# The need for reporting guidelines for early phase dose-finding trials

Dose-Finding CONSORT Extension

# The need for reporting guidelines for early phase dose-finding trials: Dose-Finding CONSORT Extension

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**To the Editor** - Early phase trials (phase I or phase I/II) are studies conducted in healthy volunteers or patients aiming at determining drug disposition (absorption, distribution, metabolism and excretion), adverse effects, drug exposure, pharmacodynamic (PD) biomarker activity and clinical activity. A critical step in treatment development, results from early phase trials directly influence decisions on further trials and whether the selected doses and schedules are sufficiently safe and have promising results on treatment activity.

Often termed dose-finding or dose-escalation studies, early phase trials account for a large number of the trials being run at any given time: A search of ClinicalTrials.gov for phase I studies first posted between 2019 and 2020 returns 8536 entries, versus 5162 phase III trials first posted over the same period. Attrition rate throughout the drug development process is high, and the success rate between phase I studies and marketing authorisation has been reported as between 9.8% and 13.8% based on several studies (1, 2), with failure being primarily attributable to either poor tolerability or lack of biological activity (79% of failed studies over the period 2016-2018) (3).

In this context, it is crucial that phase I trial results are assessed accurately, to avoid progressing candidate treatment to subsequent phase studies with a false or imprecise sense of tolerability and activity, or conversely discontinuing a tolerable and biologically active treatment. Incorrect assessment of early phase trials could waste time, resources, and may expose participants to ineffective or even harmful treatments (4). To allow accurate assessment of early phase trial results, it is crucial they are reported precisely, transparently and in sufficient detail.

Contemporaneously, phase 1 trials have also seen a trend toward the use of biology-based, hypothesis-testing and biomarker driven, more complex designs including arguably more efficient novel designs, such as model-based or model-assisted designs. A model-based design uses a model to describe the dose-toxicity relationship, whereas a model-assisted design does not; both generally use a combination of probability models and rules to drive decision-making. 1.6% (20 of 1,235 oncology phase I published trials) used such novel design approaches in 1991-2006 (5), with this increasing to 2.4% (5/212) in 2009 and 9.7% (22/226) in 2014 (6). This increased complexity of trial

design and conduct should come with increased transparency and reporting demands to ensure methods and results are reproducible.

The CONSORT (CONsolidated Standards of Reporting Trials) 2010 statement is the recognised quality standard for reporting randomised trials and the adoption of CONSORT by many scientific journals has contributed to an increase in reporting quality and completeness (7,8). However, early phase dose-finding trials may be non-randomised, and therefore may not have used the CONSORT 2010 statement to report their findings, though many of the checklist items may apply. Additionally, early dose-finding trials have specific features that are currently not covered in the original CONSORT 2010 statement. Examples of specific features that require additional reporting considerations include: starting dose and justification, recruitment and dosing process, definition of dose-limiting toxicities (including length of assessment window), interim dose decision making and recommended dose(s) selection criteria.

Therefore, there is a need for an extension to the existing CONSORT 2010 guidance aimed at dose-finding trials. Dose-finding CONSORT extension will incorporate the unique features of dose-finding trials, be applicable regardless of the specific trial design that has been implemented or disease area, and will facilitate trial interpretability and support reproducibility of methods.

To address this challenge, an Executive Committee has been assembled comprising: a multi-disciplinary team of international methodologists and clinical trialists experienced in early phase trials in both academia and pharmaceutical industries; a CONSORT group representative; and a patient and public representative. The Executive Committee will produce a robust and comprehensive international consensus-driven guidance using gold standard methodology following the methodological framework for guideline development recommended by the CONSORT group (9). A rapid methodological review of published early phase dose-finding trials will be conducted to identify deficiencies in their reporting, and inform the initial generation of the list of candidate items for the Dose-finding CONSORT Extension. The initial draft checklist will be further enriched through review of the published and grey literature (such as guidelines or reports from regulatory bodies and professional working groups) and consultation with international experts, including regulators and journal editors. A modified Delphi process will then be used to refine the checklist before an international consensus meeting, which will agree on minimum essential reporting items that should be included in the guideline.

Throughout the development process, strong international multi-stakeholder involvement will include early phase methodologists and trialists including clinicians, research nurses, trial managers and statisticians, journal editors and peer-reviewers, ethics committees, funders, regulators and patient and public partners. Involvement will ensure the produced guidance reflects the views of the wider early phase trials community. The Executive Committee will pilot test the near-final guidelines with real-world trial examples to identify any gaps, troubleshoot any problems and incorporate feedback in the final revision.

To maximise awareness and engagement as well as promote maximum uptake, a detailed dissemination strategy will be implemented. This will include workshops tailored to specific target groups such as journal editors, and the production of lay summary papers as well as publications of the various aspects of the work in academic journals.

Once published, it is expected the Dose-finding CONSORT Extension will benefit the community in several ways as shown in Table 1.

Table 1: Benefits of the Dose-finding CONSORT Extension

| Benefit |
| --- |
| Promoting transparency and adequate reporting in early phase dose-finding trials |
| Enhancing reproducibility of methods |
| Enhancing the understanding and interpretability of early phase dose-finding trials results |
| Providing a framework for peer review of early phase dose-finding trial reports by editors and peer-reviewers, as well as supporting the general readership in the critical appraisal of the quality of the trial design and methods, and the risk of bias in the reported outcomes |
| Helping researchers in designing early phase dose-finding trials |
| Used as an educational tool for researchers |
| As a result of the above benefits, the guidance will ultimately contribute to reducing research attrition and better patient care. |

In the medium to long-term, this Dose-finding CONSORT Extension will benefit society by improving the efficiency and accuracy of dose-finding trials and accelerate the safe development of novel therapies.

The Executive Committee would like to invite interested stakeholders to register their interest in taking part in the Delphi Survey process via the Dose-finding CONSORT Extension project website (10).

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**Authors Contributions:**

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**Conflicts of interest**

The authors declare no known conflict of interest.

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