ARCHIMEDES
Quantifying Healthcare

Case Study

Clinical Trial Simulation

Project objective

The intent of this project was to calculate the expected MACE (Major Adverse Cardiac Event) rate in the control arm population of a clinical trial evaluating a candidate compound targeting a novel cardiovascular biomarker. The estimated event rate was used to inform trial size.

Introduction

Phase III trials require a large investment of time and resources. One of the critical components in the success of a trial is ensuring that the event rate in the study is sufficient to power the study. Failure to achieve an appropriate event rate can lead to inconclusive results, which could require extending the current trial or, in this case, conducting a separate cardiovascular outcome trial, which could be sizable and span multiple years. In a worst-case scenario, the trial could be halted due to lack of funding.

Furthermore, regulatory authorities have become more concerned about cardiovascular (CV) safety across a number of diseases. For example, in December 2008, the FDA announced new guidelines on evaluating CV risk in new anti-diabetic therapies. The guidelines now require developers of new drug candidates to demonstrate convincingly that their agents do not result in elevated CV risk. This requirement can significantly increase the size, duration, and cost of the necessary clinical trials necessary to support regulatory approval.

A large pharmaceutical company was in the process of designing a Phase III clinical trial for a diabetic agent. In the trial design phase, they needed to develop a strategy to maximize

Virtual people participating in a simulated clinical trial.

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Numbers

- Client: Major pharmaceutical company
- Target population: US patients at increased risk of a myocardial infarction (MI) as determined by their known cardiac risk factors
- Subgroups evaluated
  - Diabetes Mellitus (DM)
  - History of Peripheral Artery Disease (PAD)
  - History of MI
  - Renal dysfunction
  - History of stroke
- Simulated duration: 5 years
- Outcome measures:
  - Primary: MACEs
  - Secondary: MI, Stroke, Coronary Heart Disease, and Death

the probability that the population they enrolled would experience a large enough incidence of MACE to ensure that the company had appropriately powered the trial.

Before beginning the trial, the company turned to Archimedes in order to explore the parameters necessary for an optimal trial size to provide conclusive results.

Project approach

Working closely with the client, Archimedes built a population of virtual patients that matched as accurately and realistically as possible the anticipated population based on the company's selection criteria. Archimedes also matched the clinical trial's duration and protocol (e.g., treatments/procedures, laboratory testing, and physician office and hospital visits). Additionally, rates of patient compliance to medications and healthcare visits were taken into account. Subpopulations of interest (diabetic, CVD, etc.) were also evaluated. Although the primary outcome measure was the overall number of MACEs, the component outcomes of MACE were evaluated individually as secondary outcomes.

Results

The Archimedes Model predicted the MACE rate in the proposed trial. Results were modeled for a period of five years. Archimedes then worked with the client to explore adjusting inclusion and exclusion criteria, elements of the trial protocol, and compliance rates to examine the effects on the primary and secondary outcomes.

Business Value

Archimedes provided the company with detailed predictions of the overall MACE rate in the trial population. Additionally, Archimedes predicted the relative contribution of each of the various inclusion and exclusion criteria that were specified. This information helped the company avoid under-powering the trial.

Archimedes clients using the Archimedes Model for clinical trial simulation are able to make informed decisions concerning expected event rates for the populations they plan to enroll in a study. This information is used in study design, resource planning, and risk mitigation strategies that avoid costly, unforeseen Type II errors. By accurately simulating a trial, pharmaceutical companies can significantly reduce the uncertainties in powering a trial and dramatically improve their chances of success.

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