

RESPECT THE RULES OF THE PROTOCOL

EARLY PHASE CLINICAL TRIALS – MAXIM #7

The clinical trial protocol, as a detailed outline of a clinical study, must be rigorously followed by the clinical trial team, not only to be in line with regulations, but also to avoid harm to participants and erroneous conclusions. As early phase trials are becoming increasingly complex, the risk of protocol deviations, necessary amendments, incorrectly gathered data and even inaccurate conclusions may increase.

Per ICH-GCP, the protocol is “the document that describes the objective(s), design, methodology, statistical considerations and organization of a trial”. Simply, it describes what you will do and how you will do it. It should be designed in such a way that it ensures participants’ safety and solid scientific answers at the same time. Flaws in the protocol will lead to deviations, violations, amendments and even to missing, invalid or uninterpretable data.

The development of a solid protocol is a stepwise process and involves various stakeholders. First, the outline of the study must be clear, defining the specific research question(s) and choosing an overall design. This step includes decision making on objectives, population (healthy volunteers or patients), and overall design (trial phase, number of cohorts, parallel or alternating, placebo-controlled).

STUDY SYNOPSIS

Once the scene is set, the study concept must be captured in a study synopsis that must include the following elements:

- Objectives, to be defined as primary, secondary and exploratory.
- Endpoints for every objective, with corresponding measurements and statistical methods.



- Design aspect: randomization, use of placebo, blinding, cohorts and study parts.
- Population: number of participants and main selection criteria.
- Details on the test product: doses and route of administration.
- A time and event schedule capturing assessments for subject safety and data collection.

Thorough decision making during synopsis development is paramount and requires input from clinical pharmacology, medical, regulatory, statistical and operational experts. Discussion points should be resolved at this stage to avoid issues at the stage of full protocol development, when the various required sections are further detailed in the official document, or even during study conduct.

COMPLEX STUDY DESIGNS

Early phase studies nowadays tend to formulate multiple objectives in one “umbrella” study. It is standard practice to combine cohorts for single ascending dosing (SAD) and multiple ascending dosing (MAD) in the same first-in-human (FIH) trial. Often a cohort to explore a food effect or to obtain a proof of pharmacology in a specific (patient)

population is also included. As such, not only the dose escalation process but also the progression to the next study part(s) needs to be described. Decision making during the trial needs to be carefully determined: who will make the decision to proceed, when and based on which data?

In combined early phase protocols, some decisions can only be made after analysis of the collected data. To avoid the need for protocol amendments after every decision, these aspects can be described in a flexible way. Examples of adaptive features are: the exact dose levels, the number of cohorts, the regimen for multiple dosing, assessments to be added or omitted, etc. As long as the changes follow what is written in the protocol, substantial amendments are not warranted. The advantage of combined, adaptive protocols lies in gaining efficiency, time and cost.

Following rules apply to make adaptive designs regulatory proof:

- Adaptations must be described in detail
- Clear boundaries must be set
- The decision-making process, including rules for stopping, must be clear

Examples of crucial decisions and possible pitfalls in a complex FIH synopsis are:

- The starting dose and maximum exposure need to be described and explained. Both the clinical pharmacology and medical expert must ensure that the dose range is safe and sufficient to make decisions on later dosing regimens.
- The exact dose escalation is to be decided, based on safety data, but collected pharmacokinetic (PK) and pharmacodynamic (PD) data may be needed as well. The compound's pharmacological profile will determine the exact data needed before going ahead. Dose levels can be left flexible in the protocol, but boundaries and decision making must be described. Importantly, enough time needs to be foreseen between cohorts and study parts to be able to obtain and analyze the required data.
- The exact population needs to be defined by in- and exclusion criteria. FIH trials often enroll healthy volunteers, but it is an emerging trend to also involve special populations (e.g. elderly) and patients. The design team needs to weigh the need for criteria, in terms of safety and data cleanliness, against the difficulty they may create for recruitment. For example, elderly people do not have normal kidney functions. One does not want to look for subjects who do not exist or are so rare that no one will be able to recruit them.
- The assessments needed to document safety and tolerability (as a primary objective of a FIH) as well as their exact timings, are to be determined by the preclinical safety data and comparison to similar drugs, if available. Medical experts need to choose accurate methods that can objectively demonstrate safety such as laboratory values, imaging techniques, or specific tests. Their correct timing in relation to the compound's predicted pharmacology (Tmax and half-life e.g.) is paramount for their validity.
- The correct time points for PK blood (and sometimes urine) sampling need to be defined based on the product profile. Also, metabolites need to be considered. With a wrong sampling schedule, no accurate conclusions can be drawn regarding the product PK profile. The sampling schema may also be left flexible to adapt in function of obtained results from precedent groups.
- Biomarkers of PD effects, including receptor occupancy, activation of cells and pathways, can provide proof of pharmacology, indicative of a therapeutic dose range.
- All safety, PK and PD assessments need to be captured in a visit schedule. Although not always possible, the aim is to obtain a PK/PD/safety relationship for the new compound.
- In the whole synopsis development process, it is of the utmost importance that the operational team carefully review and finetune all aspects: the feasibility of enrolment criteria, all assessments in the given time frames, the impact on the participants and hence the recruitment, etc.

To conclude, designing a solid study synopsis requires time and effort from a multi-disciplinary team. However, time spent and the investment to in-source specific expertise at this important stage will pay off later. After all, what is written on paper needs to be doable in real life, and you shall respect the rules of the protocol!



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