Academic Editor Guidance: Clinical Trials

Definition

PLOS adheres to the World Health Organization's definition of a clinical trial as

> *A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes [...] Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.*

PLOS staff ensure clinical trials are labeled as such before these submissions are assigned to Academic Editors. In many cases it is clear whether a manuscript is or is not a clinical trial, but borderline cases may arise. If an Academic Editor believes the manuscript has been misclassified either as a clinical trial or as a standard research article, they should contact the staff at plosone@plos.org or globalpubhealth@plos.org to discuss how to proceed.

Policies and Procedures

Manuscripts describing clinical trials are monitored throughout the review process and are subjected to increased scrutiny relative to other submission types.

Clinical trials must be registered in a WHO or ICMJE-approved registry. Trials should be registered prospectively (prior to patient recruitment). Authors must provide a clear explanation for any trials that are not prospectively registered. The registration number will be published with the manuscript if it is accepted.

Authors must include a copy of the trial protocol that was submitted to the IRB with their submission. Academic Editors are asked to compare this protocol to the methods and results reported in the manuscript to confirm that the researchers adhered to the IRB-approved procedure. The protocol is also published with the manuscript if it is accepted. Any deviations from the original protocol should be explained in the manuscript and the registry.

Authors must submit a completed CONSORT checklist (or TREND checklist, if the study was a non-randomized controlled trial) as part of the Supporting Information, which will be published with the manuscript if accepted, and CONSORT participant flowchart as Figure 1 of their manuscript.

We reserve the right to reject without review any manuscripts that do not meet these requirements.

Journal staff will invite a statistical reviewer to assess all clinical trial manuscripts and notify the Academic Editor of this action. PLOS has a Statistical Advisory Board composed of experts in a variety of areas who work to ensure that the statistical analysis underlying all reported clinical trial results was conducted rigorously.

In addition to the statistical review, we strongly suggest that the Academic Editor obtain at least two reviews from subject area experts if considering the manuscript for publication. Of course, the Academic Editor may reject the submission without review if the manuscript contains fundamental flaws that make it inappropriate for publication.

Statistical reviewers

Role of statistical reviewers

The journal works with a group of statisticians, which we refer to as our Statistical Advisory Board. At present, all clinical trials submitted to the journal are evaluated by a statistical reviewer, but we also invite statistical input for other types of studies on an ad hoc basis - typically systematic reviews, meta-analyses, and also large epidemiological studies (e.g. case-control and cohort studies). Statistical reviewers are asked to focus on improving the quality of study reporting and the rigor and appropriateness of the statistical analysis when preparing recommendations and writing comments for the authors and editors. The average workload for each statistical reviewer is two manuscripts per month, although they may be invited to handle more.

Working with statistical reviewers

Listed below are some general points that statistical reviewers bear in mind when appraising statistical reporting. In particular, they highlight some important areas that are often performed or reported poorly in papers reporting results of trials. Statistical reviewers consider general points related to good statistical practice for reporting of trials (especially randomized trials), to which PLOS would aim to adhere. Some will also apply to other biomedical studies, and more detailed guidance for other types of studies can be found in the references we include later on. Even if they believe the study is of excellent quality and they have no major criticisms, statistical reviewers will note for the Academic Editor and in-house staff that they have reviewed with respect to the aspects below and can recommend the paper for publication.

Specific points we ask statistical reviewers to note

- Is there a clear statement of the objective, source of participants, and interventions being compared?
- Are randomization procedures fully detailed? Was the randomization likely to be robust and was concealment of allocation adequate?
- Was blinding (of patients, physicians, and outcome assessors) used? If not, do the authors acknowledge possible biases resulting from a lack of blinding?
- Is the study sample size properly justified (preferably with a pre-study power calculation)?
- Does the paper report on final outcomes for the full study population, and were outcomes and analyses pre-specified?
- For trials, check the manuscript against the trial registry record and/or the study protocol document (available as supporting information) and ensure any discrepancies are explained in the paper. If you are concerned about selective reporting, comment on this in your report. We recommend taking great care with reports that describe interim analyses or seem not to report on all primary and secondary outcomes.

- Is the reporting of the study population adequate? Reasons for dropout and the CONSORT flow diagram should be fully completed.
- Is reporting of harms (adverse events/side effects) adequate and balanced?
- Do the main analyses use appropriate statistical tests and are the statistical procedures referenced or described?
- Is the correct analytical population used and do the main conclusions rest on this analysis? In most cases (particularly effectiveness trials), this will be intention-to-treat, not per-protocol.
- Are the main statistical results given using estimates of effect size and an indication of precision (uncertainty, typically 95% confidence intervals)?
- Most guidance discourages reliance on p-values, which do not enable readers to distinguish between "negative" and "inconclusive" results nor to draw clinically relevant interpretations from the observed difference between groups.
- In general is statistical material presented adequately (figures, tables etc.)? Is there appropriate correction for multiple testing? Reports should use exact p-values not notation such as stars, N.S., non-significant, etc.
- Papers should report absolute as well as relative risks, or use numbers needed to treat.
- Do authors discuss results in a balanced way (without "spin")? Be sure to evaluate this in the abstract, not just the full paper. Potential biases should be properly discussed by authors.

Quick references and guidelines on good statistical reporting

- CONSORT Statement - guideline intended to improve reporting of randomized controlled trials.
- SAMPL Guidelines - Statistical Analyses and Methods in the Published Literature
- Statistical Problems to Document and to Avoid - Vanderbilt University Department of Biostatistics checklist for authors
- Checklists for statisticians - BMJ 1996; 312

Additional points

We ask the reviewers to read our guidelines for reviewers (ONE | GPH) online to familiarize themselves with the scope, purpose, and editorial criteria of the journal.

The journal is particularly focused on methodological rigor and quality of reporting in making decisions on submitted papers. We do not consider the direction of results (i.e., whether "positive" or "negative") to be relevant to editorial decisions, providing the study is adequately powered, well conducted, and clearly reported. We ask reviewersto therefore disregard the direction of findings in their evaluations and submitted reports. We are therefore looking for a detailed review covering all aspects of quality of design, statistical analysis, and reporting of the study.

The journal supports widely endorsed community standards for trial conduct and reporting, such as the CONSORT Guidelines for registered clinical trials. The statistical reviewers are encouraged to refer to the study protocol supplied by the authors and to consider issues of reporting bias when evaluating the validity of the published paper. We ask these reviewers to ensure they highlight any protocol deviations and whether these seem to be important or not when providing their report to the journal.