Considerations for open-label clinical trials: design, conduct, and analysis

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Abstract

Randomization and blinding are regarded as the most important tools to help reduce bias in clinical trial designs. Randomization is used to help guarantee that treatment arms differ systematically only by treatment assignment at baseline, and blinding is used to ensure that during the trial the two arms are treated the same with differences only arising from the treatment received and not, for example, the expectation or desires of people involved. However, there are times when it is not feasible or ethical to conduct fully blinded trials. This poster reviews what can be done to improve the trial when fully blinding a trial is not considered possible.

Introduction

The benefits of blinding are well known. Randomization and blinding are regarded as the most important tools to help reduce bias in experimental designs.

- Randomization is used to help guarantee that treatment arms differ only by treatment assignment at baseline.
- Blinding to subject treatment assignment is used to ensure that during the trial the two arms are treated the same with differences only arising from the treatment received and not, for example, from expectations related to knowledge of the assigned treatment. It allows one to interpret evidence of differences between treatment arms as evidence of a causal effect of the treatment. Along with being randomized, studies should be fully blinded whenever possible.

Despite the known benefits of blinding, it is not used as often as it could be in clinical trials. There are times when open-label trials are unavoidable for various reasons. As is often the case in these situations, once a fully blinded trial is deemed infeasible or unethical, often no attempt at blinding is undertaken. However, even open-label trials should have some level of blinding and consideration should be given to enhance the integrity of the trial, rather than accepting that it will be of no value.

Blind as much as possible

In situations where it is not possible to conduct a fully blinded trial, blinding as many people associated with the trial as possible. Each subject’s treatment assignment should be unknown to as many individuals as feasible. Candidates for blinding include:

- Investigators.
- Investigators.
- Pharmacists.
- Laboratory personnel.
- Outcome assessors.
- Central independent adjudication committees.
- Data collectors.

Additionally, documents associated with the participants, such as digital images, case report forms, and laboratory reports should not contain treatment assignment information. The sponsor statistician/analyst should be blinded, i.e., not have knowledge of subjects’ assignments, until the database is locked and the study is officially unblinded. Exceptions can be made for the independent statistician(s) who conduct interim safety and efficacy analyses to facilitate monitoring by the DMC.

Accumulating data kept confidential

It is critical to prevent access to accumulating subject-level and group-level study data that includes information on treatment assignment (either with the treatments identified or with codes such as “A” and “B”) outside of an independent DMC and a supporting independent statistician(s) who prepares interim reports.

Knowledge of comparative summary-level interim outcome results by subjects, investigators, the sponsor, or the public can negatively impact trial conduct (e.g., recruitment, adherence, and retention) and impair ultimate interpretation of results.

Trial conduct considerations

A critical requirement for open-label trials is allocation concealment, meaning that it should be impossible to know or to predict what assignment a subject will be given before randomization. For this reason, extreme care needs to be taken regarding how subjects are randomized in open-label trials and randomization methods should be clearly explained in the protocol, study report, and manuscript.

Subject in the different treatment arms should be treated identically, except that for the treatment they are receiving, or in direct response to the treatment they are receiving. For example:

- Incomplete end of study results should be the same.
- Adverse event data collection, blood collection, and inclusion/exclusion criteria should all be the same as well.
- The timing of preliminary analyses of open-label trials needs to be the same amount of time from randomization for the various treatment arms, even if treatment duration is different across the arms.

Patient retention and follow-up of subjects may be different across treatment arms in an open-label trial. Subjects’ knowledge of their assignment might make them more or less likely to drop out of the trial, leading to differential missing data across treatment arms. For these reasons, the need to reduce the amount of missing data, and to do this equally across all arms, is exceedingly important. Blinding as much as possible can help, as can clear guidelines for how to follow all subjects that can be implemented consistently across treatment arms. This should include plans to follow and ascertain complete outcome information in all randomized subjects who maintain their participation, including those who prematurely discontinue treatment.

Handling of intercurrent events should also be considered carefully in an open-label trial. Intercurrent events, such as receipt of additional medication or discontinuation of assigned treatment, could likely be influenced by knowledge of the treatment assignment by subjects or investigators. Therefore, subjects should be blinded to the trial. Consideration should be given to the use of a treatment policy strategy which does not consider those intercurrent events in the assessment of outcome.

The protocol and statistical analysis plan should be finalized prior to the start of an open-label trial. This will help to protect the integrity of the trial, so that it is clear that the ongoing trial results did not impact the protocol or statistical analysis plan.

Conclusion

The advice provided is briefly outlined in Figure 1. The most important point is to conduct a fully blinded trial whenever at all possible and, if not possible, conduct the trial as if it were a fully blinded trial. Clearly state in the protocol, study report, and manuscript, who is and who is not blinded to subject treatment assignment and who has access to accumulating unblinded results and how that might impact the study. It is important to acknowledge the limitations and potential for bias due to the lack of a fully blinded design and the steps taken to minimize the bias.

Trials should be conducted in a way to minimize the possibility of bias, both real and perceived. A major goal when conducting an open-label trial should be to minimize bias due to differential handling of the randomized arms arising from knowledge of assigned treatment. Consider what might lead to biases in the trial at the design stage, during the conduct of the trial, and in the analysis, and what might be done to overcome those biases.

Definitions

- **Open-label trial**: a trial that is not completely blinded, typically in that subjects and physicians have knowledge of the assigned treatment. Importantly, it does not mean “uncontrolled” or “single-arm” which is often what the term “open-label” is used to describe.
- **Fully blinded trial**: a trial where no one knows the treatment assignment of individual subjects or has access to interim results that include treatment assignment information, outside of an independent statistician/pharmacist/DMC.
- **Double-blind**: often used to describe a fully blind trial, but the term double-blind is vague and, when used, should be clearly defined as to how blinding was validated as being double across both the study protocol and in the report of the trial.

- **Objective endpoint**: a test that is designed to answer a specific question. It includes a pre-defined subset of the ITT population, the population defined as all randomized subjects and considered by many to be the gold standard for the analysis of clinical trials. A commonly used reason for exclusion from an ITT population is not receiving study treatment. In a fully blinded trial, this exclusion will not lead to a bias. However, in anything other than a fully blinded trial, there is a likelihood that a population composed of only eligible subjects who received study medication may no longer be the same as the initial randomized subject population. An investigator, subject, or other individual involved in the trial might use knowledge of the treatment assignment of a subject to play into the decisions on whether or not that subject receives treatment.

The completed study should be assessed for possible differences in the amount and type of missing data across randomized arms. It is also important to consider what is the possibility for missing data to be due to knowledge of assigned treatment and expectations of those involved in the trial. As with any trial, if the amount of missing data is large, it will not be clear if the overall trial result would have differed if the data were not missing.

- **Design**
  - Use as many individuals involved in the trial to individual subject treatment assignments as possible.
  - Consider how treatment assignment information can influence results.
  - Consider blinded assessments of allocation committee.

- **Conduct**
  - Maintain confidentiality of interim results, typically by ensuring that an independent DMC and supporting statistician(s) have access to accumulating unblinded interim data and results.
  - Perform blinded review.
  - Treat randomized arms identically.
  - Use the same timing from randomization for the primary endpoint for all arms.
  - Follow all subjects using standard guidelines to prevent missing data.

- **Analysis**
  - Use an intent to treat analysis.
  - Do not exclude subjects from the analysis for not taking randomized treatment.
  - Make sure missing data handling considers potential biases, including those due to open-label design.
  - Take potential and actual bias into account.
  - Assess the trial for compromised blinding.

Figure 1. Considerations for open-label trials