



Case Study Biometrics

Model Based Drug Design (MBDD)

Therapeutic Area I: Oncology

Situation

Primary objective of using MBDD in Oncology is to generate quantitative information to improve planning of oncology drug development. This information could pertain to risk factors for survival, disease model for change of tumor size over time and relationship between tumor size related metrics (early biomarker) and overall survival.

The ultimate aim is to use these models to

- decrease attrition rate by allowing better screening of compounds early in the development phase
- optimize dose selection by targeting meaningful changes in tumor size and balancing toxicity
- increase trial success rate by designing better survival trials

Case Study I: Methodological Research applicable across all areas of Oncology

Client Situation

In Oncology trials, especially in early development, patients are switched from one treatment to another depending on certain safety or efficacy outcomes. Unlike planned crossover designs in usual Phase I trials, in such oncology trials, whether the patient is switched to another treatment is random & the timing of the switch is also random, and the randomness is based on the outcome of the treatment in every patient. Estimation of treatment effect is complicated by the presence of these two random components in the treatment effect model.

Sciformix Solution

A few methods have been proposed to estimate treatment effect in such scenarios of switching in Oncology trials. Sciformix statistician reviewed the proposed methods, and after discussion with the client's Oncology statisticians, decided to evaluate two methods – Shao's method and Branson & Whitehead method. Extensive simulations were done, in R and SAS, to compare the two methods. Simulation results were analyzed and presented to the Client.

Outcome

The client used the analysis done by the Sciformix statistician to make a presentation to the US FDA about the relative merits and de-merits of these 2 methods, and to get FDA's nod for the method to be used for the client's upcoming Oncology studies.



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Case Study 2: Prostate Cancer

Client Situation

An NIH-funded Public Health and Epidemiology project at a top-3 Medical school aimed at investigation of treatment of Benign Prostatic Hyperplasia (BPH) and prevention of prostate cancer. The focus was on evaluating the role of Prostate-specific antigen (PSA) levels as biomarkers for prostate cancer.

Sciformix Solution

Longitudinal PSA data on a large cohort of subjects enrolled with a large health care provider was extracted from health care records and cleaned. The data was used to build models for PSA levels for the group that developed cancer and the group that didn't, stratified on presence or absence of BPH and other factors.

Outcome

Such models are required to help define the right efficacy endpoints for clinical trials. The modeling that was done in the above situation has been useful towards this end.

Therapeutic Area 2: Central Nervous System (CNS)

Situation

One of the primary objectives of using MBDD is to develop innovative trial designs/endpoints/analyses to discern a 'protective drug effect'. Some of the questions that we attempt to answer through statistical modeling are:

- Which demographic factors influence the baseline clinical scores and disease progression?
- How can the progression in case of, say, Parkinson's disease, be described, by a linear model or a non-linear model?
- Why do patients drop out of these trials?

Client Situation

A small biotechnology company was conducting a Ph 2 trial with 2 treatment arms and placebo, of an add-on therapy in patients with idiopathic Parkinson's disease with motor fluctuations. Very little data on the treatment was available upfront. Thus variance estimates used in the initial sample size calculation were of low precision.



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Sciformix Solution

Sciformix statistician suggested an adaptive design, by factoring in an interim analysis with the primary purpose of sample size re-estimation, not for any kind of efficacy hypothesis test. The study design was appropriately determined. Sciformix deployed an independent team to look at the interim data and re-estimate the sample size. Moreover, the interim data was kept blinded. Sciformix statistician identified the most appropriate method to be used to estimate the variance at interim analysis. This method was described in a research paper in a journal. The required programming was done in SAS to implement this method and the sample size was re-estimated.

Outcome

The client was able to perform a study that was right-sized and had sufficient power to test the primary objective, without compromising on the trial setup and conduct, while minimizing the extra cost of doing a pilot trial to estimate the variance.

Therapeutic Area 3: Human Immunodeficiency Virus (HIV)

Situation

Presence of HIV infection in an infant can only be ascertained through viral assays in the period immediately after birth. Hence modeling maternal-to-infant HIV transmission is critical for estimation of probability of peri-natal HIV transmission. A large study funded through a public-private partnership was planned to help build such models.

Sciformix Solution

A Sciformix statistician, who specializes in the area of HIV, was assigned to this study. Specific practical issues to be addressed at the trial execution stage were identified, for e.g., how does breastfeeding affect the model for HIV transmission? This and several other factors were incorporated and the best-fitting model was constructed.

Outcome

The model provided valuable information about administration pattern of HIV therapy for prevention of maternal to infant HIV transmission, and has proven to be useful in determining study designs for future studies in this area.

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