



Innovative Proof-of-Concept Designs for Phase I/II and IIIb Studies

Ann Leung, Noemi Toiber Temin, Rick Chiu & St. Clare Chung

TORONTO, Ontario – On May 3-4, 2006, the MaRS Centre was the venue for the “Innovative Proof-of-Concept Designs for Phase I/II and IIIb Studies” seminar hosted by SciAn Services, Inc. The first of a planned annual event, this particular seminar was undertaken in part to address the FDA’s “diagnosis” of a slowed drug development process, and to bring together members of industry and the academia to discuss the challenges of designing clinical trials. Key speakers on statistical and regulatory topics included Dr. Peter Thall (MD Anderson Cancer Centre), Dr. Chyi-Hung Hsu (Novartis US) and Dr. Agnes Klein (Health Canada).

Published in March 2004, the FDA’s “Critical Path Initiative” served to bring the attention and focus of stakeholders to the need to modernize the drug development process – the Critical Path. It encompasses all research activities from preclinical to post marketing stages. Jaan Peets, Head of Clinical Sciences at Context Clinical Research, Inc., summarized the problem as being worldwide, in which the year 2004 represented a 20 year low in new development of chemical entities. Many members of industry acknowledge the challenges posed by the “Critical Path Initiative”, but also point to the lack of clarity in FDA review and approval standards – which, though conservative, are ever-increasing – as a major obstacle. The result of this initiative has been the FDA’s list of specific opportunities (published in March 2006) that, if implemented, can speed the drug development process. Of priority is the need to validate biomarkers that reflect clinical responses to treatments. Clinical trials need to be streamlined through automation (e.g. EDC) and data standardization (e.g. CDISC). Specific to this seminar, emphasis was placed on the need to bring forth innovative clinical trial designs. This, and other reasons outlined in the FDA’s Critical Path Opportunities List, are opportunities that need to be exploited. The onus is on industry to be open to and provide resources for innovation.

Traditional designs are mostly employed when running clinical trials. Industry has been slow to adapt to new methods because the perception is that regulatory agencies may not be receptive to innovative, less popular methods. Furthermore, there is an industry-wide reliance on tried-and-trusted methods rather than investing in innovation. According to St. Clare Chung, Director of Bio-Statistics and Data Management at SciAn Services, Inc., the resultant stagnation from this reliance on limited traditional designs is in part responsible for the decline in drug development. For every traditional design – e.g. dose-finding, single arm or comparative – there is an equally, if not more, efficient and effective alternative design based on a Frequentist or Bayesian approach.

In Phase I studies, the primary objective is to determine the maximum tolerated dose that can be administered to a subject with some acceptable level of toxicity. Traditional approaches have relied on the 3+3 design which exposes groups of 3 subjects to a dose level and observes the response from the subjects. Based on the number of subjects demonstrating DLT (dose limiting toxicities), the next group of 3 subjects is treated at the same (current) dose level or one level above or below. Such an approach is typically unreliable, unpredictable and likely to choose a lower, therapeutically ineffective dose. At this seminar, designs beyond this traditional approach based on the Bayesian framework were summarized. The Bayesian approach has the unique feature of “combining” previous or historical information with current information. One of the very first Bayesian-based design for dose-finding studies in Phase I is the Continual Reassessment Method (CRM, 1999). The CRM method targets a specific probability of toxicity that is computed from both historical data and data from the current group of subjects treated. To implement the CRM, the probability of toxicity at each of the selected dose levels and the desired level of toxicity must be specified. The dose-toxicity curve is evaluated and the next group of subjects is treated at the dose for which the posterior mean is closest to the target probability of toxicity. Simulations show that the CRM is much more reliable than the 3+3 method widespread use of the CRM may have been limited due to the specialized software needed. Regardless, since its introduction, there have been several variants to the original CRM method, including the Modified CRM, Extended CRM [2 stage], Restricted CRM and Tri-CRM.

Whereas the CRM and its variants focus on safety, i.e. determining the dose that produces an acceptable level of toxicity (the MTD dose), an alternative, innovative approach that combines Phase I and Phase II objectives, i.e. efficacy and toxicity has been explored. One such approach, based on Bayesian principles was presented by Dr. Thall at the seminar. The method

involves specifying 3 factors that are specified in consultation with the investigator: the upper limit for the probability of toxicity, the lower limit for the probability of efficacy and 3 desirable targets for efficacy and toxicity. The first 2 limits are motivated by the desire to limit the risk of treating patients at a dose with either unacceptably high toxicity or unacceptably low efficacy. The 3 desirable targets, π_1^* , π_2^* and π_3^* , set up the initial efficacy-toxicity trade-off contours (dimension reduction). The first target, π_1^* , represents the minimum probability of efficacy when toxicity is not expected (i.e. probability of toxicity = 0) while π_2^* is the maximum probability of toxicity when efficacy is certain (i.e. probability = 1). The final target π_3^* is an intermediate point between the smallest efficacy and largest toxicity probabilities. These construct the target contour **C** as in Figure 1. (Peter F. Thall and John D. Cook, 2004 Biometrics). As illustrated in Figure 1, π_1^* is (0.15, 0), π_2^* is (1.0, 0.55) and π_3^* is (0.25, 0.30).

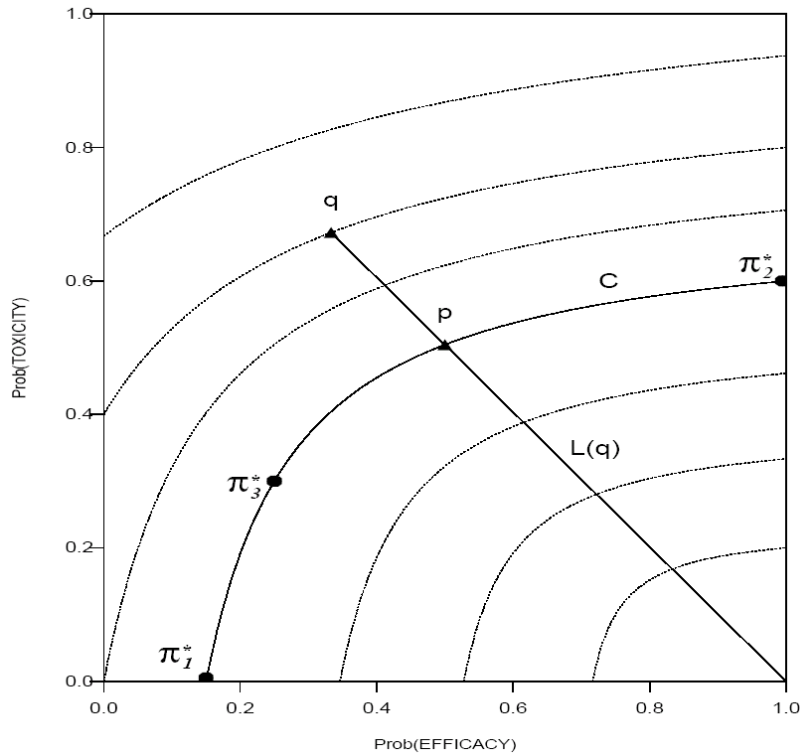


Figure 1. Efficacy-toxicity trade-off contours. The three elicited target points that determine the target contour **C** are given by round dots. The two triangular points illustrate the desirability of any pair of probabilities.

The contour C is then used to define desirable probabilities for any pair of probabilities q which in turn then determines the desirability of the doses under investigation. A family of trade-off contours can then be constructed (see Figure 1). Once this structure has been defined, the dose-finding algorithm is as follows:

1. Investigator chooses the starting dose
2. Dose x is acceptable if the dose has acceptable probabilities of efficacy and toxicity **or** if the dose is the lowest untried dose and has an acceptable probability of toxicity
3. Treat each group of subjects at the current most desirable dose
4. Do not skip untried doses
5. If no dose is acceptable, stop the trial
6. At the end of the trial, select the most desirable dose

Figure 2 illustrates the selection process with 2 pairs of points, q_1 and q_2 . The point q_2 is more desirable because its contour is closest to the desired C contour.

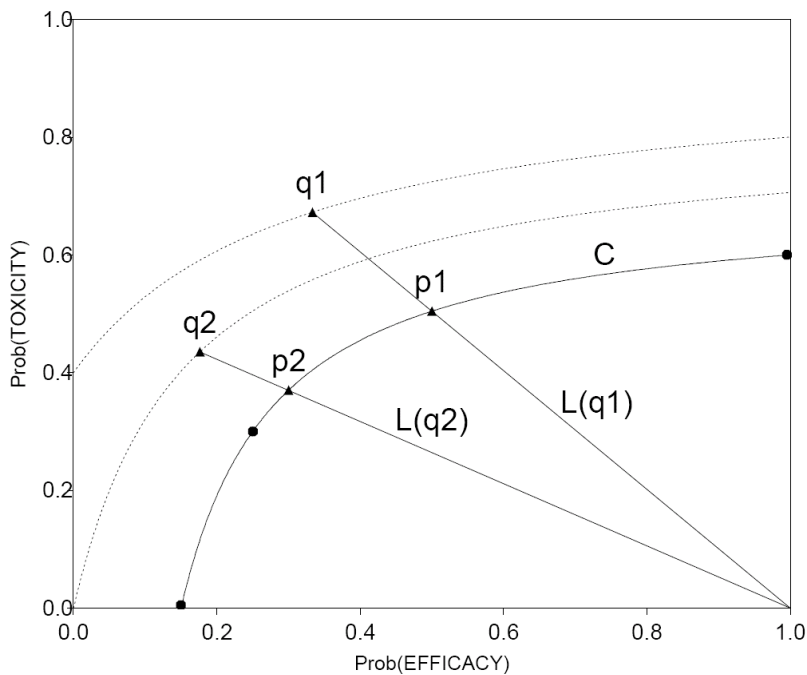


Figure 2. Efficacy-toxicity tradeoff contours – Selection

Two key advantages to this approach are: (i) the method reliably finds safe doses with high efficacy and (ii) stops if no dose is acceptable.

The proof-of-concept study represents another area that is an ideal target for innovative designs. Proof-of-concept studies are carried out to determine if there is early evidence of clinical efficacy using a small, targeted number of subjects, to warrant taking a drug further in development. Traditional designs may not be appropriate for a number of reasons: designs with a placebo arm may be unethical, designs are based on a fixed sample size and conclusions can only be drawn once the study is completed, etc. Designs that address these limitations include two-stage Simon designs, three stage designs, optimal flexible two-stage designs and adaptive two stage designs. As their name suggests, the study is implemented in stages. At each stage, the data from subjects in the study are examined and a decision is made to stop the study early or to enroll additional subjects into the next stage.

Adaptive designs refer to designs in which the design factors can be adjusted during the trial. Design factors that can be adjusted include sample size, dropping ineffective treatment arms, randomization, stopping early rules, etc. The decision is usually based on accumulating data in the current trial but can also accommodate data from other ongoing trials. Examples of adaptive designs that were summarized included: the continual reassessment method for Phase I studies, adaptive 2-stage designs for Phase II studies, adaptive randomization, and seamlessly combining the objectives of Phase II and III studies. Benefits of adaptive designs include reduction in sample size, the ability to assess predictive probabilities of statistical significance and terminate early if there is no evidence of drug effect, reduction of total drug development time and the availability of long term safety data earlier were discussed. An example of an adaptive randomization approach in a clinical trial was presented by Dr. Thall.

Dr. Thall's presentation on adaptive, covariate randomization is a Bayesian approach. Adaptive randomization in this approach utilizes interim data to compute the probability that one treatment is better (i.e. produces a better response) than the other and repeatedly updates the randomization probabilities to reflect the most recent data from the trial. With this approach, patients are randomized to the 'better' treatment, the trial is terminated if none of the treatments are efficacious or the trial terminates early if the data clearly shows one treatment is superior to the other. According to Dr. Thall, adaptive randomization is more ethically appealing than conventional balanced randomization because, on average, adaptive randomization assigns more

patients to the treatment or treatments that have higher interim success rate or lower interim adverse event rates; a design principle ideally suited to Phase IIIb or IV trials. Dr. Thall's presentation on adaptive randomization was enhanced by an application to a recently completed clinical trial on soft tissue sarcoma. A paper on the clinical trial findings will be published in the near future.

The seminar also included presentations by individuals who have used Bayesian designs in practice. In his presentation, Dr. Chyi-Hung Hsu, Associate Director of Modeling & Simulation/Statistics at Novartis Pharmaceuticals (USA) demonstrated how decision making in a proof-of-concept study could be improved with Bayesian methodology. The trial was a 4-week dose escalation study that randomized 90 dyslipidemic patients into 1 of 5 cohorts. Five ascending doses of a new compound were under consideration. In each cohort of 18 subjects, 12 were randomized into one of the 5 doses of the new compound, 3 to placebo and 3 to active control. The primary efficacy endpoint was the percentage change from baseline in non-HDL cholesterol at end of Week 4. The efficacy criterion was non-inferiority to the active control group. Based on the established limits for a test of non-inferiority, the power to detect non-inferiority was less than 60%, too low for reliable decision making. Dr. Hsu showed that with a Bayesian-modeling approach, the power would be increased to 78%. As a result, the Bayesian approach was adopted as the primary analysis in the protocol. In the incorporation of Bayesian statistics showed that this approach was more informative, had increased the power of the study with the same amount of data used in the original methodology, and provided more flexibility on decision making.

Parallel to the need for innovative statistical designs, Dr. Agnes Klein – Director of the Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics at Health Canada – outlined important considerations for a successful clinical trial design that places it in good standing for accelerated regulatory review. A clinical trial is the gold standard for drug development, so a proper trial design is crucial in clinical studies. The drug development process is not linear but iterative, and as such, a clinical trial should follow a development path that places the proposed product within the therapeutic armamentarium of the disease. It is of obvious importance to understand the disease (e.g. its incidence, prevalence, etiology, etc.), its manifestations, and its standard of care. Lessons learned from pharmacokinetic studies in animals need to be assessed for the novel product's potential applicability to humans. The choice of a validated endpoint is critical in matching study objectives to outcomes. These considerations

lay the groundwork necessary for a solid clinical foundation. Frequent consultation with regulatory authorities, transparency of methodologies, and overall attention to detail would further streamline and speed up regulatory review times.

All phases of drug development stand to benefit from the increased acceptance of innovative designs. This seminar presented approaches that were based on Frequentist and Bayesian frameworks. Frequentist and Bayesian approaches have their place in study design. For one type of protocol, a Frequentist approach may work while for another, a Bayesian approach may be more appropriate. There is no 'one-fits-all' solution and the resulting design should be a collaborative effort between medical, clinical and statistical experts. We hope that this seminar has expanded everyone's repertoire on study designs and that the designs discussed will prove to be useful in your future clinical trials. Thanks to the 57 attendees for their participation and we hope to see you again at next year's seminar.