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First in Human Studies:

Points to Consider in Study Placement, Design and Conduct

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Introduction

First in Human (FIH) clinical trials are part of the exploratory phase of drug development and represent a significant milestone in the clinical development of new medicines. When only preclinical data are available to guide dose-selection, population, study design, safety monitoring and appropriate expertise are all critical to maximise the safety of the study subjects and the quality of the data.

There has been intense focus on the risks of FIH clinical trials since the TeGenero TGN1412 incident in 2006, and much has been published on the evidence and recommendations [1, 2, 3, 4]. The European Medicines Agency's (EMA) "Guideline on strategies to identify and mitigate risks for first in human clinical trials with Investigational Medicinal Products" (IMPs) [5] provides an excellent overview of points to consider. In addition, the ABPI Guidelines for Phase I Clinical Trials [6] summarise recognised industry standards. The purpose of this document is to supplement these guidelines with practical considerations for the planning, design and conduct of FIH clinical trials. These include sections on:

- Choice of study population
- Selection of an appropriate study site and principal investigator
- Formulation and site pharmacy considerations
- Study design considerations
- Dose escalation decisions
- Informed consent considerations

Choice of study population

The majority of FIH clinical trials use healthy volunteers. This approach has the advantage of speed of recruitment and ease of scheduling cohorts of subjects throughout the study. It also removes potential confounding factors such as concomitant medication and disease pathology when reviewing adverse event and pharmacokinetic (PK) data. Healthy volunteers can generally tolerate more intensive interventions and adverse effects than would be expected from a symptomatic patient.

FIH clinical trials are part of the exploratory phase of drug development and therapeutic benefit is not an objective. Clearly healthy individuals do not stand to gain any therapeutic benefit from an investigational drug, and ethical principles dictate that they should not be exposed to any more than "minimal risk" [7]. In patients, the foreseeable risks should also be kept as low as possible. Historically, the use of patients has been commonplace for oncology agents and agents with low therapeutic index intended for life-threatening conditions.

The decision whether to conduct an FIH trial in healthy volunteers or patients should be carefully considered and fully justified on a case-by-case basis. Some pros and cons are detailed in Table 1. The safety of subjects and the value of the information that is likely to be obtained should be considered, especially:

a) the risks inherent in the type of medicinal product and its molecular target
b) potential immediate and long term toxicity predicted from non-clinical or literature information
c) the presence of the target, key biomarker or a surrogate marker in healthy subjects or in patients only, and
d) the possibility and impact of higher variability in patients versus lower external validity in healthy subjects.

Table 1. Selection of Patients versus Healthy Volunteers.

	HEALTHY VOLUNTEERS	PATIENTS
PROs	• Easier recruitment and management in the clinical unit • Recruitment quicker, resulting in more efficient study • No confounding pathology or medications • Easier to obtain blood for full PK profile • Data may be useful for several indications • Wide choice of potential FIH sites and investigators • High internal validity	• Pharmacodynamic (PD)/biomarker and surrogate data may only be obtainable in patients • Target-related safety may be tested • Possible benefit, especially at higher doses • High external validity
CONs	• Often no or limited target-related PD/biomarker data obtainable • Often difficult to justify target availability in healthy volunteers (but may be expressed at low levels) • Target-related safety may be different from patients (but off-target toxicity likely to be similar) • PK may be different from patients • No therapeutic benefit to subjects, only potential risks • Low external validity	• Recruitment and management often more difficult, resulting in less efficient study (e.g. extended timelines and higher costs) • Sites that have the patients may have no experience in FIH clinical trials or facilities for extended in-house monitoring • Concomitant disorders and medications confound interpretation of safety data • Greater variability in safety signals • Target-related safety may still be different in other indications • Single dose, or low doses, may not provide adequate therapeutic benefit to justify entering very ill patients into the study, and may preclude participation in subsequent trials • Potentially more difficult to obtain blood for PK (consider sparse sampling for population PK) • Ethical concerns around placebo use

Volunteers.

Certain study designs may include "bridging" between healthy volunteers and a patient population once the expected therapeutically relevant dose is achieved in the escalation paradigm. This allows a more time- and cost-efficient early evaluation of PK, PD and safety parameters at lower doses in healthy subjects to facilitate improved dose-selection and/or regime at higher doses in the target patient population, in whom more informative safety or PD data can be generated.

Inclusion of women as early as possible in drug development programmes is encouraged. The ICH M3 Revision 2 (R2) guideline [8] describes the nonclinical study guidelines for enrolling women of child-bearing potential into clinical studies. In the FIH clinical trial, women will typically be of non-child bearing potential. In addition, a risk evaluation should be conducted to establish the need for protection from seminal IMP exposure, or the need to add a highly effective method to avoid pregnancy for the women of child-bearing potential who are partners of male subjects in the FIH clinical trial. Highly effective methods to avoid pregnancy are defined in the ICH guideline [8] as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.

It is important to confirm the medical history of the volunteers or patients prior to inclusion in a FIH clinical trial, which is usually done by contacting the primary care physician.

Choice of research site

The sponsor should conduct a site evaluation to consider the site's capabilities to meet the specific demands of a particular protocol such as appropriate medical governance, drug-specific biomarker methodologies or sample acquisition/analysis, the ability to recruit study participants, and pharmacy capabilities.

FIH clinical trials of IMPs with identified factors of risk (as discussed in [Appendix 1]) should be conducted in research units with sufficient expertise and know-how and which, in the UK, have been awarded the MHRA Phase 1 Supplementary Accreditation [9] as they will have undergone a comprehensive scrutiny of their emergency equipment, procedures and training. However, this does not negate the importance of a site-evaluation by sponsor staff. Furthermore, the MHRA Phase 1 Accreditation is voluntary, i.e. there is no mandatory requirement for it. Site assessment by the sponsor staff should include, but not be limited to, evaluation of the experience of the site with FIH clinical trials and the ability to carry out appropriate safety monitoring, the site's experience with IMPs of all levels of risk, the site's process and experience with dose escalation decisions, the site's facilities and ability for stabilising individuals in an acute emergency and the site's ability to conduct resuscitation, the proximity to hospital and the access to Intensive Care Services, and ready availability of Intensive Care Unit facilities.

In FIH clinical trials where there is a predictable risk of certain types of severe adverse reaction, the sponsor should specifically address risk mitigation in the protocol, which should include considerations for treatment of such reactions. The sponsor and research site should ensure the specific antidotes will be readily available, where they exist, as well as a clear plan of supportive treatment, including the pre-arranged contingency availability of intensive care facilities or specialty consultation. The research site should assess the study-specific requirements for clinical cover and ensure that an appropriate level of staffing, with medical doctors during and after dosing, will be present.

For IMPs other than those with identified factors of risk, the sponsor should consider similar factors than previously discussed, on a case by case basis. As a minimum, the sponsor must assess facilities, training and experience of personnel, and the evidence that unit medical staff are appropriately qualified and trained in handling emergency situations.

The principal investigator and unit staff responsible for the care of subjects in FIH clinical trials should always be appropriately qualified and experienced. In the UK, the principal investigator will hold a post-graduate qualification related to pharmacology, such as the Diploma of Human Pharmacology [10], or equivalent, as described in the MHRA Phase 1 Accreditation scheme [9]. The sponsor should ensure that the investigator knows enough about the agent, its target, mechanism of action and potential adverse events to be in a position to manage the informed consent process with the subject, and to make informed clinical judgments during the study. The investigator must also understand the intricacies of executing FIH clinical trials, including the potential need to adjust doses during the study as human data become available.

The sponsor should give consideration to the pharmacy licence, which is discussed in the section below.

Finally, it is critical that subjects taking part in FIH clinical trials have not been recently exposed to other investigational products. Therefore sites using web-based systems to monitor for "over-volunteering", e.g. TOPS [11] or NVR [12], provide a valuable safeguard against the "professional volunteer".

Formulation and site pharmacy

When designing an FIH clinical trial, the sponsor development team must consider the formulation that will be used and the need for flexibility to permit adjustment of doses in real-time as safety and PK data become available. Unless an open-label study is planned, matching placebo will also be required for blinding purposes.

The formulations used in FIH clinical trials have generally not yet been optimised, and the sponsor should therefore identify as soon as possible whether the dosage form will require specific preparation at the research site (for example, dilution for preparation of an intravenous infusion, or preparation of a suspension). The sponsor should pay great attention to the type of licence held by the research site's pharmacy to ensure the study is placed at a site that can perform the preparation. The research site should have an equipped investigational drug pharmacy, staffed with qualified pharmacist/s and/or technician/s who have experience preparing special dosage forms typically used in FIH evaluations (e.g. oral powder for constitution, intravenous formulations requiring dilution steps, etc). The sponsor should ensure that the site pharmacy holds the appropriate manufacturing and assembly licence, such as the MIA (IMP) licence awarded by the MHRA, and that this licence is referenced in the IMPD submission to the MHRA, for all sites based in the UK. The sponsor should check that the specific manufacturing or assembly activities that are required for the study are authorised on the licence (e.g. importation of IMPs, sterile products, biological medicinal products, packaging and labelling, storage, blinding). In addition, the sponsor should check that the site pharmacy has timely access to a Qualified Person (QP) who can facilitate issues around release of final product for human administration [13]. If possible, 24-hour "in-use" stability of the constituted dosage form should be provided, as this will ease the burden on the site in terms of the timing of the preparation vs the timing of dose administration.

The most flexible formulation is intravenous, as doses can be adjusted easily, and administration stopped during the infusion should significant adverse events occur. Intravenous infusions using a controllable infusion pump are preferable to bolus administration. FIH clinical trials for oral compounds are often conducted using oral powder for constitution, which results in administration of either a solution or a suspension to the subject, or powder-in-capsule, a minimally formulated capsule fill.

If tablet formulations are used, the sponsor should plan maximum reasonable flexibility with the pharmaceutical development team, so that combinations of dose strengths can be used to span a wide dose-range and allow for unscheduled dose adjustments during the clinical trial. Administration of

large numbers of tablets or capsules to a subject as a single dose is sub-optimal and can be avoided by adequate pre-planning and communication between the product development team and the pharmaceutical development groups within the sponsor company.

Study Design Options

In choosing design options for FIH clinical trials, it is important to consider factors linked to the compound characteristics (e.g. level of risk, PK, PD, number of dose levels to investigate, etc) and factors linked to the timelines and site logistics (e.g. number of doses per subject, number of subjects to be dosed per day relative to capacity of the clinical research unit to handle unexpected adverse events (AEs), risk of dropouts with multi-period study, flexibility to changes in the study design as clinical data are generated, etc).

Once the development team has agreed the compound's level of risk [5], they should consider whether the FIH design will include use of sentinel subjects or not. The EMA advises that it is usually appropriate to design the administration of the first dose so that a single subject receives a single dose of the active IMP, with justification of the period of observation before the next subject receives a dose. Should the sponsor consider that the level of risk of the compound does not warrant such a design, documented justification will generally be expected. Naturally consensus in these discussions will include key staff from the research site staff (e.g. principal investigator).

There is no regulatory need for a strict double-blind design in FIH clinical trials, and adoption of a single-blind design may be envisaged; however, the teams should consider the risk of resulting bias in decision-making and in the review process for dose-escalation decisions.

In a **parallel group design**, each cohort is assigned only one dose of active drug and subjects within a cohort are randomly assigned to receive either active drug or placebo, e.g. six on active and two on placebo (Table 2). Doses are escalated sequentially with each cohort. For six doses, this design would require approximately three times the number of subjects required for the crossover design. A parallel group design may be appropriate when the projected half-life of a compound or metabolite is longer than can be accommodated in an interlocking cohort, crossover design. In addition, it may be used when there is a concern about exposing subjects to more than one dose of active drug, or for biologics where neutralising antibodies could be formed.

Table 2. Parallel Group Design

SINGLE ASCENDING DOSE ESCALATION IN HEALTHY VOLUNTEERS (NOMINAL DOSES SHOWN, P=placebo, A to F are ascending active doses of IMP); in each cohort, 2 subjects receive P, 6 receive IMP						
PERIODS	I	II	III	IV	V	VI
Cohort 1 (2 P, 6 IMP)	'A' mg					
Cohort 2 (2 P, 6 IMP)		'B' mg				
Cohort 3 (2 P, 6 IMP)			'C' mg			
Cohort 4 (2 P, 6 IMP)				'D' mg		
Cohort 5 (2 P, 6 IMP)					'E' mg	
Cohort 6 (2 P, 6 IMP)						'F' mg

Crossover designs are generally favoured over parallel designs because they allow more efficient use of subjects who serve as their own controls with respect to safety, PK and PD, thereby reducing variability. Both within-subject

and between-subject dose escalation is evaluated, allowing estimation of within-subject PK variability for calculation of sample size in subsequent studies. In addition, the crossover design allows evaluation of the influence of food on PK, which can only be done properly by studying within subject changes in PK parameters.

However, as the subject receives increasing single doses of the IMP several times, at intervals, in this design attention will be given on a case-by-case basis to the characteristics of the compound to analyse the factors of risk and to justify this choice of design and the dose escalation increments and intervals. This design may be well suited to small chemical molecules with a short half-life and where the identified risks and the toxicology preclinical data support multiple drug exposures within a subject. In addition, the potential for PK and/or PD carryover, the limitations in the number of blood samples that can be collected, subject dropouts, and time dependence in drug clearance or metabolic profile should be evaluated when considering a crossover design. For example, crossover design is impractical for drugs with prolonged PK profiles or PD half-lives – this is particularly true for biological agents (e.g. humanised antibodies).

By using **Sequential Cohorts**, in which doses are escalated within a cohort, and each subject receives two to three ascending single doses of the IMP plus

single dose of placebo (i.e. a 3- or 4-way crossover), within-subject dose increments are small, and a wider dose range can be covered. An example of this design is shown in Table 3. The dosing interval for an individual subject should be initially determined on the basis of predicted human PK, and confirmed following availability of human PK and/or PD effect of the IMP in question.

Table 3. Crossover Study Design (Standard)

SINGLE ASCENDING DOSE ESCALATION IN HEALTHY VOLUNTEERS (NOMINAL DOSES SHOWN, P=placebo, A to F are ascending active doses of IMP); in each cohort, 2 subjects receive P, 6 receive IMP						
WEEKS (nominal)	0	3	6	9	12	15
Cohort 1 (2 P, 6 IMP)	'A' mg	'B' mg	'C' mg			
Cohort 2 (2 P, 6 IMP)				'D' mg	'E' mg	'F' mg

Using **interlocking cohorts** (Table 4) is an efficient design allowing for a longer washout period between subjects. This may reduce the risk of PD and/or PK carryover and thus may be suitable for a compound where the parent or an active metabolite has a long half-life. However, dose increments in this design are often larger and the longer study participation time may increase subject dropouts.

Table 4. Crossover Study Design (Interlocking Cohorts)

SINGLE ASCENDING DOSE ESCALATION IN HEALTHY VOLUNTEERS (NOMINAL DOSES SHOWN, P=placebo, A to F are ascending active doses of IMP); in each cohort, 2 subjects receive P, 6 receive IMP						
WEEKS (nominal)	0	3	6	9	12	15
Cohort 1 (2 P, 6 IMP)	'A' mg		'C' mg		'E' mg	
Cohort 2 (2 P, 6 IMP)		'B' mg		'D' mg		'F' mg

In summary, the choice of design should be tailored to the needs of the specific compound and development programme. The main factors to consider when choosing the design concern the compound and the logistics aspects, as discussed above. From a statistical standpoint, a crossover design with placebo insertion is preferred because it results in more precise and better controlled estimates of parameters of interest. However, given that FIH clinical trials are generally not powered for formal hypothesis testing, this represents only a minor advantage for the design.

Dose escalation decisions

The sponsor must put in place agreements with the investigator and research site staff to review and discuss safety and tolerability data, and PK and PD data when available, throughout the ongoing clinical trial. Under the MHRA Phase 1 Accreditation scheme, the site should have procedures in place for dose escalation [9]. A set of stopping rules should be identified clearly in the protocol, at cohort level and at subject level. The minimum data set required to make a decision and the number of subjects required for this data set should be decided in advance. In addition, there should be prior agreement on the minimal list of both sponsor and staff from the research site who need to be present for such decision-making meetings to be quorate. The minimum safety and tolerability data should comprise adverse events, preferably with the investigator's assessment of the relationship to clinical trial medication, physical examination, electrocardiogram (ECG) or cardiac monitoring (e.g. telemetry and Holter monitoring), vital signs, clinical laboratory parameters, at pre-dose and relevant post-dose time points, in comparison with the screening data. These data should be documented and commented in an interim report by the principal investigator. In addition, PK data at pre-specified dose levels may be required especially when exposure data are part of the stopping rules of the protocol. The dose escalation meetings should be scheduled in advance to occur after each dose level cohort is completed and before escalation to the next dose level. Ad hoc meetings may be needed if emerging data require more immediate action, or if the dates of dosing change during the clinical trial. These formalised meetings (described in the protocol) are in addition to the 24-hour availability of the sponsor medical monitor (or defined delegate) for the clinical trial principal investigator to contact regarding any urgent issues.

The protocol will describe the conditions under which dose escalation must not occur and the need for the investigator to contact the sponsor, for example occurrence of:

- Severe adverse event/s assessed by the principal investigator as being related to IMP
- Clinically significant ECG or cardiac monitoring abnormalities (e.g. arrhythmias), or clinically significant changes in vital signs assessed by the principal investigator as being related to IMP
- Other findings that, at the discretion of the principal investigator, indicate that the dose escalation should be halted and are assessed by the principal investigator as being related to IMP
- Predefined criteria for organ function based on target organs identified from animal toxicology data

- Systemic exposure for a dose that is anticipated to exceed pre-determined exposure limits based on preclinical toxicology data and/or already available human PK data; in that case, dose escalation should generally be stopped.

An assay will ideally be available and validated to permit rapid analysis of the PK samples from the FIH clinical trial, as it is generally expected that PK data will be available prior to the administration of the next planned dose. There are situations when PK may not be available, for example after the start dose, and justification of dose escalation without PK data should be agreed in advance of the clinical trial between the sponsor and the unit, and documented. The status of the bioanalytical data for dose escalation in term of its quality check or quality assurance sign-off should be predefined. If an acceptable biomarker for PD activity is available however, this may replace the need for PK data. The PK assay should permit characterisation of the parent compound and any metabolite thought to be important to an understanding of the clinical pharmacology of the compound. Additionally, a process must be in place for the rapid transport of biological samples to the assay laboratory, so that there is time for sample analysis and PK summarisation prior to the next scheduled dose. This is especially important if strict exposure-based stopping rules are employed as is recommended in the case of exploratory clinical trial applications in which more limited preclinical toxicology data are available.

It is important to adequately document dose escalation decisions and their communication between sponsor, investigator and site pharmacy to avoid dosing errors. The list of attendees at the dose escalation meetings should be included in the meeting minutes. The evidence of the communication may be scrutinised in regulatory audits if they occur. If decisions are made to alter the planned doses, preparations must be made between the sponsor and the site regarding how those decisions will be communicated. For example, if the study staff members are to remain blinded, but sponsor personnel are unblinded, then direct communication with the unblinded pharmacist must be possible so that instructions on dosage changes can be provided without compromising the integrity of the blinding. The study team must consider these and operational factors around dosing and dose adjustment at the time of choosing the site. The study team must put in place, in advance of the study start, a plan to enable flexibility to be maintained without compromising objective decision-making. This will include assurance that the pharmacy will be able to perform the dose adjustments and obtain the release of the IMP by the QP, possibly at short notice. It is useful to write the protocol with flexibility around the doses to allow for dose alterations within predefined constraints of systemic exposure, without the need for a protocol amendment.

Informed consent considerations

The written informed consent form and any other written information to be provided to subjects for an FIH trial present unique challenges to the author, who must provide an interpretation of risk derived solely from preclinical data and knowledge of the pharmacological target in a way that is easily understood by a lay person. In the choice of site, the sponsor should check that the site has robust consent procedures in place, and should consider the principal investigator's experience in writing or reviewing informed consent documents. Some specifics of the informed consent documentation for FIH clinical trials are different from those of later trials or later phase trials. For example, in most cases with FIH clinical trials, the written informed consent form is drafted by the unit staff rather than the sponsor, and it must contain the rationale in lay language for the start dose and the maximum dose. The critically important information on the drug characteristics (pharmacological and toxicological) to support the start dose and the maximum dose should be provided by the sponsor who also bears a responsibility for the wording being chosen to be easily understood by a lay person. Otherwise, the elements of the informed consent discussion and the written informed consent form must comply with the Good Clinical Practice standards, which are, for example, documented in the Note for guidance on Good Clinical Practice of the European Medicines Agency [14].

Conclusion

In conclusion, study design and site selection for an FIH clinical trial are critical to the safety and wellbeing of the study participants and to the scientific validity of the study. The study design and the selection of the study population (healthy volunteers or patients) are dictated by the characteristics of the IMP. The research site will have safety of study participants as a fundamental and overarching operating principle. The selection of the site will also be guided by the site's capabilities to meet the specific demands of a particular protocol such as appropriate facilities for pharmacy, volunteer recruitment, biomarker methodologies or sample acquisition/analysis, and the site's ability to conduct clinical trials meeting all legal, regulatory and ethical obligations.

Appendix 1.

Risk Assessment of Investigational Medicinal Products

The potential risk of an IMP should be assessed by the sponsor development team, as early in the development lifecycle of the IMP as possible (preferably around the time of candidate selection). The European Medicines Agency's "Guideline on strategies to identify and mitigate risks for first in human clinical trials with Investigational Medicinal Products"[5]provides advice on the factors of risk to consider for FIH clinical trials, as listed here for ease of reference; in FIH clinical trials the following situations require special attention:

- where the mode of action involves a target that is connected to multiple signalling pathways (target with pleiotropic effects) eg leading to various physiological effects or targets that are ubiquitously expressed
- acting (directly or indirectly) via a cascade system where there may be an amplification effect which might not be sufficiently controlled by a physiological feedback mechanism
- acting (directly or indirectly) via the immune system with a target or mechanism of action which is novel or currently not well characterised.
- where there is novelty in the structure of the active substance eg a new type of engineered structural format such as those with enhanced receptor interaction as compared with the parent compound
- where the level of expression and biological function of the target receptor may differ between healthy individuals and patients with the relevant disease
- where there is insufficient available knowledge of the structure, tissue distribution, cell specificity, disease specificity, regulation, level of expression and biological function of the human target, including down-stream effects
- acting via a possible or likely species specific mechanism or where animal data are unlikely to be predictive of activity in humans
- acting via a new target or poorly defined mechanism of action which is not well characterised and for which no previous experience in humans is available.

In the UK, expert advice may be sought from the Clinical Trials Expert Advisory Group [15].

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