Ensuring Appropriate and Reliable Data is Collected for Conclusive First-in-human/Phase I Trials

The purpose of clinical trials is to find answers to a research question by generating data to prove or disprove a hypothesis. By their very nature, first-in-human (FIH) and most Phase I trials are exploratory, and are conducted without a statistical hypothesis; and so their aim is to obtain reliable information on the safety, tolerability, pharmacokinetics and mechanism of action of a drug.

Various data are captured from FIH trials, and despite their exploratory character, these data need to be relevant, accurate and appropriately analysed to obtain meaningful results that are useful for future clinical development.

There are four main steps in clinical data processing:

(e)CRF: (electronic) Clinical Research Form, TLFs: Tables, Listings and Figures

Data Planning

The first step is the planning of the data at an early stage when developing the study design / protocol / case report form (CRF). The clinical team must evaluate which measurements need to be taken, when exactly in the study these will be carried out, for how long and how frequently. These questions concern all the assessments within the FIH, such as patient safety, drug tolerability, and pharmacokinetics (PK) and pharmacodynamics (PD). Often, planning is not very targeted since the only supporting information available at this stage is preclinical data with human predictions; moreover, there is no precise statistical endpoint.

Data Collection

Once the study starts, data are collected by the operational staff of the Research Unit on an ongoing basis. Any use of inappropriate methodology or non-adherence to protocol / manuals / CRF may have a critical influence on data reliability and can introduce unintended bias to the results. Therefore, it is critical that staff overseeing the study are fully trained and aware of the importance of their work and the precision needed in the detail of both the timing and methodology of data collection.

It also goes without saying that the staff cannot overlook the safety and care of the study subjects. The relatively high-risk nature of FIH studies and the absence of therapeutic benefit for participants 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 the appropriate 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 (the use of software, standard automatic process, electronic CRFs, electronic data review) should be adopted.

Data Analysis

At the end of the trial, the data must be analysed 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 proceed or not to the next phase of development, and to give initial indications on how to design the next study.

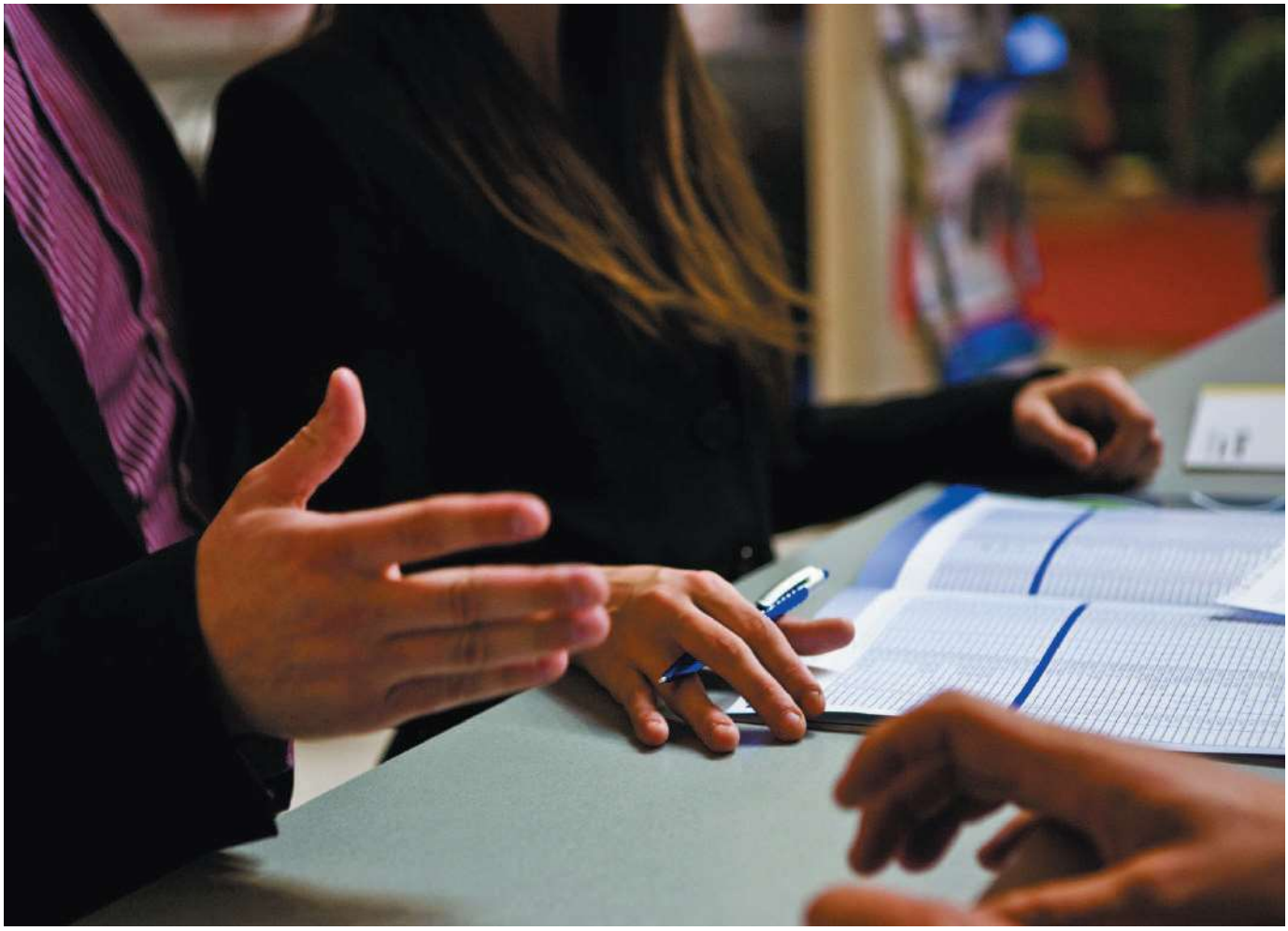
As with many aspects of clinical design, ensuring meaningful data are achieved is enhanced with the experience of the clinicians undertaking the studies. It may be the case that protocols need to be adaptive and flexible to meet the objectives of the studies, especially in FIH and early phases which are exploratory. Two scenarios are outlined below which demonstrate this:

- Scenario 1: A substantial amendment was introduced, and study conduct changed because of inappropriate PK data planned in an initial version of the study protocol

During a complex FIH study, including both single ascending dose (SAD) and multiple ascending dose (MAD) parts, the PK sampling until 24h needed to be analysed before the next dosing in the SAD escalation part. This time point was based on a predicted human short half-life of the compound, and the next dosing was fixed to start 14 days after the preceding dose.

The starting dose was very low and, in most subjects, the plasma drug concentrations were very low or even non-quantifiable. As such, PK parameters (including half-life) were not relevant; therefore, the 14-day interval was sufficient but perhaps in this instance, unnecessary. Interestingly, with the third and fourth doses, the 24h PK sampling period proved to be too short, and so 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.

This scenario highlights the fact that FIH trials are exploratory, with PK as one of the primary objectives, and 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.

- Scenario 2: After a specific adverse event (AE), the safety data collection method 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 I MAD study, frequent gastrointestinal (GI) events were observed in the first two dose groups, increasing with the higher dose. As usual protocol, 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/diarrhoea only occurred once in each subject or multiple consecutive times and if so, how often and within what time frame. The observational staff suggested starting collecting details for each particular GI AE, i.e. a separate record for each vomiting/diarrhoea 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 were collected in the clinical pharmacology unit.

This event reinforces the need for specific and detailed safety information to be collected. Clinical sites should be reactive and ready to adapt the data collection process in response to ongoing observations to ensure that the data collected are as useful as possible.

In summary, high-quality data are needed in all clinical studies including exploratory FIH. These should meet the protocol-specified parameters and comply with the protocol requirements. However, the unpredictability of the studies mean that clinicians must be flexible and adaptive to ensure as much data as possible available to assist in the progression of a drug through the development process.

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