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 diminished quality compared to a fully blinded trial.

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 conducted and who exactly was blinded both in the study protocol and in the report of the trial.

Blind as much as possible

In situations where it is not possible to conduct a fully blinded trial, blind 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

- subjects,
- caregivers,
- physicians,
- other healthcare personnel,
- laboratory personnel (i.e., microbiologists, pathologists),
- outcome assessors,
- central independent adjudication committees,
- data collectors
- anyone else involved in the trial.

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, as is done for fully blinded trials.

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 external 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.

Endpoint less prone to bias

Two considerations for endpoints for trials that are not fully blinded:

- **blinded endpoint assessor or committee:** The use of a blinded endpoint committee or blinded outcome assessors can be considered if the physician cannot be blinded and the outcome requires an assessment. Care should be given to the information provided to the committee or assessor so that they are not influenced by potential biases of the investigators.
- **objective endpoint:** If the outcome assessor cannot be blinded, then the outcome should be modified to remove any subjective components or a completely objective endpoint be used to reduce bias.

Note, it is important to consider whether the primary endpoint directly captures or reliably predicts how a subject feels, functions or survives. For example, it would not be appropriate to switch to an objective biomarker as the endpoint if the biomarker is not validated as a surrogate endpoint, i.e., has not been shown to reliably predict benefit in terms of how a subject feels, functions or survives.

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 prior to 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 for the treatment they are receiving, or in direct response to the treatment they are receiving. For example,

- Visit schedule and procedures should be the same.
- Adverse event data collection, blood collection, and inclusion/exclusion criteria should all be the same as well.
- The timing of primary endpoints for landmark analyses of open-label trials need 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 consent, including those who prematurely discontinue treatment.

Analysis considerations

Subjects should not be excluded from the analysis for not receiving study medication. In some trials, the primary analysis population is conducted in 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 fairly commonly used reason for exclusion from an ITT population definition is not receiving study treatment. In a fully blinded trial, this exclusion will likely not lead to bias. However, in anything other than a fully blinded trial, there is a likelihood that a population composed of only subjects who received study medication may no longer be the same across treatment arms. 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. In open-label trials there 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.

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 that are not blinded. 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 feasible and, if not feasible, 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 having 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.

- **Design**
  - Blind as many individuals involved in the trial to individual subject treatment assignments as is possible
  - Consider endpoints that are less prone to bias (but still reliably reflect how subjects feel, function, or survive)
  - Consider blinded assessors or adjudication committees
- **Conduct**
  - Maintain confidentiality of interim results, typically by ensuring that an independent DMC and supporting statistician(s) have sole access to accumulating unblinded interim data and results
  - Use allocation concealment
  - 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 therapy
  - Make sure missing data handling considers potential biases, including those due to open label design
  - Finalize protocol and SAP prior to start of the trial
  - Assess the trial for compromised blinding

Figure 1. Considerations for open-label trials