Clinical Trial Simulation in Early Market Access Planning

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Introduction

Health technology assessments (HTAs) of a new treatment often require the manufacturer to justify its economic value through analyses that make inferences from the trial data to predict long term outcomes, costs, and quality of life. When challenges arise in the clinical data needed to support market access, the opportunity to address those issues unfortunately no longer exists. These challenges can be particularly acute in therapeutic areas in which single arm studies or very long duration trials are necessary. This risk can be mitigated with an improved understanding of the interaction between the potential trial outcomes and market access needs.

In this article, we discuss how clinical trial simulation (CTS) can support early market access planning by predicting a range of feasible trial results of a new treatment that can be fed into an economic model, making it possible to anticipate challenges to the economic value story. By understanding these challenges at the trial design phase, adjustments to the trial protocol and preparations for additional evidence generation can be made to improve the chances for a successful launch.

### CTS Enables Earlier Integration of Market Access Strategy

To better prepare for HTAs' assessments of economic value, manufacturers are beginning to integrate market access planning throughout the product development lifecycle to allow more time to build out the economic value story. They are undertaking activities well in advance of launch, such as systematic literature reviews of economic models in the same indication and building economic models using early phase trial data to predict cost-effectiveness drivers and challenges. However, these approaches are limited by
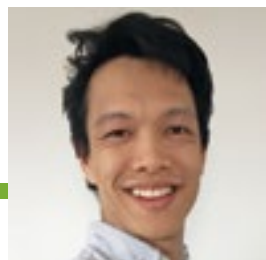
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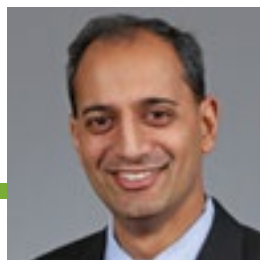
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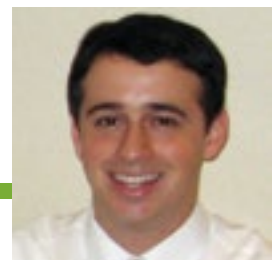
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their inability to evaluate and predict trial outcomes in new therapeutic areas where data or prior modeling may be scarce. Moreover, it may be challenging to understand the implications of heterogeneity in treatment response or other trial outcomes on economic modeling without patient level data. As an example, a common challenge in HTA reviews is the uncertainty associated with statistical extrapolations of survival curves, and so to get an early sense of this challenge, manufacturers may produce parametric fits from published curves or earlier phase trial data. However, both sources may not fully represent the heterogeneity seen in a later phase trial or reasonably match the pivotal trial population, which are needed to understand the limitations of extrapolations or the planning of subgroup analyses. Another increasingly common question is whether indirect treatment comparisons (ITC) are able to address patient heterogeneity (for example in NICE TA440[1]). With simulated patient-level data, early economic analyses can more accurately test statistical extrapolations and ITC approaches such as matching adjusted indirect comparisons (MAIC).

Market access planning should begin when trials are being designed, where there are still opportunities to provide input to the protocol and data collection or time to explore other routes of evidence generation. However, this requires a good understanding of the implications of trial design options and uncertainties on outcomes relevant to an economic model. This can be achieved through CTS, which mimics patient outcomes longitudinally within the context of a trial using existing data. CTS yields simulated patient level data which is then analyzed using standard statistical techniques and can be fed into an economic model or an indirect treatment comparison. This yields a complete integration between the trial design and the economic value assessment (Figure 1).

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Existing Data Can Inform CTS Prior to the Start of a Trial

CTS requires a longitudinal, patient-level dataset of patients that, at a minimum, contains a baseline observation and an event observation. The dataset can be derived from various sources including prior clinical trials, real-world evidence (e.g., claims data), and disease simulator output (Figure 2). Clinical trials accessible to the manufacturer are the most relevant data and can be specific to the trial setting, but offer the least opportunity for exploration beyond the manufacturer's own research experience, such as new therapeutic areas or populations. Also, trial data, especially early phase trial data, generally may not involve long-term

Figure 1. Linking Trial Design to Economic Analysis Via CTS
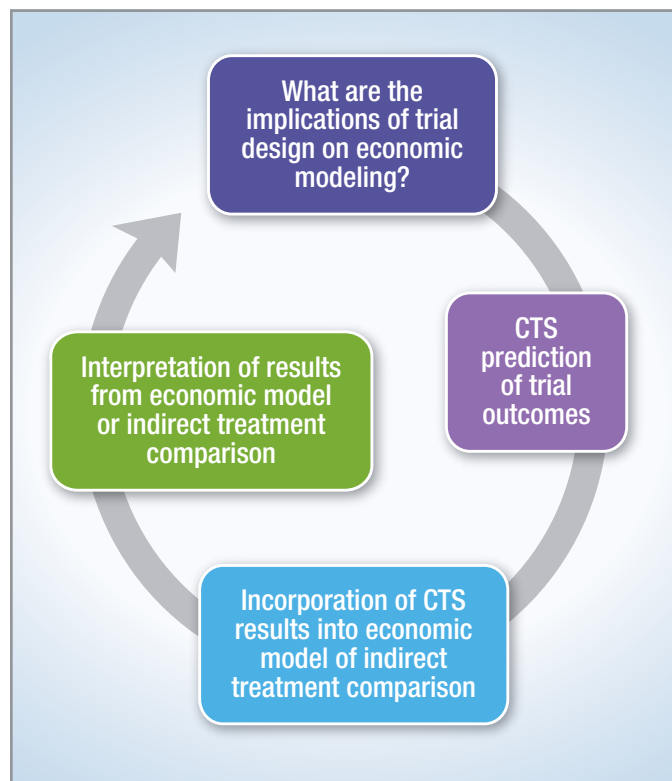
follow up. Real-world evidence, on the other hand, may include long-term data and offer a broader pool of patients that can cover therapeutic areas in which the manufacturer may not have experience; however, the form and granularity of data may not meet the level expected of a trial, limiting the aspects of the trial which can be explored. Moreover, data on early decline or disease progression are generally difficult to find. Disease simulators can offer the most flexibility and predictive power, and even serve as a bridge between trial data and real-world evidence, but, construction of disease simulators can take time and must be carefully validated before being used for decision making (see *Disease Simulation in Drug Development – External Validation Confirms Benefit in Decision Making* in this issue of *The Evidence Forum*).

Disease simulators use predictive equations based on trial or observed data to model the course of key markers over time and any interconnected clinical relationships to predict outcomes. As an example, previous Evidera CTS studies in Alzheimer's Disease (AD) have relied on simulated patient data from a disease simulator, the Alzheimer's Disease Archimedes Condition-Event (AD ACE). The AD ACE uses predictive equations derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and Assessment of Health Economics in Alzheimer's Disease (AHEAD) to estimate the progression of AD in terms of multiple interacting trajectories for key biomarkers, cognition, behavior, function, and dependence markers.[2] By coupling the simulated longitudinal patient level data from a disease simulation with CTS, we can understand the interaction between trial operations and disease progression and the

Figure 2. Flow of Data for CTS
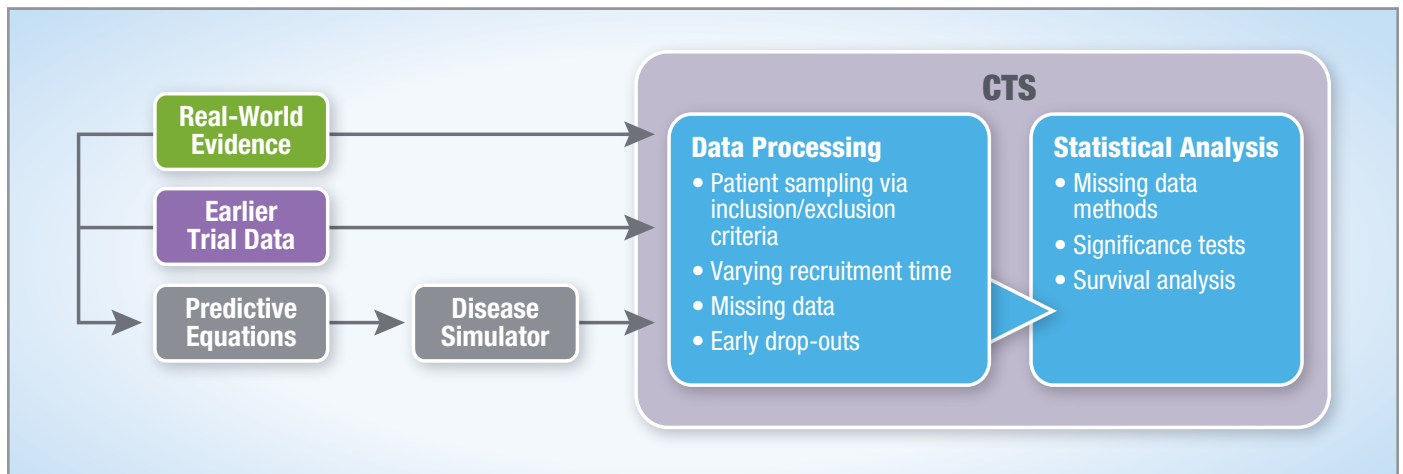
impact on the observed treatment effect. The data from the disease simulation can undergo additional processing to mimic data derived from an actual trial, including missing data, varying times of recruitment, and early dropouts (Figure 2). As an example of the importance of understanding the effect of trial operations on outcomes, a recent AD study suggested the observed treatment effect of a disease modifying drug can be influenced by the number of patients in a trial that are prone to faster disease progression and a higher likelihood of dropping out early.[3]

CTS Employs Robust Statistical Methods to Produces Trial-Like Data and Outputs

CTS can perform most standard statistical methods used in trial analyses. Survival analysis is among the methods, and the generation of the Kaplan-Meier (KM) curves allows for estimation of median survival time, hazard ratios, and evaluation of the overall difference between curves with log-rank test. This analysis coupled with simulation makes it applicable in the evaluation of cancer trial designs, which are becoming more challenging to show efficacy, as crossover or switching to other effective treatments in market can dilute the overall survival (OS) signal. For example, Evidera conducted a CTS study examining the effect of subsequent life-extending therapies on OS in a non-metastatic prostate cancer trial of a hypothetical treatment with a OS hazard ratio of 0.70.[4] Coupled with a disease simulator in prostate cancer,[5] the CTS of a scenario in which 75% of patients continued onto an effective subsequent treatment (similar OS hazard ratio as the initial treatment) produced OS KM curves that showed separation at around two to three years. The difference became significant at about four years (Figure 3).

As the level of subsequent treatment use lowered, time to show benefit in OS shortened as expected.

CTS Can Benefit Planning of Evidence Generation for Optimal Market Access Success

Given CTS's ability to provide trial-like results, it can be used to inform early economic models or comparative effectiveness such as indirect treatment comparisons. In a similar fashion to how early economic models are used, using CTS to conduct early comparative effectiveness assessments can help identify challenges to market access. For example, the method of extrapolation is often scrutinized by HTAs; as such, the process to determine the most appropriate approach can be time consuming and

Figure 3.
Example Prediction of Overall Survival Accounting for Subsequent Treatments
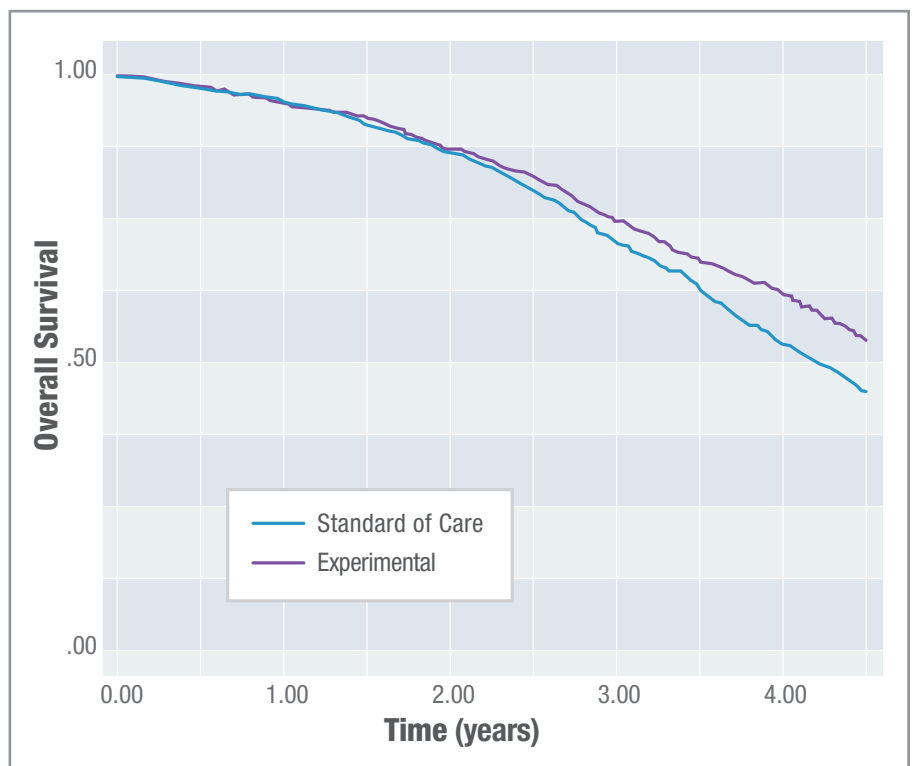
require the input of various experts in health economics outcomes research (HEOR), medical affairs, payer affairs, and outside clinicians. With CTS generating potential KM curves to base extrapolations and accompanying statistics, the discussion with, and preparation of, various stakeholders can take place earlier and facilitate clinical input to the economic analysis plans.

Discussion

With the number of factors outside the trial data to be considered in an economic analysis, there is no guarantee that a trial meeting its primary end points translates to a positive economic evaluation, which is why manufacturers are integrating market access planning throughout the product development lifecycle. CTS can be a tool to enhance this integration by providing the means for clinical operations and market access operations to more effectively collaborate. CTS allows the relationship between trial design and market access needs to be understood earlier in the process, when there is still the opportunity to address any potential issues. This can be particularly important in new therapeutic areas where prior information is limited; when there may not be a track record of HTA successes to follow; or, more novel trial designs are being considered. CTS can help understand the implications of trial designs on economic modeling, identify potential challenges, form constructive feedback at the trial design phase, and assist in the planning of studies for additional evidence generation to support market access. ■

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