



Optimizing Trial Design

Incorporating MCDA into Trial Simulation

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Introduction

Efforts by regulatory agencies to balance the need to ensure rapid access to new drugs with the need to gather data on efficacy and safety have produced a number of innovations in regulatory science.¹ This paper is concerned with two such innovations - the use of modeling and simulation and the use of patient-preference data. Our objective is to consider how they are currently supporting regulators, and how they can be used in combination to improve the efficiency of clinical development, identify differences in benefit-risk balance, and support proactive risk management.

Trial Simulation

Modeling and Simulation (M&S) is being used more and more to understand the likely impact of trial design

scenarios on the outcome of an intervention, not only with the objective of preventing failures, but also to increase the probability of success.² M&S is used to predict variations in treatment response with factors such as dose, time on treatment, different physiological and pathological conditions, and covariates such as disease severity, co-medication, co-morbidities, and compliance. This insight can be used to perform *in silico* clinical trials, also known as clinical trial simulations (CTS), which enable optimization of the design of prospective trials, including decisions such as the dose, comparator, population, inclusion/exclusion criteria, sample size, and endpoints. By doing so, attrition can be reduced and consequently development costs are lowered. Most importantly, these technologies allow for a kill-fast approach, enabling tough decisions to be made in a timely manner.

The past decade has seen an increase in the appreciation by regulators of the role of M&S in drug development, and an increased influence of M&S on risk/benefit assessment and labeling decisions.^{3,4} This interest initially focused on using pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PKPD) models to understand dose-response relationships. These principles were already embedded by the U.S. Food and Drug Administration (FDA) in the publication *Guidance for Industry: Population Pharmacokinetics*⁵ in 1999 and *Guidance for Industry: Exposure-Response Relationship – Study Design, Data Analysis, and Regulatory Applications* in 2003.⁶ This was later complemented by additional guidance, as the applications and demand for M&S increased.

- In 2009, the FDA published its *Guidance for Industry: End-of-Phase 2A Meetings*,⁷ encouraging sponsors to seek regulatory meetings at the end of Phase 2A to discuss trial simulation.
- Regulators' collated examples of the impact of M&S on approval. The FDA has published a number of reviews regarding how M&S enabled approval of unstudied dose regimens, provided confirmatory evidence of effectiveness, and utilized primary endpoints derived from model-based approaches.⁸ Similar efforts have been undertaken by the European Medicines Agency (EMA), which has organized two major workshops on the subject since 2011.⁹
- Modeling and simulation approaches are included in the FDA's published strategic priorities and are expected to be incorporated in the 2017 Prescription Drug User Fee Act (PDUFA) reauthorization.¹⁰

In parallel with these developments, industry has been systematizing its approach to using M&S for drug development. For instance, in 2007 Pfizer published its approach to model-based drug development (MBDD), outlining how decision points throughout the development of their drugs are informed by MBDD, and how PKPD and disease models could be combined with trial performance metrics and decision criteria to support decision making and prioritize compounds. The same approach was used to gather quantitative insight into competitors.¹¹ Further, industry has evaluated the costs and benefits of using M&S in product development: Pfizer estimated that it enabled a reduction in the annual clinical trial budget of \$100 million and increased late-stage clinical study success rates; and Merck & Co./MSD has reported cost savings of \$0.5 billion through impact of MBDD on decision-making.²

Case Study

An example of the concept has recently been published by Bellanti and collaborators.¹² Clinical trial simulation was used to characterize the time course of five clinical endpoints relevant for the evaluation of iron chelation therapy in pediatric patients affected by chronic iron overload. Partial values and weights for these endpoints were obtained from experts and aggregated into an overall benefit-risk score. The analysis identified alternative regimens that would benefit sub-groups of patients, which was linked back to their different pharmacokinetics and pharmacodynamics. The study demonstrates the feasibility of integrating PKPD relationships into benefit-risk methodologies such as multi-criteria decision analysis (MCDA).

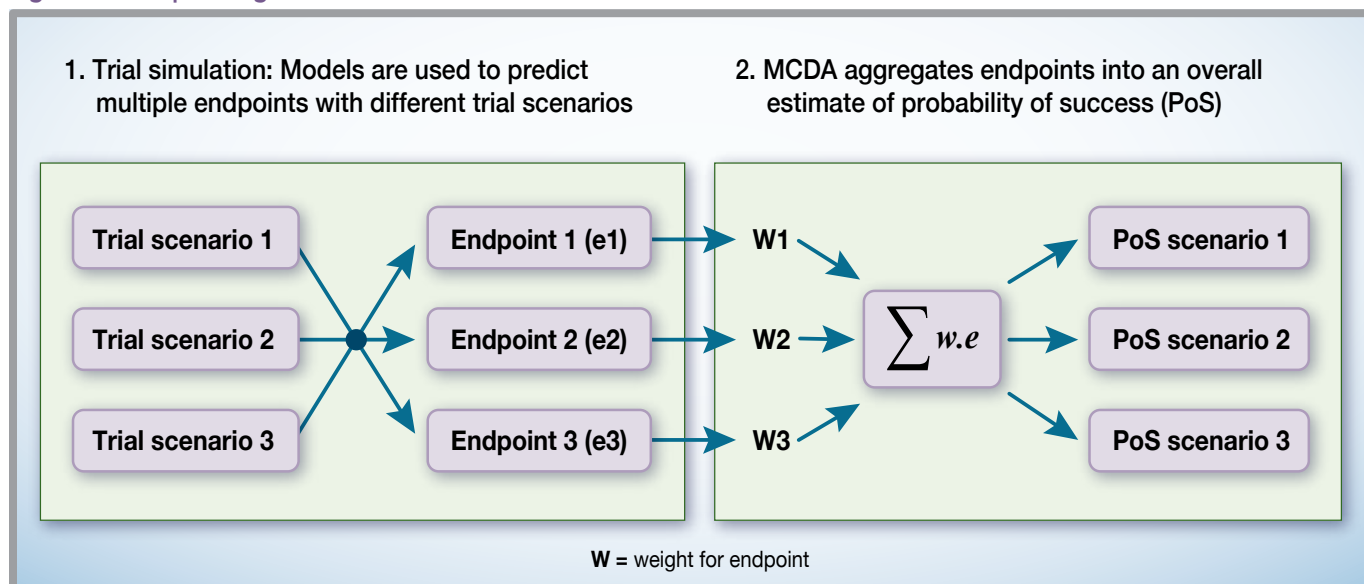
Multi-Criteria Decision Analysis

Multi-Criteria Decision Analysis (MCDA) refers to a collection of analytical methods for supporting decision making and evaluation in the face of multiple, often conflicting, criteria. A number of common steps are often used to define MCDAs, including: defining the decision problem, identifying criteria, measuring the performance of treatments against criteria, eliciting preferences for criteria, and aggregation.¹³ The use of MCDA in healthcare has increased over the last 10 years, and it is used to inform many decisions, including: portfolio optimization, approval, reimbursement, and prescription decisions.¹³ Given this increased interest in MCDA, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recently published guidance on good practice in the use of MCDA in healthcare.¹⁴

In the regulatory space, MCDA is often referred to as quantitative benefit-risk assessment (BRA). The use of MCDA/BRA to support regulatory decision making has been endorsed by a number of authorities, including: the EMA's BRA Methodology project,¹⁵ IMI PROTECT,¹⁶ and ISPOR's working group on risk-benefit management.¹⁷ For instance, the EMA's BRA methodology project concluded that, where the benefit-risk balance was marginal, MCDA could support the approval process.

More recently, both the EMA and the FDA have been investing in projects to determine how to incorporate patients' preferences into regulatory decisions using quantitative BRA. The FDA's Center for Devices and Radiological Health (CDRH) has produced guidance on when and how patient preferences should be elicited to support regulatory decisions.¹⁸ In 2016, CDRH achieved a milestone by approving a weight-loss device, that had failed its primary endpoints, based on work to elicit

Figure 1: Incorporating MCDA into Trial Simulation



patients’ preferences, which suggested that patients would accept the mortality risks associated with the device in exchange for the weight loss it generated.¹⁹ Staff at the EMA have also been piloting methods for the elicitation of preferences from patients.²⁰

Using MCDA to Support Trial Simulation

While the last decade has seen increased attention of regulators to both MCDA and trial simulation, they have to date been considered separately. There is, however, potential for them to be applied in combination, further enhancing the efficiency of drug development. This is acknowledged in a recent paper authored by two FDA employees, which states:

In the near future, CDER plans to issue a series of guidances to enable patient groups, and others, to collect and provide structured input on patient preferences in determining benefit-risk trade-offs, the burden of disease, and patient assessment of present treatments. This input will be used to inform subsequent CDER guidances on ensuring that the structure and assessment of clinical trials are meaningful to patients ...²¹

Specifically, MCDA can support trial simulation by providing a means to reliably estimate the ‘probability of success’ associated with different trial designs in a manner that reflects stakeholders’ preferences. Most importantly, it enhances the value of clinical trial simulations, as it creates the basis for virtual patients, in that both desirable and undesirable effects can be generated at individual patient-level. A trial simulation will invariably predict responses to treatment using multiple endpoints. Comparison of trial

design simulations will, therefore, involve trading off performance on these endpoints (Figure 1).

To date, the notion of ‘probability of success’ employed by trial simulation models has tended to be defined from a commercial perspective, predicting how sales will vary with changes in endpoint predictions.²² This perspective is still relevant for manufacturers. The use of MCDA can, however, help incorporate relevant perspectives into trial simulations to better predict the probability of approval and reimbursement success. Moreover, it provides insight into patient acceptance and eventually improves the prediction of uptake and sales.

Without MCDA, those responsible for designing trials will continue to do so without understanding what really

Table 1: Perspectives that Can be Incorporated into Trial Simulation Using MCDA

Perspective	Description
Internal	Elicitation of the preference for trial endpoints from multiple internal stakeholders, and facilitation of discussion about which trial scenario is preferred
Regulatory	Elicitation of patient preferences for trial endpoint, and estimation of the probability of which trial scenario would generate the highest benefit-risk balance
Reimbursement	Elicitation of payer preferences for endpoints, and estimation of the probability that a price will be acceptable with each trial scenario

matters to different stakeholders, whose preferences for changes may be different for each endpoint. MCDA offers a weighting mechanism to account for preferences and provides a stronger basis for the probability of success of multiple trial scenarios, as well as the impact of the uncertainty in all these considerations.

Regardless of the perspective, MCDA can facilitate the judgement of how simulation outcomes relate to the probability of success. Depending on the objective of the analysis, MCDA can facilitate multiple perspectives (Table 1).

Conclusion

Clinical drug development is fraught with attrition; benefit–risk assessment should be an integral part of the decision making process in R&D, as it already is for regulators. Whereas historically BRA has been performed retrospectively, the use of M&S can be combined with MCDA to support the evidence synthesis as well as evidence generation before clinical trials are performed or an application is made for market authorization. It is imperative to understand the implications of multiple stakeholders' preferences before implementing costly clinical protocols. We now have the tools to do so. ■

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