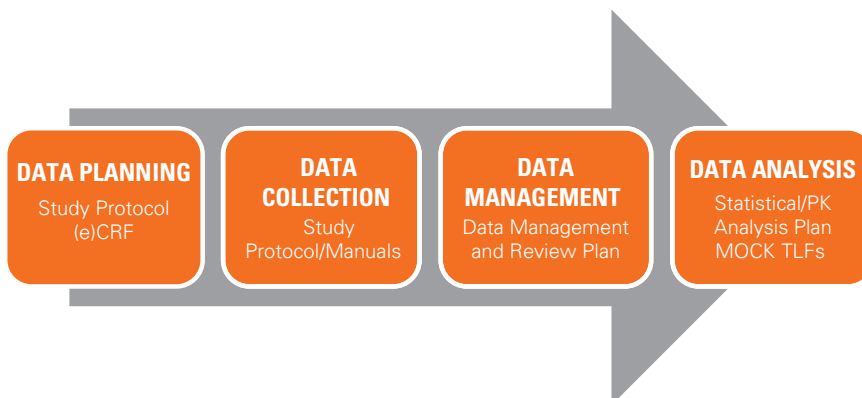


APPROPRIATE AND RELIABLE DATA REQUIRED FOR CONCLUSIVE FIH/PHASE 1 TRIALS

EARLY PHASE CLINICAL TRIALS

Clinical trials are intended to find answers to a research question by generating data to prove or disprove a hypothesis. First-in-Human (FIH) and most Phase 1 trials by their very nature are exploratory, without a statistical hypothesis. They are aimed at obtaining reliable information on the safety, tolerability, pharmacokinetics and mechanism of action of a drug.

Various data is captured from FIH trials. Despite their exploratory character, this data needs to be relevant, accurate and appropriately analyzed to obtain meaningful results that are useful for future clinical development. We can highlight four main steps in clinical data processing:



DATA PLANNING

The first step is the planning of data at an early stage when developing the study design/protocol/CRF: which measurements to foresee, when exactly, for how long and how frequently? These questions concern all the assessments in the FIH, i.e. safety, tolerability, PK and PD. Often, planning is not very targeted since the only supporting information available at this stage is preclinical data with human predictions and because there is no precise statistical endpoint.

DATA COLLECTION

Once the study starts, data is collected by the operational staff of the Research Unit on an ongoing basis. Any inappropriate methodology and non-adherence to protocol/manuals/CRF may have a critical influence on data reliability and introduce bias. Thus, trained and punctual staff, aware of the importance of their work, are mandatory, without ignoring the training and preparation of the study subjects. The relatively high-risk nature of FIH studies and the absence of therapeutic benefit brings with it the ethical obligation to limit the number of exposed subjects, stressing even more the need for good quality data capture and handling.

DATA MANAGEMENT

Clinical Data Management (CDM) is the process of collecting, cleaning, coding and managing subject data in compliance with regulatory standards. The primary objective of CDM processes is to provide good quality data and gather the maximum data for analysis. To meet this objective, best practices (software, standard automatic process, eCRF, electronic data review) should be adopted.

DATA ANALYSIS

At the end of the trial, the data is analyzed to "become results". If appropriate methods of analysis are used with the appropriate data, it will be possible to interpret results and come to a conclusion. In the case of FIH studies, the conclusion should allow a decision to go, or not go, to the next phase of development and to give initial indications on how to design the next study.

In summary, 'high-quality' data is needed in all clinical studies including exploratory FIH. These should meet the protocol-specified parameters and comply with the protocol requirements.

CASE STUDY 1:

Major role of appropriate PK data planning in FIH study

A substantial amendment was introduced, and study conduct changed because of inappropriate PK data planned in an initial version of the study protocol

SGS was in charge of the conduct and analysis of a complex FIH study including SAD and MAD parts. In the SAD escalation part, the PK sampling until 24h needed to be analyzed before the next dosing. This time point was based on a predicted human short half-life of the compound. Accordingly, the planning in the Clinical Pharmacology Unit at SGS was fixed to start next dosing 14 days after the preceding dose.

The starting dose being very low, in most subjects the plasma drug concentrations were very low or even non-quantifiable. Hence PK parameters (including half-life) were not relevant; therefore, the 14 day interval was sufficient but perhaps "not needed".

Interestingly, with the third and fourth doses, the 24h PK sampling proved to be not long enough, and thus the half-life could not be estimated correctly (as it was longer than predicted in the protocol).

The protocol was amended after the fourth dose, and additional subjects were included to repeat the third and fourth doses with PK sampling up to 72h and 96h post-dose, respectively, before escalating to the fifth and final dose in the SAD part.

Take home message: FIH trials are exploratory, with PK as one of the primary objectives. It is obvious that PK data/assessments cannot always be precisely planned in the initial protocol. Therefore, an adaptive approach can be used with careful and tailored PK data review steps.

CASE STUDY 2:

Importance of rigorous safety data collection in a Phase 1 study

The safety data collection method, for a precise AE, was changed after two MAD groups to obtain the necessary information on drug/dose relationship, severity and actions to be taken during further clinical development

During a Phase 1 MAD study conducted at the SGS Clinical Pharmacology Unit (CPU), frequent GI events were observed in the first two dose groups of subjects, increasing with the higher dose: in around 70% of subjects. As usually done, and as foreseen by the CRF, the date/time and severity of this AE was reported by the clinical site. However, since it was a frequent AE, related to dose and might occur multiple times in the same subject, it became of interest to know if vomiting/diarrhea only occurred once in each subject or multiple consecutive times and if so, how often and within what time frame. So far, the CPU medical team and sponsor suggested to start collecting details for these particular AEs, i.e. a separate record for each vomiting/diarrhea episode for each subject. No amendment to the CTP or other actions related to the CRF were needed, but only a modification to the way data was collected in the CPU.

Take home message: the more granular the safety information collected, the more useful the data. Clinical sites should be reactive and ready to adapt the data collection process in response to ongoing observations.



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