Statistical Simulation in Master Protocols: Components & Communications Considerations

Master protocol studies require significant pre-trial statistical simulation – a technique, often requiring the use of specialized computer software, that evaluates the operating characteristics of a clinical trial across multiple scenarios – to define and make decisions about key operating characteristics of the trial, including interim analyses, adaptive randomization, inferential power, subgroups, biomarker assessment, and recruitment. The use of statistical simulation enables the study sponsor and key stakeholders to get a sense of how different design choices will affect the study prior to study execution, thereby enhancing the quality and feasibility of the trial. Additionally, statistical simulation is an important tool that can be used to communicate the strengths, weaknesses, and ethical considerations of a master protocol study to key stakeholders.

This tool provides early adopters with (1) an overview of components of statistical simulation and (2) tips for how to organize presentations of simulated trials to key stakeholder groups.

BUILDING A SIMULATION STRATEGY

Simulation Module	Description
Definition of Plausible Scenario	◆ This module holds all the parameters required to define an assumed "reality" for the simulation. This includes patient characteristics, sub-study assignments, treatment assignment, and outcomes, to name a few. ◆ Note: Not all possible scenarios should be simulated. Simulations should focus on scenarios that possible within the design and/or are of key interest to regulators.
Virtual IMP Module:	◆ Demonstrates how different investigational medical products (IMPs) will enter the trial and complete the trial at different times. This allows stakeholders to understand how the trial will perform with variations in the number of arms that are open for randomization at a time.
Virtual patient generator	◆ Generates virtual patients, including necessary baseline characteristics and time-of-enrollment ◆ In light of assumed treatment effect(s) defined by the scenario(s), generates virtual patient outcomes, including time-to-information; potential patterns of compliance; or missing data ◆ Calculates possible accrual rates

COMPONENTS OF A SIMULATION STRATEGY

Simulation Module	Description
Interim Analyses Module	◆ Determines when an interim analysis should be triggered (e.g., by patient enrollment, maturity of outcome data, and/or sufficient follow-up) ◆ Applies interim analysis algorithm to interim data, resulting in pre-specified adaptations (e.g., to randomization ratios, inclusion/exclusion criteria, dose selection, or application of criteria for early stopping)
Final Analyses Module	◆ Once final sample size is achieved and final outcomes determined, applies final primary analyses strategy to determine overall trial outcome, average sample size, estimate of treatment effect, and other factors
Module to Summarize Operating Characteristics	◆ Accumulates characteristics of individual trial simulations to determine operating characteristics (e.g., type I error rates, power), distributions of sample size, average bias in treatment effect estimation, and precision of estimates ◆ Generates graphical and other summaries of trial performance ◆ Compares of trial performance across scenarios (e.g., as a function of assumed treatment effect, accrual rates)

FACILITATING STAKEHOLDER ENGAGEMENT

Stakeholder Group	Engagement Goal
Patients	◆ Statistical simulation can be used to get early feedback from patients on the design of the trial. Patients may be interested in key questions such as: • Will the design reduce the number of patients deemed to be ineligible (e.g. potential to randomize patients to a different concurrent or future arm)? • Will the design decrease probability of being randomized to placebo/standard of care? • Can the design improve the probability of a patient in the clinical trial receiving the most promising treatment for their disease?
IMP Developers	◆ Explain the benefit of joining a master protocol study versus developing their asset independently: • Interested in the same things as the regulators (e.g. type 1 error, power) • General trial operating characteristics, specifically the average number of participants who will be enrolled in their arm for drug supply considerations • Length of time to completion for their participation in the master protocol
Funding Agencies	◆ Provide a succinct summary of how simulation trial results justify the proposed design approach
Regulators	◆ Before trial launch: • Demonstrate how key aspects of the trial will work (e.g. control of bias in treatment estimation, control of type 1 error) ◆ After trial completion: • Demonstrate that the type 1 error risk protection was really maintained • Demonstrate that the trial operating characteristics were not impacted adversely
IRBs	◆ Show the risk benefit balance for individual subjects and how the risk benefit balance might change over time ◆ Communicate about patient burden, ethics, and informed consent ◆ Communicate about high-level trial performance characteristics (e.g. similar concerns as regulators)
Sites	◆ Discuss the operational implications of the design • The need for close-to-real-time data entry • How will the need for rapid and frequent interim analysis impact site staff burden? ◆ Discuss patient-centered considerations • Informed consent considerations • What considerations have been made to reduce patient burden?

COMMUNICATING SIMULATED TRIAL RESULTS

Presenting simulated trial results in the following order is very important to avoid confusing key stakeholders. The use of tables and graphs, versus long narratives, is encouraged.

1.

Describe how you developed your simulation framework:

- What are the key assumptions that guided the development of the simulation framework?
- What data was used to inform assumptions (e.g. historical data)?

2.

Examine individual trial trajectories. Examples include:

- What is the adaptation that may arise at each of the interim analyses?
- When does a platform trial drop a treatment arm and when would one be added?

3.

Summary of trial characteristics for a single scenario:

- Sample size distribution
- Illustrate the impact on trial characteristics based on deviation from assumptions or scenarios

4.

Summary of trial characteristics across multiple scenarios:

- Relationship between power and assumed treatment effect, relationship between the required number of patients and the treatment effect, etc.