

Innovative Designs for Successful Decision-Making In Early Clinical Drug Development

By St. Clare Chung, M.Math

Early drug development (clinical phases I-II) is focused on exploring the efficacy and safety of drugs.

Phase I trials typically employ some types of dose-escalation designs such as the "3+3" design, while Phase II trials rely on parallel group or in certain indications, single-arm designs. Such designs are considered de-facto standards and have appealing properties such as being 'robust' and 'rigorous.' However, these designs are notoriously ineffective in answering the questions of early drug development or require unreasonably high number of patients and therefore take considerably longer to complete. Proof-of-concept and other early-phase clinical studies require flexibility and effective decision-making so that overall development time is reduced.

Throughout the past 5 years, novel designs for Phase I and II studies have appeared in journals and discussed by statisticians at industry meetings. Innovative designs are gaining momentum because they offer several potential benefits including:

1. Ability to address complex, clinically more meaningful questions, for example:
 - Determining an optimal dosing schedule as opposed to an optimal dose of a single cycle of a combination treatment.
 - Addressing efficacy and toxicity

within a single trial

2. Potential to reduce sample size/shorten study duration for many dose-finding and other phase II studies aimed at identifying the target patient population and concomitant therapies.

3. Ability to treat patients in the trial more effectively/ethically: patients are always allocated to the treatment regimen estimated to be the most effective (ensures increased enrollment rate and treatment compliance).

Miklos Schulz, CEO for SciAn Services Inc., believes Bayesian designs are ideally suited for early phase studies.

"Current drug development is obsessed with the elusive 5 percent p-value. The truth is, in early drug development, you want to make decisions, not conduct hypothesis testing. This represents a significant shift in thinking and the reality is that traditional designs do not have the flexibility or framework for making decisions; Bayesian designs do, and they do so in a scientifically rigorous and credible manner," Schulz said.

A Bayesian design borrows strength by combining historical/prior information with accumulating data in a trial as it becomes available. The probability that a drug is effective is calculated and compared to the probability calculated before the new data came in. As a result, it is essentially looking at 'prior' and 'posterior' probabilities. This differs from the tradi-

tional approach which determines the likelihood that a drug's efficacy could have happened by chance.

A relatively simple example of a Bayesian design is the Bayesian counterpart for the traditional "1-in-3" design used in Phase I trials, namely the "Continual Reassessment Method" (CRM). Before the trial begins, a model defining the dose-toxicity relationship is determined. A probability of toxicity is assigned to each dose level, representing the prior information. Patients are treated at a starting dose and the number of dose-limiting toxicities (DLTs) is observed. Based on the model, the prior information and the current data (number of DLTs), subsequent patients are assigned to the dose level at which currently available evidence indicates to be the MTD. Simulations have shown that the CRM design estimates the MTD more effectively than the "1-in-3" design (Fig. 1).

Complex Bayesian applications include designs that:

- Determine the MTD based on efficacy and toxicity tradeoffs.
- Determine the maximum tolerated schedule of a drug based on repeated administrations of a drug.
- Identify the best combination of dose, patient population/co-morbidities and concomitant therapies for a phase 3 program.
- Seamlessly combine the objectives of Phase II and III trials into a single design.
- Adaptive, covariate randomization.

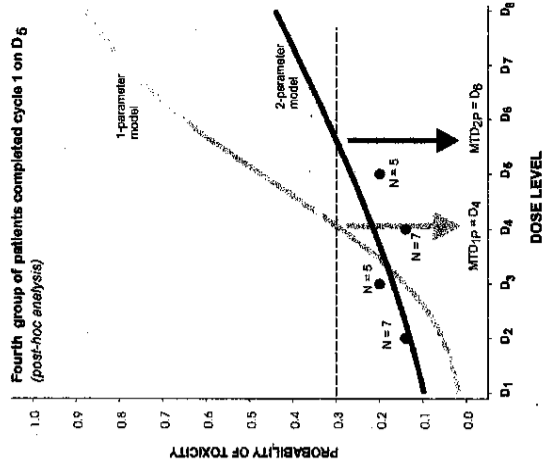


Figure 1 Illustration MTD Determination.

Summary

To give a company the best chance to identify the most successful indication of a drug within a reasonable timeframe and budget, it is paramount for the company to consider utilizing recent advances in clinical trial methodologies, such as adaptive designs, especially Bayesian approaches.

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