Biotech Essential Statistics: Study Design Considerations for Biotechs.

Successful product development starts with robust study design, a vitally important yet hugely complex process that relies on statistical methodologies and insights. Successful evidence-based decision-making will therefore require a team to engage effectively with statisticians at the earliest possible stage.

As part of Phastar's **Biotech Essential Statistics Series of webinars**, **Stephen Corson, Associate Director of Statistics and Technical Solutions,** outlined some of the main study design considerations, from navigating the estimand framework and randomization, to understanding the role of blinding and determining sample size.

> ❝ The hope is that those with limited kind of statistical training will gain an understanding of why these terms are important, and what we mean by them, and give them the tools they need to engage more effectively with their statistical colleagues at the earliest possible opportunity. ❞

Adequate and well-controlled investigations

Clinical investigations are the tools that are used to distinguish the effect of a drug from other influences, such as a spontaneous change in the course of a disease, a placebo effect, or biased observations. With the reports from these trials providing the primary basis for determining whether there is substantial evidence to support claims of effectiveness for new drugs, robust study design can be the difference between success and failure.

FDA regulations state that evidence for efficacy should come from **"adequate and well-controlled"** studies, meaning **they need to include a clear statement of the objectives and a summary of the analysis methods.** Crucially, they must be based on a design that permits a valid comparison with control that provides a quantitative assessment of drug effect – a design that carefully considers concepts such as estimands, randomization, blinding, and sample size.[1]

Navigating the estimand framework

Estimands can best be described as a precise description of the treatment effects reflecting the clinical questions posed by a given clinical trial objective.[2]

A study comparing the impact of a Type 2 diabetes medication on HbA1c to placebo, would need to specify how the use for rescue medication will be handled. Allowing rescue medication to be administered and then "ignoring" values after the initiation of rescue medications is a completely different clinical question to using all data values before and after rescue medication. Each of these "estimands" dictates different study design and analysis methods, making them an essential early consideration in any clinical trial.

The **ICH E9(R1)** guideline, which has been adopted by regulatory authorities including the **EMA, FDA, and NMPA,** provides a framework for navigating this complex process. It starts with considering the trial objective, in the context of the therapeutic setting and treatment intention, which is then followed by a process to identify intercurrent events, or events occurring after treatment initiation that could impact interpretation of the results. Examples include treatment discontinuation due to adverse events (AE), the use of rescue medication, treatment switch, or death. Cross-functional teams, comprising of the sponsor, clinical scientists, physicians, statisticians, and other disciplines, should then discuss strategies to address intercurrent events, construct the estimands, and propose them to regulators for agreement.[2]

Randomization

Randomization is the process of assigning subjects to treatment arms in a way that minimizes the differences between treatment groups and enables results to be generalized to the target population. An essential part of any pivotal study design, it has **three broad approaches,** each of which will be suited to different trials.

The simplest method makes each new treatment allocation without considering any previous allocations, either by the use of a coin toss or sealed envelopes. While it is easy to implement, it can sometimes lead to inequalities between groups, which can be particularly detrimental to small studies. **The block approach** builds on this by making allocations in "blocks" of a pre-specified size, e.g. a block of six would

see three participants randomized to arm "A" and three participants randomized to arm "B". While this can be useful, it can lead to predictability when used in large cohorts or near the end of the block.

Stratified randomization is an extension of block allocation that balances groups both by numbers in each treatment group and a pre-determined set of factors that may impact study outcome. These may include sex and age, for example. When using this approach, it is important to remember that too many stratification variables can lead to imbalances in the treatment groups and that well-balanced arms in a study do not guarantee balance when looking at subgroup analyses.

Blinding

Blinding is a tool to keep study participants and/or investigators unaware of which treatment is being received. By ensuring each subject is treated the same, it can help minimize differences in assessment, data collection, analysis, and ensure robust interpretation.

While **double blinding**, where both the subject and investigator are unaware of the treatment administered, is the gold standard in comparison to single blinding, where just the subject is unaware, it is not always possible to implement. Trials where there are different methods of administration will require the investigator to be unblinded, for example in trials that require a surgical procedure. Maintaining the blinding in a study is an equally important consideration. Factors such as AE profile, lab results, and even drug expiratory dates can all provide clues to group allocations. As such, study teams will need to consider the most appropriate blinding approach, and any necessary mitigating factors, early on.

Sample size

Sample size calculations, which give the minimum number of participants needed for a study, are an important part of ethics approval and protocols. While they may sound simple, they are a complex balancing act whereby we balance available resources, costs, assumptions, and risk.

An oversized study, which can include more subjects than is strictly necessary, exposes more people to risk and can divert resources away from other worthwhile research. Conversely, an undersized study runs the risk of being unable to demonstrate treatment effect adequately which can lead to shifting of resources away from areas where patient benefits can still be attained.

Statisticians base these complex calculations on a number of assumptions, including the **probability of a false positive claim (the significance level), and the probability of finding a difference if one exists (power).** They also need to consider what is expected to happen in the control group, the variability of results, and how many participants may be lost to follow-up. It is a process, then, that requires a large degree of cross-functional discussion and collaboration.

Teamwork

Robust study design is crucial to the success of any drug development process, and it relies on the ability of all members of the team to align their goals and share their knowledge.

From defining estimands to calculating sample sizes, sponsors, clinical scientists, physicians, and statisticians need to work together from the earliest stages, tailoring their approach to the trial, and ensuring their studies are adequate, well-controlled, and have the very best chance of success.

Learn more: Watch the full webinar here

References:

1. FDA. CFR - Code of Federal Regulations Title 21. (2023). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.126 Last accessed: 3rd January 2024

2. EMA. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. (2020). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en. pdf Last accessed: 3rd January 2024