ADAPTIVE TRIALS, SOLID RESULTS

When Innovation is Surer than Convention

Disease area: Cardiology—Acute Coronary Syndrome (ACS)

Trial design: Population selection/enrichment and sample size re-estimation in phase 3 confirmatory trials

Challenge

Typical cardiovascular clinical trials are expensive, large-scale studies enrolling tens of thousands of patients over long periods of time. For a promising new therapy for Acute Coronary Syndrome (ACS), however, relatively low event rates and diverse patient populations suggested that the conventional approach was too risky.

Staging an expensive, protracted exploratory trial just to identify the most promising patient subgroups might jeopardize funding and approval of the follow-on confirmatory phase. The sponsor turned to Cytel to design a state-of-the-art adaptive trial with interim analyses-based options for early stopping, sample size re-estimation and population enrichment that actually reduced their exposure to population uncertainties and other nuisance parameters.

The Cytel Advantage

The statisticians of Cytel pioneered the science and technology of adaptive trial design and have literally trained thousands of health sciences industry biostatisticians, clinicians, and regulatory staff. Benefiting both sponsors and patients, Cytel experts have designed more validated adaptive trials than anyone else.

The trial design and implementation services of Cytel Pharmaceutical Research Services place our study innovation experience at the disposal of your clinical research and development programs. From trial simulation and process development to independent data assessment and regulatory review, Cytel stands with you every step of the way.

Cytel
STATISTICAL SOFTWARE & SERVICES

Cytel Adaptive Trial Case Study #1

Adaptive Group Sequential Design of a Cardiology Trial with Sample Size Increase and Population Enrichment.

Response

- Cytel designed and developed special adaptive trial simulation software that proved pivotal in the business decision-making of the sponsor by predicting probable outcomes of a variety of study approach scenarios.
- FDA/CDER statistical review committee members received the same simulation software in advance of the review meeting to demonstrate the rigor and validity of the proposed adaptive trial design.
- In conjunction with the sponsor, Cytel created an innovative adaptive group sequential design with early-stopping points for efficacy or futility. The statistical procedures of the design were structured to strongly control type-1 error in the face of multiple hypothesis tests and sub-group selection scenarios.
- Cytel composed a detailed description of the advanced methodology for the confirmatory statistical analysis plan of the study.

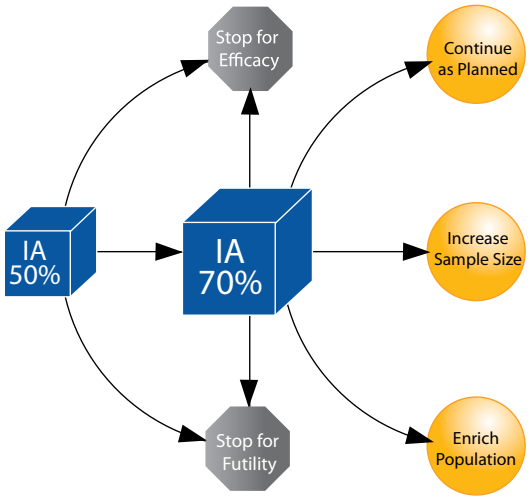
Outcome

- Cytel together with representative of the sponsor presented and successfully defended the innovative trial design at an FDA statistical review meeting.
- Adaptive designs lower economic risk while increasing development options. Stopping early for futility saves money. Stopping early for efficacy speeds time to market. Focusing on the most promising sub-populations optimizes return on investment.
- Adaptive trials have many patient benefits. Compared to traditional clinical trials, the statistics behind adaptive designs inherently "play the winners" – increasing attention on the most promising treatments. For patients it means a higher likelihood of receiving an effective medicine more rapidly than in typical conventional studies.

Adaptation

- The resulting FDA-approved adaptive trial design provides an early stopping option at the first interim analysis IA-50% if the drug either does not work or is more efficacious than predicted, while further increasing probability of approval if it works best on a sub-population.
- At IA-70% - the second interim analysis - the sponsor has multiple options including increasing the sample size, and if beneficial, to "enrich" the study population by enrolling new patients only in subgroups appearing to benefit from the new therapy.
- An Independent Interim Analysis Committee, including a Cytel biostatistical expert, was formed by the sponsor to recommend adaptive changes based on the unblinded interim analysis data.

Two Trials in One



Avoiding two traditional trials, Cytel designed one innovative confirmatory trial that adapts based on the "early looks" of the trial data: interim analysis IA-50% and IA-70%

IA-50% allows for early stopping for efficacy or futility

IA-70% options include "enriching" the population by enrolling new trial patients only into the most responsive subgroups

Cytel's work on the trial design, simulation and the discussion with the FDA was instrumental in obtaining regulatory acceptance for the proposed methodology in implementing a groundbreaking adaptive trial.

-Vice President, Medical Science