compounds in this area. As such, it was an ideal case study

for this thesis, since there was expertise available from recent experience and the area remains of interest to the pharmaceutical industry in general.

5.3. Pharmacodynamic Endpoints

One of the primary limitations of the linked pharmacometric-pharmacoeconomic modelling approach relates to the scale of uncertainty in early drug development. The linkage requires that pharmacodynamic endpoints be used as inputs to a pharmacoeconomic model. Pharmacodynamic endpoints could take the form of the clinically relevant events which can be assigned health and cost outcomes, or surrogate outcomes that require additional modelling to estimate clinically relevant consequences, such as sUA in gout. Not all disease areas and treatments will have these characteristics which may make a linked pharmacometric-pharmacoeconomic approach unfeasible. For example, direct oral anticoagulants (DOACs) for atrial fibrillation were considered as an additional case study for this thesis. The clinically relevant outcomes include bleeding and strokes, relatively rare events, for which a dose response relationship may not be observable in early phase trials. Furthermore, the evidence to link the level of factor X inhibition, the relevant biomarker, to clinical events is much sparser than that linking sUA concentrations to the occurrence of acute gout flares.

5.4. Validation

The purpose of this work was not to provide a proof of concept, this has been addressed in previous studies (Pink, Lane and Hughes, 2012; Pink *et al.*, 2014). Instead, this thesis has sought to extend the scope of potential applications of linked pharmacometric-pharmacoeconomic modelling and to frame it within an MID3 paradigm (Marshall *et al.*, 2016). However, the validation of the models and the ways in which they have been used is an important and challenging aspect of this methodology. Pharmacometric model validation is well established in the field and there will often exist data enabling internal and external validation of a model used for simulation (Mould and Upton, 2012). Validation of pharmacoeconomic models is more challenging owing to an absence of external evidence for comparison and is less well developed.

From the perspective of the reimbursement authority the methods and evidence used in economic evaluation, and their validity, is of great importance since this affects decisions regarding the allocation of significant health care resources. From the perspective of the pharmaceutical industry, however, the issue is not whether the pharmacoeconomic model used is the ‘right’ one, or its validity per se, but only whether the methods employed meet a reimbursement authority’s requirements for economic evidence in support of an application for reimbursement. The objectives and the risks surrounding resource allocation decisions differ depending on the perspective being considered and,

therefore, the appropriate modelling methods and the requirement for validation is also context specific.

Where possible in chapters 2-5 comparisons have been made between published data and the simulation results, whether in terms of treatment response rates or the modelled downstream economic consequences. Simulations were found to be broadly in line with the observed data, however differences in simulation assumptions regarding drug adherence and patient characteristics inevitably result in a range of possible outcomes before considering the impact of parameter uncertainty. This is a retrospective comparison since the models were developed with knowledge of the results of the pivotal clinical trials and economic evaluations used to make comparisons.

Previous studies have used linked pharmacometric-pharmacoeconomic models to retrospectively reproduce cost effectiveness metrics obtained in HTA based on real-world trials data with a reasonable degree of accuracy (Pink, Lane and Hughes, 2012; Pink *et al.*, 2014). These studies also predicted the clinical outcomes and subsequent economic evaluations for trials that had not completed. Had the results of these trials been available at the time of writing, this thesis would have included the comparison between the simulated and observed economic outcomes. The ultimate validation of this approach must be addressed in the long run according to whether its implementation within the MID3 toolkit is associated with an increase in drug development efficiency.

5.5. Adherence Selection Bias

The subjects in clinical trials are likely to vary in the extent to which they adhere to the study medications. An individual's level of adherence may be related to other characteristics that also impact on the efficacy of the medications in question. Subjects who adhere well may not, therefore, be representative of subjects as a whole; a form of selection bias (Comté *et al.*, 2009). Simulation models of adherence should, where possible, account for relationships between subject characteristics and dose taking behaviour in order to generate a realistic trial cohort. In the absence of available evidence for gout patients to characterise any such relationships between dose taking behaviour and subject covariates, the current work has simulated dose taking independent of any other subject covariates. This is acknowledged to be a limitation of the approach to modelling medication adherence.

5.6. Uncertainty and Assumptions

Early economic modelling is subject to a greater level of uncertainty owing to the absence of large scale trial data, and will be burdened by a greater reliance on assumptions. However, as with pharmacoeconomic modelling in support of reimbursement using pivotal study data, under a Bayesian

decision theoretic approach the optimal decision is that with the greatest expected payoff regardless of the uncertainty associated with the decision (Claxton, 1999). Furthermore, economic modelling at any stage using a decision analytic model provides a framework for evidence synthesis that allows the consequences of combining uncertainty from multiple sources to be quantified. This measures the risk associated with decision making and may itself support the optimisation of development strategies.

Early economic modelling is predicated on being able to quantify the value placed on potential benefits of a drug by prospective reimbursement authorities. This will depend on the consistency and transparency of the processes adopted by specific reimbursement authorities. This thesis has focussed on a UK context and it is one that is on the whole consistent and transparent. However, for other jurisdictions this is likely to be less straightforward. If the prices a reimbursement authority is prepared to pay to access new medications appears to vary over time, or between disease areas in a non-predictable way then it will be very difficult to value potential benefits of drugs in development. To mitigate this problem, increasingly, reimbursement authorities are working with the pharmaceutical industry in order to define and communicate their priorities and value propositions.

Not only is it more difficult to assign value to potential treatment benefits for some reimbursement authorities while in the early phases of development, but this process will need to be repeated for authorities in all potential markets. Furthermore, these markets are not independent as prices set in one market influence prices in others. This increases the complexity of integrating early pharmacoeconomic modelling within the decision making process, compared with the case study in this thesis that has only considered a single payer.

6. Future Research

Given that drug development is, in part, an exercise in designing and executing clinical studies in order to reduce uncertainty regarding a drug's efficacy and safety, it would appear suited to the application of value of information approaches. Further research is needed on the potential applications of value of information to inform planning of research programmes and study design. In particular, research questions include whether the approach adopted in Chapter 5 could be applied to other case studies, and the extent to which its limitations can be resolved. These include simultaneously optimising the design of multiple phase 3 studies and of developing a model of return on investment that incorporates an environment where there are multiple reimbursement authorities and where market share is a function of the trial evidence. The method could also be applied to consider a wide range of design issues, including duration, inclusion/exclusion criteria, dose, regimen, or the addition of adherence enhancing interventions.

The continued development and increasing use of Model-Based Meta-Analysis (MBMA) (Upreti and Venkatakrishnan, 2019) is likely to remove some of the barriers to implementing linked pharmacometric-pharmacoeconomic modelling. MBMA makes use of pharmacometric models to provide pharmacologically plausible dose response relations and allow for a wider range of data sources to inform model parameters. Pharmacometric models are then placed within a framework that allows for the synthesis of a wide array of evidence sources which may include internal or external data from multiple trials, as well as aggregate or individual patient data for both clinical and preclinical development phases. Since this approach can also be used to synthesise evidence relating to the pharmacology of potential competitor compounds, the resulting models could provide inputs to comparative economic models.

Quantitative Systems Pharmacology (QSP) uses computational mathematical models to represent biological and disease processes and study their interaction with a drug based on its pharmacology. It is increasingly being used to inform decision making in drug discovery and the early stages of drug development (Visser *et al.*, 2014). Amongst the possible ways in which QSP could facilitate early pharmacoeconomic modelling via pharmacometrics, two are given here. The first is to enable early market assessments, where clinical evidence does not exist QSP models could provide a basis for understanding the pharmacological profiles that would be required in order to produce a target level of benefit. The second is as a tool for linking surrogate to clinical endpoints. This has the potential to address a significant limitation of linked pharmacometric-pharmacoeconomic modelling, that the clinical outcomes of interest to reimbursement authorities may not be observable prior to phase 3 trials.

Despite the development of the linked pharmacometric-pharmacoeconomic methodology since the first publications in this area (Hughes and Walley, 2001; Poland and Wada, 2001), there remain few published examples of it being applied in a real-world drug development context. This is unsurprising given the commercial sensitivity of information regarding development candidates. However, this makes it a challenge for academia and industry, without first-hand experience, to assess the value of investing the time of analysts to attempt such exercises. It is hoped that in time, further publications will emerge and the pharmaceutical industry experience of the success or failure of implementing linked pharmacometric-pharmacoeconomic modelling will be shared more widely.

7. Conclusion

Drug development is under growing pressure from increasingly stringent requirements from regulators and reimbursement authorities at the same time as the availability of low cost generic medications is increasing. The objectives of drug development must be aligned with those of reimbursement authorities as well as regulators, in order to sustain future drug development and deliver the benefits that are of value to society. Linked pharmacometric-pharmacoeconomic modelling provides a framework for integrating reimbursement authority value into drug development decisions, whilst also enabling evidence synthesis and measurement of the cost of uncertainty. By expanding the scope of linked pharmacometric-pharmacoeconomic modelling and adding to the library of applications available in the literature, this thesis aims to facilitate and promote a wider use of the methodology. The iterative application of this methodology within a Model-Informed Drug Discovery and Development framework has the potential to enhance drug development efficiency and communication of product value to external decision-makers.

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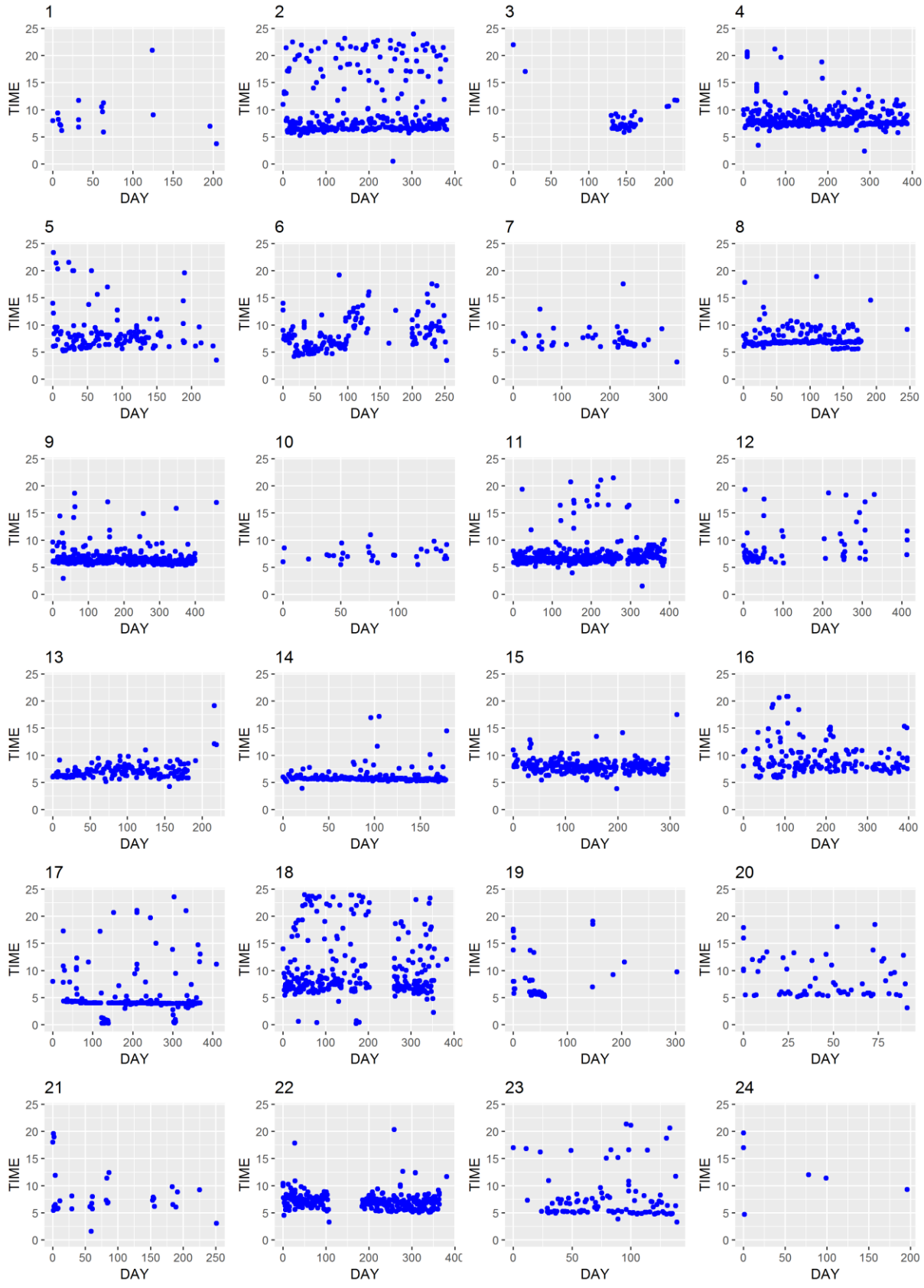
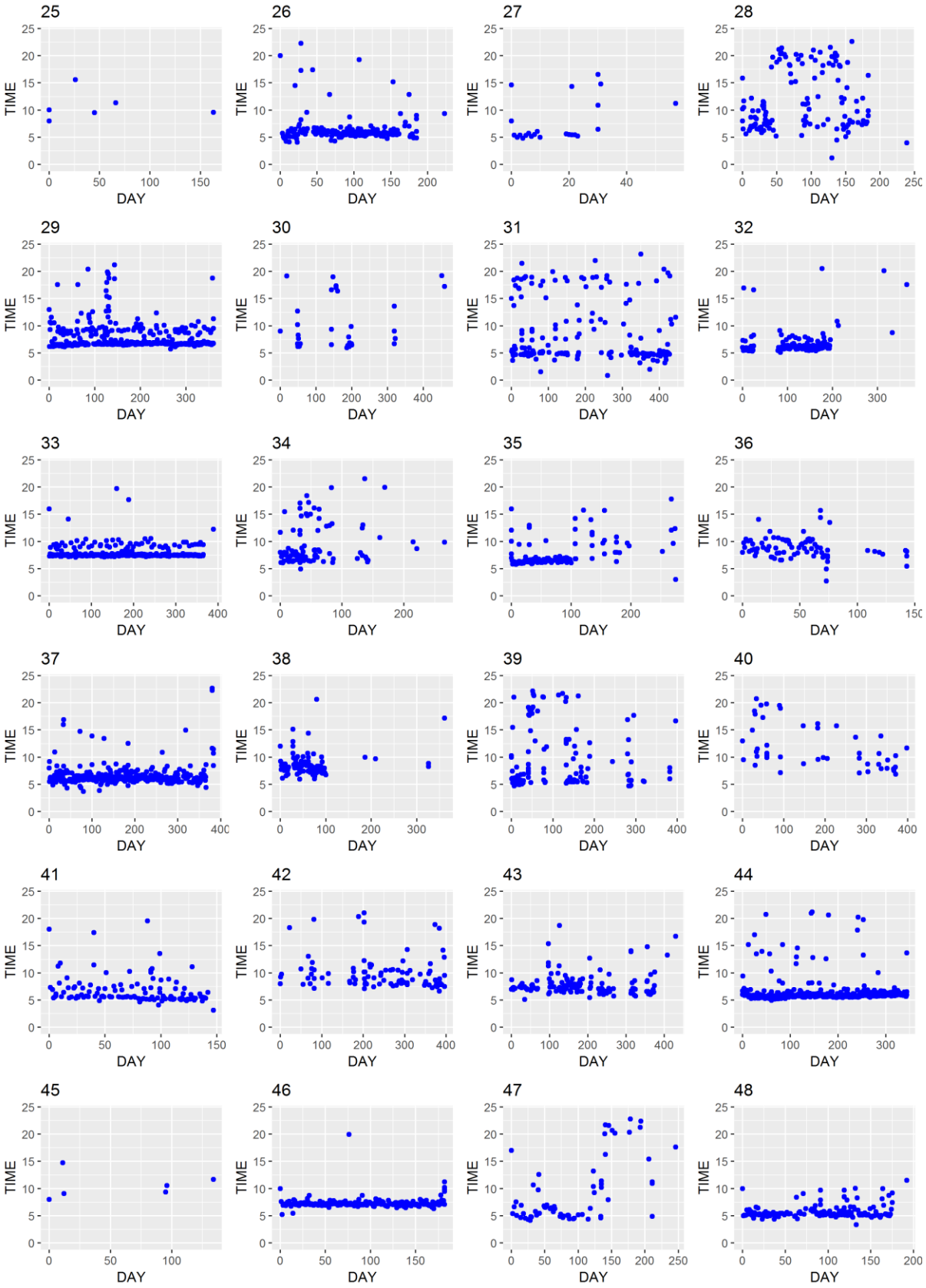
Appendices

MEMS data used for simulation in Chapter 4.



Subjects 1 - 24



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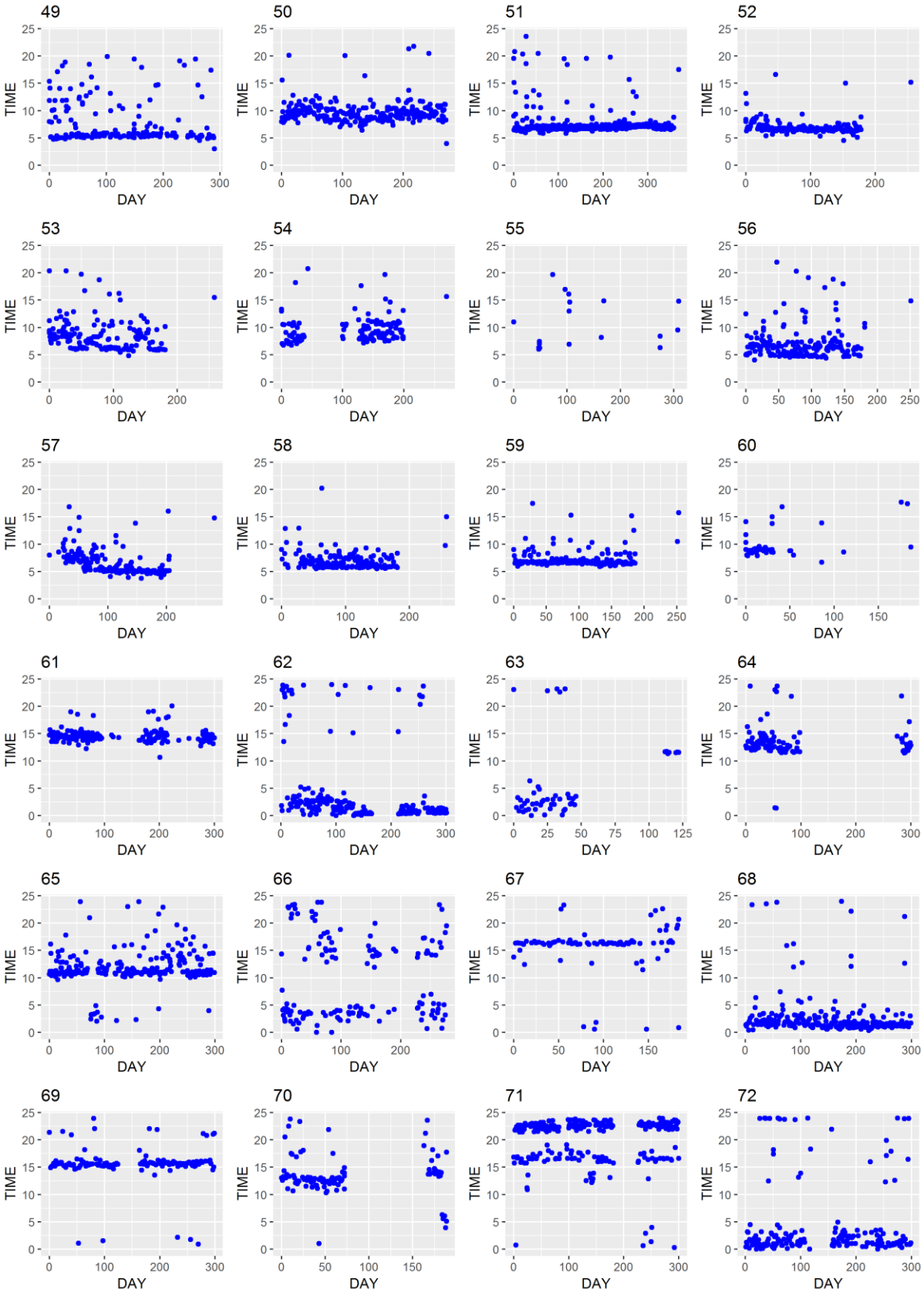

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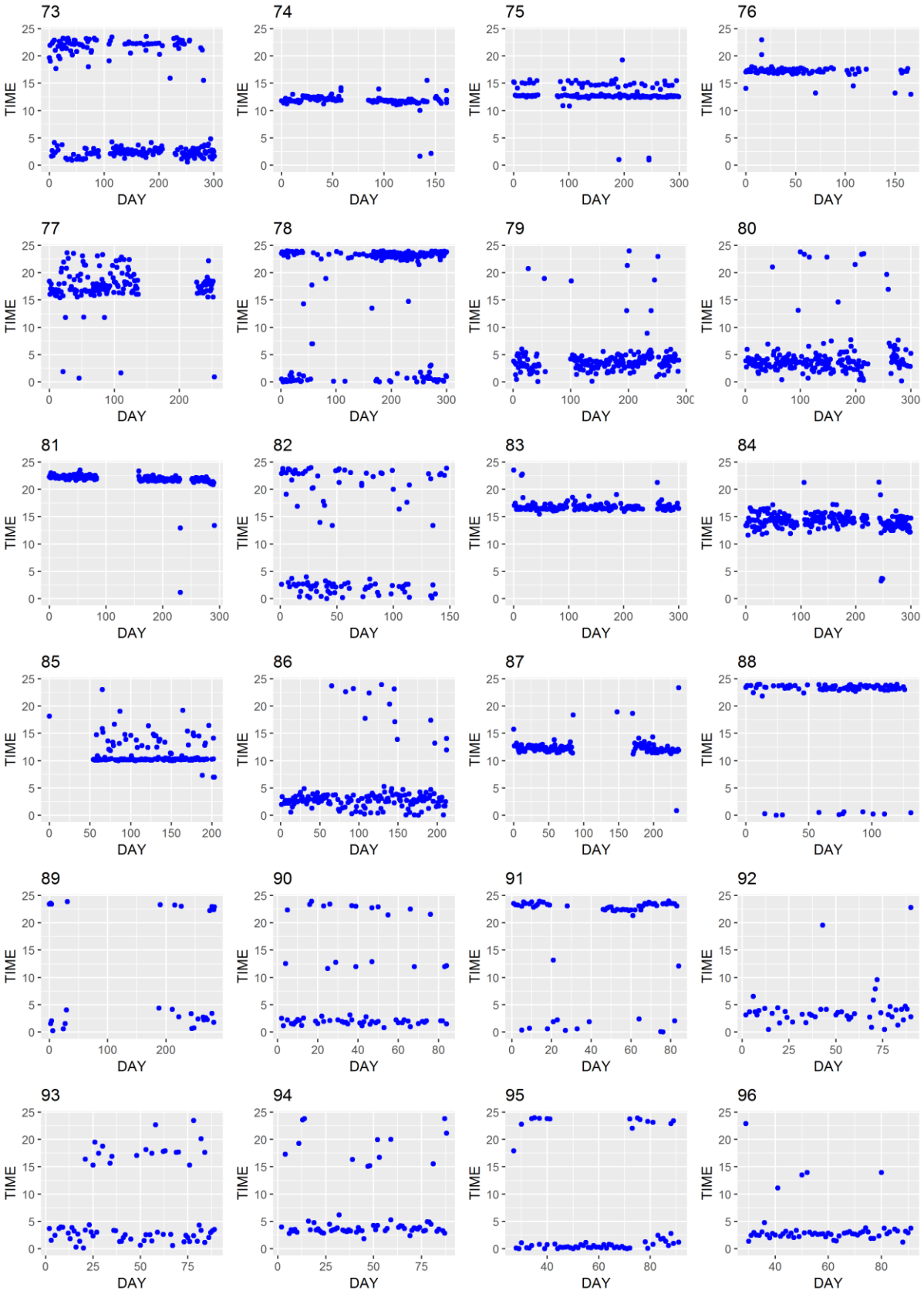

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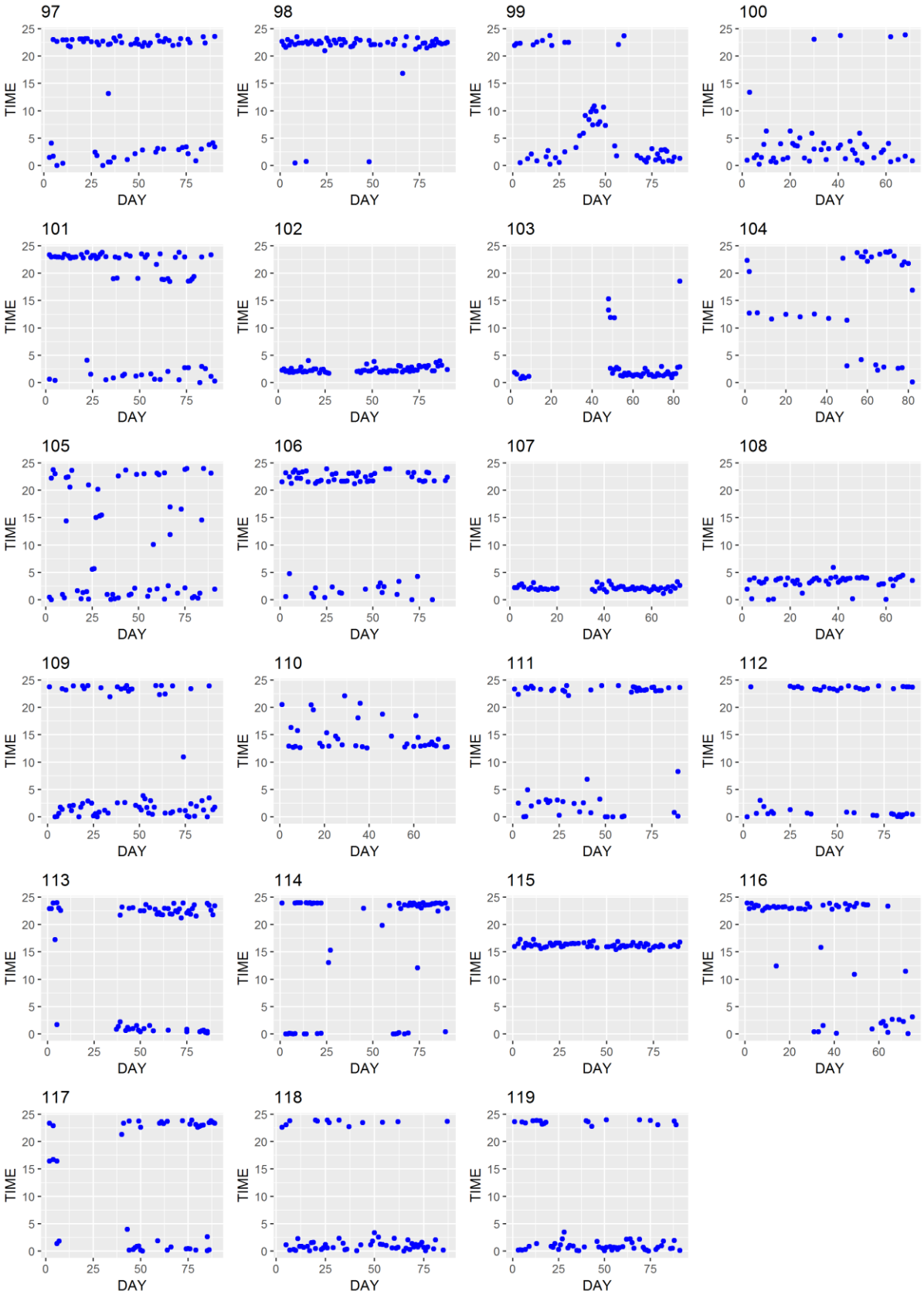

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THERAPEUTICS

Impact of non-adherence on the safety and efficacy of uric acid-lowering therapies in the treatment of gout

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Keywords febuxostat, hyperuricosuria, lesinurad, pharmacodynamics, pharmacokinetics, urate-lowering therapy

AIMS

Dual-urate-lowering therapy (ULT) with xanthine oxidase inhibitor and uricosuric medications is a treatment option for severe gout. Uricosuric agents can cause hyperuricosuria, a risk factor for nephrolithiasis and acute uric acid nephropathy. The aims of the present study were to simulate the relationship between suboptimal drug adherence and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving mono- and dual-ULTs.

METHODS

The impact of poor medication adherence was studied using two-compartment pharmacokinetic (PK) models based on published evidence, and a semi-mechanistic four-compartment pharmacodynamic (PD) model. The PKPD model was used to simulate mono and dual-ULT in gout patients with either under-excretion (lowered clearance) or overproduction of uric acid, with sub-optimal adherence modelled as either a single drug holiday of increasing duration or doses taken at random.

RESULTS

Simulation results showed a surge in urinary uric acid occurring when dosing is restarted following missed doses. For under-excreters taking a 20-day drug holiday, the addition of 200 mg (or 400 mg) lesinurad to 80 mg febuxostat increased the percentage of patients experiencing hyperuricosuria from 0% to 1.4% (or 3.1%). In overproducers, restarting ULTs following drug holidays of more than 5 days leads to over 60% of patients experiencing hyperuricosuria.

CONCLUSIONS

Suboptimal medication adherence may compromise the safety and efficacy of mono- and dual-ULTs, especially in patients with gout resulting from an overproduction of uric acid. Clinicians and pharmacists should consider counselling patients with respect to the risks associated with partial adherence, and offer interventions to improve adherence or tailor treatments, where appropriate.

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BJCP

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Uricosuric agents, used for the treatment of gout, increase the risk of hyperuricosuria and therefore also acute kidney injury.
- Adherence to urate-lowering therapies for treating gout is among the worst of any chronic disease.

WHAT THIS STUDY ADDS

- Restarting uricosuric treatment following a drug holiday increases the rate of episodic hyperuricosuria.
- Suboptimal medication adherence may compromise the safety and efficacy of mono- and dual-urate-lowering therapies, especially in patient groups such as those with gout resulting from an overproduction of uric acid.
- Clinicians and pharmacists should consider counselling patients with respect to the risks associated with partial adherence, and offer interventions to improve adherence or tailor treatments, where appropriate.

Introduction

Gout is a painful and disabling chronic disease which affects a large and increasing number of people and has proven difficult to treat [1]. Long-term treatment with urate-lowering therapies (ULTs) aims to reduce serum uric acid (sUA) concentrations to below the point of saturation (approximately 6 mg dl^{-1}). When treatment with a **xanthine oxidase** inhibitor (XOI) alone is unsuccessful, a uricosuric agent can be administered as a co-treatment [2]. Historically, the use of uricosuric agents for long-term therapy has been limited owing to possible hepatotoxicity (benzbromarone) and drug–drug interactions (**probenecid**). However, the **uric acid transporter-1** (URAT-1) inhibitor **lesinurad** has recently gained regulatory approved and is intended for long-term therapy in combination with an XOI (such as **allopurinol** or **febuxostat**) [3].

As they increase the renal excretion of UA, uricosuric agents such as lesinurad can cause hyperuricosuria (urinary excretion of UA ≥800 mg day^{-1} in men; ≥750 mg day^{-1} in women) [4]. High levels of urinary UA (uUA) can cause kidney damage, which may be acute – for example, through stone formation (nephrolithiasis) [5] or intrarenal obstruction (acute urate nephropathy) – or chronic, as in chronic (or gouty) nephropathy. Acute kidney injury can occur when UA concentrations in renal tubules reach supersaturation, which also depends on urine pH [6, 7]. Chronic nephropathy is thought to result from long-term hyperuricosuria, in which UA concentrations may be below supersaturation. The existence of chronic nephropathy remains controversial [8] but is supported by animal models and some epidemiological studies [9]. The harmful effects of UA on the kidney are a possible explanation of the association, in recent clinical trials, between lesinurad and an increase in the rate of raised serum creatinine and, for higher doses, with serious renal adverse events [10].

Adherence to ULT is known to be among the lowest of any chronic disease treatment [11, 12], with 70% of patients having a drug holiday of at least 60 days over 6 years. Poor adherence to allopurinol monotherapy is associated with lower treatment success rates [13]. While dual therapy increased response rates compared with monotherapy in clinical trials [14–16], an interruption in dosing (drug holiday) could result in high peaks in uUA concentration when treatment is restarted. Suboptimal implementation of the dosing regimen (e.g. late doses, skipping a dose or drug holidays) [17] may therefore increase the risk of renal adverse events caused by UA nephropathy.

The present study aimed to simulate the relationship between poor implementation of dosing and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving mono- and dual-ULT.

Methods

Strategy

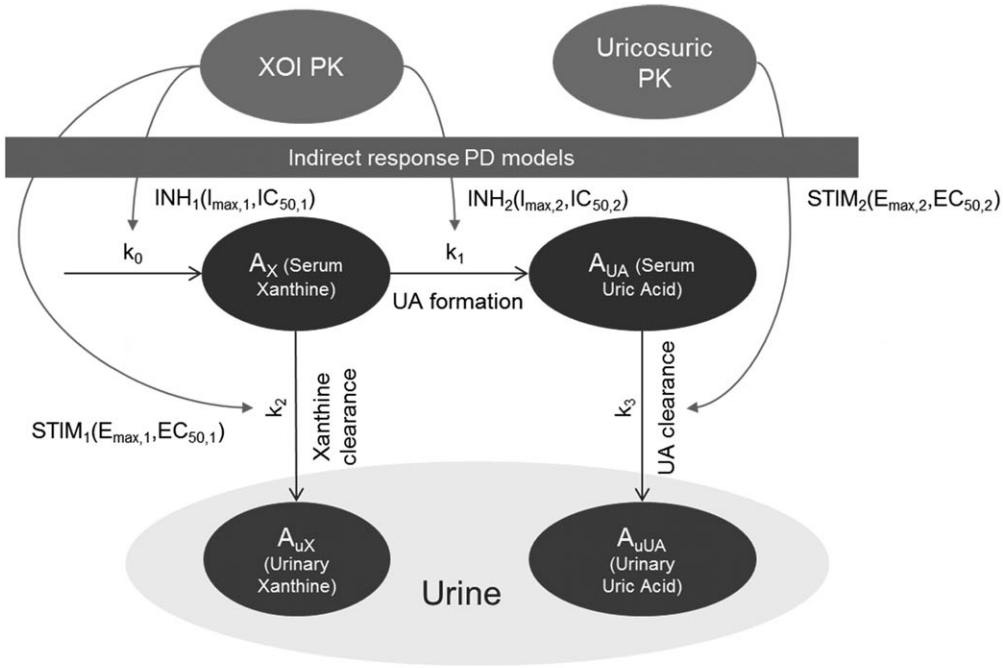
A semi-mechanistic pharmacokinetic–pharmacodynamic (PKPD) model, based on previous research on the systems pharmacology of the purine metabolic pathway [18], was developed to capture the pharmacology of ULTs (Figure 1). The system comprised four compartments utilizing a zero-order production rate (k_0) governing the formation of xanthine and first-order production rates characterizing its biotransformation to UA (k_1) and the elimination of xanthine (k_2) and UA (k_3) into the urine. These, in turn, were parameterized in terms of volumes and clearance terms.

The PD model characterizes the time course of sUA, uUA, xanthine and urinary xanthine. Two inhibitory indirect response (turnover) models were used to account for the effect of multiple doses of febuxostat on k_0 and k_1 [19]. A stimulatory indirect response [20] equation acting on the k_2 rate parameter was incorporated to model the increased xanthine renal clearance associated with febuxostat [21]. The clearance of UA upon multiple doses of lesinurad was modelled using a stimulatory indirect response equation acting on the k_3 rate parameter.

The system and drug PD model parameter estimates were obtained from the literature and other publicly available sources. As described below, some parameters values were taken directly from the literature, while others were estimated using nonlinear mixed-effects models and clinical trials data**.** The parameters required to characterize the pharmacodynamic model are given in Table 1.

PK

Two-compartment models with first-order absorption for febuxostat and lesinurad obtained from the literature [22, 23] were used to simulate typical and individual subject drug



System dynamics equations:

$$\frac{dA_X}{dt} = k_0 * INH_1 - k_1 * INH_2 * A_X - k_2 * STIM_1 * A_X \quad \text{(Eq. 1)}$$

$$\frac{dA_{UA}}{dt} = k_1 * INH_2 * A_X - k_3 * STIM_2 * A_{UA} \quad \text{(Eq. 2)}$$

$$\frac{dA_{uX}}{dt} = k_2 * STIM_1 * A_X \quad \text{(Eq. 3)}$$

$$\frac{dA_{uUA}}{dt} = k_3 * STIM_2 * A_{UA} \quad \text{(Eq. 4)}$$

No treatment steady-state:

$$k_2 = \frac{CLX}{VX} \quad \text{(Eq. 5)} \qquad k_3 = \frac{CLUA}{VUA} \quad \text{(Eq. 6)}$$

$$k_1 = \frac{k_3 * BUA}{BX * (M_{UA}/M_X)} \quad \text{(Eq. 7)} \qquad k_0 = \frac{k_1 * BX}{k_2 * BX} \quad \text{(Eq. 8)}$$

Pharmacodynamic models:

$$INH_1 = \frac{IC_{50,1}}{IC_{50,1} + C_F(t)} \quad \text{(Eq. 9)} \qquad INH_2 = \frac{IC_{50,2}}{IC_{50,2} + C_F(t)} \quad \text{(Eq. 10)}$$

$$STIM_1 = 1 + \frac{E_{max,1} * C_F(t)}{EC_{50,1} + C_F(t)} \quad \text{(Eq. 11)} \qquad STIM_2 = 1 + \frac{E_{max,2} * C_L(t)}{EC_{50,2} + C_L(t)} \quad \text{(Eq. 12)}$$

Figure 1

Diagrammatic and mathematical representations of the pharmacodynamics (PD) of dual-urate-lowering therapies. A_X and A_{UA} are the total time-varying amounts of xanthine and uric acid in serum respectively; A_{uX} and A_{uUA} are the total time-varying amounts of xanthine and uric acid in urine respectively; BUA, baseline amount of uric acid; BX, baseline amount of xanthine; $C_F(t)$ and $C_L(t)$ are the plasma concentrations of febuxostat of lesinurad, respectively; CLUA, renal clearance of uric acid; CLX, renal clearance of xanthine; $EC_{50,1}$ and $EC_{50,2}$ are drug concentrations corresponding to 50% of the maximum possible level of stimulation in the pharmacodynamic drug models $STIM_1$ and $STIM_2$ respectively; $E_{max,1}$ and $E_{max,2}$ are the maximum possible levels of stimulation in the pharmacodynamic drug models $STIM_1$ and $STIM_2$ respectively; $IC_{50,1}$ and $IC_{50,2}$ are the drug concentrations corresponding to 50% of the maximum possible level of inhibition in the pharmacodynamic drug models INH_1 and INH_2 respectively; INH1 and INH2 are inhibitory pharmacodynamic model drug functions; k_0, k_1, k_2 and k_3 are the rate parameters for the production of xanthine, xanthine to uric acid conversion, removal of xanthine to urine and removal of uric acid to urine, respectively; $STIM_1$ and $STIM_2$ are stimulatory pharmacodynamic model drug functions; VUA, volume of uric acid distribution; VX, volume of xanthine distribution

plasma concentration–time courses. The PK parameters, covariate effects and associated between-subject variability (BSV) are reproduced in Table 2.

PD

Parameters obtained from the literature. The mean rates of renal clearance of UA and xanthine (CLUA and CLX) in

Table 1

Pharmacodynamic (PD) parameters for febuxostat and lesinurad: literature and statistical estimates combined

Model	Name	Source	Parameter estimates		BSV (SD^2)	
System PD parameter	BX (mg)	Estimated	θ_1	8.94		NE
	VX (dl)	Estimated	θ_2	333		NE
	CLX (dl h^{-1})	Literature	θ_3	10.57		NE
	BUA (mg)	Estimated	θ_4	703		NE
	VUA (dl)	Estimated	θ_5	154		NE
	CLUA (dl h^{-1})	Literature	θ_6	4.11		NE
Febuxostat PD parameter	$E_{max,1}$	Assumed	θ_7	3		NE
	$EC_{50,1}$	Assumed	θ_8	0.001		NE
	$I_{max,1}$	Assumed	θ_9	1		NE
	$IC_{50,1}$	Estimated	θ_{10}	0.1320	η_3	0.2
	$I_{max,2}$	Assumed	θ_{11}	1		NE
	$IC_{50,2}$	Estimated	θ_{12}	0.00113	η_3	0.2
Lesinurad PD parameter[a]	E_0	Literature	θ_{13}	6.77		NE
	E^D_{max}	Literature	θ_{14}	−2.55	η_4	0.346
	b_{CrCl}	Literature	θ_{15}	0.564		NE
	EC^D_{50}	Literature	θ_{16}	0.0974		NE

BSV, between-subject variability; bCrCl, covariate effect parameter for creatinine clearance (ml min^{-1}); BUA, baseline amount of uric acid; BX, baseline amount of xanthine; CLUA, renal clearance of uric acid; CLX, renal clearance of xanthine; E_0, baseline sUA concentration; $EC_{50,1}$, drug concentration corresponding to 50% of the maximum possible level of stimulation $E_{max,1}$; $EC_{50}{}^D$, drug concentration corresponding to 50% of the maximum reduction in sUA; $E_{max,1}$, maximum possible level of stimulation for model $STIM_1$; $E_{max}{}^D$, maximum possible reduction in sUA; $I_{max,1}$, maximum possible level of inhibition in equation INH_1; $I_{max,2}$, maximum possible level of inhibition in equation INH_2; $IC_{50,1}$, drug concentration corresponding to 50% of maximum possible inhibition $I_{max,1}$; $IC_{50,2}$, drug concentration corresponding to 50% of maximum possible inhibition $I_{max,2}$; INH_1 (acting on k_0) and INH_2 (acting on k_1) are inhibitory pharmacodynamic model drug functions; k_0, k_1, k_2 and k_3, rate parameters for the production of xanthine, xanthine to uric acid conversion, removal of xanthine to urine and removal of uric acid to urine, respectively; NE, not estimated; SD, standard deviation; $STIM_1$ (acting on k_2), stimulatory pharmacodynamic model drug function; VUA, volume of uric acid distribution; VX, volume of xanthine distribution
Error model used: $\theta_i = \theta_u \exp(\eta_i)$
[a]Lesinurad: Parameters of the direct Emax model used to derive the corresponding parameters of the indirect response model in Figure 1

Table 2

Pharmacokinetic parameters for lesinurad and febuxostat

	Febuxostat		*Lesinurad*	
Parameter	**Estimate**	**BSV (CV%)**	**Estimate**	**BSV (CV%)**
CL/F_0 (dl h^{-1})[a]	49.3	18.3	69.9	63.4
b_CrCl	0.142	NA	0.322	NA
b_WT	0.155	NA		NA
Vc/F_0 (dl)[b]	322	NE	241	12.2
b_WT		NA	0.511	NA
Vp/F (dl)	222	NE	83	20.5
Q/F (dl h^{-1})	55.7	NE	4.48	NE
Ka (h^{-1})	13.7	176	0.69	121.7
Tlag (h)	0.23	NE	0.233	38.9

BSV, between-subject variability; CL/F, apparent clearance; CrCl, creatinine clearance rate; CV%, percentage coefficient of variation; Ka, first-order absorption; NA, not applicable; NE, not estimated; Q/F, intercompartmental clearance rate; Tlag, absorption time-lag; Vc/F, volume of the central compartment; Vp/F, volume of the peripheral compartment; WT, individual body weight (kg)
[a]Febuxostat: CL/F = CL/F_0 + b_CrCl*CrCl + b_WT*WT; Lesinurad: CL/F = CL/F_0 * (CrCl/87)^b_CrCl
[b]Lesinurad: VC/F = VC/F_0 * (WT/70)^b_WT

healthy volunteers, along with the BSV, were obtained using summary data from a phase I dose-escalation study of 154 healthy volunteers receiving febuxostat [24]. The reported average clearance in each group and standard deviations (see supplementary material) were used to obtain a weighted average estimate of population typical value and the BSV.

This trial also found that the CLX rate in subjects taking febuxostat, even at doses as low as 10 mg day^{-1}, increased three- to fivefold from baseline. This may result from the saturation of active transport processes responsible for the reabsorption of xanthine from the renal tubules [21]. A step function was assumed using a stimulatory E_{max} drug function (Equation 11 in Figure 1), with an $EC_{50,1}$ of 0.001 mg dl^{-1} (a low concentration associated with the 10 mg dose) and $E_{max,1}$ of 3.

A previous PD model of lesinurad used a direct-effect E_{max} model to relate the steady-state average plasma concentration of lesinurad to the individual's sUA concentration [23]. The parameters of the indirect model ($E_{max,2}$, $EC_{50,2}$) were derived from those given in the published direct model (E^D_{max} and EC^D_{50}) using the steady-state equations [19] (see supplementary material). The published model includes a covariate effect of creatinine clearance on the maximum reduction in UA, E^D_{max}. The stimulatory model drug function $STIM_2$ is given by Equation 12 in Figure 1, while the equations used to derive $E_{max,2}$ and $EC_{50,2}$ are given below.

$$E_{\max,2} = \frac{E_0}{E_0 - \left(E^D_{max}\left(\frac{CrCl}{87}\right)^{b_{crcl}}\right)} - 1$$

$$EC_{50,2} = \frac{E_{\max,2}\, EC^D_{50}}{E_0 / \left(E_0 - \left(\frac{E^D_{max}}{2}\right)\right) - 1} - EC^D_{50}$$

CrCl is the individual's creatinine clearance rate and E_0 is the baseline sUA concentration of trial participants used to derive the direct E_{max} model parameters.

Estimations using statistical modelling. All other parameters were estimated using nonlinear mixed-effects modelling and febuxostat phase I trial summary data on daily area under the plasma concentration–time curve (AUC) and 24-h urinary excretion of xanthine and UA [24] (see supplementary material). This was conditional on the clearance estimates and drug PD function parameters obtained directly from the literature in the previous section. A NONMEM dataset was created using the AUC and urinary data and the trial dosing schedule. Each value was an average across all individuals within a dose group and has, therefore, been replicated according to the number of subjects within the group, in order to weight by sample size.

The PKPD modelling was conducted using NONMEM 7.3 (ICON Development Solutions, Hanover, MD, USA) and the ADVAN6 routine for solving differential equations. The PD model was coded using the differential equations in Figure 1, where Equations 3 and 4 correspond directly to published data on 24-h urinary excretion [24]. However, additional sUA and serum xanthine accumulation compartments were added to compute the area under the concentration–time curve at 24-h intervals. Parameter estimation used the first-order algorithm, and different initial parameter estimates were tested. No random effects were included on system parameters estimated in NONMEM as the data points did not come from individual subjects. The inhibitory model drug functions INH_1 and INH_2 are given by Equations 9 and 10, respectively, in Figure 1.

In order to simplify the modelling procedure and make use of all available evidence, the statistical modelling was performed in two stages. The first stage used a published PKPD model of febuxostat that used an indirect inhibitory response model applied to a zero-order rate of UA production [22]. Rewriting UA production in the differential equations in our model as zero order, the literature parameter estimate of 0.0239 mg dl^{-1} was assumed for $IC_{50,2}$ and the remaining parameters were then estimated. In the second stage, the UA production was returned to being first order, such that it was a function of changing xanthine levels, and a new parameter estimate was made of $IC_{50,2}$ with all other parameters fixed.

Gout patient simulation model

We assumed that the febuxostat PD parameters estimated for healthy volunteers could be applied to gout patients with hyperuricaemia. However, systems parameters have been adjusted to be representative of a patient population. A typical patient sUA concentration was assumed to be 8.83 mg dl^{-1} (standard deviation 1.53) as this was the pretreatment sUA concentration for patients in the CRYSTAL (Combination Treatment Study in Subjects With Tophaceous Gout With Lesinurad and Febuxostat (NCT01510769)) trial, which compared febuxostat with lesinurad [25]. We considered two phenotypes – overproducers and under-excreters of UA [26, 27] – and modified the healthy subject system parameters accordingly. For overproducers, the amount of xanthine was scaled up, and for under-excreters the clearance of UA was scaled down in proportion to the sUA concentration (Table 3). This assumes the same volumes of distribution of xanthine and UA for patients as for healthy subjects.

Table 3

Individual system parameters for healthy subject and gout patients

Parameter	Healthy subject	Gout patient	
		Under-excreter	Overproducer
sUA (mg dl^{-1})		LN(8.83,1.53)	LN(8.83,1.53)
BX (mg)	θ_1	θ_1	θ_1*(BUA/θ_4)
VX (dl)	θ_2	θ_2	θ_2
CLX (dl h^{-1})	θ_3	θ_3	θ_3
BUA (mg)	θ_4	θ_5*sUA	θ_5*sUA
VUA (dl)	θ_5	θ_5	θ_5
CLUA (dl h^{-1})	θ_6	θ_6*(θ_4/BUA)	θ_6

BUA, baseline amount of uric acid; BX, baseline amount of xanthine; CLUA, renal clearance of uric acid; LN; Lognormal (mean, standard deviation); sUA, serum uric acid; VUA, volume of uric acid distribution; VX, volume of xanthine distribution

The model was used to simulate treatment with 120 days of ULT in a hypothetical cohort of 1000 patients with baseline characteristics corresponding to the CRYSTAL trial. The cohort was all male (95% were male in CRYSTAL) and baseline sUA, weight and age were assumed to be log-normally distributed, with mean and standard deviations taken from CRYSTAL (study 304) [28]. CrCl, calculated using the Cockcroft–Gault equation [29], overestimated the distribution of the trial participants. All estimates were reduced by 15 ml min^{-1}, and estimates below 30 ml min^{-1} were excluded to obtain a better representation of the trial population CrCl. The variability of drug effects in INH_1 and INH_2 could not be estimated and the IC_{50} parameters were assumed to vary according to η_3 with a coefficient of variation of 20%. Steady state was assumed following 30 days of simulated treatment and only the latter 60 days was used to derive results.

The outcomes of interest were the simulated time course of sUA and uUA concentrations, from which we estimated the proportion of patients responding (sUA below ≤5 mg dl^{-1} on day 120) and the proportion of patients experiencing hyperuricosuria (uUA ≥800 mg day^{-1} on any day). The normal range of the 24-h volume of urine is 0.5–1 ml kg^{-1} h^{-1} but is likely to be lower in the elderly [30, 31]. On this basis, a representative daily urine output for a 99 kg male of 15 dl was assumed for the purpose of estimating uUA concentrations. The soluble limit for UA is highly sensitive to urine pH, being much greater in alkaline than in acidic urine. For a given uUA concentration, the pH at which saturation would occur was estimated by fitting a linear model to literature data [32] to obtain: saturation pH = 6.36–40.96/[uUA].

Modelling adherence

The impact of poor adherence was studied for four different ULT options – namely, febuxostat 80 mg monotherapy and lesinurad 400 mg monotherapy, and febuxostat 80 mg combined with either lesinurad 200 mg or 400 mg. All are once-daily regimens, and it was assumed that doses are taken at the same time each day. Two types of poor adherence were considered. The first was a single drug holiday of increasing duration, from 1 day to 20 days, to assess the impact on uUA burden of restarting treatment following increasing lengths of drug holiday. The second assessed the impact of poor implementation on response rates and peaks in uUA by simulating doses taken completely at random, with a probability ranging from 1 to 0.1. For all dual-ULTs, missed doses included both drugs being missed simultaneously. A total of 30 simulations were conducted for each adherence scenario, which used random samples of the model parameter BSV, and the results were averaged over the range of simulation results.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [33], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [34, 35].

Results

The combined set of PD parameters and corresponding BSVs, which were derived or estimated from the literature, are presented in Table 1. Goodness-of-fit plots and visual predictive checks for the nonlinear mixed-effects modelling are provided as supplementary material.

With perfect adherence, uUA concentrations are maintained at low levels under the combined action of febuxostat 80 mg and lesinurad 200 mg (see plots for a typical patient in Figure 2). During a simulated drug holiday of 8 days, urinary concentrations increase as sUA concentrations return towards baseline. After dosing is restarted, peaks in uUA concentrations occur; for the typical under-excreter, the peak reached 39 mg dl^{-1}, which exceeds the typical average concentration for a healthy person (30 mg dl^{-1}). For the typical overproducer, the peak uUA concentration was 85 mg dl^{-1}, which exceeds the threshold for the typical average uUA concentration of an individual with hyperuricosuria (53 mg dl^{-1}). For the typical under-excreter, uUA concentrations after restarting treatment following an 8-day drug holiday could become supersaturated if the urinary pH was towards the acidic end of the normal range (pH <5.3; normal range 4.5–8.0). For the typical overproducer, peak uUA concentrations after restarting treatment are more likely to reach supersaturation at closer to the mid-point of the normal range, at approximately 5.9.

Across the population, increasing the length of a drug holiday increases the proportion of patients whose daily amount of UA excreted exceeds the threshold for hyperuricosuria upon restarting treatment (Figure 3). The proportion of patients with hyperuricosuria increases with increasing doses of lesinurad and is greatest for lesinurad 400 mg monotherapy. For under-excreters taking a 20-day drug holiday, the addition of 200 mg (or 400 mg) lesinurad to 80 mg febuxostat increased the percentage of patients experiencing hyperuricosuria from 0% to 1.4% (or 3.1%). In overproducers, restarting ULTs following drug holidays of more than 5 days led to over 60% of patients experiencing hyperuricosuria. In both patient groups, 1- or 2-day drug holidays were well tolerated compared with longer holidays, with only moderate increases in the rates of hyperuricosuria.

With perfect adherence, the proportion of patients treated to target (sUA ≤5 mg dl^{-1} on day 120) was greater than was observed in the CRYSTAL trial (Figure 4). However, success rates fell rapidly as an increasing proportion of doses were missed at random. For daily doses of febuxostat 80 mg, febuxostat 80 mg with lesinurad 200 mg, febuxostat 80 mg with lesinurad 400 mg and lesinurad 400 mg monotherapy, the success rates at 100% of doses taken in under-excreters were 87.2%, 94.5%, 96.0% and 15.4%, respectively. At 50% of doses taken at random, these success rates fell to 27.2%, 42.6%, 47.3% and 7.4%, respectively. The corresponding plots for overproducers are provided in the supplementary material.

Increasing the proportion of doses missed at random resulted in higher rates of hyperuricosuria due to randomly occurring drug holidays, especially in the presence of a uricosuric agent (Figure 4). The baseline daily uUA excreted in under-excreters was below healthy baseline levels and none of the simulated cohort showed hyperuricosuria in the absence of ULT. For dual-ULT with a uricosuric agent, however, randomly occurring drug holidays resulted in increasing

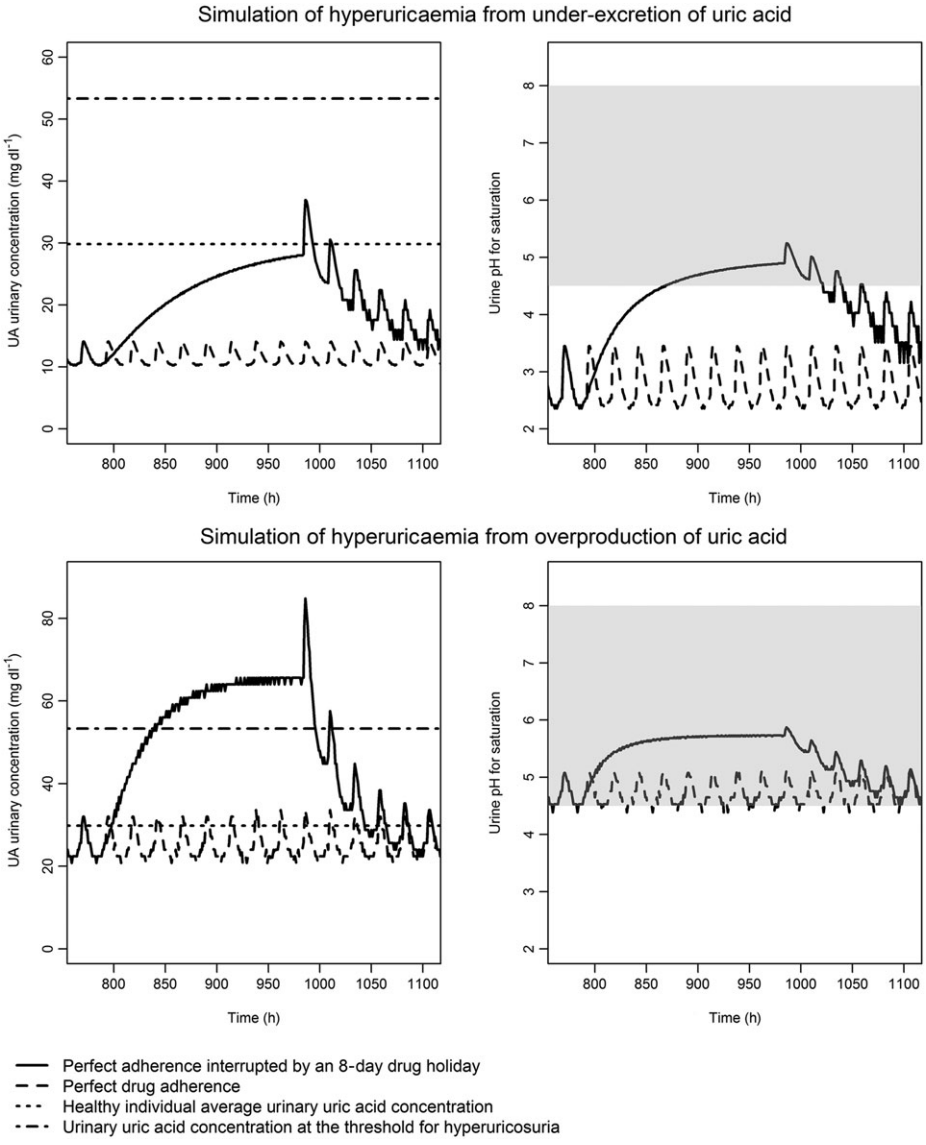


Figure 2

Simulated urinary uric acid (uUA) concentration and estimated pH for uric acid supersaturation, assuming a daily volume of urine of 15 dl. The simulated uUA concentration over time (left-hand panels) and the estimated pH at which this concentration would become supersaturated (right-hand panels). Imperfect adherence is modelled as an 8-day drug holiday (beginning on day 33). The shaded area represents the normal range for urine pH. The upper plots are the central estimates from the pharmacokinetic–pharmacodynamic model for a gout patient with hyperuricaemia from a reduced rate of uric acid clearance, and the lower plots for hyperuricaemia due to overproduction of xanthine. The urate lowering therapies used in these simulations were febuxostat 80 mg and lesinurad 200 mg, both once daily

rates of hyperuricosuria. For example, at 30% of doses taken, for febuxostat 80 mg with lesinurad 200 mg, febuxostat 80 mg with lesinurad 400 mg and lesinurad 400 mg monotherapy, the rates of hyperuricosuria were 1.3%, 3.2% and 4.9%, respectively.

Discussion

The use of uricosuric agents, either as monotherapy or in combination with an XOI, results in transient increases in uUA concentrations when dosing is restarted after a drug holiday. As a result, supersaturation of UA in urine can occur at pH values within the normal expected range, and therefore precipitation of UA in the renal tubules is more likely to occur during routine clinical practice. This effect is likely to be greater following a drug holiday from dual-ULTs than when starting treatment for the first time, where, as per the regulatory approval of lesinurad, patients must already have been taking an XOI. Specifically, our simulations indicated that peak uUA concentrations reach the threshold for supersaturation at a urinary pH of 5.3 for under-excreters and of 5.9 for overproducers, so that crystal formation may occur for a urinary pH at or below this level.

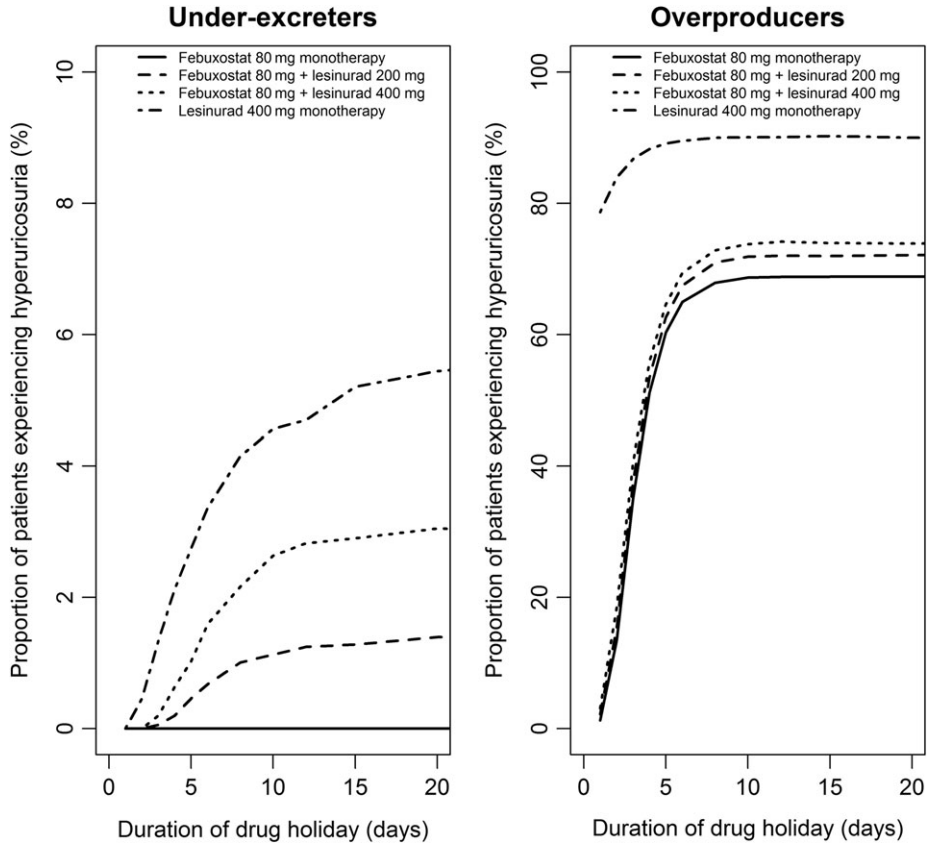


Figure 3

Proportion of simulated patients with 1-day hyperuricosuria following a single drug holiday taking place after 1 month of perfect adherence

Increasing the length of a drug holiday increased the proportion of patients whose daily amount of UA excreted exceeded the threshold for hyperuricosuria. The increase was more rapid for patients with overproduction, suggesting poorer drug forgiveness in this population. Treatment outcomes deteriorated rapidly as an increasing proportion of doses were missed at random. For under-excreters taking febuxostat 80 mg with lesinurad 200 mg, treatment-to-target rates fell by more than 50% when adherence reduced from 100% to 50%.

Approximately 90% of gout patients have hyperuricaemia caused by the renal under-excretion of UA [27]. In these cases, unless sUA concentrations are very high, or urinary volume is also lowered, uUA concentrations are likely to be lower than in healthy subjects. However, in simulations of drug holidays, after restarting dual-ULT, under-excreters had uUA concentrations raised to above the baseline levels for healthy subjects, and a small proportion exceeded the threshold for hyperuricosuria. For these patients to be at an increased risk of kidney damage, either a very low urinary output volume or a low urine pH (although still within the typical pH range) would probably be required. Urine pH is itself a primary predictor of nephrolithiasis as the solubility of UA is highly sensitive to small changes in pH [32].

Genetic disorders or a high-purine diet can be the cause of an overproduction of UA in the remaining 10% of gout patients [36]. Hyperuricosuria is a defining feature of UA overproduction [26], putting these patients at an increased risk of kidney injury without treatment. Our simulations suggest that in the case of very good medication adherence (≥80% of doses taken), dual-ULT would result in sustained reductions in sUA concentrations and also, therefore, uUA excreted. Regular drug holidays, however, would result in episodes in which uUA output was raised above its already high baseline. For this reason, uricosuric agents may not be appropriate for patients with hyperuricaemia due to UA overproduction [37], but no cautions are provided in the label for lesinurad [38].

To our knowledge, the present study was the first to investigate the relationship between medication adherence and the efficacy and safety of dual-ULT therapy for the treatment of gout. This was especially timely, given the recent approval of lesinurad for use in combination with an XOI in patients who have not responded on an XOI alone [39]. Our analysis benefited from having used a semi-mechanistic PD model which provides a level of complexity capable of capturing the nonsteady-state system dynamics. The effects of treatments were investigated in two distinct patient subgroups, the cause of hyperuricaemia being either an overproduction or under-excretion of UA. When comparing our simulation results with the findings from clinical trials, all of our perfect adherence simulations produced higher treatment success rates than had been reported in trials. Mathematical models such as this could be used to anticipate the problems resulting from suboptimal adherence, and potentially to help to identify the properties of more forgiving uricosuric agents.

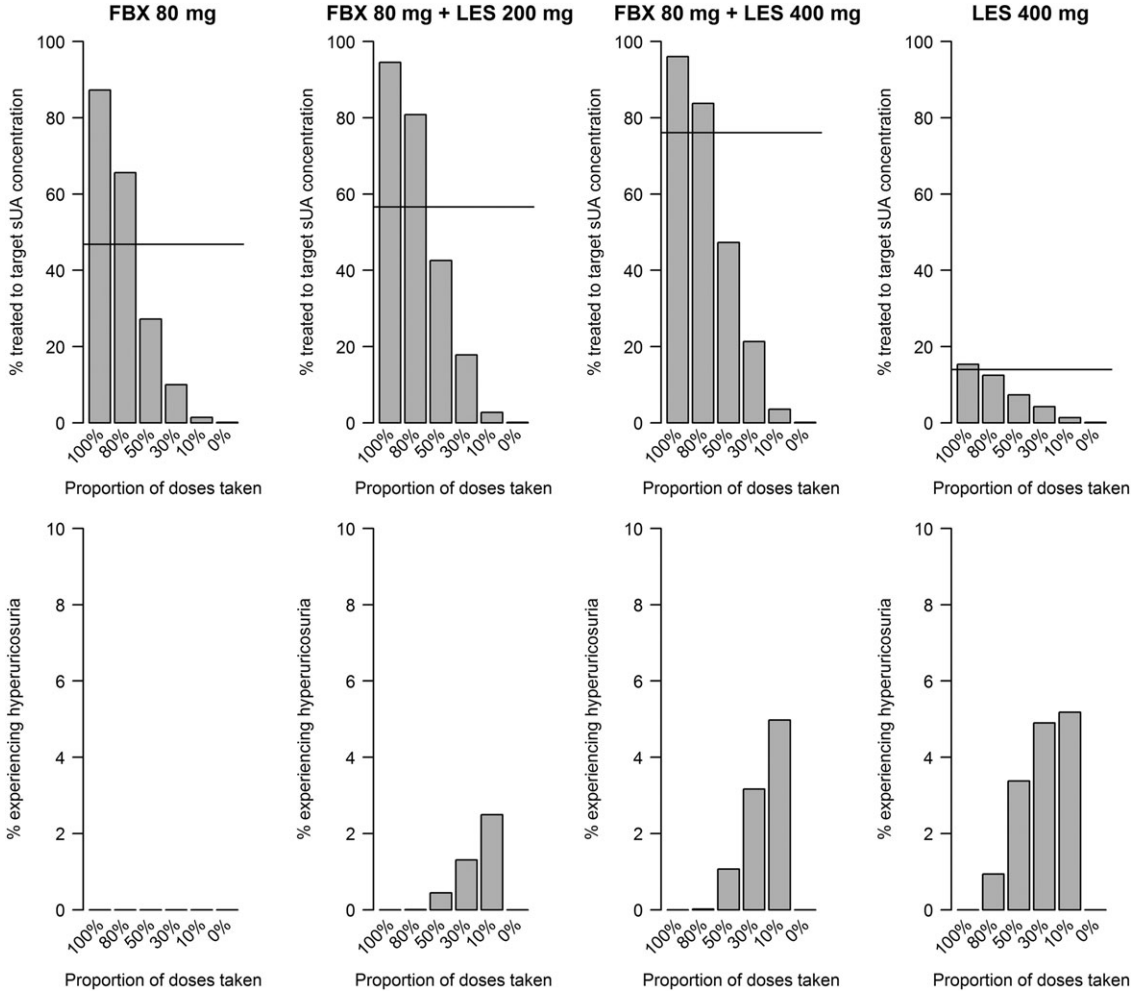


Figure 4

Treatment success rates (top row) and the proportion of patients experiencing 1-day hyperuricosuria during 2 months of urate-lowering therapy (bottom row). Horizontal lines provide the reference response rates for this treatment arm from the CRYSTAL trial comparing febuxostat and lesinurad, and Study 303 [25] for lesinurad 400 mg monotherapy. Results are for under-excreters of uric acid only; for overproducers, see the supplementary material. FBX: febuxostat; LES, lesinurad; sUA, serum uric acid

The main limitation of the study was our reliance on different sources of data from different populations. This limited our ability fully to quantify the variability and co-dependencies; nonetheless, we consider the model to be representative of existing dual-ULTs. We assumed that the nonrenal clearance of UA, which is responsible for around a third of total excretion [40], was negligible. Nevertheless, the contribution of nonrenal clearance relative to renal clearance will be lower in scenarios where a uricosuric agent is taken. Finally, the analysis focused on the XOI febuxostat but allopurinol is by far the most commonly prescribed ULT. However, we have no reason to believe that these findings do not extend to other XOIs (allopurinol) and uricosuric agents (probenecid and benzbromarone).

With the currently available ULTs, a large proportion of patients do not achieve sustained reductions in sUA to below saturation concentrations. The potential reasons for treatment failure include poor implementation of the treatment regimen (adherence), under-dosing, variation in treatment response and the underlying cause of hyperuricaemia [41]. Persistence with ULTs is known to be among the lowest of any chronic disease treatment [11, 12] and previous studies have provided evidence both for long [42] and short [43] drug holidays. The present study showed that renal safety may also be compromised by suboptimal medication adherence and highlights the need to improve adherence and adapt treatments to poorly adherent populations. This could include instructions on drug labelling [44], indicating a number of doses which can be missed based on the forgiveness of the drug to missed doses [45]. Such measures may improve the safety profile of future uricosuric agents, which for lesinurad may have influenced reimbursement decisions [46].

If gout patients adhere well to dual-ULT, then it appears to offer a means of further reducing sUA concentrations with a negligible increase in uUA output. However, regular drug holidays, which are commonplace among gout patients using ULTs, result in much lower rates of long-term treatment success and increased rates of hyperuricosuria when treatment is restarted. This has the potential to increase the risk of kidney damage in all patients, but especially those with

hyperuricaemia due to overproduction of UA. Further research is needed into the impact of adherence patterns on treatment success rates and kidney safety in order better to understand how dual-ULT could be used optimally in the treatment of hyperuricaemia in patients with gout. However, at present, counselling patients with respect to the risks associated with poor adherence should be advised.

Competing Interests

S.M. and E.S. are, or were, employees of Pfizer. The other authors have no competing interests to declare.

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Contributors

D.H.-M., E.S., S.M., S.L. and D.A.H. contributed substantially to the study conception or design, or the acquisition, analysis or interpretation of the data. D.H.-M. drafted the manuscript and E.S., S.M., S.L. and D.A.H. revised it critically for important intellectual content. D.H.-M., E.S., S.M., S.L. and D.A.H. gave final approval of the version to be published. D.A.H. agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13427/suppinfo

Appendix A Study information and data tables for TMX-99-001
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Economic Evaluation

Impact of Non-Adherence and Flare Resolution on the Cost-Effectiveness of Treatments for Gout: Application of a Linked Pharmacometric/Pharmacoeconomic Model

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ABSTRACT

Background: Dual urate-lowering therapy (ULT) with lesinurad in combination with either allopurinol or febuxostat is an option for patients with gout unsuccessfully treated on either monotherapy. Treatment failure is often a result of poor medication adherence. Imperfect adherence in clinical trials may lead to biased estimates of treatment effect and confound the results of cost-effectiveness analyses. **Objectives:** To estimate the impact of varying medication adherence on the cost effectiveness of lesinurad dual therapy and estimate the value-based price of lesinurad at which the incremental cost-effectiveness ratio is equal to £20,000 per quality-adjusted life-year (QALY). **Methods:** Treatment effect was simulated using published pharmacokinetic-pharmacodynamic models and scenarios representing adherence in clinical trials, routine practice, and perfect use. The subsequent cost and health impacts, over the lifetime of a patient cohort, were estimated using a bespoke pharmacoeconomic model. **Results:** The base-case incremental cost-effectiveness ratios comparing lesinurad dual ULT with monotherapy ranged from £39,184 to £78,350/QALY gained using allopurinol and £31,901 to £124,212/QALY gained using febuxostat, depending on the assumed medication adherence. Results assuming perfect medication adherence imply a per-quarter value-based price of lesinurad of £45.14 when used in dual ULT compared with allopurinol alone and £57.75 compared with febuxostat alone, falling to £25.41 and £3.49, respectively, in simulations of worsening medication adherence. **Conclusions:** The estimated value-based prices of lesinurad only exceeded that which has been proposed in the United Kingdom when assuming both perfect drug adherence and the eradication of gout flares in sustained treatment responders.

Keywords: adherence, cost-effectiveness analysis, economic evaluation, gout, pharmacometrics

Introduction

Gout is a painful and disabling condition and one that is relatively common in developed countries [1]. When the concentration of uric acid in serum exceeds the saturation point (hyperuricemia), it may crystallize in peripheral joints and surrounding tissues, which can lead to gout symptoms. Treatment guidelines recommend that serum uric acid (sUA) be reduced to less than a target of either 5 or 6 mg/dl [2] to allow for the dissolution of monosodium urate crystals from affected joints [3]. Besides preventing the progression to more severe disease (e.g., tophaceous gout) and, albeit controversially, reducing the potential of cardiovascular and renal comorbidities, long-term treatment reduces and may eventually eliminate the painful flares that characterize gout [4].

The mainstay of therapy is the xanthine oxidase inhibitor (XOi) allopurinol; however, a large proportion of patients are not treated successfully [5]. Treatment failure has been postulated to result from suboptimal dosing or nonadherence, or a combination of both over the long (often symptom-free) treatment period [6]. Medication adherence is known to be especially poor for urate-lowering therapies (ULTs) [7,8] and, if not recognized and managed appropriately, can result in unnecessary switching to more expensive ULTs such as febuxostat or combined XOi therapy with a uricosuric, such as lesinurad.

Medication adherence can be decomposed into three distinct phases: 1) the initiation of treatment, 2) the degree to which a patient's dose-taking matches the prescribed regimen while nominally adhering (implementation), and 3) the discontinuation

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of treatment (persistence) [9]. Persistence can often be accounted for in the analysis of clinical trials and although implementation can be recorded using electronic pill dispensers [10], this is seldom done in clinical trials. Imperfect implementation may lead to biased estimates of treatment effect [11] and confound the results of cost-effectiveness analyses.

Key influences on the decisions not to recommend lesinurad or febuxostat as first-line treatment in the United Kingdom were the uncertainties in their effects on acute flares and their lack of cost effectiveness as estimated using economic modeling [12–14]. Nevertheless, an important limitation of conventional economic models is their limited capacity to account for the impact of poor implementation (i.e., missed or delayed doses) on health outcomes and costs. Pharmacokinetic-pharmacodynamic (PKPD) models together describe the relationship between doses taken and the observed drug effects via the time course of drug concentration. By specifying variable dose implementation as an input function, this offers a method for predicting the influence of nonadherence on the clinical effectiveness and cost effectiveness of drug treatments [15].

The aim of this study was to estimate the impact of varying dose implementation and persistence on the cost effectiveness of the uricosuric lesinurad as an add-on treatment in patients nonresponsive on either allopurinol or febuxostat alone.

Methods

A published PKPD model of lesinurad and febuxostat [16] was extended to include allopurinol and used to simulate the time course of sUA concentration among patients with differing adherence to the dosing regimen. A bespoke pharmacoeconomic model was developed, with reference to previous economic evaluations of ULTs [17,18], and linked to the PKPD model to estimate the costs and quality-adjusted life-years (QALYs) accrued over patients' lifetimes for different treatment and adherence scenarios. All PKPD simulations were performed using NONMEM 7.3 (ICON Development Solutions, Hanover, MD) [19].

ULT PKPD Model

The lesinurad and febuxostat PKPD model [16] was used without modification. A separate study presenting PKPD modeling of allopurinol [20] was used to obtain the PK relationships and associated parameter estimates that were also used without modification. Nevertheless, because a direct-effect sigmoid E_{max} PD model had been used to relate sUA concentrations to oxipurinol (allopurinol's active metabolite) plasma concentrations, a semimechanistic indirect-response model [21] was derived from the estimated parameters. This allows for the expected delay between the PK and PD of XOis [16] and is better suited to modeling patterns of imperfect adherence. Details of the necessary steps are given in the Supplemental Materials found at doi:10.1016/j.jval.2018.06.002, where tables of all PKPD model parameters are also provided.

Patient Population

A cohort of 500 patients with gout was created for simulations based on the population characteristics of the recently completed CLEAR 1 clinical trial of lesinurad [22]. Individual age and weight, which account for some of the variability in PKPD model parameters, were sampled at random from log-normal distributions using CLEAR 1 mean body weight of SD = 23 kg and age of SD = 11 years. Creatinine clearance, a covariate in the PK models, was estimated using the Cockcroft-Gault equation [23]. The resulting distribution was reduced by 15 ml/minute and estimates less than 30 ml/minute were excluded (as per protocol criteria) to adjust for the underlying degree of renal impairment and obtain an approximation of the broad creatinine clearance categories available for the CLEAR 1 trial population [22]. In accordance with gout epidemiology, patients were also assigned to have gout resulting from either an overproduction or an underexcretion of uric acid in the ratio of 1:9 [24,25].

PKPD Simulation Modeling

The PKPD model was used to generate 12 sUA concentration distributions from the patient cohort using 4 ULT options and 3 models of medication adherence. These 12 distributions then provide the treatment effectiveness inputs in subsequent pharmacoeconomic modeling. We have considered two scenarios for first-line ULT, these being patients with gout eligible for ULT being prescribed either allopurinol 300 mg or febuxostat 80 mg once daily. The recommended dose for febuxostat is 80 mg [12], and 300 mg is the most commonly used dose for allopurinol [26]. If a patient did not achieve a reduction in the 6 mg/dl target on a monotherapy, then dual therapy was used as second-line treatment with lesinurad 200 mg once daily.

The first method of modeling adherence (adherence model 1) represents the hypothetical best-case scenario in which all patients persist with treatment and implement perfectly. The second and third adherence models are broadly intended to represent a phase 3 clinical trials setting and a routine practice, respectively. With the second adherence model (adherence model 2), treatment persistence was based on discontinuation observed in lesinurad pivotal trials [18], and patients implemented doses randomly according to a probability that was sampled from a beta(2.4,0.6) distribution, such that the population average was 80% of doses with an SD of 20%. The third adherence model (adherence model 3) also used treatment persistence from lesinurad pivotal trials [18] and dose implementation sampled from a beta(2.6,2.6) distribution, such that the population average was 50% of doses with an SD of 20%.

For each ULT option and adherence model, treatment in each patient was simulated for 120 days, with the initial 30 days used only to achieve steady state on first-line monotherapy. On day 30, those patients in the dual ULT simulation scenarios whose sUA concentration was higher than 6 mg/dl had lesinurad as second-line treatment added to their daily dosing schedule. Days 30 to 60 were then used to establish those patients who were newly switched to dual therapy at steady state. The final days from 60 to 120, for all four ULT options, provided the treatment effects that drive the pharmacoeconomic model, including the distribution across sUA concentration categories on day 120 as well as the proportion of days for which each patient was below the target of 6 mg/dl. The sUA concentrations were divided into four categories (<6, 6 to <8, 8 to <10, and ≥10 mg/dl), which provide the distribution across sUA substates in the pharmacoeconomic model and are static throughout pharmacoeconomic model simulations (Fig. 1).

Pharmacoeconomic Model

Overview

Consistent with previous economic evaluations of gout treatments [17,18], we used a Markov state transition model to estimate lifetime costs and QALYs in a cohort of patients eligible for ULT. Although treatment was simulated for individual patients in the PKPD model, the economic model used a cohort approach. The model adopts the perspective of the National Health Service in the United Kingdom and has a cycle length of 3 months and a lifetime (50 years) time horizon. Costs and QALYs were both discounted at a rate of 3.5% per annum [27]. The economic model was implemented in R statistical software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) [28].

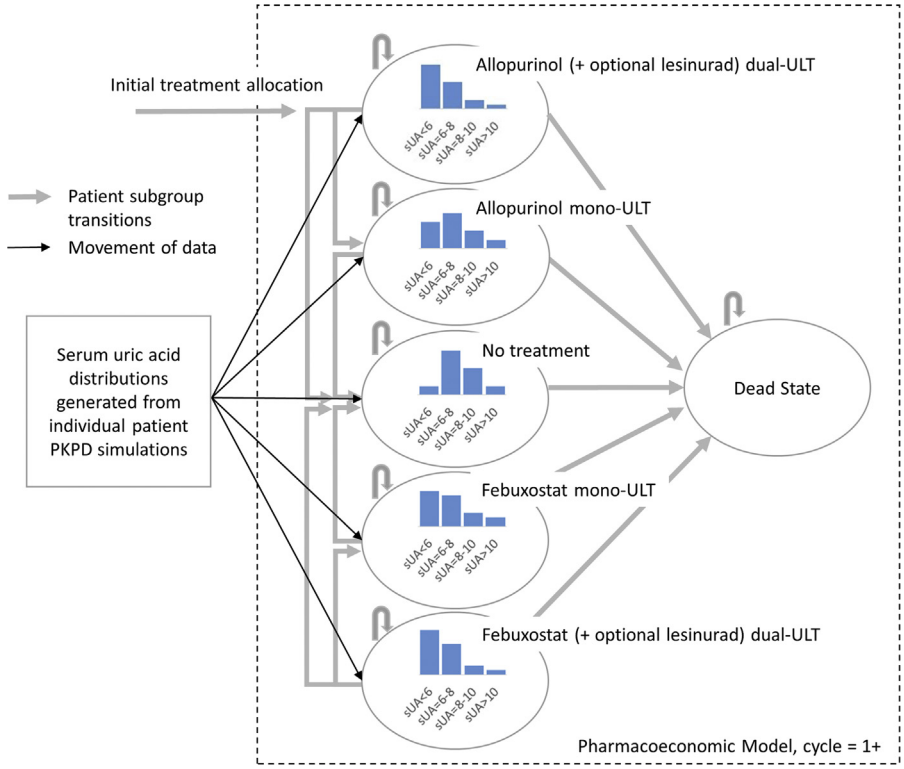

Fig. 1 – Illustration of the structure of the pharmacoeconomic model showing patient subgroup transitions and the sUA distributions set by PKPD simulations. In this example, the model estimates the lifetime costs and QALY gains resulting from all patients being initially allocated to allopurinol with optional lesinurad dual ULT. This process is repeated using three adherence models and four initial ULT allocations to compare treatments options. PKPD, pharmacokinetic-pharmacodynamic; QALY, quality-adjusted life-year; sUA, serum uric acid; ULT, urate-lowering therapy.

Treatments and transitions

The Markov model consisted of six main health states that included four possible ULT options, no treatment, and an absorbing dead state. Within each of the five treatment options, patients were distributed between the 4 sUA concentration substates such that there was a total of 21 model states. The distribution across the sUA concentration substates for each treatment depended on the level of dose implementation and was generated using the PKPD model (Fig. 1).

In each pharmacoeconomic simulation, all patients are initially allocated to a single ULT option, where they remain unless they discontinue (nonpersistence). A proportion of patients on monotherapy could, therefore, transition to the no-ULT health state and a proportion of those on a dual therapy could transition to either the no-ULT health state or the XOi monotherapy health state if only discontinuing the uricosuric component. It was assumed that no patients will discontinue a XOi while continuing to take lesinurad because it is not licensed as a monotherapy [29]. The patients transitioning to either a no-ULT or a monotherapy (Fig. 1) were redistributed according to the sUA concentration distribution of this new treatment. Per-cycle treatment discontinuation probabilities were calculated using the results of clinical trials of febuxostat [30] and lesinurad [18]. After every cycle, a proportion of patients transitioned to the death state according to all-cause mortality probabilities derived from life tables for England and Wales in 2015 [31].

Gout flares

Sufferers of gout experience acute episodes of intense pain and inflammation known as flares whose frequency is directly proportional to sUA concentration [32]. Clinical trials of newer ULTs have not demonstrated a reduction in the frequency of gout flares when compared with allopurinol; economic evaluations have instead relied on observational data to estimate the reduction in flares resulting from reduced sUA concentrations.

In the base-case analysis, we modeled the frequency of gout flares within sUA concentration substates using the results of a cross-sectional survey in which 172 out of 620 participants provided both a most recent sUA measurement and a number of flares in the previous 12 months [33]. This was used to derive quarterly flare frequency distributions across five categories (0, 1-2, 3, 4-5, $\geq$6) for each sUA concentration substate assuming a constant rate of occurrence. These survey data, however, reporting a single sUA measurement may not be representative of patients who maintain low sUA concentrations. To assess the potential quality of life and cost implications of a trial being able to demonstrate clear benefits in sustained responders and therefore not relying solely on survey data, we developed a second, alternative, model of flare reduction. This assumed that patients with gout who sustain an sUA concentration of less than 6 mg/dl on more than 80% of days will become flare-free after 2 years, whereas the survey data flare rate distributions are applied to all other patients. This is broadly in line with a study that found that 86% of patients whose average sUA concentration was less than 6 mg/dl had no recurrent gouty attacks during the 2-year follow-up [3,34].

The initiation of ULT is known to initially result in an increase in the risk of experiencing gout flares [3] that is proportional to the extent of sUA reduction [17,35]. This was modeled by fitting a linear model to data on the mean number of flares during the first

3 months of treatment and treatment response rate for four different ULTs [17]. The predicted number of flares for a zero response rate and for a response rate after treatment was used to calculate a multiplier that is used to increase the baseline number of quarterly flares. This multiplier was applied to every flare frequency category in the first model cycle only; further details are provided in the Supplemental Materials.

Costs

The daily cost of lesinurad 200 mg was assumed to be £0.93 [13], allopurinol 300 mg £0.03, and febuxostat 80 mg £0.87 [36]. We assumed that for all patients, gout flare prophylaxis was provided by 0.5 mg colchicine daily for the full 6 months as recommended [2]. This would require 200 tablets at a cost of £28.56 and it was assumed that unused doses would be discarded.

The average cost of treating a flare was assumed to be £43.78 (2016 prices) and the proportion of flares requiring treatment to be 26.7% [18]. The National Institute for Health and Care Excellence (NICE) recommends quarterly monitoring of sUA concentration and renal function during the first year of ULT and annually thereafter. The estimated average cost of a treatment monitoring visit for lesinurad (£153.07) was assumed for all treatments. Although monitoring may vary between treatments (e.g., liver function tests with febuxostat and urinary uric acid tests with lesinurad [37]), in the absence of data on the frequency of such testing no difference in overall cost was assumed.

Health state utilities

A literature review and a range of trial-derived health state utility values are presented in recent reports submitted to NICE as part of the reappraisal of lesinurad in the United Kingdom [18]. As in these published reports, we adopt a base case that uses the mean six-dimensional health state short form scores in CLEAR 1 and CLEAR 2 clinical trials [22,38] stratified by flare frequency. These annual health state utilities, stratified according to flare frequency, were used to calculate an average decrement of 0.043 utilities per flare. This was used to reduce the utility of those experiencing flares from the reference health state utility of 0.768 for patients with gout experiencing no flares for 12 months. We did not model any impact of sUA concentration on mortality, on the basis of a lack of substantiated evidence of such an association [39].

Sensitivity Analyses

A total of 500 iterations of the PKPD model were conducted, each simulating 120 days of treatment in 500 patients. Each iteration produced an sUA concentration distribution that provided inputs to 10 pharmacoeconomic model simulations, resulting in a total of 5000 simulations. The mean incremental costs and QALYs are presented in later sections and the distribution of these results in the cost-effectiveness plane is given in Appendix D in Supplemental Materials found at doi:10.1016/j.jval.2018.06.002.

Results

PKPD Model Results

The results of the PKPD simulations (Table 1) suggest that febuxostat 80 mg could be nearly 100% effective in patients who adhere perfectly to their dosing regimen, and only a small number of patients would be eligible for dual ULT with lesinurad. For allopurinol 300 mg, even with perfect adherence, only 57% of patients were estimated to achieve the sUA concentration target of less than 6 mg/dl, but this is increased to 83% with the addition of lesinurad. As expected, the proportion of patients achieving target concentrations fell with worsening adherence across all treatments, whereas the proportion eligible for dual ULT rose. The rank of treatments by response rate remained constant across the three adherence scenarios. Suboptimal adherence has a larger impact on sustained response (<6 mg/dl on >80% of days) than the single time point response (day 120).

Table 1 – Distribution of patients across sUA concentration categories after ULT with varying levels of dose implementation using 500 PKPD simulations

ULT option*	Percentage of subjects in sUA category (mg/dl) at day 120				Percentage <6 mg/dl on ≥80% of days	Percentage receiving lesinurad
	<6	6–<8	8–<10	≥10		
100% dose implementation						
ALL 300 mg	57	40	3	0	56.6	NA
ALL 300 mg + optional lesinurad 200 mg	83	17	0	0	83.0	43.7
FBX 80 mg	97	3	0	0	97.3	NA
FBX 80 mg + optional lesinurad 200 mg	99	1	0	0	99.3	2.6
80% dose implementation						
ALL 300 mg	41	49	10	0	35.7	NA
ALL 300 mg + optional lesinurad 200 mg	63	33	5	0	52.5	59.6
FBX 80 mg	81	15	4	0	71.3	NA
FBX 80 mg + optional lesinurad 200 mg	84	14	3	0	74.6	18.4
50% dose implementation						
ALL 300 mg	19	53	24	3	12.7	NA
ALL 300 mg + optional lesinurad 200 mg	36	46	16	2	21.0	80.1
FBX 80 mg	49	36	14	1	25.1	NA
FBX 80 mg + optional lesinurad 200 mg	53	34	12	1	30.2	49.5
No treatment	0	21	57	22	0	NA

ALL, allopurinol; FBX, febuxostat; NA, not applicable; PKPD, pharmacokinetic-pharmacodynamic; sUA, serum uric acid; ULT, urate-lowering therapy.

* Allopurinol 300 mg once daily; FBX 80 mg once daily; lesinurad 200 mg once daily.

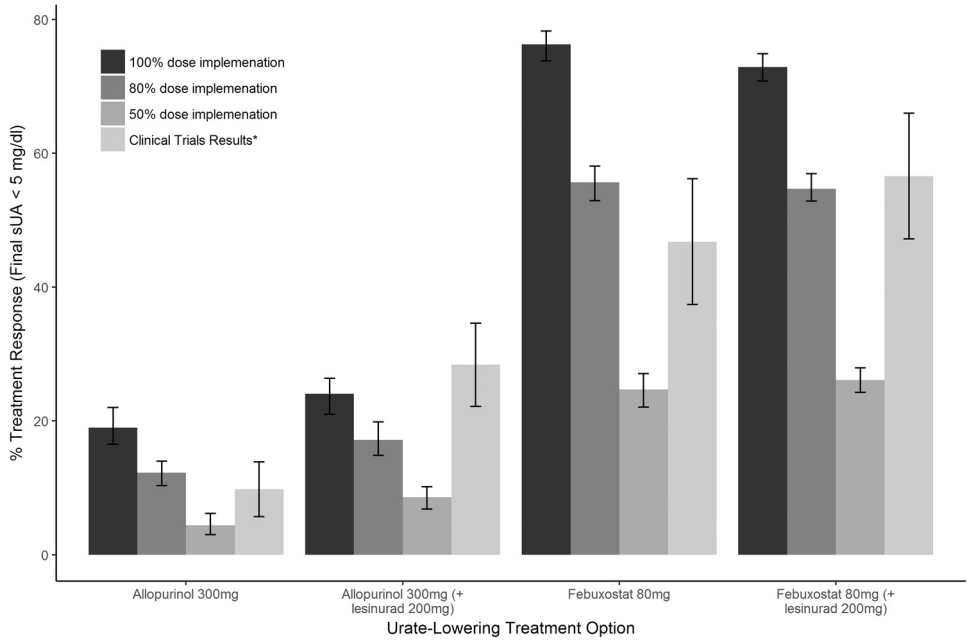

Fig. 2 – Simulated treatment response rates for three adherence models and the treatment response in the corresponding treatment arm in clinical trials. The threshold for treatment response has been defined as 5 mg/dl. Clinical trial results are at 6 months and assume nonresponder imputation for patients who discontinued. Discontinuation rates were also applied to simulated results assuming equal probability of discontinuation among responders and nonresponders. Confidence intervals on PKPD simulations account for patient heterogeneity and parameter random effects, but not uncertainty in parameter estimates or within individual residual variability. *Allopurinol 300 mg and allopurinol 300 mg + lesinurad 200 mg response rate is 9.8% and 28.4%, respectively, from CLEAR 1 and CLEAR 2 trials; febuxostat 80 mg and febuxostat 80 mg + lesinurad 200 mg response rate is 46.8% and 56.6%, respectively, from the CRYSTAL trial. PKPD, pharmacokinetic-pharmacodynamic; sUA, serum uric acid.

Figure 2 provides a comparison between the results of pivotal clinical trials and the simulated response rates. Treatment response is defined as sUA less than 5 mg/dl (because <6 mg/dl was unavailable for all treatments), and the simulated results have been adjusted to account for treatment discontinuation at 6 months in the corresponding trial arm to provide a more appropriate comparison. Although our simulated results are broadly in line with the results from pivotal trials, the differences may be difficult to interpret because of the many factors that have not been accounted for in the PKPD modeling.

Economic Model Results

Table 2 presents the simulated total costs and QALYs accrued over the lifetime of the patient cohort, with allopurinol 300 mg as first-line and lesinurad add-on as second-line ULT. In the base-case method of calculating flare frequency and with perfect medication adherence (adherence model 1), the incremental cost-effectiveness ratio (ICER) of allopurinol with optional lesinurad dual ULT compared with allopurinol alone was £39,184/QALY gained. This is considerably higher than the £20,000/QALY threshold of cost effectiveness used in the United Kingdom. The ICER increased to £47,848 and £78,350/QALY gained in adherence models 2 and 3, respectively, in which patients discontinue treatment over time and have implementation rates of 80% and 50%, respectively. The ICERs were lowered using the alternative flare frequency methodology to £19,019, £31,803, and £77,903/QALY gained across adherence models 1, 2, and 3, respectively.

Patients not eligible for first-line treatment with allopurinol may be prescribed febuxostat and, if not adequately controlled, may subsequently be offered dual ULT with lesinurad. In both perfect adherence scenarios (Table 3), the ICER of febuxostat with optional lesinurad dual ULT compared with febuxostat alone was £31,901 and £15,376/QALY gained in the base-case and alternative flare frequency models, respectively. The simulations suggest that it would be more cost-effective to provide lesinurad to non-responders on febuxostat than on allopurinol monotherapy, assuming perfect adherence. Nevertheless, in adherence models 2 and 3, it appears that lesinurad is more cost-effective with allopurinol than with febuxostat.

Value-Based Price

For each probabilistic economic simulation we calculated the price of lesinurad at which the ICER comparing dual ULT to allopurinol or febuxostat monotherapy is equal to the £20,000/QALY threshold (value-based price). The resulting distributions of prices are plotted in Figure 3 along with a line indicating the price of lesinurad originally proposed for the UK market [18]. Using the base-case methodology for flare frequency, very few value-based prices of lesinurad are more than, or equal to, the price originally proposed for the UK market, regardless of the adherence model that was assumed. The simulations resulting in the highest proportion of value-based prices greater than, or equal to, the proposed price used the alternative flare frequency methodology and required adherence models 1 (53% vs. allopurinol and 61% vs. febuxostat). In scenarios of imperfect adherence, the value-based prices of lesinurad often fall below 0. This is primarily due to dual ULT being associated with lower rates of treatment discontinuation (an assumption we used on the basis of clinical trial data),

Table 2 – Economic model results in patients with allopurinol 300 mg monotherapy as first-line treatment and add-on lesinurad 200 mg in nonresponders as second-line treatment

ULT treatment option*	Lifetime cost (£)	Lifetime QALYs	ΔCost vs. ALL (£)	ΔQALYs vs. ALL	ICER vs. ALL (£)
Base-case flare frequency methodology					
Adherence model 1					
ALL 300 mg	3,757	13.36	–	–	–
ALL 300 mg + optional lesinurad 200 mg	6,352	13.42	2,594	0.066	39,184
Adherence model 2					
ALL 300 mg	2,246	13.22	–	–	–
ALL 300 mg + optional lesinurad 200 mg	4,068	13.26	1,822	0.038	47,848
Adherence model 3					
ALL 300 mg	2,277	13.19	–	–	–
ALL 300 mg + optional lesinurad 200 mg	4,796	13.22	2,519	0.032	78,350
Alternative flare frequency methodology					
Adherence model 1					
ALL 300 mg	3,614	13.49	–	–	–
ALL 300 mg + optional lesinurad 200 mg	6,139	13.63	2,525	0.133	19,019
Adherence model 2					
ALL 300 mg	2,221	13.24	–	–	–
ALL 300 mg + optional lesinurad 200 mg	4,024	13.30	1,804	0.057	31,803
Adherence model 3					
ALL 300 mg	2,277	13.19	–	–	–
ALL 300 mg + optional lesinurad 200 mg	4,784	13.23	2,507	0.032	77,903

Note. The ICER was calculated as the difference in lifetime costs divided by the difference in lifetime QALYs. Costs and effects were discounted at 3.5%.

ALL, allopurinol; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; ULT, urate-lowering therapy.

* Adherence model 1: perfect adherence to dosing regimen; adherence model 2: treatment discontinuation and 80% average implementation; adherence model 3: treatment discontinuation and 50% average implementation.

Table 3 – Economic model results in patients with febuxostat 80 mg monotherapy as first-line treatment and add-on lesinurad 200 mg in nonresponders as second-line treatment

ULT treatment option*	Lifetime cost (£)	Lifetime QALYs	ΔCost vs. FBX (£)	ΔQALYs vs. FBX	ICER vs. FBX (£)
Base-case flare frequency methodology					
Adherence model 1					
FBX 80 mg	9,157	13.46	–	–	–
FBX 80 mg + optional lesinurad 200 mg	9,311	13.46	154	0.005	31,901
Adherence model 2					
FBX 80 mg	5,094	13.28	–	–	–
FBX 80 mg + optional lesinurad 200 mg	5,803	13.29	709	0.010	74,136
Adherence model 3					
FBX 80 mg	5,122	13.23	–	–	–
FBX 80 mg + optional lesinurad 200 mg	7,015	13.25	1,893	0.015	124,212
Alternative flare frequency methodology					
Adherence model 1					
FBX 80 mg	8,884	13.70	–	–	–
FBX 80 mg + optional lesinurad 200 mg	9,034	13.71	149	0.010	15,376
Adherence model 2					
FBX 80 mg	5,024	13.34	–	–	–
FBX 80 mg + optional lesinurad 200 mg	5,724	13.36	700	0.017	40,078
Adherence model 3					
FBX 80 mg	5,151	13.23	–	–	–
FBX 80 mg + optional lesinurad 200 mg	7,031	13.25	1,880	0.022	86,870

Note. The ICER was calculated as the difference in lifetime costs divided by the difference in lifetime QALYs. Costs and effects were discounted at 3.5%.

FBX, febuxostat; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; ULT, urate-lowering therapy.

* Adherence model 1: perfect adherence to dosing regimen; adherence model 2: treatment discontinuation and 80% average implementation; adherence model 3: treatment discontinuation and 50% average implementation.

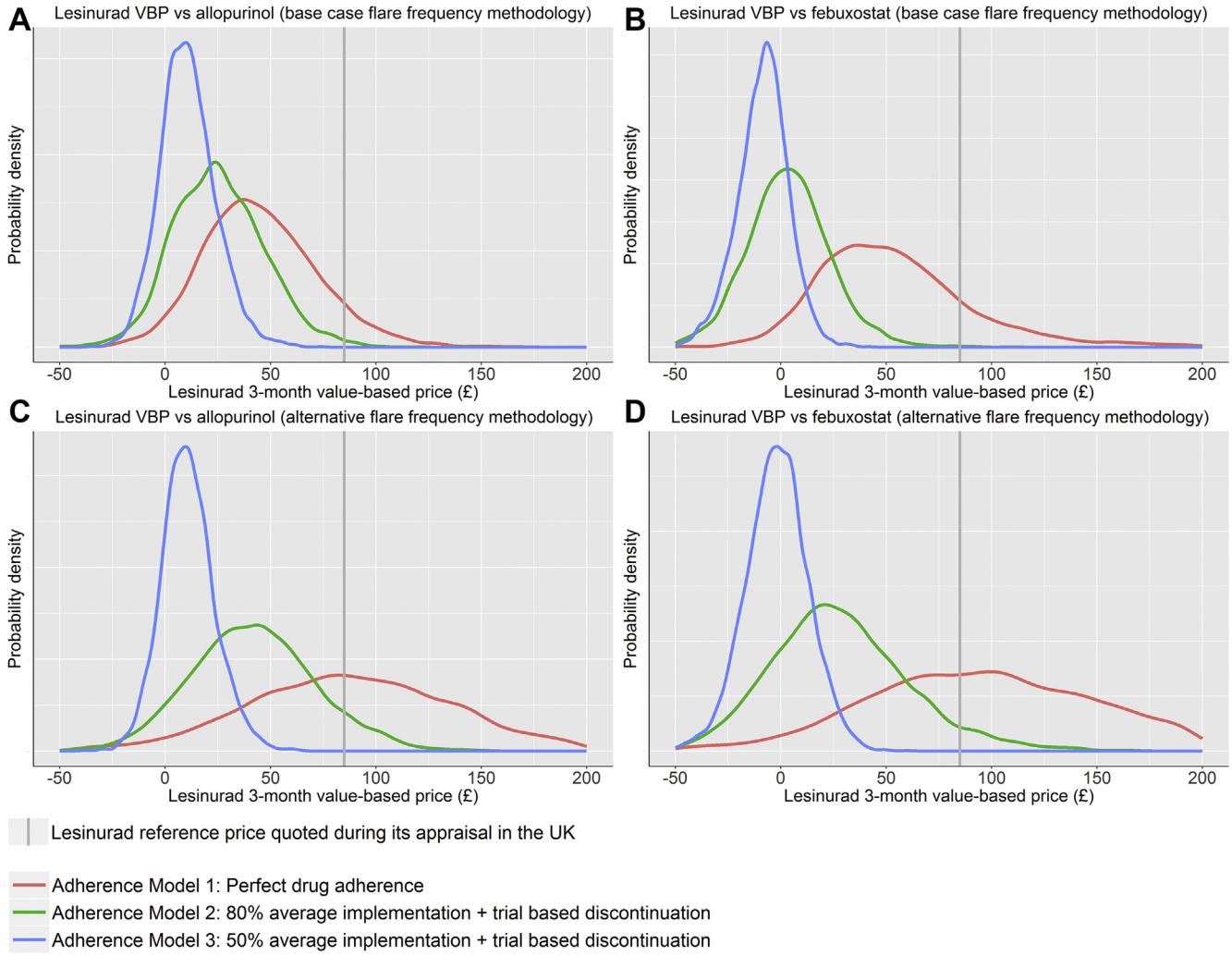

Fig. 3 – The value-based price of lesinurad as part of dual ULT in combination with either febuxostat or allopurinol in patients not responding to either monotherapy alone. The value-based price distributions are obtained using the results of 5000 probabilistic economic model simulations. Value-based price is defined as the price of lesinurad at which the modeled incremental cost per QALY comparing dual ULT to mono ULT is equal to the £20,000 threshold. The vertical line indicates the price of lesinurad quoted during its appraisal in the United Kingdom. QALY, quality-adjusted life-year; ULT, urate-lowering therapy; VBP, value-based price.

therefore accruing higher costs from the XOi component of dual therapy.

Discussion

This was a study of the effectiveness and cost effectiveness of lesinurad as a second-line ULT after first-line treatment with either allopurinol 300 mg or febuxostat 80 mg, adopting an approach to cost effectiveness that is consistent with a UK NICE appraisal [40]. A population PKPD model used to simulate monotherapy and dual ULT showed that although treatment could be highly effective at reducing sUA concentrations to below the target, response rates rapidly fell as adherence was reduced by allowing treatment discontinuation and reducing dose implementation from an average of 100% down to 50%. Using the price of lesinurad originally proposed for the UK market, there was only one scenario in which the ICER of dual therapy with lesinurad compared with allopurinol or febuxostat monotherapies was lower than the higher end of the cost-effectiveness threshold of £30,000/QALY. This was using treatment effectiveness simulated using perfect drug adherence and a pharmacoeconomic model that used the alternative flare frequency methodology in which sustained responders become flare-free. By calculating the value-based price at a threshold of £20,000/QALY, we have shown the extent to which the pricing of a uricosuric for second-line ULT depends on drug adherence.

Our results broadly agree with the results of previous economic evaluations of lesinurad. On the basis of the manufacturer's evidence and independent review, a NICE appraisal committee considered the most plausible ICER for lesinurad plus allopurinol compared with allopurinol alone to be at least £62,298/QALY gained [14]. Our base-case estimates range from £39,184 to £78,350 depending on the level of medication adherence assumed.

Linked PKPD and pharmacoeconomic modeling provide a means of studying the implications of drug pharmacology and adherence on the economic potential of new medicines [41]. These methods can reveal the best-case economic value of new

treatments in the case of perfect drug adherence and estimate the rate at which this changes with worsening persistence or dose implementation. The linkage of these two disciplines is increasingly being implemented to study various issues in drug development [41–46]. We are, however, not aware of any studies that have estimated the impact of changing levels of drug adherence on modeled economic outcomes. Because treatment discontinuation and imperfect dose implementation are both features of latter stage clinical trials and routine practice use of medicines, understanding how these may affect cost effectiveness could be of use to both manufacturers and health care providers.

Although PKPD simulation allows rapid analysis of previously untested treatment scenarios, it may not always provide a substitute for clinical trials. The mixture of data sources informing the models, possible model mis-specification, simplifying assumptions, and differences in time or in the patient population can all result in predictions that differ from what would be observed in a trial setting [47]. Furthermore, we have assumed that within the data from which the PKPD models were constructed, patients adhered to their dosing regimen. This may not be the case and could result in biased model results [48]. The adherence patterns we assumed were not based on real-world evidence of adherence to ULTs because of an absence of studies that disentangle persistence from implementation. The possible treatment strategies for gout are more nuanced than was considered in this study. Guidelines recommend that allopurinol be used as first-line treatment but that it should be initiated at a low dose (e.g., 100 mg) before being titrated up to 900 mg/d or until response is achieved. Similarly, febuxostat could also be initiated at 40 mg and titrated up to a possible 120 mg. The economic evaluation did not consider the potential adverse drug reactions: allopurinol is known to cause rare hypersensitivity reactions, there are possible cardiovascular complications associated with febuxostat, and lesinurad is associated with renal complications that may be exacerbated by poor medication adherence [16].

Gout remains a condition that is typically poorly managed, even in a clinical trials setting with newer ULTs. For health care payers, our results provide an indication of the extent to which poor adherence to ULTs erodes the cost effectiveness of these medicines when translating from clinical trials to routine practice. Development of ULTs with greater drug forgiveness [49] would to some extent mitigate the effects of poor implementation and result in greater effectiveness relative to existing treatments. Pharmaceutical companies conducting future clinical trials of novel ULTs should be mindful that achieving sUA end points alone, without also showing reductions in gout flares, is not likely to provide an attractive value-based price. This is due, in part, to uncertainty in the rate and scale of reductions in gout flares after a reduction in sUA and the weak evidence base linking sUA to other potential health outcomes, such as cardiovascular diseases. Designing clinical trials to demonstrate the eradication of gout in sustained responders, which is expected in most patients [3], is likely to increase the potential value-based price of new ULTs. An alternative approach could be a substudy designed to bridge the evidence gap between sUA concentration and flares. For example, Jutkowitz et al. [50] have estimated the potential value of conducting various 1-year studies.

Conclusions

This study has found that medication adherence has a significant influence on the potential cost effectiveness of second-line dual ULT with lesinurad compared with either allopurinol or febuxostat alone. Nevertheless, although treatment effect is enhanced under perfect medication adherence, dual ULT is not expected to be cost-effective relative to either monotherapy at a threshold of £20,000/QALY. The estimated value-based prices of lesinurad only exceeded that which has been proposed in the United Kingdom when assuming both perfect drug adherence and the eradication of gout flares in sustained treatment responders.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.06.002.

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Integration of Pharmacometrics and Pharmacoeconomics to Quantify the Value of Improved Forgiveness to Nonadherence: A Case Study of Novel Xanthine Oxidase Inhibitors for Gout

Daniel Hill-McManus[1], Scott Marshall[2], Elena Soto[2] and Dyfrig A. Hughes[1,*]

Linked pharmacometric and pharmacoeconomic models provide a structured approach for assessing the value of candidate drugs in development. The aim of this study was to assess the utility of such an approach for identifying the properties of xanthine oxidase inhibitors (XOi) providing improved forgiveness to nonadherence and estimate the maximum reimbursement price. The pharmacometric and pharmacoeconomic models were used to simulate the time course of serum uric acid concentrations and estimate quality-adjusted life years and costs for the XOi febuxostat and a range of hypothetical analogues. Compounds with reduced clearance or increased potency were more forgiving to missed doses, however, even following relatively large changes in these properties the predicted maximum reimbursement prices represented an increase of only 19% above febuxostat 80 mg. Linked pharmacometric and pharmacoeconomic modeling methods have the potential to inform early drug development by providing an indication of pricing options that may permit reimbursement.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Linked pharmacometric and pharmacoeconomic modeling has been shown to have potential utility across a range of different applications.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study has sought to extend linked pharmacometric and pharmacoeconomic models to quantify the value of drugs with improved forgiveness to missed doses.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The relationship between increased potency or reduced clearance, drug forgiveness, and maximum reimbursement price was estimated for hypothetical xanthine oxidase inhibitors for treating gout. This novel framework provides a direct link between drug pharmacology and cost-effective while explicitly accounting for realistic medication adherence.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These methods have the potential to inform early drug development by providing an indication of whether drug candidates possess the properties that would result in a maximum reimbursement price that justifies their progression through the long and costly drug development process.

Linked pharmacokinetic-pharmacodynamic-pharmacoeconomic (PKPDPE) models can provide a framework capable of testing the influence of drug pharmacology on long-term clinical and economic outcomes, such as cost-effectiveness and value-based pricing.[1–4] This offers distinct advantages over conventional pharmacoeconomic analyses during clinical drug development by making explicit consideration of the relation between dose taking, dose response, health outcomes, and costs. Linked PKPDPE modeling can be used to predict the likelihood of therapeutic success and quantify the implications for pricing. One application, which exploits the mechanistic properties of this approach, is in determining the influence of nonadherence on the value of treatments. This represents a natural extension to previous research in which different patterns of adherence serve as inputs to PK[5,6]

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and PKPD[7–9] models, and provides a basis for estimating cost-effectiveness in preference to cost-efficacy.[10]

Imperfect medication adherence can limit the benefit of treatments, result in poorer outcomes for patients, and increase healthcare costs.[11] Medication adherence can be decomposed into three distinct phases: (i) the initiation of treatment, (ii) the degree to which a patient's dose taking matches the prescribed regimen while nominally adhering (implementation), and (iii) the discontinuation of treatment (persistence).[12] The design of medicines that remain effective when dose implementation is erratic—a property known as "forgiveness"[13,14]—may improve treatment effectiveness under conditions of routine care and provide added value. Conventional PK and PD modeling can offer insights into the impact of variable dosing on clinical endpoints;[15,16] however, to our knowledge, there are no published methods for predicting the value of improving treatment forgiveness.

Despite the availability of effective urate-lowering therapies (ULTs) for gout, such as xanthine oxidase inhibitors (XOi) allopurinol and febuxostat, many patients fail to achieve serum uric acid target concentrations. Within clinical trials, allopurinol 300 mg/day reduced serum uric acid (sUA) concentrations to below target (6 mg/dL) in 12–41% of patients[17–21] and febuxostat 80 mg/day in 57–76% of patients.[17–19] Rates of target attainment in routine practice are also low, with estimates of 22% (US primary care or rheumatology clinic),[22] 38% (UK primary care),[23] and 45% (UK rheumatology).[24] A principal cause of treatment failure is nonadherence, with as few as 40% of patients being classed as adherent (medication possession ratio >0.8) using prescription claims data but with higher estimates obtained using other methods.[25,26]

One potential way in which the next generation XOi could add value is through improved forgiveness. Of the many structurally dissimilar candidate lead compounds,[27] the potential for one to have such a property, e.g., through reduced clearance or increased potency, could result in improved use-effectiveness.[28] More forgiving drugs that retain greater effectiveness under real-world adherence would be expected to result in quality of life benefits, and potentially impact on costs, compared with existing treatments. Many jurisdictions operate a form of value-based pricing where the maximum reimbursement price is linked to the added value of a medicine, in terms of both cost and health impacts. A higher maximum reimbursement price makes it more likely that a pharmaceutical company would achieve a return on investment.

This study uses real-world adherence data and PKPDPE modeling to simulate the effectiveness and determine the value of a series of hypothetical XOi. The aim was to assess the utility of using a PKPDPE model to link pharmacology to treatment effectiveness to the maximum reimbursement price in order to inform early decision making based on the predicted value that could be gained from developing a more forgiving drug.

RESULTS

The time courses of drug concentration in plasma and sUA concentration following single doses are presented in **Figure 1** to illustrate the differences in PK and PD between febuxostat and hypothetical

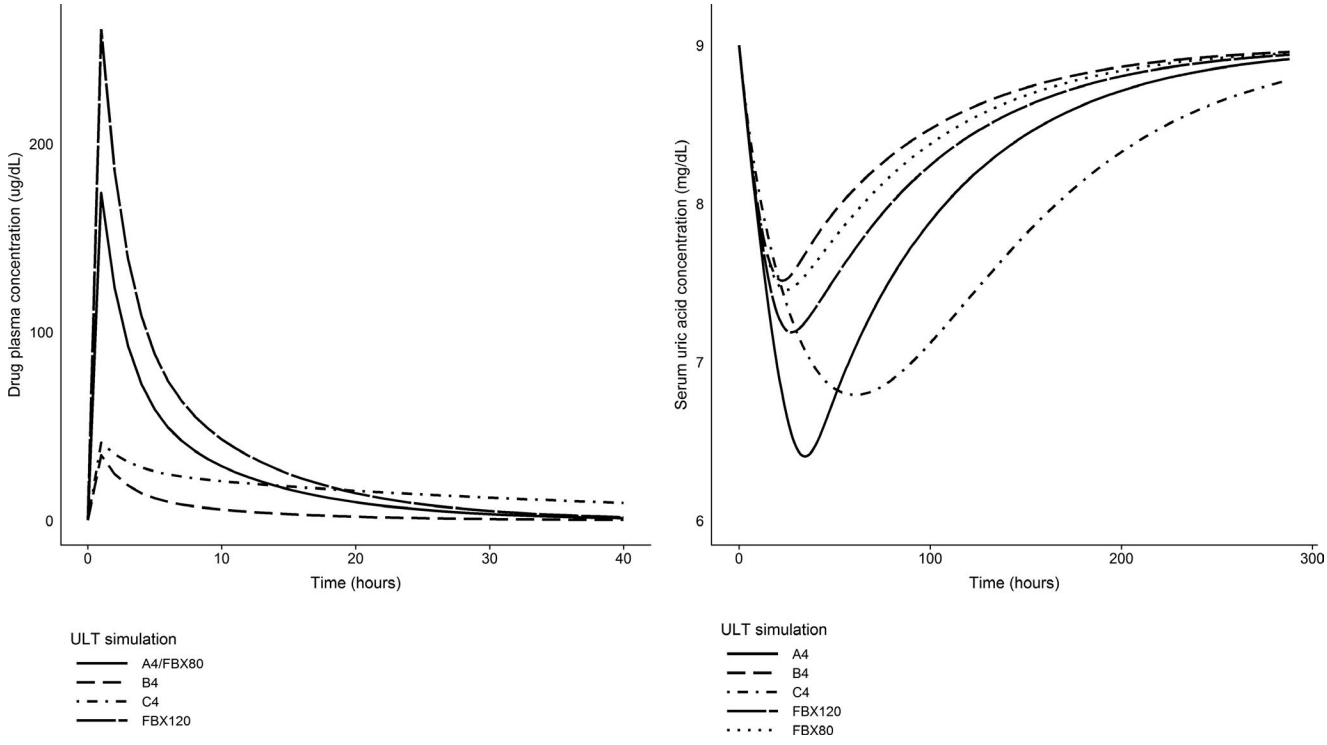

Figure 1 Simulated drug plasma concentration and serum uric acid time course following a single oral dose (taken at hour 12) of febuxostat 80 mg or 120 mg as well as 3 hypothetical ULTs (simulations used a reference subject of age 60, weight 100 kg, and baseline sUA of 9 mg/dL). sUA, serum uric acid; ULT, urate-lowering therapy.

ULTs. The doses of hypothetical ULTs of group B (reduced half maximal inhibitory concentration (IC_{50}) and dose) and C (lower clearance and dose reduction) are reduced, and consequently plasma concentrations of B4 and C4 are lower than febuxostat at 80 and 120 mg. A4 (reduced IC_{50}) results in the greatest reduction in sUA concentration, but its effect is transient relative to C4 with an extended elimination half-life.

The predicted response rates for the hypothetical cohort over all PKPD model simulations are summarized in **Table 1**, where several possible measures of response have been presented. Febuxostat 80 mg and 120 mg were predicted to result in 55% and 64% of subjects with a mean sUA concentration below a 6 mg/dL target, respectively. The hypothetical ULTs leading to the greatest proportion of responders was C4 (extended half-life with dose reduction) and A4 (increased potency without dose reduction), both achieving <6 mg/dL in 75% of subjects. Scenarios assuming a greater potency and a reduced dose resulted in slightly lower response rates, down to 51%, relative to febuxostat 80 mg.

Average response rates (<6 mg/dL) over all PKPD simulations by dose implementation groups, as shown in **Table S1**, are presented in **Figure 2**. There is very little differentiation between the ULTs when implementation is below 20% or above 90%, with the best-worst treatment differences being between 0.8 and 10.3 percentage points. Greater differentiation occurs between 20% and 90%, where the best-worst treatment difference ranges from 15.1 to 38.8 percentage points. A more pronounced pattern is observed for sustained treatment response, **Figure S1**, where there is no response predicted until at least 40% dose implementation. Only once implementation exceeds 70% of doses taken are high response rates (>50%) achieved.

Table 2 presents the estimated maximum reimbursement prices at which treatments are cost-effective, based on differences in estimated lifetime quality-adjusted life years (QALYs) and costs, resulting from expected changes in flare frequency. Prices are given using either febuxostat 80 or 120 mg as the comparator. The highest maximum reimbursement prices are achieved by A4 and C4, which are expected to be cost-effective at an annual price of £376, an increase of 19% on febuxostat 80 mg at a threshold of £20,000 per QALY.

Figure 3 shows the relationship between the responder rate and the pricing of a hypothetical ULT vs. the comparator febuxostat 80 mg. The price axis is the difference between the maximum reimbursement prices at every response rate compared with the price of febuxostat 80 mg, hence the price at the response rate of 55% is fixed at £0. The two curves plot the relationship for a £20,000 per QALY cost-effectiveness threshold and a probability of 10% and 50% of being cost-effective at or below this threshold. This curve provides an estimate of the maximum reimbursement price for any response rate, and indicates that with 100% responder rate the maximum reimbursement price would be £140 above the annual cost of febuxostat 80 mg.

DISCUSSION

This study has demonstrated the application of linked PKPDPE models to inform drug development by estimating the maximum reimbursement price from drug pharmacology, using real-world data on medication adherence. In this case study, hypothetical XOi with reduced dose and extended duration of action were predicted to increase the proportion of treatment responders to a similar extent as those with increased potency alone. Simulations estimated a proportion of patients responding to treatment for

Table 1 Summary of PKPD simulations including % of subject simulations below target thresholds and the proportion of subject simulations below 6 mg/dL on at least 60%, 70% or 80% of days

	Mean sUA conc.		% of subjects below target on >x% of days[a]		
Urate-lowering therapy	<5 mg/dL, %	<6 mg/dL, %	80% days, %	70% days, %	60% days, %
FBX80	35.88	55.23	32.02	41.90	52.12
FBX120	47.06	63.86	37.90	48.40	58.87
A1	41.79	60.00	35.07	45.40	55.71
A2	48.92	64.98	38.66	49.18	59.80
A3	57.12	70.08	42.80	53.15	63.69
A4	66.02	75.24	47.78	57.43	67.87
B1	35.56	54.89	31.74	41.53	51.68
B2	34.97	54.39	31.30	41.00	51.11
B3	34.04	53.51	30.54	40.12	50.10
B4	31.86	51.43	28.98	38.20	48.08
C1	42.31	60.61	36.08	46.44	56.76
C2	49.49	65.76	40.82	50.96	61.38
C3	56.77	70.55	46.09	55.58	65.83
C4	64.04	75.16	52.50	60.72	70.24

PKPD, pharmacokinetic-pharmacodynamic; sUA, serum uric acid.
[a]For each adherence pattern and PKPD simulation the proportion of simulated days below 6 mg/dL was calculated, then the proportion of these results above 80%, 70% or 60% are shown here.

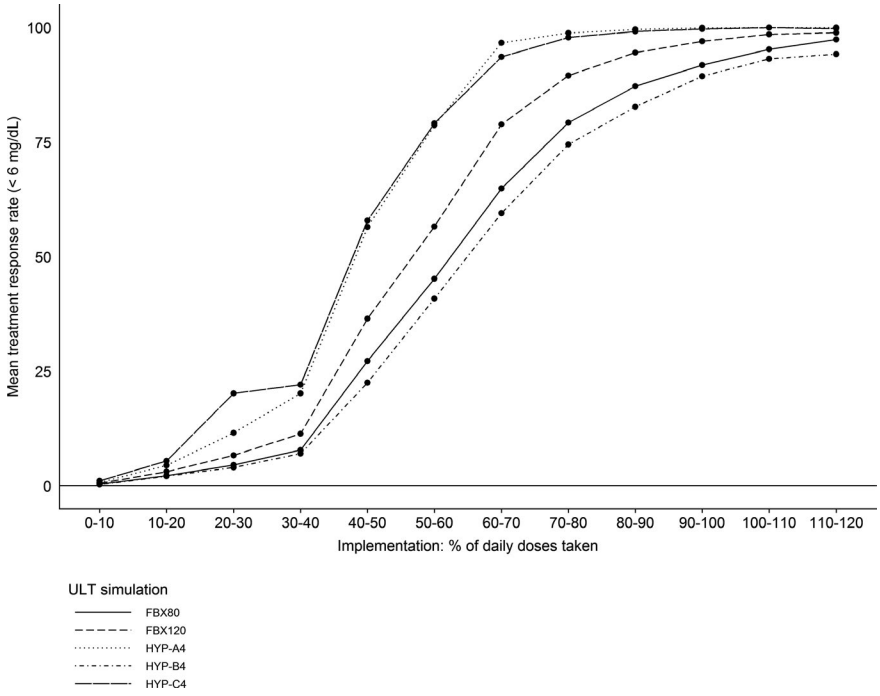

Figure 2 Mean treatment response rates for hypothetical ULTs compared with febuxostat 80 mg by dose implementation using response defined using mean daily sUA concentration below 6 mg/dL target. sUA, serum uric acid; ULT, urate-lowering therapy.

Table 2 The maximum cost-effective annual price (£) of hypothetical ULTs based on mean lifetime QALYs, costs, and number of cycles of drug required in 5,000 simulations and using 119 real-world adherence patterns

ULT	Lifetime QALYs	vs. Febuxostat 80 mg		vs. Febuxostat 120 mg	
FBX80	13.272	–	–	–	–
FBX120	13.283	–	–	–	–
A1	13.278	331.63	+ 4%	306.48	– 4%
A2	13.284	346.16	+ 9%	321.01	+ 1%
A3	13.291	360.92	+ 14%	335.77	+ 6%
A4	13.297	376.08	+ 18%	350.92	+ 10%
B1	13.272	316.77	0%	291.62	– 8%
B2	13.271	315.22	– 1%	290.07	– 9%
B3	13.270	312.56	– 2%	287.41	– 10%
B4	13.267	306.38	– 4%	281.23	– 11%
C1	13.279	333.45	+ 5%	308.30	– 3%
C2	13.285	348.54	+ 10%	323.39	+ 2%
C3	13.291	362.66	+ 14%	337.51	+ 6%
C4	13.297	376.61	+ 19%	351.46	+ 11%

The percentage change columns compare the estimated prices with that of febuxostat (80 or 120 mg) with an annual price assumed to be £317.72. QALYs, quality-adjusted life years; ULT, urate-lowering therapy.

these more "forgiving" ULTs of between 60% and 75% compared with 55% for febuxostat 80 mg. Based on this improvement and assuming that treatment benefit is limited to a reduction in the frequency of acute gout flares, maximum reimbursement prices were estimated of between 4% and 19% above the £317.72 current annual cost of febuxostat using a cost-effectiveness threshold of £20,000 per QALY gained.

The results of this study suggest that, under conditions of imperfect adherence, reduced clearance is of equal value as a target for early candidate selection as increased potency. The identification of compounds with long elimination half-lives, while maintaining bioavailability and potency may be challenging. However, some structurally diverse and highly potent XOi molecules have been identified, and these may offer some potential lead candidates[27] so further research

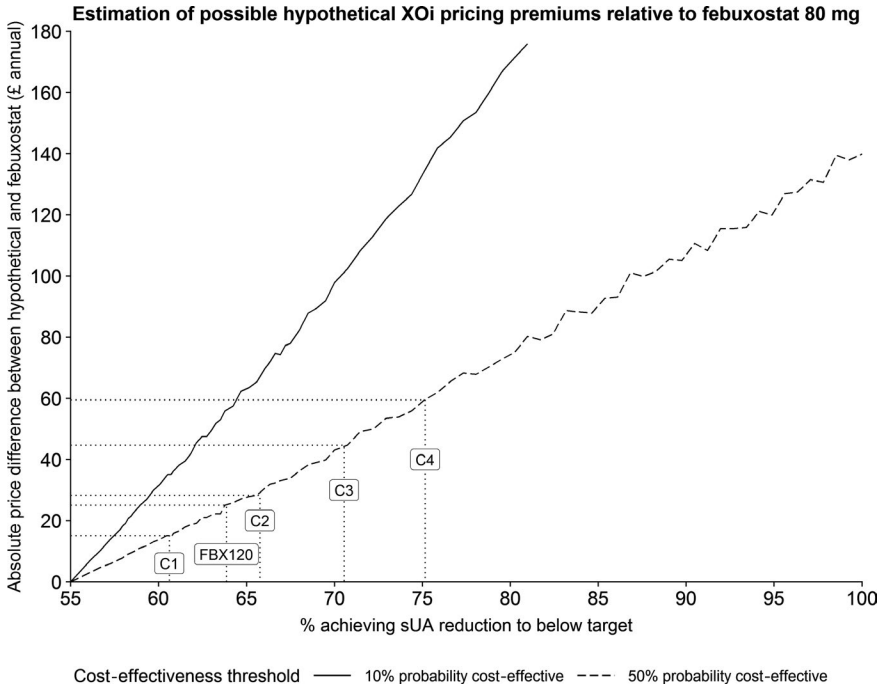

Figure 3 Curve of estimated pricing to achieve cost effectiveness vs. febuxostat 80 mg with probability of 50% and 10% at a willingness to pay threshold of £20,000. sUA, serum uric acid; XOi, xanthine oxidase inhibitor.

and drug discovery endeavors could be justified. While there are alterative ULT mechanisms, such as uricosurics, which lower sUA by stimulating its renal excretion, these have had limited success due to safety concerns.[29] Similarly, administration of the enzyme uricase (e.g., pegloticase) that converts uric acid into the more soluble component, allantoin, is not widely used due to occurrence of antidrug antibodies, injection site reactions, and its high cost.[30]

The linkage of pharmacometrics with pharmacoeconomics remains relatively novel, and there are few published examples, but it has potential across a range of applications from early drug research and development,[2] in estimating cost-effectiveness in alternative subgroups and treatment protocols,[31] in the evaluation of complex pharmaceutical interventions such as pharmacogenetic testing,[32] and modeling health economics of treatments for use during pandemics.[33] Pharmacometrics has been used to study issues relating to medication adherence for some time (for example, Vrijens *et al.*[34]). This study is the first, of which we are aware, to combine adherence, pharmacometrics and pharmacoeconomics to inform early drug design decisions. In doing so, this further demonstrates the value of an interdisciplinary approach and the need to interconnect existing methods to improve efficiency in drug development. As such, linked PKPDPE modeling may be seen as an additional component within the model-informed drug development paradigm.[35]

This study has advantages over conventional pharmacometric studies that do not assess the future value of compounds beyond market authorization; and conversely, it has advantages over standard PE practices which do not account for exposure response relationships. It has benefited from a semimechanistic pharmacodynamic model that can account for the system dynamics resulting from intermittent dose taking. Unlike in some previous economic evaluations of ULTs,[36–38] in this study, the clinical benefits of lowering sUA concentration have been assumed to be limited to reduced frequency of flares alone. However, this is consistent with the findings of recent meta-analyses.[39]

Limitations of this study include the assumptions which were necessary in order to develop a model structure and to obtain parameters estimates. It has been assumed that the structure of the pharmacometric and PE models provide a sufficiently accurate representation of ULTs and their impacts to make predictions. The PKPD model was developed from a variety of published sources without fully accounting for the additional uncertainty this introduced. Aspects of the PE modeling, such as the frequency of acute gout flares, relied on survey data obtained from a small number of patients. We have not considered the safety aspects of hypothetical XOi that would inform dose selection and would need to be accounted for in pharmacoeconomic models in terms of the cost and health implications. The adherence data were not collected in gout patients but do contain a wide variety of adherence patterns, and the overall low level of adherence is consistent with studies on the routine use of ULTs.

Many jurisdictions make use of economic evaluations as a part of the decision-making process of whether to reimburse medicines having obtained marketing authorization. A new medicine failing to meet the criteria for cost-effectiveness may not be marketable at a commercially viable price or gain sufficient market penetration for adequate return on investment. The framework used here provides a direct link between pharmacology and the probability of a medicine being cost-effective. These methods have the potential to inform early drug development by providing an indication of whether drug candidates possess the properties that would result in a maximum reimbursement price that justifies their progression through the long and costly drug development process.

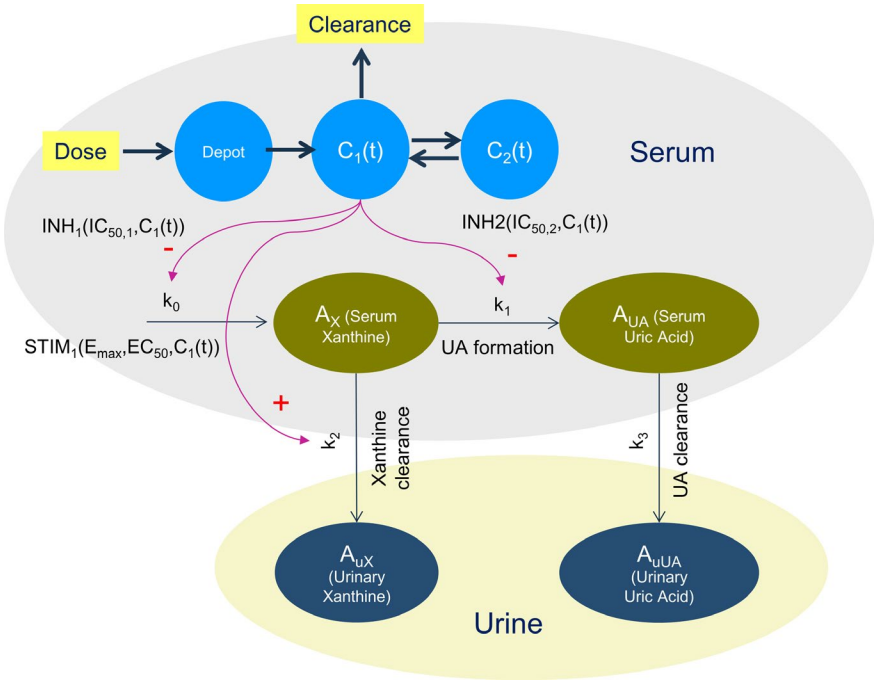

Figure 4 Diagrammatic and mathematical representations of the pharmacodynamics of dual-urate lowering therapies. k_0, k_1, k_2, and k_3 are the rate parameters for the production of xanthine, xanthine to uric acid (UA) conversion, removal of xanthine to urine and removal of uric acid to urine, respectively. INH_1, INH_2, and $STIM_1$ are the pharmacodynamic model drug functions. A_X and A_{UA} are the total time-varying amounts of xanthine and UA in serum, respectively. A_{uX} and A_{uUA} are total amounts of xanthine and UA removed to urine, respectively. $C_1(t)$ and $C_2(t)$ are the plasma concentrations of drug in the central and peripheral pharmacokinetic compartments respectively. E_{max}, maximum stimulatory effect achievable; EC_{50}, half maximal stimulatory concentration; IC_{50}, half maximal inhibitory concentration.

Table 3 Summary of urate-lowering therapies used in PKPD simulations

		Parameter (units)			
Scenario description	ULT ID	Dose (mg)	CL/half-life[a] (dL h^{-1}/ hours)	IC_{50}[b] (mg/dL)	Steady-state sUA conc. perfect adherence[a] (mg/dL)
Febuxostat 80 mg	FBX80	80	75.9/6.5	1.13×10^{-3}	3.33
Febuxostat 120 mg	FBX120	120			2.48
Hypothetical ULTs with reduced IC_{50}	A1	80	75.9/6.5	9.04×10^{-4}	2.86
	A2			6.78×10^{-4}	2.30
	A3			4.52×10^{-4}	1.60
	A4			2.26×10^{-4}	0.74
Hypothetical ULTs with reduced IC_{50} and dose	B1	64	75.9/6.5	9.04×10^{-4}	3.34
	B2	48		6.78×10^{-4}	3.37
	B3	32		4.52×10^{-4}	3.42
	B4	16		2.26×10^{-4}	3.55
Hypothetical ULTs with lower clearance and dose reduction	C1	64	60.7/7.7	1.13×10^{-3}	2.91
	C2	48	45.5/9.7		2.52
	C3	32	30.3/13.8		2.20
	C4	16	15.2/26.2		1.97

IC_{50}, half maximal inhibitory concentration; PKPD, pharmacokinetic-pharmacodynamic; sUA, serum uric acid; ULT, urate-lowering therapy.
[a]Simulations used a reference subject of age 60, weight 100 kg, and baseline sUA of 9 mg/dL. [b]The ULTs are xanthine oxidase inhibitors and inhibit the rate of conversion of hypoxanthine to xanthine and xanthine to uric acid. The IC_{50} given here is for the inhibition of xanthine to uric acid conversion. The IC_{50} for hypoxanthine to xanthine is assumed to scale proportionately.

METHODS

Overview

In the first stage, the time course of sUA was simulated based on real-world dose-taking histories and using a range of drug models, representing both real-world and hypothetical XOi. This stage was repeated a large number of times with resampling from probability distributions for patient characteristics, including baseline sUA concentration, age, and weight. In the second stage, the posttreatment

sUA was used to predict the annual frequency of acute gout flares over the patients' remaining lifetime and to estimate the overall costs and impacts on QALYs.

Pharmacometric and PE models

An existing two-compartment PK model and multicompartment semi-mechanistic PD model developed for febuxostat[7] was used to simulate sUA concentrations. The structure of the PD model has been reproduced in **Figure 4**, while PK and PD model parameters are provided in the **Supplementary Material**. In addition to febuxostat at approved daily doses of 80 and 120 mg,[40] twelve "hypothetical" ULTs were assessed by changing the values of potency or clearance parameters for febuxostat (**Table 3**).

The rationale for the clearance, potency, and dose adjustments is that (i) reduced clearance prolongs residual drug concentration (and therefore extends the duration of action), but for an unbiased comparison a dose reduction was made to maintain the same drug exposure (area under the concentration curve); and (ii) for a given concentration, a more potent drug will result in greater effect and we have, therefore, tested scenarios with and without dose adjustments. In reality, decisions concerning dose would be guided by a consideration both of the efficacy and the safety profiles of a candidate compound. We have not considered safety in this study.

The PE model used a Markov state-transition structure with a 3-month time cycle to estimate costs and QALYs in a cohort of patients eligible for ULT. An overview of the model structure is given in **Figure S2**, model parameters are provided in the **Supplementary Material**, and a comprehensive description of the model can be found elsewhere.[1] The approach to modeling cost-effectiveness is consistent with the methods of the National Institute for Health and Care Excellence in the UK,[41] adopting the cost perspective of the National Health Service in the UK, a lifetime (50-year) time horizon, and costs and QALYs both discounted at a rate of 3.5% per annum.[42] The model was implemented in R version 3.5.1.[43]

For each ULT in **Table 3,** a nominal 10,000 patients are initially allocated to treatment and distributed between four sUA substates (<6, 6 to <8, 8 to <10 and ≥10 mg/dL) based on the results of PKPD simulations. In each model cycle, a proportion of patients discontinue treatment and are redistributed between the sUA sub-states to an untreated sUA distribution. A proportion also move to a dead state according to all-cause mortality probabilities derived from life tables for England and Wales in 2015.[44] The model conservatively assumes that the only benefit of reducing sUA concentrations is to reduce the frequency of acute gout flares. A flare frequency distribution was derived from cross-sectional survey data[45] across five categories; 0, 1–2, 3, 4–5 and 6+ flares per annum. Fewer gout flares then result in improved quality of life and reduced treatment costs.[45]

Adherence data

Adherence to ULTs was assumed from real-world data on chronic treatment (119 subjects, 15,959 individual doses and follow up between 90 and 529 days[46,47]) using electronically recorded pill bottle cap opening times[48] (MEMS, Aardex Group). Many of the adherence patterns are characterized by an implementation phase of varying levels of adherence followed by a complete cessation of doses prior to the end of the observation period. Instances of nonadherence following the implementation phase were discarded, as discontinuation was modeled separately in the pharmacoeconomic model. The distribution of dose implementation is given in **Table S1**, while figures showing all doses taken by every subject are provided in **Figures S3–S7** in the **Supplementary Material**.

Simulation modeling

Linked PKPDPE simulations were performed for each of the 14 ULTs. The pharmacometric stage was performed for each of the 119 real-world adherence patterns ranging from 57 days to 529 days of dose implementation. Each simulation was repeated 500 times with resampling from individual random effects and from the probability distributions (based on clinical trial baseline data[19]) assumed for subject covariates including age (log-normal), weight (log-normal), and baseline sUA concentration (normal). However, uncertainty in the parameter estimates, in the estimates of the random effects parameters and residual variability was not included in PKPD simulations.

The simulated sUA time courses were used to generate posttreatment sUA concentration distributions across four states for use in the PE model. These were obtained by taking the mean of the simulated daily sUA levels for days beyond day 50 but before discontinuation. The primary measure of treatment response for a ULT, equivalent to the primary outcome measure used in many clinical trials,[17–19] is the proportion of subject simulations in the <6 mg/dL state. Further alternative measures of treatment response were derived using daily sUA concentrations for all available days beyond day 50 but before discontinuation. The proportions of subject simulations which were <6 mg/dL for at least 80%, 70%, or 60% of days have been calculated to measure sustained response. Although not reported in clinical trials, this measure is more likely to be associated with a reduction in gout symptoms.[49]

In each iteration of the pharmacoeconomic model, the process of collapsing sUA concentration measurements on to the four sUA states was repeated with random sampling to bootstrap and propagate PKPD variability. Other pharmacoeconomic model inputs, such as flare frequency distributions, health state utilities, and discontinuation rates, were also varied according to probability distributions used to represent uncertainty regarding their true value. Further details of the model parameters and probability distributions are summarized in the **Supplementary Material**. A total of 5,000 PE models were performed for each unique ULT and adherence pattern combination.

The outputs of the pharmacoeconomic model for each ULT are the mean per patient lifetime QALYs and costs associated with gout following the initiation of treatment and the mean number of cycles of drug supplied. All hypothetical ULTs were compared with febuxostat 80 or 120 mg, both with an annual price of £317.72.[40] Cost-effectiveness thresholds were used to determine whether a higher cost treatment is sufficiently effective to justify reimbursement. We have used a cost-effectiveness threshold of £20,000 per QALY gained, which is routinely used in the United Kingdom.[50]

Where a hypothetical ULT is more effective than febuxostat 80 mg, we have estimated the maximum price at which the hypothetical ULT would be cost-effective using the mean QALY and cost differences. The maximum cost-effective price can be found by solving Equation 1 for P_b when net monetary benefit (NMB) is equal to zero.

$$\mathrm{NMB} = \lambda \Delta Q - \left(\Delta C_{\mathrm{ND}} + \left(S_b * P_b - S_f * P_f\right)\right) \qquad (1)$$

NMB is the net monetary benefit, λ is the cost-effectiveness threshold, ΔQ is the difference in lifetime QALYs, ΔC_{ND} is the difference in non-drug costs, S_f is the number of cycles febuxostat 80/120 mg, P_f is the price of febuxostat 80/120 mg, S_b is the number of cycles of hypothetical ULT, and P_b is the price of the hypothetical ULT.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Supplementary Table S1. Levels of dose implementation in MEMS dosing histories (Individual mean number of doses taken 60.4%)
Supplementary Material: PKPD Model Equations
Supplementary Table S2. Subject covariate distributions
Supplementary Table S3. PK parameters for febuxostat
Supplementary Table S4. PD parameters for febuxostat
Supplementary Table S5. Quarterly treatment discontinuation probabilities

Supplementary Table S6. Quarterly mortality probabilities
Supplementary Table S7. Distribution of annual frequency of flares by sUA level
Supplementary Table S8. Health state utilities by frequency of gout flares
Supplementary Table S9. Daily drug costs, patient monitoring cost and cost of treating flares
Supplementary Figure S1. Mean treatment response rates for hypothetical ULTs (urate-lowering therapies) compared with febuxostat 80 mg by dose implementation using response defined using proportion of subject simulations responding (<6 mg/dL) on 80% or more of days (sustained response).
Supplementary Figure S2. Model diagram showing the linkage between PKPD and pharmacoeconomic components and the basic structure of the pharmacoeconomic model.
Supplementary Figure S3. Subjects 1–24
Supplementary Figure S4. Subjects 25–48
Supplementary Figure S5. Subjects 49–72
Supplementary Figure S6. Subjects 73–96
Supplementary Figure S7. Subjects 97–119

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CONFLICT OF INTEREST

S.M. and E.S. are, or were, employees of Pfizer. D.H-M. and D.A.H. have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

D.H.-M., E.S., S.M., and D.A.H. wrote the manuscript; D.H.-M. and D.A.H. designed the research; D.H.-M. performed the research; D.H.-M. analyzed the data.

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