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Short Communication

An Overview on Primary & Secondary Research of Clinical Trails

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Most errors in clinical trials are a result of poor planning. Fancy statistical methods cannot rescue design flaws. Thus careful planning with clear foresight is crucial. Issues in trial conduct and analyses should be anticipated during trial design and thoughtfully addressed. Fundamental clinical trial design issues are discussed.

The objective of clinical trials is to establish the effect of an intervention. Treatment effects are efficiently isolated by controlling for bias and confounding and by minimizing variation. Key features of clinical trials that are used to meet this objective are randomization (possibly with stratification), adherence to intent-to-treat (ITT) principles, blinding, prospective evaluation, and use of a control group. Compared to other types of study designs (e.g., case-control studies, cohort studies, case reports), randomized trials have high validity but are more difficult and expensive to conduct [1].

The design of every clinical trial starts with a primary clinical research question. Clarity and understanding of the research question can require much deliberation often entailing a transition from a vague concept (e.g., "to see if the drug works" or "to look at the neuro-biology of the drug") to a particular hypothesis that can be tested or a quantity that can be estimated using specific data collection instruments with a particular duration of therapy. Secondary research questions may also be of interest but the trial design usually is constructed to address the primary research question [2,3].

There are two strategies for framing the research question. The most common is hypothesis testing where researchers construct a null hypothesis (often "no effect" or "no difference") that is assumed to be true and evidence is sought to disprove it. An alternative hypothesis (the statement that is desired to be claimed) is also constructed (often the presence of an effect or difference between groups). Evidence is sought to support the alternative hypothesis. The second strategy is estimation. For example a trial might be designed to estimate the difference in response rates between two therapies with appropriate precision. Appropriate precision might be measured by the width of a confidence interval of the difference between the two response rates.

Clinical trials are classified into phases based on the objectives of the trial. Phase I trials are the first studies of an intervention conducted in humans. Phase I trials have small sample sizes (e.g., <20), may enroll healthy human participants, and are used to investigate pharmacokinetics, pharmacodynamics, and toxicity. Phase II trials are typically conducted to investigate a dose response relationship, identify an optimal dose, and to investigate safety issues. Phase III trials are generally large trials (i.e., many study participants) designed to "confirm" efficacy of an intervention. They are sometimes called "confirmatory trials" or "registration trials" in the context of pharmaceutical development. Phase IV trials are conducted after registration of an intervention. They are generally very large and are typically conducted by pharmaceutical companies for marketing purposes and to gain broader experience with the intervention.

Although clinical trials are conducted prospectively, one can think of them as being designed retrospectively. That is, there is a visionof the scientific claim (i.e., answer to the research question) that a project team would like to make at the end of the trial. In order to make that claim, appropriate analyses must be conducted in order to justify the claim [4]. In order to conduct the appropriate analyses, specific data must be collected in a manner suitable to conduct the analyses. In order to collect these necessary data, a thorough plan for data collection must be developed. This sequential retrospective strategy continues until a trial design has been constructed to address the research question.

Once the research question is well understood and associated hypotheses have been constructed then the project team must evaluate the characteristics of the disease, the therapies, the target population, and the measurement instruments. Each disease and therapy will have its own challenges. Neurologic data has many challenging characteristics [2-4]. First, some neurologic outcomes can besubject to lots of variation (e.g., cognitive outcomes). Second, some neurologic outcomes are subjective in nature (e.g., pain, fatigue, anxiety, depression). Thirdly, some neurologic outcomes lack a gold standard definition or diagnosis (e.g., neuropathy, dementia).

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Forth, neurologic outcomes can be high dimensional (e.g., neuro-imaging outcomes or genomic information, that cannot be captured using a single numeric score). Fifth, composite outcomes are common (e.g., cognitive measures, instruments assessing depression or quality of life). Consider a trial to evaluate treatments for pain. Researchers should consider the subjective and transient nature of pain, the heterogeneity of pain expression, the placebo effect often encountered in pain trials, and the likely use of concomitant and rescue medications [5]. Design must be customized to address these challenges. The goal of design is to construct the most efficient design within research constraints that will address the research question while considering these characteristics.

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