Clinical trial design: Considerations for medical writers developing clinical trial protocols

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Abstract
Clinical trial protocols must provide a clear trial design to meet the study objectives. Medical writers must understand and be ready to review and discuss aspects of the trial design with the protocol development team, in order to write a clear and accurate protocol. This article reviews some of the main trial design concepts medical writers should expect to find when writing protocols.

Introduction
Clinical trial protocols for trials evaluating pharmacological products are complex documents that describe the medical, ethical, and regulatory foundations of the trial. Medical writers work together with protocol development teams of subject matter experts (including medical experts, statisticians, regulatory experts, operational experts, and pharmacokineticists) to write clear protocols that will address the proposed medical questions and protect participant safety and rights. To accomplish this, writers must understand and be able to communicate clinical trial design concepts that are often complex. Moreover, although International Council for Harmonisation (ICH) Good Clinical Practice (GCP)[1] provides recommendations on what a trial protocol should include, and efforts have been made to harmonise the structure of trial protocols (e.g., TransCelerate Common Protocol Template[2] and SPIRIT Statement[3]), a standard similar to ICH E3[4] for trial reports, defining what information to present and how is not available. This creates an additional challenge for writers.

This article reviews the main concepts affecting trial designs presented in protocols and how to address them from a medical writing

Table 1. Protocol writing tips and considerations for key sections

Introduction
- The introduction section should include a literature review covering the indication, available therapeutic options, and test treatment(s)
- Present the scientific rationale of the trial, identifying its primary purpose, what it aims to achieve, and its importance

Objectives
- Confirm consistency between the rationale and objectives
- Write SMART objectives (see Table 2 opposite)

Population
- Define the target population and present a list of inclusion/exclusion criteria
- Confirm that the inclusion/exclusion criteria are consistent with the objectives

Endpoints
- Write short descriptions of the endpoints, which should be measurable
- Confirm consistency between the objectives and endpoints
- Confirm that all variables are captured in the schedule of assessments
- Confirm consistency between the defined estimands, objectives, endpoints, and analyses

Trial design
- Confirm that the trial design is clear and consistent with the objectives, endpoints, and schedule of assessments
- Confirm that bias minimisation methods are presented. If randomisation and/or blinding are not used in a comparative trial, this should be justified

Control groups
- Confirm that the control group is clearly identified and justified
- Confirm that the control group is aligned with the design and objectives
- Confirm that all test treatments (including placebo) are clearly identified and characterised

Statistical considerations
- Confirm consistency between statistical considerations and trial endpoints
- Confirm that all variables analysed are collected at the appropriate times in the schedule of assessments
- Avoid too much detail when presenting the statistical analysis methods, referring to the statistical analysis plan when appropriate

perspective while ensuring compliance with ICH GCP. Operational, regulatory, and ethical concepts are not discussed.

Table 1 summarises some writing tips for each key section of the protocol.

Rationale

Clinical trials assess the efficacy, safety, and/or pharmacological characteristics of medicinal products in human participants. The protocol must present a rationale that identifies the primary purpose of the trial, usually in the "Introduction" section (Table 1). At trial conception, the protocol development team should consider:

- If the rationale is clear
- If the trial is clinically relevant and feasible
- If an unnecessary risk/burden will be posed to trial participants

Objectives

Trial objectives are the actions proposed to fulfil the trial's rationale. The objectives should be conceived by the protocol development team and written by the medical writer according to the SMART principles (Table 2).[5,6]

Objectives in clinical trials can be divided into three categories:[7]

- **Primary** (typically one): aims to directly answer the primary purpose of the clinical trial
- **Secondary**: other actions relevant to and/or indirectly associated with the rationale
- **Exploratory**: hypothesis-generating objectives that can be confirmed in dedicated studies

Population

Protocols should briefly define the **target population** (i.e., the set of people throughout the world for which the trial results may be generalised).[8] A detailed **list of inclusion and exclusion criteria** should follow, specifying:[8,9]

- Demographic characteristics (e.g., age, sex, body mass index)
- The medical indication under study,

Table 2. Example of a SMART written objective

To assess the efficacy of paracetamol 1000 mg per os versus placebo in adult patients with fever of unknown origin (body temperature >37.5°C) 2 hours after administration.

Specific: identifies the action (to assess efficacy), medication(s) (paracetamol and placebo), population (adults), and indication (fever of unknown origin)
Measurable: temperature is a measurable variable
Achievable: feasible and not burdensome to the participant (to be confirmed by the trial medical expert)
Relevant: objectives should be clinically relevant (to be confirmed by the trial medical expert)
Time based: in this example, a 2 hour timeframe is specified

acceptable/prohibited comorbidities, and acceptable/prohibited concomitant medications
- Ethical requirements for participation (e.g., informed consent)
- Exclusion criteria that may bias result interpretation or pose an unnecessary risk to the participant

Endpoints

In clinical trials, variables are the parameters (sociodemographic, clinical efficacy and safety, laboratory/imaging-related, etc.) that will be measured. Variables can be independent (variables that potentially influence health outcomes, e.g., treatment, age, sex, smoking history) or dependent (health outcomes, e.g., vital signs, laboratory parameters).[8]

An **endpoint** is defined by Spilker as "*an indicator measured in a patient or biological sample to assess safety, efficacy or another trial objective.*[10] Each objective must be matched with at least one endpoint, to ensure that the right variables will be captured and that all questions posed by the trial will be addressed. As an example, let's consider the following objective:

- *To assess the efficacy of paracetamol 1,000 mg per os versus placebo in adult patients with fever of unknown origin (body temperature >37.5°C) 2 hours after administration of the test treatment*

Two possibilities for the corresponding endpoint can be proposed (the best possibility should be selected with the protocol development team based on clinical relevance and feasibility):

- *Proportion of patients with a body temperature higher than 37.5°C 2 hours after test treatment administration*
- *Mean body temperature 2 hours after test treatment administration*

The protocol development team is responsible for defining the endpoints, while the medical writer should ensure that they are clearly written (Table 1).

Endpoints are classified in accordance with the corresponding objectives (primary, secondary, exploratory). The primary endpoint should provide the most clinically relevant and convincing evidence directly related to the primary objective of the trial and its selection should reflect the accepted norms and standards in the relevant field of research.[11]

Endpoints should be measurable and should be concisely described in the protocol, while details of how the endpoints will be captured can be provided in one or more dedicated protocol sections. All endpoints and variables must also be captured in a schedule of assessments that identifies which variables will be measured at each trial visit and that provides summarised procedural information for quick reference to the trial site teams.

> The protocol defines the procedures by which a clinical trial is conducted, and its writing requires careful assessment of all concepts surrounding trial design for accuracy and consistency.

Estimands were recently introduced in ICH E9 (R1) and describe the treatment effect with consideration of specified post-randomisation events and whether the outcome would be under different conditions.[12] Four interrelated attributes are considered for this purpose:[12,13]

- Population: participants targeted by the trial
- Variable/endpoint
- Post-randomisation events: events that happen to participants that may affect results (e.g., death, treatment discontinuation, use of rescue medications)
- Population-level summary statistics for the endpoint: the basis for treatment comparisons

A summary of the use of estimands in clinical trials can be found in a publication by Bridge and Schindler.[13]

Trial design

The trial design will dictate participant treatment and follow-up, the number of treatment groups, and data collection, among other aspects.

Single group design

In single group trials, variables are compared in the same participant before and a certain time after exposure to the test treatment (intra-participant analysis).[8] These are typically early phase trials or are conducted where limited participant pools are available. Results are usually preliminary since it is not possible to blind the treatment.[14]

Comparative design

In comparative trials, two or more test treatments

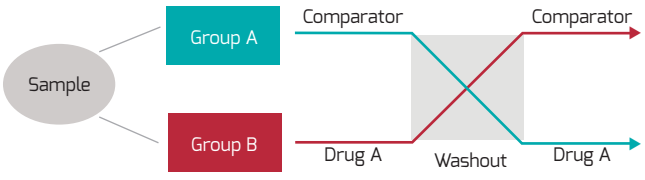

Figure 1. Crossover design

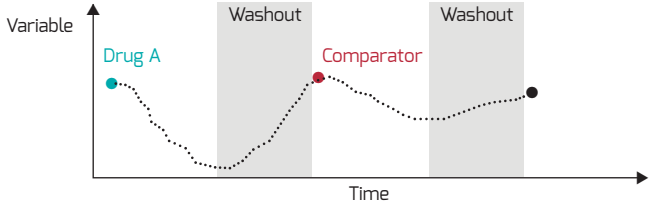

Figure 2. Ideal crossover trial variable

are compared. In a **parallel design**, participants will keep the same treatment until trial completion or discontinuation. At defined time points, variables are compared between groups (interparticipant analysis).[15]

In a **crossover design**, participants receive all treatments in a randomised sequence. Administration of different treatments is separated by a washout period, where no active treatment is given. This is done to prevent the effect of the previous treatment from biasing the new treatment, i.e., carryover effects (Figure 1).[8,15] Because the same participant receives different test treatments, intraparticipant analyses are possible.

Crossover trials are useful when assessing stable variables and conditions that produce a response during treatment and return to near-baseline levels during washout (Figure 2).[8,14]

Factorial designs compare different treatments given as monotherapy or in combination, creating groups for each possibility (Table 3). These trials assess various possible interactions and complementary effects. However, they can be complex if a high number of groups is required.[14]

Table 3. Factorial design (2^2)

Product A	Product B	
	Yes (+)	No (–)
Yes (+)	Group 1 ++	Group 3 + –
No (–)	Group 2 –+	Group 4 – –

Minimising bias in comparative trials

Comparative trials typically include measures to minimise bias and ensure groups are comparable. **Randomisation**, in which trial participants are randomly assigned to the different study treatments, is the standard method to obtain treatment groups with similar baseline characteristics (e.g., age, sex). Randomisation increases the likelihood that baseline characteristics that could confound treatment effects will be distributed equally among treatment groups.[8] Randomisation lists with the participant codes and respective treatment allocations are informatically generated by different methods:

- Simple randomisation: based on a single sequence of random assignments (like tossing a coin), it is useful for large samples, but can create unequal treatment groups in smaller samples.[15-17]
- Block randomisation: blocks of equal size are defined with all possible treatment orders and are picked randomly to generate the randomisation list (Figure 3).[8,16,17]
- Stratified randomisation: the sample is stratified by key baseline characteristics (e.g., sex, age). Participants are randomised so that these characteristics are distributed equally between treatment groups.[8,16,17]

Another allocation method is adaptive randomisation, where the first participant is randomised, while subsequent participants are allocated non-randomly to minimise group imbalances regarding key baseline variables.[16,17]

After ensuring that all treatment groups are comparable, it is important to confirm that participant follow-up and outcome assessments are not biased.[8] The key trial procedure here is **blinding** (or masking): the process of ensuring that the Investigator and/or participant is unaware of the treatment assigned. The main types of blinding include:[15]

- Double blinding: both the Investigator and the participant are unaware of the treatment given. This is the preferred type of blinding as it avoids biased assessment of outcomes by both the Investigator and the participant
- Single blinding: only the Investigator or the participant is aware of the treatment given
- Open label: both the Investigator and the participant are aware of the treatment given

Double blinding requires test treatments to be indistinguishable (shape, colour, smell, taste), which is sometimes not possible (e.g., comparing two active treatments with different formulations). One way to overcome this is to perform a **double dummy trial**, where each treatment has a matched placebo (dummy), so each participant receives one active treatment and the placebo version of the comparator.[15]

Control groups

The choice of the control group in comparative trials should consider the rationale and objectives, along with regulatory, operational, and ethical aspects.

Placebo

Placebos are formulations without any active pharmaceutical ingredient used in double blind trials.[15] These must be indistinguishable from the test treatment in terms of packaging, labelling, size, shape, opacity, coatings, viscosity, colour, smell, flavour, and route of administration.[18] Placebos are useful to minimise bias and distinguish the real effects of the test treatment and "noise" effects, such as:[15]

- Normal physiology and spontaneous disease fluctuations
- External factors that can alter the participant response (e.g., increases in liver transaminase levels after a long period of hospitalisation in a clinical trial unit due to a strict diet, lack of exercise, or other lifestyle changes)

On the other hand, placebo groups may not be appropriate in some settings, such as serious

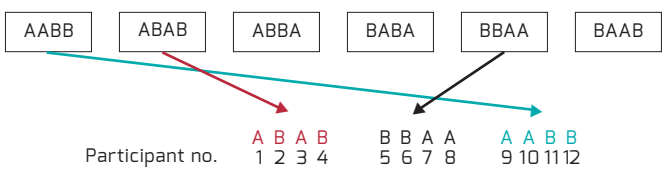

Figure 3. Block randomisation for treatments A and B

Twelve participants are randomly allocated to treatment A or treatment B using three randomly selected blocks of 4, each containing a unique sequence of treatment options.

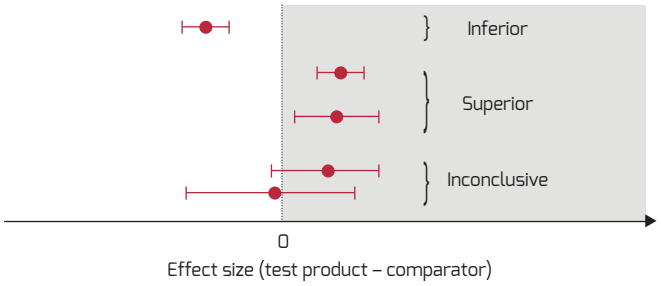

Figure 4. Possible outcomes of a superiority trial
Data are shown as the point estimate and 95% confidence interval.

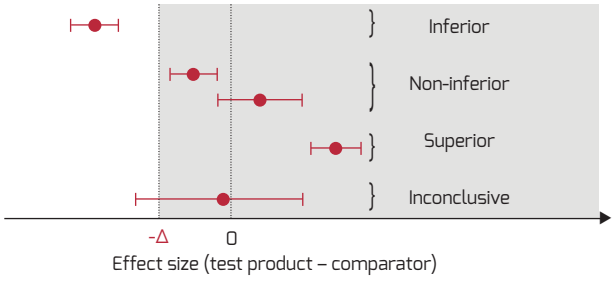

Figure 5. Possible outcomes of a non-inferiority trial
Data are shown as the point estimate and 95% confidence interval.

diseases with available therapeutic alternatives (e.g., oncology, infectious diseases).[15]

Active comparator

When comparing a test treatment against an active comparator, different trials can be considered.

Superiority trials aim to demonstrate the superiority of the test treatment against the active comparator regarding the primary endpoint. If the difference between the test treatment and comparator and 95% confidence interval (CI) are higher than 0 for the primary endpoint, the test treatment is considered superior (Figure 4).[19]

Sometimes, a different test treatment may not be superior in terms of efficacy but may offer other advantages (e.g., a better toxicity profile, more convenient administration).[15] Here, **non-inferiority trials** can be considered. These trials evaluate whether the test treatment is as good as or worse to an acceptable degree compared to the reference. Here, a non-inferiority margin (-Δ in Figure 5) is defined.[8,20,21] If the difference between the test treatment and comparator and 95% CI for the primary endpoint is higher than -Δ, the test treatment is considered non-inferior (Figure 5).[19] If the 95% CI lies entirely above 0, there is evidence of superiority at the two-sided 5% significance level ($p<0.05$).

A justification for the non-inferiority margin, typically provided by the trial statistician, should be included in the protocol.

Bioequivalence trials compare two products with the same active pharmaceutical ingredient (i.e., different formulations of the same product or generic versus comparator).[22] Two products are considered bioequivalent if they produce the same plasma concentration-time profiles, i.e., if the 90% CIs for the geometric mean ratios for the area under the curve from time 0 to last measurable concentration (AUC_{0-t}) and maximum plasma concentration (C_{max}) for the test and reference products lie entirely within the interval 80% to 125%.[22,23] Examples are shown in Figure 6.

Other control groups

Other potential control groups include:

- **No treatment**: this method is not blindable and can be unethical unless it is confirmed that participants will not be subjected to an unacceptable risk[24]
- **Standard of care** (treatment as usual, routine care): this can be employed to compare the test treatment with existing practice. However, "standard of care" can vary between study sites and countries, hampering an objective definition[25]
- **Active placebo**: a placebo that mimics the adverse effects of the test treatment. This can be useful when the risk of unblinding due to characteristic adverse events is high[26]

Statistical considerations

Statistician support is needed when developing the statistical sections of the protocol. When applicable, other experts should also be consulted (e.g., a pharmacokinetics/pharmacodynamics expert, quality of life expert). The protocol should present a **rationale for the calculated sample size** with the necessary statistical and clinical assumptions (based on the primary endpoint). In addition, the **statistical analysis methods** should be summarised for all endpoints, with full details being provided in a separate statistical analysis plan.

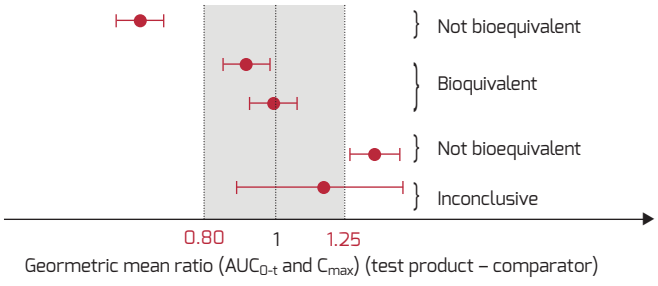

Figure 6. Possible outcomes of a bioequivalence trial
Data are shown as the geometric mean ratio and 90% confidence interval for the area under the curve from time 0 to last measurable concentration (AUC_{0-t}) and maximum plasma concentration (C_{max}).

Final remarks

The protocol defines the procedures by which a clinical trial is conducted, and its writing requires an assessment of all concepts surrounding trial design. Medical writers must understand these concepts and work with the protocol development team to communicate them clearly. This will protect the scientific integrity of the trial and the safety of the participants.

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Disclaimers

The opinions expressed in this article are the author's own and are not necessarily shared by his employer or EMWA.

Conflicts of interest

The author declares no conflicts of interest.

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