

UNDERSTAND RISKS IN DRUG DEVELOPMENT THROUGH SIMULATION

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ABSTRACT

In all phases of a clinical program, the design of a trial plays a crucial role. Aspects range from number of treatment arms, total number of patients and duration of a trial to more complex considerations such as stopping a trial early for futility or for efficacy, or re-adjusting design parameters at the trial interim to boost the probability of trial success. Trials are carefully regulated by the FDA, and the control of Type-I error (declaring a drug efficacious when it is actually not) is mandated. Traditionally, asymptotic theory is used to guide a design. But as trials become more complex, theoretical solutions are no longer adequate. In this talk I want to discuss the role of simulation in clinical trial design, how the practice of it has benefited greatly from advances in the "Big Data" revolution, and how it has enabled us to find designs that have the highest probability of making the right decision at the earliest time point, all within the realistic constraints of clinical, commercial and regulatory parameters.

Simulating a clinical trial almost always involves two steps, a data step and an analysis step. During the data step, the data generating process has to be devised to match what we expect the reality is to be. There are at least three aspects to be modeled.

First, there is the patient outcome, the quantitative measurement that assesses a patient's disease progression. It varies depending on the disease under study, ranging from continuous to binary to time-to-event. Either an appropriate statistical distribution can be used to generate empirical observations, or often one rely mechanistic models (e.g. Pharmacokinetic/Pharmacodynamic models) to provide a more realistic simulation of how a drug is absorbed by the body and reacted against by it (a.k.a modeling & simulation). Usually patients are followed up repeatedly during the course of a trial, and multiple endpoints are taken at each follow up to monitor different aspects of a disease. Hence longitudinal (serially correlated) outcomes that are themselves correlated must be simulated. Typically we want to use longitudinal data to boost the precision of whatever estimates we need to make. But the sensitivity of results on longitudinal assumptions must be examined.

Second, there is the recruitment process of patients to consider. This can vary from simple exponential or uniform processes to more complicated scheme where the recruitment rate increases over time. Still more complicated processes allow for dependency on patient characteristics, and/or regional variations.

Third, patients will have various reasons to be discontinued from a study. How much this happens, and for what reason it happens, will have great impact on the outcome of a trial. For example, patients can quit due to adverse events experienced, due to lack of treatment effect, or other reasons such as death. Missing data as a result of each of these cases need to be treated differently to avoid biasing one's experimental outcome.

A development program is often made up of many studies of different phases. In the earliest clinical phase I, the safety of the drug needs to be established. In phase II, an appropriate dose is selected. Then in phase III the efficacy and safety of the drug is confirmed through very large trials. The ultimate goal is to show statistical significance against control (sometimes an existing competitor) while maintaining

adequate safety profile. In this respect, what to demonstrate is also very important, as any claim must be verified statistically. Commercial considerations and competitive landscape must weigh in here for the usual trade-offs: an easily demonstrated benefit might not have any commercial viability, but on the other hand, in order to beat a competing drug, a bigger/longer/more complicated trial might be required. In all this, from the design perspective, the question is how to find a clinical development program such that, at the minimal cost and earliest timing, will be able to demonstrate a drug's clinical and commercial viability. This implies that simulation must go beyond one single study, and a trial design must be optimized with respect to the overall likelihood of program success.

Simulation is but a platform on which different design parameters and analytical methodologies can be compared quantitatively. Thus the second main step of trial design is the application of appropriate statistical analysis to the synthesized data. Of course there are many choices to be made. Particularly interesting are dose finding phase II studies, where the right question is probability of selecting the correct dose for phase II, rather than showing statistical significance of a treatment-control comparison. I have already mentioned the handling of missing data. If there are a large proportion of patients discontinuing, then how missing data is imputed will impact the outcome of the analysis, and must be examined carefully.

After presenting the general concept of clinical trial simulation and discussing some details, I plan to talk about a case study of a large phase III study where multiple endpoints will be collected over time. I will show how design choices in a few areas are made with the aid of simulation:

1. testing strategies to control type-I error while maximizing study power;
2. early stopping rules to save cost in the event the drug has no effect;
3. maximizing the probability of overall program success.

Lastly, I will spend some time discussing a crucial enabler of "Big Data", cloud computing, that allows provisioning of a cluster computer thousands of nodes in size. Such scalability is what makes large scale simulations possible. What would otherwise have taken a week to finish now can be completed overnight. Simulation by design is always an iterative process with many dialogues between statistical, clinical and commercial stakeholders. Quick turn-around time thanks to the cloud makes the whole premise of simulation based design feasible and valuable.