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## Linked Pharmacometric-Pharmacoeconomic Modeling and Simulation in Clinical Drug Development

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## **MANUSCRIPT TITLE**

Linked Pharmacometric-Pharmacoeconomic Modelling and Simulation in Clinical Drug Development

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S.M. and J.L. are, or were, employees of Pfizer, and R.W. is a Pfizer retiree. All other authors declared no competing interests for this work

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Linked pharmacometric-pharmacoeconomic modelling, early economic evaluation, translational health economics, modelling and simulations, clinical trial simulation, early pharmacoeconomics

## **1. Abstract**

Market access and pricing of pharmaceuticals are increasingly contingent on the ability to demonstrate comparative effectiveness and cost-effectiveness. As such, it is widely recognised that predictions of the economic potential of drug candidates in development could inform decisions across the product lifecycle. This may be challenging when safety and efficacy profiles in terms of the relevant clinical outcomes are unknown or highly uncertain early in product development. Linking pharmacometrics and pharmacoeconomics, such that outputs from pharmacometric models serve as inputs to pharmacoeconomic models, may provide a framework for extrapolating from early phase studies to predict economic outcomes and characterise decision uncertainty. This article reviews the published studies that have implemented this methodology and used simulation to either inform drug development decisions and/or optimise the use of drug treatments. Some of the key practical issues involved in linking pharmacometrics and pharmacoeconomics, including the choice of final outcome measures, methods of incorporating evidence on comparator treatments, approaches to handling multiple intermediate endpoints, approaches to quantifying uncertainty, and issues of model validation, are also discussed. Finally, we have considered the potential barriers that may have limited the adoption of this methodology and suggest that closer alignment between the disciplines of clinical pharmacology, pharmacometrics, and pharmacoeconomics, may help to realise the potential benefits associated with linked pharmacometric-pharmacoeconomic modelling and simulation.

## 2. Background

Many jurisdictions across OECD countries require evidence of cost-effectiveness to secure the reimbursement and formulary inclusion of new medicinal products.<sup>1</sup> Economic evaluations, conducted as part of a broader health technology assessment (HTA), are often the preferred approach to demonstrate value; that is, whether the benefits of a new treatment are sufficient to justify any additional cost. There is a trend of increasing requirements for cost-effectiveness to secure reimbursement, including in the United States.<sup>2</sup> As pricing and market access has become increasingly contingent on the ability to demonstrate cost-effectiveness, there has emerged the potential for the pharmaceutical industry to benefit from methods of quantifying the economic potential of drug candidates earlier in development.

Earlier value assessments are especially pertinent in the context of the high and increasing cost of drug development that is skewed toward the later phases. The return on investment in pharmaceutical R&D has also steadily declined since 2010,<sup>3</sup> although returns would not appear to have yet fallen below those for other large companies.<sup>4</sup> The mean cost of phase 3 development has been estimated to exceed the cost of phase 2 by more than a factor of four.<sup>5</sup> It is, therefore, desirable to fail development candidates at the earliest stage possible before incurring large costs – hence the mantra “fail fast, fail cheap”. While it does appear that there has been some success in shifting project terminations towards earlier phases in recent decades, the proportion failing at phase 3 remains high.<sup>6</sup>

Studies of attrition rates show inadequate efficacy at phase 3 to be the primary reason for termination but that 22% failed for commercial reasons<sup>7</sup> and 24% for strategic reasons.<sup>8</sup> Even if marketing authorisation is granted there may be difficulty securing reimbursement. In the UK, for example, in a sample of drug appraisals only around half of funding decisions were positive without restrictions.<sup>9</sup> Considerations of the requirements for drug reimbursement ought to be integrated within the drug development decision-making process. Failure to do so may risk 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.

Early economic evaluation during drug development aims to increase R&D efficiency through earlier termination of commercially non-viable drugs and, inform pricing strategies by predicting the price reimbursement authorities would be willing to pay.<sup>10</sup> Economic evaluation should ideally be applied iteratively, beginning in the pre-clinical phase and subsequently updated as clinical data emerges<sup>11,12</sup> and used beyond go/no-go and pricing decisions, to also inform strategic, data collection and risk management decisions.<sup>11</sup> However, the methods and data sources required to parameterise early economic models have not been well described, including how to address the issue that outcomes in terms of the safety and efficacy of treatments will either be unknown or highly uncertain.

It has been proposed that safety and efficacy inputs to early economic models may be obtained using pharmacometric models, by extrapolating from early phase data along with the associated uncertainty.<sup>13</sup> In this approach, pharmacometric models, developed routinely in the early clinical phases of drug development, are used to simulate the potential range in outcomes from proposed pivotal clinical trials<sup>14</sup> which in turn serve as inputs to a pharmacoeconomic model. As pharmacometric models provide a mathematical description of the exposure-response relationships, whilst also accounting for inter-individual variability, inputs to pharmacoeconomic models could be simulated for specific patient subgroups, doses, regimens, or drug adherence scenarios. It also provides a framework that allows uncertainty in safety and efficacy to be captured and propagated through to the economic endpoints, which is essential in order to quantify decision uncertainty and the value of conducting further research.<sup>15</sup>

In this article we refer to this methodology as linked pharmacometric-pharmacoeconomic (PMPE) modelling and simulation. Our aim in this study was to review the published literature for applications of linked PMPE modelling and simulations since the original publications in this area; to identify categories of decisions and timings when this approach may have potential to add value to decisions

making; to describe the key challenges in implementing the methods in practice, and; consider what barriers may have limited the extent to which this has been applied during drug development.

### **3. Types of Early Economic Evaluation in Drug Development**

The concept of early economic evaluation, which may be defined as ‘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’,<sup>16</sup> first appeared in the literature in the early the nineties.<sup>10</sup> Published applications of early economic evaluation in drug development are limited<sup>16,17</sup> and appear to be less numerous than those for medical device development.<sup>18</sup> Review articles of early economic evaluation have presented various means of classifying or categorising the types of early economic evaluation that are possible, in terms of their methodology and the types of research question which they address.<sup>19,20</sup>

Linked PMPE modelling is one approach available to enable and enhance early economic evaluation in drug development. We consider three broad categories of drug development problems to which linked PMPE could be applied: i) applications where the primary focus is on ‘go/no-go’ decisions; ii) applications whose primary focus is to inform study design and development strategy; and iii) applications used primarily to inform decisions relating to pricing, reimbursement or market access (PRMA) strategies (Table 1). A fourth category is presented for completeness, to include those published PMPE studies that are not focussed on drug development questions but may be used to inform resource allocation decisions from a payer perspective.

#### 4. Economic Evaluation of Pharmaceuticals

Health technology assessment (HTA) is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.<sup>21</sup> This often includes economic evaluation, defined as the process of conducting an analysis of alternative courses of action in terms of both their costs and consequences, taking the perspective of society, a health care provider or payer.<sup>22</sup> This process is inherently comparative and is commonly applied when a medicine has received marketing authorisation, to inform the decision of whether, and to what extent, it will replace the existing standard of care (SoC). An important source of evidence providing inputs to such evaluations, in particular relating to efficacy, are the pivotal phase 3 clinical trials.<sup>23</sup> However, other sources of evidence may also be required and pharmacoeconomic modelling involves methods for linking surrogate and clinical endpoints, evidence synthesis, generalising trial findings, extrapolation to appropriate time horizons and quantifying decision uncertainty. This is represented by 'late stage HTA' in Figure 1, whereby costs and outcomes of two treatments,  $R_1$  and  $R_2$ , are informed from pivotal clinical trial(s) and provide inputs to an economic evaluation.

An important outcome measure in the context of HTA is the quality-adjusted life year (QALY), developed in order to facilitate comparisons across different disease areas and interventions. QALYs are based on utilities, which are preference-based valuations of health-related quality of life, and measured on a scale where perfect health = 1 and death = 0.<sup>24</sup> QALYs are calculated as the integral of utility scores over time, often over a patient's lifetime. Aggregated QALYs therefore represent an overall measure of length of life weighted by quality of life.<sup>25</sup> Weights are intended to represent societal preferences for being in a given health state and are obtained via survey methods. The evidence for the utilities associated with different states of health, for use in HTA, is often collected within pivotal clinical trials but may also be taken from external sources and applied to observed health states or clinical events. The ratio of incremental health benefit (e.g. QALYs) to the incremental



cost is known as the incremental cost-effectiveness ratio (ICER). Some reimbursement authorities make decisions by relating ICERs to threshold values of willingness to pay, above which health technologies are deemed not cost-effective.<sup>1</sup>

## **5. Linked Pharmacometric-Pharmacoeconomic Case Studies**

We conducted a literature research to identify studies that had used linked pharmacometric and pharmacoeconomic models in order to address questions relating to drug development or the use of existing medicines. We searched PubMed, Medline, EconLit, Embase and BIOSYS Previews for articles published between January 2001 and April 2020. Search terms included: 'pharmacometric', 'pharmacokinetic pharmacodynamic', 'drug development' and 'investigational compound'. These terms were searched in combination with the terms 'cost-effectiveness', 'pharmacoeconomic', 'health economics' and 'economic evaluation'. The relevant articles that this search identified were used to identify additional relevant studies by examining study references. We also used the results of previous reviews on early economic evaluation in medical product development.<sup>16,17</sup>

We identified ten publications implementing linked PMPE models since the first publication by Hughes et al., outlining the methodology in 2001.<sup>13</sup> Following the study by Poland & Wada,<sup>26</sup> there was a considerable delay until the subsequent studies began to emerge, the first being Pink et al.<sup>27</sup> in 2012. There may, however, have been applications of linked PMPE performed within the pharmaceutical industry that have not been published. The following subsections summarise each of the published studies in turn, grouped according to the type of analysis as outlined in Table 1. The important characteristics of each study including the disease area, the perspective adopted, the approximate timing within, or beyond, drug development to which the approach would be most applicable, the type of decision addressed and specific research questions, are summarised in Table 2. A summary of the types of sub-models the studies included, model structures and specific analyses performed is provided in Table 3.

### **5.1. Drug Development Applications**

#### *5.1.1. Go/no-go decisions*

The economic viability of a project should be assessed at every stage of drug development as new data becomes available. This includes decisions ranging from whether to initiate a drug discovery effort to whether to continue into phase 3 clinical trials. Economic evaluations performed at very early stages, during drug discovery or in pre-clinical phases, could help identify target product profiles most likely to achieve the types and scale of benefits that would be required to obtain a price in a range that may justify further R&D investment. Subsequently, as biomarker or early outcome data from clinical studies emerge, pharmacometric models can be used to extrapolate early results to late stage pharmacoeconomic outcomes to assess whether efficacy and safety thresholds are likely to have been met and justify continued development.

An early stage economic evaluation using linked PMPE was conducted by Hill-McManus et al. to assess the potential for new xanthine oxidase inhibitors to achieve price premiums relative to the existing treatment options.<sup>28</sup> The pharmacology of the comparator, another xanthine oxidase inhibitor, was described using a compartmental pharmacokinetic (PK) model and multicompartment semi-mechanistic pharmacodynamic (PD) model. This was linked to a pharmacoeconomic model which predicted rates of clinical events and extrapolated to a longer-term time horizon to estimate incremental costs and QALYs. Hypothetical compounds were simulated by modifying the clearance and potency parameters of the existing comparator, to estimate the value-based price of such drugs under conditions of “real world” drug adherence. Simulations predicted a distribution of possible hypothetical drug prices that would meet a cost-effectiveness threshold of £20,000 per QALY. The results showed only modest price premiums would be acceptable even for much more potent, or slowly cleared (more forgiving<sup>29</sup>) hypothetical drugs; suggesting that discovery and development of such compounds is unlikely to be commercially viable unless therapeutic benefit in addition to reduction in gout flares could be identified.

Slejko et al. reported a PD model-based meta-analysis (MBMA) linked to a pharmacoeconomic model to assess the cost-effectiveness of a hypothetical drug for chronic obstructive pulmonary disease

(COPD).<sup>30</sup> The purpose of the analysis was to predict the threshold of drug efficacy that would be cost-effective. The MBMA was used to predict (as non-linear functions) the COPD exacerbation rates given changes in FEV<sub>1</sub> with placebo or drug treatment, which then served as inputs to a Markov microsimulation pharmacoeconomic model estimating costs and QALYs over a 1-year period. The results indicated that a hypothetical anti-inflammatory drug that increased FEV<sub>1</sub> by 50ml, decreased exacerbations by 26%, and if priced at €35 per month, would be associated with an ICER ranging from €13,000 to €207,000 per QALY gained across different patient subgroups, with the lowest ICER in patients with severe COPD. The simulations identified which COPD drug profiles are most likely to be cost-effective and in which patient population this is most likely to be achieved.

Early estimates of cost-effectiveness, or of pricing options, may be useful in planning for product launch and approaches to market access. A linked PMPE model of rituximab for the treatment of follicular lymphoma, undertaken as a proof of concept, was used to predict the trial-based cost-effectiveness of a trial that had yet to report.<sup>27</sup> Using a population PK model and a PD model which linked serum drug concentrations to progression-free survival, the analysis simulated a phase III randomized controlled trial comparing rituximab, fludarabine and cyclophosphamide to rituximab, cyclophosphamide, vincristine and prednisolone induction chemotherapies for the treatment of stage II–IV follicular lymphoma. Utility and cost estimates for Markov model states representing disease progression, no progression, or death were used to project lifetime estimates of QALYs and health service costs. Two further analyses of rituximab as first line and maintenance therapy were compared with economic models based on completed trial results used by the National Institute for Health and Care Excellence (NICE). The predicted ICERs in these analyses were found to differ by 25% or less.

#### *5.1.2. Research and development (R&D) strategy and trial design*

Applications that are used to inform R&D strategy or trial design cover a wide range of possible decisions. Examples could include portfolio decisions or compound selection, choice of target patient population or dose and regimen selection. The influence of trial designs on economic outcomes may

be studied by examining the impact of imperfect drug adherence (or interventions to improve adherence), the choice of comparator or the inclusion/exclusion criteria. It may also be possible to determine optimal sample sizes of clinical trials with respect to the value provided by reduced uncertainty in expected value-based prices, e.g. Brennan & Breeze (2014)<sup>31</sup> and Dranitsaris et al. (2012)<sup>32</sup>, but there are no published examples of this being done using pharmacometric models. Another potential application is to inform decisions regarding clinical trial data collection, beyond sample size, according to the resulting reduced cost of the uncertainty in inputs to economic models, i.e. value of information.<sup>15</sup>

Poland & Wada (2001)<sup>26</sup> presented a real-world prospective case study of an HIV protease inhibitor drug in late-stage development. The objective was to evaluate alternative development strategies that differed in terms of the doses and regimens for treatment naïve or experienced patients. Models of patient adherence, PK, PD and viral dynamics were linked to an economic model in order to compare the development strategies in terms of their predicted net present value (NPV). The results highlighted the importance of adherence if using once-a-day dosing and suggested there would be high value to a longer lasting – more forgiving – drug formulation.<sup>33</sup> Many details of the modelling were omitted from the publication in order that the drug and pharmaceutical company involved could not be identified.

Van Hasselt et al. developed a PMPE model to assess the toxicity, dose intensity, disease progression, and cost-effectiveness of eribulin for castration-resistant prostate cancer.<sup>34</sup> The analysis utilized a semi-physiological model for neutropenia, the major dose-limiting toxicity of eribulin, a disease progression/clinical outcome model relating prostate-specific antigen dynamics to overall survival, and an economic model that incorporated quality of life and treatment-related costs. The motivation for the analysis was to illustrate how trial design and decision-making in oncology could be further informed using a model-based approach early in clinical drug development. Simulations evaluating

alternative treatment regimens, disease progression criteria, dose reduction rules, patient population and comparators were performed, and QALYs and ICERs were presented for a range of scenarios.

Hill-McManus & Hughes demonstrated how linked PMPE modelling could be used to optimise phase 3 trial design, focussing primarily on sample size determination.<sup>35</sup> This case study adopted a Bayesian decision theoretic approach to trial design in which the optimal design is that which is predicted to result in the greatest expected utility. The utility function employed was the expected pharmaceutical company return on investment. A prior distribution for the efficacy of a new treatment was obtained via pharmacometric based clinical trial simulation and used to calculate a posterior distribution given a proposed sample size. Posterior treatment efficacy was converted to a value-based drug price distribution via a pharmacoeconomic model and subsequently to company return on investment. This enabled uncertainty to be propagated from aspects of drug pharmacology through to the predicted return on investment, where drug prices are contingent on the results of phase 3 testing. Such an approach may have value in supporting trial design decisions and in identifying costly sources of uncertainty, and thus inform future research and development strategies.

#### *5.1.3. Pricing, reimbursement and market access decisions*

Linked PMPE modelling may be able to inform pricing decisions such as price setting to ensure sufficiently high likelihood of reimbursement, or to assess differences in potential prices across different markets and inform market entry strategies. A case study of urate-lowering therapies for treating gout showed how, prior to proceeding into phase 3 testing, a probability distribution of drug prices could be simulated based on target cost-effectiveness thresholds.<sup>36</sup> The simulations used uncertainty in PKPD model parameters to estimate the likelihood of cost-effectiveness over a range of drug prices and tested alternative biomarker to clinical outcomes modelling approaches and adherence scenarios. The results highlighted the importance of adherence in clinical trials for these medications in terms of its impact on effectiveness estimates and subsequent economic outcomes.

## 5.2. Other Applications

Linked PMPE modelling has been applied to research questions beyond drug development, adopting a societal, regulatory or payer perspective. This can enable reimbursement authorities or regulators to assess cost-effectiveness of treatments, or treatment strategies, where there is an absence of direct trial evidence. Published case studies using linked PMPE have been applied to assess the cost-effectiveness of pharmacogenetic-guided warfarin dosing algorithms,<sup>37</sup> to compare influenza pandemic treatment scenarios in terms of cost-effectiveness<sup>38</sup> and to make early predictions of the potential cost-effectiveness of generic versions of the direct oral anticoagulant dabigatran.<sup>39</sup>

Pink et al. used pharmacometric-based prediction of time within international normalized ratio (INR) range for warfarin based on a genetic dosing algorithm, to estimate the cost-effectiveness of different oral anticoagulation treatment strategies in patients with non-valvular atrial fibrillation.<sup>37</sup> Justification for taking this approach was based on there being many possible dosing algorithms – far more than might be conceivably tested in a clinical trial; and the magnitude of the differences in both benefits and costs being small, requiring a prohibitively expensive trial to demonstrate differences in haemorrhagic or stroke outcomes. The authors used a pharmacometric model that described the effects of *CYP2C9* and *VKORC1* genetic polymorphisms, alongside other clinical parameters, on the relationship between warfarin dose and INR response. Linked to this, the economic model utilized evidence from an indirect comparison of treatment options, a meta-analysis of the association between time in INR range and risk of haemorrhagic events and strokes, and costs and utilities derived from published sources. The principal finding, of an ICER for genotype-guided warfarin versus clinical algorithm–dosed warfarin of £13,226 per QALY gained compared favourably with a later analysis using trial data.<sup>40</sup> This example provided further evidence of the feasibility of applying a linked PMPE approach to estimate cost-effectiveness.

Kamal et al. developed an integrated modelling framework, including pharmacometric, epidemiology and economic models, to compare treatments under influenza pandemic scenarios for which it is not

practical to conduct clinical trials.<sup>38</sup> This utilized a PKPD model linked to a compartmental epidemiological susceptible, exposed, infected, recovered model, and economic model of costs and health outcomes. The number of infected patients per population of susceptible individuals was simulated for a series of pandemic scenarios, varying oseltamivir dose, basic reproductive number, and drug uptake. The study assumed the perspective of a potential US payer and used QALYs as the measure of benefit and assessed cost-effectiveness using ICERs. The results indicated that across all pandemic scenarios, 75 mg twice-daily oseltamivir was cost-saving and more effective compared to no treatment, with QALY gains of 430 per 100,000 population over 1 year in a scenario of low transmissibility and low severity. The authors concluded that this approach has the potential to inform government planning for an effective and cost-effective response to influenza pandemics. We consider that there is broad scope for linked PMPE in the assessment of value of antimicrobials, where this value depends on a drug's properties as well as where it is positioned in the strategic use of antimicrobials.<sup>41</sup>

Wang et al. applied linked PMPE modelling and simulation to assess the effectiveness and cost-effectiveness of potential future generic versions of the direct oral anticoagulant (DOAC) dabigatran.<sup>39</sup> DOACs have a narrow therapeutic range, and there is concern that future generics at the outer limits of bioequivalence may not be equivalent in terms of clinical effectiveness and might not be cost-effective versus the branded drug despite the difference in price. The authors used a previously published PKPD model and adapted and reproduced a previously published economic model. The models were used to simulate clinical event rates and to predict QALYs and ICERs for hypothetical generic dabigatran at the typical limits of bioequivalence of 80% and 125% systemic exposure, as well as at the more conservative bioequivalence limits of 90% to 112.5%. The results showed that generics with 80% systemic exposure relative to the branded medication were predicted to result in higher QALYs and lower costs, whereas those with 125% systemic exposure showed worse cost-effectiveness due to increase in bleeding events. The authors acknowledge that these simulations represent the worst-case scenario in terms of bio-inequivalence, however, the work highlights that cost-



effectiveness prediction may be useful in assessing the value of generic substitution particularly where there are steep concentration-effect relationships.

## **6. Considerations in Linking Pharmacometrics and Pharmacoeconomics**

In this section we consider five important concepts in the application of linked PMPE models during drug development and how they have been dealt with in the published case studies. These concepts are i) value outcomes, typically these have been based on QALYs, but this may not always be appropriate; ii) evidence on comparators, which is an essential input for linked PMPE models; iii) the approach to linking multiple intermediate endpoints; iv) dealing with model uncertainty, and; v) the challenge of model validation.

### **6.1. Value Outcomes**

All but one of the case studies identified used the QALY as the outcome measure for use in a cost-effectiveness calculation. There may, however, be other treatment effects, beyond those captured in QALYs, which may contribute to how patients or society value new treatments and their opportunity costs.<sup>42,43</sup> These could include convenience (e.g. dose frequency, method/route of administration or treatment monitoring), as well as measures that incorporate patient preferences and/or risk aversity over the distribution of outcomes, and broader societal considerations (e.g. equity or work productivity). Where reimbursement decisions are known to be based on a range of different criteria, the task of early economic evaluation is likely to be more challenging.

In theory such additional dimensions of treatment effect could be incorporated within early economic evaluations if the necessary studies are performed at an earlier point in development. Methods such as discrete choice experiments<sup>44</sup> are available for assessing the relative weights that patients, or payers, place on different treatment outcomes. The results could then be represented by willingness-to-pay for product characteristics or translated into health state utility increments for use in cost-effectiveness analysis.<sup>45</sup> Alternatively, reimbursement decision making involving a range of criteria can be modelled using multi-criteria decision analysis (MCDA).<sup>46</sup> Regardless of the approach adopted, an understanding of the decision-making process for the relevant reimbursement authorities is required.

## 6.2. Evidence on Comparators

Pharmacoeconomic evaluations are inherently comparative; in HTA this will typically involve assessing the incremental benefit and cost of a new treatment relative to another that is often the current standard of care (SoC). The relevant comparators are those that the reimbursement authority considers would be most widely used in the clinical context, and it is essential that these are identified. Whilst from a drug development perspective, the only data available on a development candidate may be that which is generated 'in-house' through the conduct of clinical studies, evidence on comparators could come from a wide range of sources. Incorporating evidence on comparators in PMPE models may be achieved using point estimates from previous studies, published PKPD models or meta-analytic approaches for evidence synthesis.

A variety of approaches have been used to incorporate comparator evidence in the published examples of linked PMPE. Van Hasselt (2015)<sup>34</sup>, Hill-McManus (2019)<sup>28</sup>, Kamal et al. (2017)<sup>38</sup> and Wang et al. (2020)<sup>39</sup> effectively focussed on a single drug and so additional evidence on active comparators was not required. Poland and Wada (2001)<sup>26</sup> did not conduct a comparative economic evaluation and, therefore, did not explicitly consider the likely outcomes of comparators. Hill-McManus et al. (2018)<sup>36</sup> and Hill-McManus & Hughes (2020)<sup>35</sup> used published PK models for the comparators and constructed a PD model based on published phase 1 trial data and other published models but did not use a meta-analytic framework. Pink et al. (2012)<sup>27</sup> used trial results for comparators as well as data from an existing meta-analysis of clinical trials. Both Pink et al. (2014)<sup>37</sup> and Slejko et al. (2016)<sup>30</sup> employed meta-analyses that linked an intermediate biomarker endpoint to clinical endpoints. This latter example used an MBMA and could, therefore, predict economic outcomes for a range of drug efficacies as well as trial design inputs.

Meta-analyses of published data have become the main sources of evidence on comparative effectiveness and safety.<sup>47</sup> Traditional meta-analysis focuses on head-to-head comparisons of drugs administered in the same trials and ignores the (often considerable) data available from other studies

involving these drugs. Network meta-analysis (NMA) combines direct and indirect evidence, allows comparisons of multiple treatments<sup>48</sup>, and thereby synthesises a greater share of the available evidence than a traditional meta-analysis.<sup>49</sup> NMA is often used in HTA for simultaneous indirect comparison of effects of multiple treatments using studied doses and treatment durations<sup>50</sup>, and therefore, has limited potential to extrapolate to different doses and durations.

MBMA is a meta-analysis that incorporates parametric pharmacology models for the effect of treatment and patient population characteristics (e.g. different baseline disease severity) on outcomes.<sup>51</sup> In a drug development setting, MBMA models are useful to predict different doses, time points, patient populations, and endpoints when progressing from one phase of development to the next. MBMA may inform i) quantitative criteria for the target product profile to position a new drug relative to the SoC and/or emerging competitors, ii) probability of success (e.g. being preferred over SoC and/or emerging competitors), iii) early insights into best-in-class potential and iv) probability of technical success in demonstrating superiority or non-inferiority in an actual head-to-head trial. Additional examples of strategic integration of MBMA across the drug research-development–utilization continuum are provided by Upreti & Venkatakrishnan (2019)<sup>51</sup>. More recently, a framework for dose-response and time-course model-based network meta-analysis (MBNMA) has been proposed that combines, often nonlinear, MBMA modelling with the statistically robust properties of NMA.<sup>52,53</sup>

### **6.3. Handling of Multiple Endpoints**

Within the context of drug development, the purpose of PMPE modelling is to provide a framework wherein patient relevant outcomes forming the basis for reimbursement decisions (e.g. survival and quality of life) can be estimated from drug exposure. However, a direct relationship between drug exposure and such outcomes is unlikely to be characterised during drug development, especially in early phases. Efficacy and safety are instead measured using intermediate endpoints, often biomarkers, which may change during drug development as the scale and nature of clinical testing evolves. Intermediate/biomarker outcomes may also be accepted by regulatory agencies and

reimbursement authorities (e.g. leukemia<sup>54</sup>) as the basis for decisions making and, therefore, used as primary surrogate endpoints in pivotal phase 3 clinical trials.<sup>55</sup> The nature and validity of surrogate endpoints, and whether surrogates are accepted by regulators/reimbursement authorities, may influence how, and whether, PMPE modelling is informative.

The use of biomarker and clinical endpoints in published PMPE studies is summarised in Table 4, using definitions taken from the Biomarkers Definition Working Group study.<sup>56</sup> A diagrammatic representation of the linking of intermediate and final endpoints in three of the published case studies is given in Figure 2. Two studies did not use biomarker endpoints at all, and drug exposure was linked directly to the rates of clinical events. These studies were either assessing the use of a drug in a new indication<sup>27</sup> or as a generic version of an already marketed drug. Therefore, these benefitted from the availability of numerous clinical studies having been reported, including pivotal phase 3 trials.

Most PMPE case studies used a biomarker as an intermediate endpoint that was then linked to clinical event rates. Typically, the relationship between biomarker and clinical events was well evidenced and had been used previously for other therapies in the same, or similar, indication. For example, Pink et al. (2014)<sup>37</sup> performed a meta-analysis of the relationship between INR and bleeding and thromboembolic events; and, Slejko et al. (2016)<sup>30</sup> used MBMA to combine data across many studies to describe the relationship between FEV<sub>1</sub> and COPD exacerbations. Two case studies in gout used a biomarker, serum uric acid, whose relationship to the relevant clinical event rates is poorly evidenced.<sup>28,36</sup> This biomarker, however, although not validated,<sup>57</sup> was used as a surrogate outcome in the clinical trials. The linking of these endpoints was thus undertaken as part of the pharmacoeconomic component of the modelling.

#### **6.4. Modelling Uncertainty**

Methods to quantify the extent of uncertainty in modelled outcomes and to examine the relative contribution of model inputs to that uncertainty are used in both pharmacometrics<sup>58</sup> and pharmacoeconomics.<sup>59</sup> In both disciplines, sources of uncertainty can be broadly classified as either

relating to the model parameters (usually due to sampling) or to model structural assumptions. That similar approaches to handling these types of uncertainty have emerged in both disciplines suggests these may be readily applied to linked PMPE models. To examine parameter uncertainty, pharmacometrics and pharmacoeconomics both use similar methods of Monte Carlo simulation for sensitivity analyses in which models are evaluated multiple times with parameters varied simultaneously over the entire parameter space. In pharmacometrics this is known as global sensitivity analysis (GSA)<sup>60</sup>, while in pharmacoeconomics, it is known as probabilistic sensitivity analysis (PSA).<sup>61</sup> Approaches to assessing structural uncertainty include transforming to parametric uncertainty<sup>62,63</sup> and model averaging.<sup>64,65</sup>

The published PMPE case studies considered model uncertainty using a variety of one-way (or local) sensitivity analyses and probabilistic (or global) sensitivity analyses. The studies using a probabilistic sensitivity analysis approach generated a distribution of outcomes by assigning probability distributions to model inputs and using Monte Carlo simulation to generate model outputs using new sets of input parameters.<sup>27,28,30,36,37</sup> Where the influence of specific parameters was assessed this was only undertaken using one-way (or local) sensitivity analyses, not using methods that account for model outputs being non-linear in input parameters. More useful for R&D decisions and study design is likely to be the relative contribution of the uncertainty in specific model parameters to the overall uncertainty in modelled outcomes. There are methods from both pharmacometrics/systems pharmacology and pharmacoeconomics for this purpose,<sup>60</sup> for example, pharmacoeconomic models have applied methods taken from Bayesian decision theory.<sup>66</sup> One of the case studies did adopt a value of information approach<sup>35</sup> but stopped short of computing the expected value of partial perfect information for model parameters. None of the studies attempted to examine the impact of structural uncertainty beyond some one-way sensitivity analyses testing alternative modelling assumptions.

## **6.5. Model Validation**

By model validation we are referring to the process of evaluating whether a model is a proper and sufficient representation of the system it is intended to represent in view of an application. This encompasses whether the model is in accordance with what is known about the system and the extent that the results can serve as a solid basis for decision making.<sup>67</sup> Validation is an important element in model development and is relevant to a number of different aspects, such as the conceptual model, the selection and processing of input data and the outputs of the operational model.<sup>68</sup> Other terms are also used to describe this process, such as model qualification in the disciplines of pharmacometrics and quantitative systems pharmacology.<sup>69,70</sup> Linked PMPE models may be more difficult to validate owing to the additional uncertainty introduced as compared with application of the individual components.<sup>30</sup> The common technique of comparison of model outcomes with external data is often problematic for pharmacoeconomic models where such empirical data may only become available years in the future, if at all.

Few of the published linked PMPE case studies have included significant reporting of efforts to validate the models. Here we summarise efforts described to validate model outcomes by comparing these to empirical data. Pink et al. (2012)<sup>27</sup> compared simulated ICERs with two actual trial-based economic evaluations, and observed differences of 18% and 25%, although the 95% central ranges of predicted ICERs also included the trial-based results. The authors predicted the cost-effectiveness for a comparison between treatments based on a trial that had yet to begin (NCT01303887), which will provide a valuable opportunity to assess model validity when this trial reports. Pink et al. (2014)<sup>37</sup> performed external validation of the PKPD model by comparing simulated versus actual time in therapeutic range. These authors also showed comparable ICERs when using simulated and trial-based biomarker response data,<sup>40</sup> based on incremental QALY gains (warfarin genotyping vs standard dosing) of 0.003 and 0.004, and costs of £41 and £26 from each study, respectively. Slejko et al. (2016)<sup>30</sup> conducted external validation of a MBMA using published trial results. Hill-McManus et al. (2018)<sup>36</sup> obtained ICERs of between £39,000 to £78,000 per QALY gained, depending on assumed drug adherence, as compared with an ICER of at least £62,000 per QALY gained reported by NICE.<sup>71</sup>

## 7. Discussion

Linked PMPE modelling and simulation has been recognised as a methodology that can enable and enhance economic evaluation during drug development and beyond. There is a small but growing literature of applications to drug development decisions problems and to those regarding optimisation of existing therapies. We identified ten examples from the published literature which are summarised in this paper. These span a wide range of drugs and disease areas; with applications concerning drug go/no-go; R&D strategy and trial design; and PRMA decisions. Other identified applications include estimating the cost-effectiveness of complex pharmaceutical interventions (such as in the context of pharmacogenomics), generic medicines with narrow therapeutic indices, and treatments of infectious diseases.

During early drug development, compared to conventional pharmacoeconomic evaluations, linked PMPE may potentially enable a far broader range of research questions to be addressed by exploiting pharmacometric models of the exposure response relationships. As the published case studies show, this can include consideration of the economic outcomes associated with treatment of specific patient subgroups, alternative doses or regimens, or protocol deviations such as non-adherence. The overarching objective is that incorporating such approaches within the decision-making process will contribute to reducing drug development costs by improving decisions regarding project termination and trial design. However, linked PMPE may be of no greater value to decision makers than existing approaches where there is limited patient data, lack of evidence on comparators or poorly characterised relationships between biomarkers and clinical outcomes.

It would seem that there is currently a great deal of interest in early economic evaluation and the coming years are likely to see a growth in the number of applications, furthering our understanding of the potential of such innovative interdisciplinary methods. The recent article by Grutters et al.<sup>18</sup> and the subsequent commentaries<sup>72</sup> provides a valuable discussion from multiple perspectives on some of the same issues raised in this review, although in the context of non-drug interventions and early



economic modelling in general. An article published whilst ours was under review, aimed towards a health economics audience, also discusses the literature on incorporating pharmacometrics into pharmacoeconomics.<sup>73</sup> These authors conclusions, in line with our own, point to the potential of this methodology to inform drug development decision-making and the need for greater collaboration between the pharmacoeconomics and pharmacometrics communities.

Nearly all the case studies adopted incremental QALYs as the measure of treatment benefit, which yields an ICER as a metric of cost-effectiveness when combined with incremental costs. The application of early economic evaluation will be more complicated in situations where QALYs do not capture all the important treatment benefits, and when payers do not apply ICER-based decision rules or their process and criteria for decision making is not transparent. This may necessitate the use of additional techniques such as MCDA and other measures of treatment value. Early engagement with payers is clearly important in order that emerging therapies can be assessed against appropriate criteria, and so that future studies are designed to generate evidence that satisfies the requirements of decision makers.

The linked PMPE modelling framework provides a tool to combine and propagate the uncertainty from inputs to an estimate of uncertainty in economic outcomes, such as cost-effectiveness or drug price. We found that most of the published case studies had performed a probabilistic assessment of outcome uncertainty in which input parameters were varied simultaneously over the entire parameter space. The linked PMPE methodology, in which a series of models link across multiple intermediate endpoints, will typically require a large number of input parameters that may be highly uncertain early in drug development. This would then result in highly uncertain economic outcomes with limited value to decision makers. In this case, value of information analysis<sup>74</sup> may be more useful than the point estimates, enabling the cost associated with sources of uncertainty to be identified and valuing study designs according to the extent that they reduce uncertainty.<sup>15</sup> Only one of the case studies used a value of information approach, where trial design was optimised by comparing the value of the

resulting evidence in terms of its influence on drug prices.<sup>35</sup> This framework could be readily extended to assess the influence of parameters on decision uncertainty (expected value of partial perfect information<sup>66</sup>) and to direct future research efforts. These methods are well established in healthcare resource allocation decisions from a societal perspective, but there are few examples published taking a pharmaceutical industry perspective.<sup>31,75</sup> We consider that value of information may have considerable potential to add value during drug development and would benefit from further research.<sup>15</sup>

Each of the published case studies has the form of a standalone exercise designed to inform a drug development decision or optimise the use of existing therapies. Early economic models, however, could be applied iteratively throughout drug development, incorporating emerging data on treatment efficacy, safety and pharmacology to provide increasingly robust assessments of the commercial potential of development candidates. This approach has long since been encouraged<sup>11,12</sup> but, as far as we are aware, economic modelling during drug development is not routinely applied in this way. The pharmacoeconomic model for a specific disease area, target population and type of treatment may, structurally, not change substantially over the drug development timeline. Safety and efficacy profiles, providing inputs to pharmacoeconomic models, will be estimated with increasing confidence as further studies are conducted and pharmacometric models may then enable applications to a wider range of research questions. This could involve an iterative process of Bayesian updating of model inputs, synthesising evidence across the development timeline, such as has been demonstrated for medical device development.<sup>76</sup>

The concept of a framework in which quantitative methods are applied iteratively to inform decision making during drug development is an established principle of the model informed drug development (MIDD) paradigm.<sup>77</sup> MIDD embraces the integration of systems pharmacology and pharmacometric modelling approaches; empirical time course analysis including disease progression modelling, empirical to semi-mechanistic PKPD modelling and MBMA approaches. The application of these

methods in dose/trial optimisation, to inform labelling and R&D decision-making is well established.<sup>77-</sup>

<sup>79</sup> There is a growing appreciation of the value of these methods in enabling more efficient development and regulatory acceptance of novel medicines.<sup>80,81</sup> It is also increasingly being accepted by regulators that MIDD offers an alternative approach to risk-benefit evaluation where there is high unmet medical need and/or there are difficulties in conducting trials.<sup>80-83</sup> Incorporating early pharmacoeconomic modelling within the MIDD framework would naturally promote linkage between these methods and associated disciplines.<sup>84</sup>

This review was limited by only having access to applications of linked PMPE modelling and simulation that were published. This may, in fact, only be a small proportion of all such analyses that have taken place, since the majority may be being performed by the pharmaceutical industry in-house and deemed unpublishable due being considered too commercially sensitive. Nevertheless, the published literature contains a small number of examples that demonstrate the range of therapies, disease areas and decisions for which insights can be gained through the use this interdisciplinary approach.

A potential barrier to the integration of pharmacoeconomic modelling within drug development decision making is the historical separation of clinical development and commercial functions within the pharmaceutical industry, with technical experts and modellers in separate organisational arms linked only by high-level review and governance. It has been suggested that substantial changes to the pharmaceutical industry operating model, including the breaking down of functional silos, are needed to help reverse the trend of declining R&D productivity.<sup>3,85</sup> Our view is that optimal functioning, with respect to effective integration of predictive modelling within a defined organisational structure, needs to be driven by common and integrated goals that promote cross-functional collaborative end to end working. With this in mind the R&D business process, starting with the desired target product profile, needs to foster greater cross-functional and interdisciplinary alignment to enable innovative interdisciplinary activities such as linked PMPE modelling and simulation becoming a more standard component of clinical development plans.

Relevant to both the early engagement with payers to understand what constitutes value and to the bridging of company clinical development and commercial functions are initiatives to foster dialogue between regulators, payer/HTA/reimbursement organisations and the pharmaceutical industry. These include the US FDA paired meeting pilot program for providing regulatory input on MIDD issues<sup>80</sup> and the availability of parallel scientific advice from both the EMA and HTA bodies<sup>86</sup>. These may naturally encourage cross-functional collaboration and provide information regarding the payer landscape which is essential to early pharmacoeconomic modelling. Early pharmacoeconomics is also relevant to the risk minimization and management efforts and could promote the development of commercial risk management plans. Furthermore, it has been proposed that risk minimization may be operationalised in a way that serves as a bridge between clinical drug development and commercial functions within organisations.<sup>87</sup>

Other barriers to the application of linked PMPE modelling and simulation include technical issues such as the appropriate software platforms, and the challenge of communicating novel interdisciplinary methods to decision makers. Widespread application of this methodology may benefit from a common data science platform for managing data and associated expertise. The use of certain software packages within each discipline may also restrict integration, such as the prevailing use of NONMEM (pharmacometrics) and MS Excel (pharmacoeconomics). The use of more flexible (and open source) solutions such as R, Python or Julia is becoming more widespread and this would support a collaboration between disciplines. The disciplines also differ to some extent in the standard terminology used to describe the same, or similar, modelling issues, presenting a potential source of confusion. Finally, decision makers across R&D and commercial functions may require education in relation to the potential productivity gains to be achieved through novel or interdisciplinary approaches, such as linked PMPE modelling and simulations, as is occurring in relation to Artificial Intelligence.

In conclusion, while linked PMPE modelling and simulation remains relatively novel, with few published case studies, it has potential across a range of applications from early drug development to post-marketing. It 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 pharmacoeconomic practices which do not utilise exposure response relationships. Closer integration and collaboration between the disciplines of clinical pharmacology, pharmacometrics and health economics, is needed in order to realise the potential benefits and promote greater acceptance of this methodology.

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#### **AUTHOR CONTRIBUTIONS**

DH-M drafted the manuscript and SM, JL, RW and DH revised it critically for important intellectual content; DH-M, SM, JL, RW and DH gave final approval of the version to be published; DH 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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## TABLES

Perspective	Type of decision	Timing	Examples
Pharmaceutical industry/drug development	Go/no-go	Drug discovery	Combine payer value criteria, disease area knowledge and comparator data to inform decision of whether to initiate drug discovery
		Early development	Update economic models as clinical data becomes available and model potential pricing options and market size to inform decision to continue development
		Late development	Simulation of phase 3 trial to predict pricing options or cost-effectiveness to inform decision to progress into phase 3 testing
	R&D strategy and trial design	Any	Prediction of cost-effectiveness or pricing for a range of scenarios to inform selection of indication, target product profile, dose or dosing regimen Quantify the impact of uncertainty in economic model inputs to inform the data collection objectives of later studies
	PRMA	All stages	Prediction of benefit and cost-effectiveness over comparators under different scenarios to enhance value proposition Predict the probability of reimbursement at different prices in order to inform price setting decisions
Society/payer	Optimise resource allocation	NA	Predict the cost-effectiveness of interventions where trials would be difficult/impossible (e.g. choose among many treatment strategies)

**Table 1. Classification and purpose of linked PMPE applications\***

\*Pricing, reimbursement and market access



Study	Disease area	Drug(s)	Perspective <sup>1</sup>	Approximate timing <sup>1</sup>	Type of decision <sup>1</sup>	Research questions
Poland & Wada (2001)	HIV	Not stated	Pharmaceutical industry/drug development	Early development	Research strategy and trial design	Dose selection Dose regimen selection Adherence monitoring
Pink et al. (2012)	Follicular non-Hodgkin's lymphoma	Rituximab	Pharmaceutical industry/drug development	Late development	Go/no-go	Early cost-effectiveness Go/no-go
Pink et al. (2014)	NVAF	Warfarin	Applicable to multiple perspectives	Post-marketing	Optimise treatments	Cost-effectiveness of pharmacogenetic dosing
Van Hasselt et al. (2015)	Castration Resistant Prostate Cancer	Eribulin	Pharmaceutical industry/drug development	Late development	R&D strategy and trial design	Early cost-effectiveness
Slejko et al. (2016)	COPD	NA	Pharmaceutical industry/drug development	Early development	Research strategy and trial design	Cost-effectiveness by subgroup
Kamal et al. (2017)	Influenza	Oseltamivir	Applicable to multiple perspectives	Post-marketing	Optimise resource allocation	Dose selection by pandemic scenario
Hill-McManus et al. (2018)	Gout	Allopurinol; febuxostat; lesinurad	Pharmaceutical industry/drug development	Late development	PRMA	Impact of non-adherence on cost effectiveness
Hill-McManus et al. (2019)	Gout	Febuxostat	Pharmaceutical industry/drug development	Drug discovery	Go/no-go	Value of more potent/extended half-life ULT
Wang et al. (2020)	Atrial fibrillation	Dabigatran etexilate	Applicable to multiple perspectives	Post-marketing	Optimise resource allocation	Cost-effectiveness of generic dabigatran
Hill-McManus & Hughes (2020)	Gout	Febuxostat	Pharmaceutical industry/drug development	Late development	Research strategy and trial design	Optimise trial design to maximise company return on investment

**Table 2. Summary of applications of PMPE in terms of disease area and type approach and decision problem\***

<sup>1</sup> See Table 1

\* PRMA: Pricing, reimbursement and market access; NVAf: Non-valvular atrial fibrillation; ULT: Urate-lowering therapy

Study	PK Model?	Disease progression model?	Pharmacoeconomic model structure	Assessed non-adherence?	Assessed doses/regimens?	Assessed subgroups?
Poland & Wada (2001)	Yes	Yes	Company profit model	Yes	Yes	No
Pink et al. (2012)	Yes	No	Markov model	No	No	Yes
Pink et al. (2014)	Yes	No	DES	Yes	No	Yes
Van Hasselt et al. (2015)	Yes	Yes	IPS	No	Yes	Yes
Slejko et al. (2016)	No	Yes	Individual Markov	No	No	Yes
Kamal et al. (2017)	Yes	Yes	Decision tree	No	No	No
Hill-McManus et al. (2018)	Yes	Yes	Markov model	Yes	No	No
Hill-McManus et al. (2019)	Yes	Yes	Markov model	Yes	No	No
Wang et al. (2020)	Yes	No	Markov model	No	No	No
Hill-McManus & Hughes (2020)	Yes	Yes	Markov model	Yes	Yes	No

**Table 3. The types of sub-models and specific analyses employed in available examples of PMPE studies**

PK: Pharmacokinetic; DES: Discrete event simulation; Individual patient simulation.

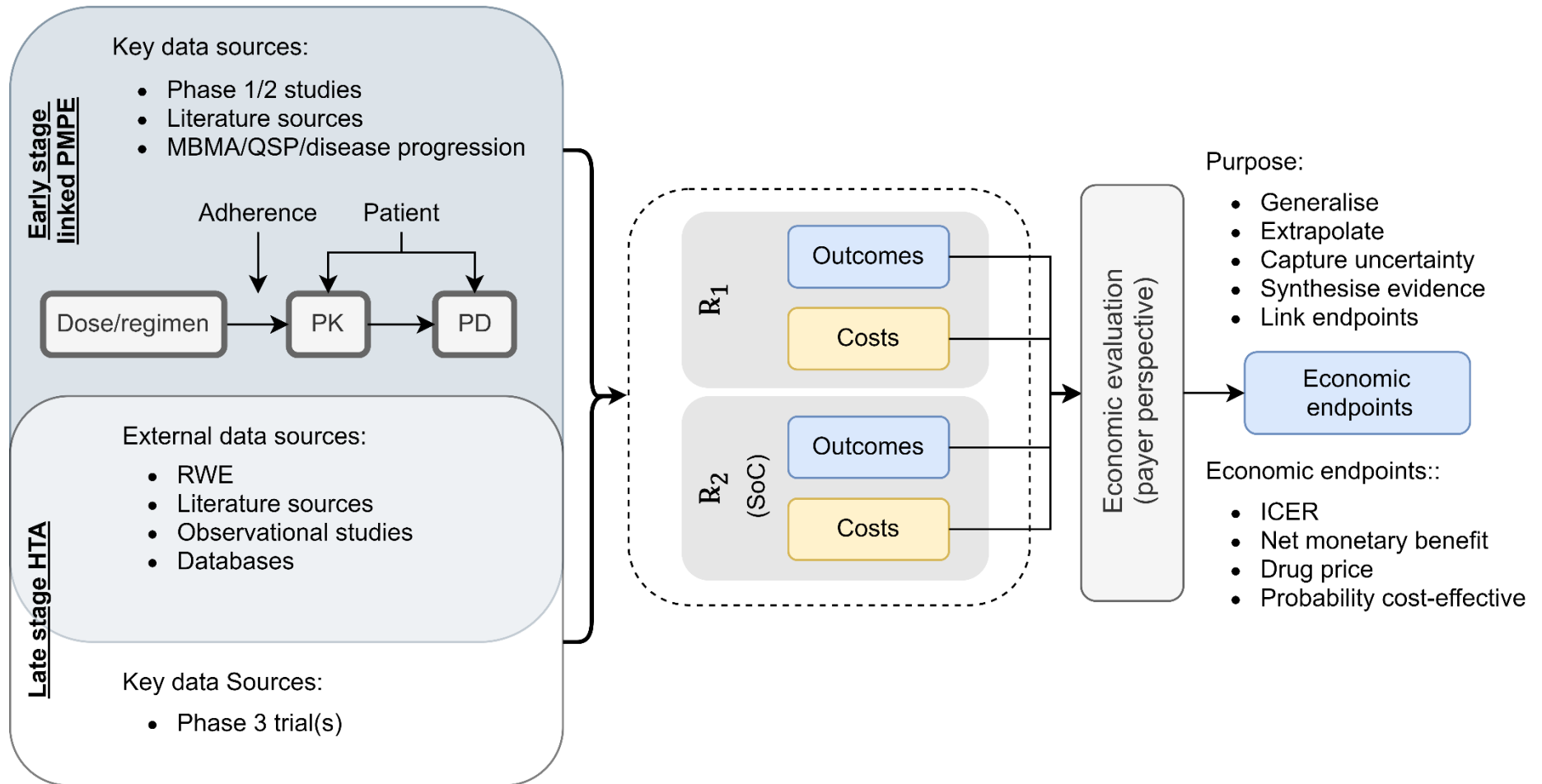
Study	Biomarker endpoints	Trial surrogate endpoints?	Clinical endpoints	Pharmacoeconomic endpoints	Cost-effectiveness metric	Uncertainty
Poland & Wada (2001)	HIV viral load	NA	NA	NPV	NPV	Elicitation One-way
Pink et al. (2012)	NA	No	Progression-free survival (clinical outcome)	Costs & QALYs	ICER	PSA
Pink et al. (2014)	International normalized ratio	No	Strokes & major bleeds	Costs & QALYs	ICER	PSA
Van Hasselt et al. (2015)	Prostate-specific antigen	No	Quality of life & survival	Costs & QALYs	ICER	One-way SA
Slejko et al. (2016)	Forced expiratory volume 1 second	NA	COPD exacerbations	Costs & QALYs	ICERs	PSA
Kamal et al. (2017)	Time to cessation of viral shedding	No	Influenza-related complication & death	Costs & QALYs	ICERs	One-way SA
Hill-McManus et al. (2018)	Serum uric acid concentration (biomarker)	Yes	Acute gout flares	Costs & QALYs	ICERs	PSA (PKPD model)
Hill-McManus et al. (2019)	Serum uric acid concentration (biomarker)	Yes	Acute gout flares	Costs & QALYs	Drug price	PSA (PKPD model)
Wang et al. (2020)	NA	No	Strokes & major bleeds	Costs & QALYs	ICERs	PSA
Hill-McManus & Hughes (2020)	Serum uric acid concentration (biomarker)	Yes	Acute gout flares	Costs & QALYs	Drug price/ROI	PSA (PKPD model)

**Table 4. The types of endpoints used at stages in available examples of PMPE studies\***

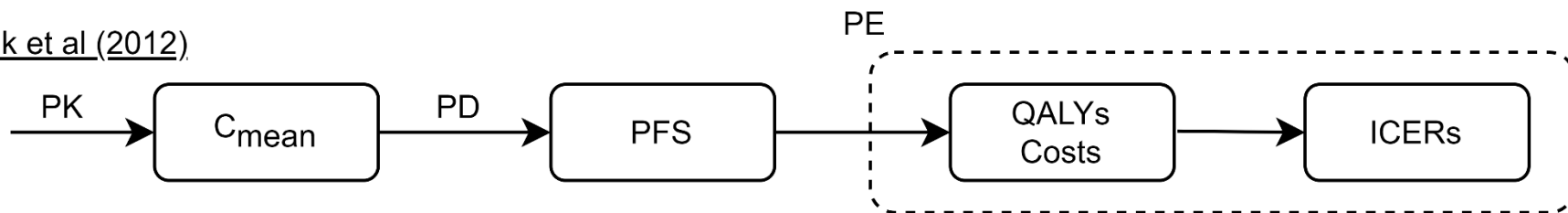
QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; SA: sensitivity analysis; PKPD: pharmacokinetic-pharmacodynamic; NPV: Net present value; ROI: Return on investment.

\* Biomarker: a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention; surrogate: a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence; clinical endpoint: a characteristic or variable that reflects how a patient feels, functions, or survives.<sup>1</sup>

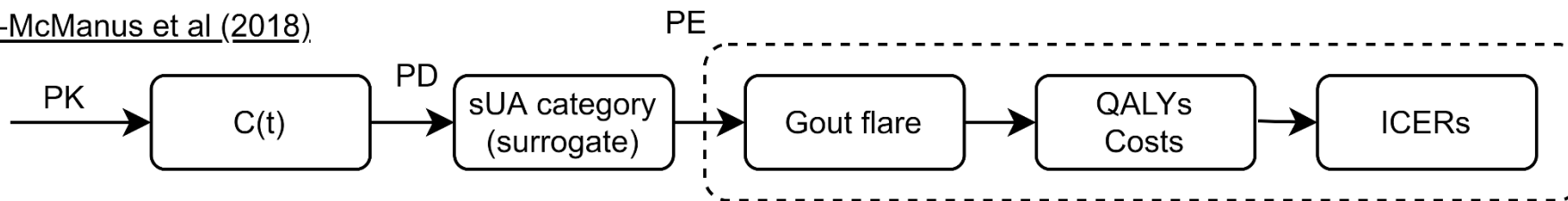
**FIGURES**



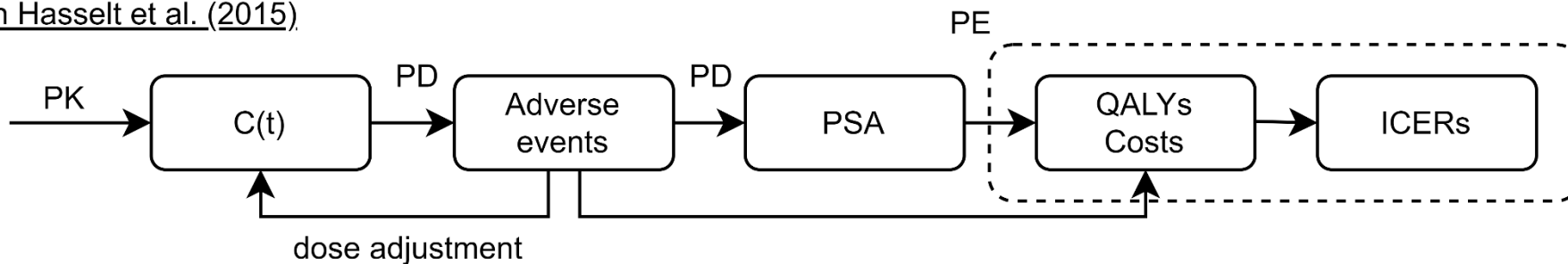
Pink et al (2012)



Hill-McManus et al (2018)



Van Hasselt et al. (2015)



## FIGURE LEGENDS

**Figure 1.** Use of evidence sources within pharmacoeconomic evaluations for late-stage health technology assessment, and early stage linked PMPE modelling where costs and outcomes of one or more drugs are informed via pharmacometric modelling and simulation.

R: treatment; SoC: standard of care; ICER: incremental cost-effectiveness ratio; PK: pharmacometrics; PD: pharmacodynamics; RWE: real-world evidence; MBMA: model-based meta-analysis; QSP: quantitative systems pharmacology

**Figure 2.** Examples of the simplified endpoint modelling sequences or causal pathways implemented in published PMPE case studies

PK: pharmacokinetics; PD: pharmacodynamics; C: drug plasma concentration; sUA: serum uric acid concentration; PFS: progression free survival; PSA: prostate specific antigen; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio.