

The literature on dose-finding trials is considerable, and there is specific terminology associated with the field. The box below gives a glossary of key terminology used in the SPIRIT-DEFINE and CONSORT-DEFINE checklists.

Definitions of key technical terms

<p>Bias: the systematic tendency for the treatment effect estimates to deviate from their “true values”; including the statistical properties (such as error rates) to deviate from what is expected in theory (such as pre-specified nominal error rate).</p>
<p>Cohort size: this refers to cohorts of participants for the dose-escalation phase, which could be one or more participants</p>
<p>CONSORT: Consolidated Standards of Reporting Trials. It encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomised controlled trials.</p>
<p>DEFINE: DosE FIndiNg Extensions for SPIRIT and CONSORT guidelines.</p>
<p>Dose: quantity of a medicine (e.g., drug, radiotherapy, repetition of an exercise in non-drug trial) to be administered or extent to which a participant may be exposed to a therapy.</p>
<p>Dose-finding trial: early phase trial where increasing doses/regimens of the investigated therapy are administered to sequential groups of participants, with interim assessments of the safety/tolerability and activity of the treatment, to identify safe dose(s) for further testing.</p>
<p>Dose limiting toxicity (DLT): unacceptable adverse events that prevent further administration of the investigated therapy at that dose level.</p>
<p>Dose regimens: specific ways how a treatment is delivered, including route of administration, dose, interval and duration</p>
<p>Early phase: the development of a new medical intervention typically follows a series of clinical research from early phase 1 to late-stage phase 3. The purpose of early phase trials is to investigate how much of the treatment is safe to give, side effects and tolerability.</p>
<p>Expansion cohort: a phase in a clinical trial that aims to accrue additional participants, after an initial dose-escalation component, with different or targeted eligibility criteria in order to collect additional information on safety or activity.</p>
<p>In silico: computational methods (e.g., modelling, machine learning) to capture, analyse, simulate and extrapolate biological and medical data (e.g., toxicological assessment, dose optimisation).</p>
<p>In vitro: studies conducted on biologic materials outside of the materials origins, e.g., observing the growth of cells derived from blood samples.</p>
<p>In vivo: studies conducted on living subjects such as animals or plants to investigate the overall effects of a drug, for example, on a living subject.</p>
<p>Interim analysis: a statistical analysis or review of accumulating data from an ongoing trial (interim data) to inform trial adaptations (before the final analysis), which may or may not involve treatment group comparisons.</p>
<p>Lay summary: a plain language (lay) summary outlining the article content, aimed at non-specialists in the field and written in a way that they can easily understand.</p>

Maximum tolerated dose (MTD): the highest tested safe dose with acceptable toxicity.

Model parameters: a parameter is a true value describing a population (e.g., average age of all stroke patients). Sometimes one or more parameters may have an effect of an outcome (e.g., survival). Varying and tuning parameters in a simulation model would allow investigators to check how they would affect the design, outcomes and results.

Nonclinical: there are two types of nonclinical research: in vitro and in vivo. Nonclinical trials are done before testing the drug in people.

Operational bias: occurs when knowledge of key trial-related information influences changes to the conduct of that trial in a manner that biases the conclusions made regarding the benefits and/or harms of study treatments.

Operating characteristic: performance of a trial design under various specified conditions (done using simulation).

Pharmacodynamic (PD): pharmacodynamic study is to assess the effect of the drug on the body, e.g., the effect from the drug's molecular, biochemical, or physiologic interactions with the body's biological structures or targets.

Pharmacokinetic (PK): pharmacokinetic study is to assess the effect of the body on the drugs, i.e., the absorption, distribution, metabolism and elimination of drug(s) from the body.

Preclinical: see nonclinical.

Pre-planned adaptations or adaptive features: changes or modifications to be made to aspects of an ongoing trial, defined a priori in the trial documentation (such as the protocol), and where results from interim data analysis are used to trigger the modifications, without undermining the trial's integrity and validity.

Recommended phase 2 dose (RP2D): dose of a drug or treatment recommended to be taken forward for phase II trials following an early phase dose finding study

Simulation: a computational procedure performed using a computer program to evaluate statistical properties of the trial design by generating pseudo data according to the design, under a number of scenarios and repeated a large number of times.

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

Unplanned changes: ad hoc modifications to aspects of an ongoing trial, often requiring a formal amendment to the trial documentation.