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PLANNING YOUR FIRST-IN-HUMAN TRIAL

- Determine the Necessary Regulatory Interactions
- Select the Starting Dose
- Design the Trial
- Plan for Participant Safety
- Identify and Mitigate Potential Risks
- Recruit, Educate, and Retain Study Participants
- Plan Resources and Conduct the Trial

Introduction

A first-in-human (FIH) clinical trial is a significant milestone in the development of a potential new drug in that it will be the first opportunity for a drug development sponsor to evaluate the impact of their new chemical entity (NCE) or biologic in humans. Typically, FIH trials with compounds intended for treatment of diseases other than cancers or certain rare non-malignant diseases are conducted using normal healthy volunteers (NHVs), unless there is an ethical concern (such as known toxicity) in administering the investigational drug to an otherwise healthy population.

During a FIH study, objectives may include:

- Evaluating safety and tolerance
- Determining pharmacokinetics (exposure and dose proportionality)
- Identifying early pharmacological activity relative to exposure level, either based on measured physiologic responses, or on biomarkers of response identified during preclinical testing
- Assessing observed effects on subsets of participants based on age, gender, or ethnicity
- Evaluating the therapeutic outcomes in a small group of patients suffering from the targeted disease

At this stage of the investigational product's (IP) lifecycle, a drug may fail simply because the human participant does not respond to the drug in the same manner that was suggested by preclinical testing.

Mitigate risks with this stepwise approach, and by partnering with an experienced and skilled CRO/CDMO.*

INVESTIGATIONAL NEW DRUG (IND) APPLICATION

Regulatory agencies will look at the FIH program's ability to clarify any uncertainties associated with the treatment being tested.

The strategy for proving safety and proactively addressing risks must be apparent in the design of the trial, including plans for clinical conduct and reporting. The plan must be supported by a well-documented scientific rationale and be responsive in adapting to trial data as it emerges. These efforts are supported by the investigational brochure (IB).

The following questions can be used to identify potential risks to subject safety:

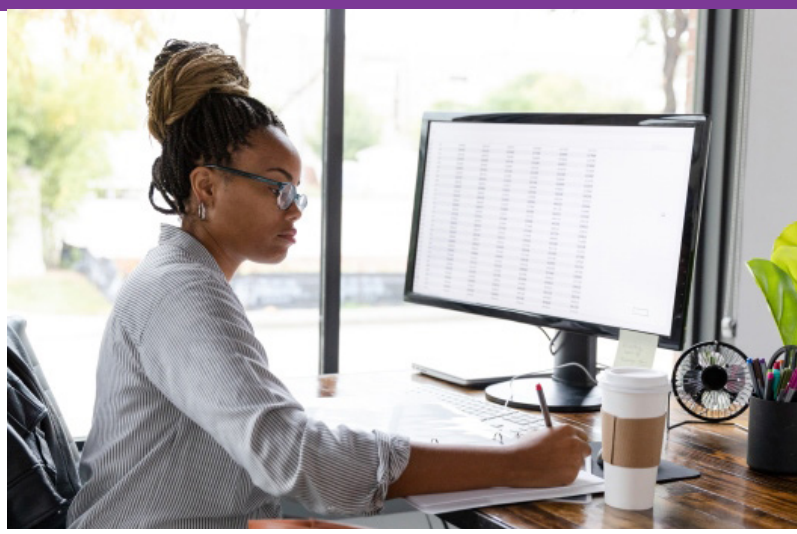
1. Were certain signs and symptoms observed during preclinical testing that should be specifically monitored during the FIH studies?
2. Have specific biomarkers for on-target or off-target activity been identified preclinically that should be evaluated during the FIH studies?

These analyses must be included in the IND application. Prior to submitting an IND, it can be beneficial to schedule a pre-IND meeting with the FDA to receive feedback on the plan which may affect the trial design. A productive pre-IND meeting helps ensure that the clinical plan addresses any FDA concerns, and thus mitigates the risk of a clinical hold on the application.

*The information assumes that a Sponsor has completed or is nearing completion of their preclinical testing and will soon be preparing for regulatory submission.

For the pre-IND meeting, come prepared with a detailed study synopsis and the following gap analyses:

- Available data versus regulatory expectations for management of the IP
- Available pharmacology support for the intended medical indication versus regulatory expectations for preclinical evidence in support of the intended medical indication
- Available toxicology support for the intended medical indication versus regulatory expectations for toxicology to support the early development program



Select the Starting Dose

An appropriate starting dose is imperative to the success of any FIH trial. The dose level needs to mitigate the risk of toxicity while being high enough to produce observable pharmacologic activity in participants. Starting the dose too low or escalating too slowly can lead to increased overall study size (and as a result, higher costs and lengthier conduct timelines). Starting a dose too high or escalating too quickly can lead to safety and adverse event issues.

Several methods for selecting the starting dose are commonly used, dependent upon the therapeutic being evaluated:

- Calculating the Maximum Recommended Safe Starting Dose (MRSD)
- Calculating the Minimum Anticipated Biologic Effect Level (MABEL)
- Referencing starting doses for therapeutics with a similar mechanism of action
- Pharmacokinetic/pharmacodynamic modeling

Design the Trial

FIH trials are typically designed as dose-escalation studies, where subjects receive increasing doses of the IP based on desired protocol-specified outcomes. Most often, both single ascending dose (SAD) and multiple ascending dose (MAD) studies are included in the early development program. The dose is increased once the safety, PK, or other protocol-specified requirements have been confirmed by a Safety Review Committee (SRC).

Single Ascending Dose (SAD)

SAD studies are commonly double-blind and placebo-controlled to accurately attribute observed effects of the IP. In a SAD design, a small group of subjects receive a single dose of the IP and are observed at the clinical testing site for any relevant adverse events or toxicity. If adverse events are not observed in a pre-determined number of subjects, the dose is increased as per the study protocol. Dose escalation continues until a pre-determined PK exposure safety level is achieved, or intolerable adverse events are experienced.

A common safety strategy of the SAD design includes sentinel dosing as an added safety precaution. In sentinel dosing, only two participants are dosed (one with the active drug, the other with placebo), and observed for adverse events. If none are observed, the rest of the cohort is dosed at the same level. If concerning adverse events are noted, the cohort may be halted, or the design or dosing plan may be adjusted. It is critical that the protocol contain clear stopping and escalation criteria specific to the known risks of the IP and drug class. Sentinel dosing can identify safety issues early, in as few subjects as possible.

Multiple Ascending Dose (MAD)

MAD trials usually follow SAD trials to further assess the safety, tolerance, PK, and PD of the IP. In a MAD trial, participants within a single cohort are given multiple doses at specific intervals, and dose levels are informed by the data generated in the preclinical work and SAD trial. The dosing regimen is designed to reach therapeutic levels, so that safety and PK can be monitored over several days. Three or more dose levels are assessed to ensure safety as the trial moves forward.

During MAD studies, adequate and timely biomarker, PK, and PD sampling is imperative. If samples are collected too infrequently or at incorrect times, the data generated may not provide sufficient information. Conversely, sampling too often will increase the burden on study participants and trial personnel without producing significant information. The appropriate sampling schedule will often be informed by the pharmacokinetic and biomarker results of the SAD study. The MAD study will often also include additional safety assessments, developed based on the expected mechanism of action, therapeutic class, and expected indication. Trials will often include assessments for vital signs, safety ECG/telemetry, early precision QT assessments, cognitive testing, and questionnaires.

While the MAD study is traditionally conducted after completion of the SAD study, significant time can be saved by including the designs under a single, integrated, and adaptive study protocol. Increased levels of planning, flexibility, and more stringent criteria allow for the MAD portion to initiate prior to completion of all the SAD cohorts.

The MAD study is typically where dose levels can be evaluated in highly adaptive cohorts, allowing for maximum flexibility to apply the learnings from the previous cohorts. Examples of adaptations that can be built into the protocol are:

- Dosing and dose regimen changes
- Sample size adjustment
- Addition or elimination of specific treatment arms

While the incorporation of adaptive cohorts can serve to expand knowledge of the IP's attributes, this design requires restrictive start and stopping criteria to ensure subject safety.

Plan for Subject Safety

When testing a drug in humans for the first time, detailed consideration must be given to the risks that exist in any early phase trial, and also the risks that can be extrapolated from observations in the preclinical testing phase.

In addition to demonstrating to regulatory authorities that the trial has been properly designed to ensure participant safety, Institutional Review Boards (IRBs) will assess whether subject risk has been minimized, and that the potential risks are justifiable in relation to any anticipated benefits. In addition to reviewing the protocol, informed consent, and IB, IRBs will review safety monitoring plans, including the membership and establishment of a Safety Review Committee (SRC), dose escalation criteria, stopping criteria, reporting of dose-limiting toxicity (DLT), and adverse events.

Safety Review Committee

Once safeguards are in place, subject safety is assessed during and after each dose level administration, and data-driven decisions are made regarding dose escalations.

1. **What is the responsibility of the SRC?** The fundamental responsibility of the SRC is to make recommendations regarding trial safety. For FIH trials, the primary decision is whether the dose level should be escalated. The SRC reviews important safety data generated from each cohort, such as the frequency and severity of any adverse events, stopping criteria, biomarker and PD data, and, in many cases, PK results. All decisions made by the SRC must be guided by the study protocol and safety management plan, and be rigorously documented for the study file.

2. **Who should be a part of an SRC?** When selecting members of an SRC, it is important to ensure that both the clinical site and sponsor representatives are included, as well as any appropriate third-party members.
   - Principal Investigator
   - Project Managers/Clinical Study Managers, PK scientists
   - Clinicians with relevant clinical specialties
   - Medical Monitor
   - Biostatistician
   - Scientific Consultant (e.g., medical expert in the therapeutic area of interest)

3. **How do SRCs operate?** Typically, SRCs operate under written charters that include well-defined procedures for meetings and allow for a thorough, objective documentation of discussions. This charter may be requested for review by regulatory authorities and other interested parties. By documenting meeting activities, concerns around biases arising from interim data can be reduced. The charter:
   - Includes a schedule and format of meetings
   - Describes guidelines for the presentation of data and the safety review decision-making process
   - Outlines a list of persons who participate on the SRC and who must be present for decision making
   - Provides a list of individuals who may be unblinded during the review, where appropriate
   - Specifies the methods of documenting and communicating decisions and actions

Protocol-Defined Safety Monitoring Plan

An effective Safety Monitoring Plan (SMP) outlines the methods for data collection and the frequency of data review, and provides guidance for how the study should proceed based on the generated data. Outside of the protocol, the SMP is the main guidance used by the SRC to plan for decision making during the trial.

In general, the SMP should address how to summarize data collected during each cohort, and how and when the SRC will review it in order to make safety and escalation decisions. The SMP will dictate what data is needed for review and generally includes:

- Subject demographics
- Adverse events, including severity and relatedness to study drug administration
  - If specific AEs are anticipated due to preclinical testing, include more thorough information on the collection measures regarding AEs
- Use of concomitant medications
- Trends or abnormalities in vital signs and ECGs
- Clinical laboratory evaluations
- Physical examinations
- If any subject has met dose escalation or individual stopping criteria
- Specialty safety or pharmacodynamic assessments, biomarkers, and PK
- Assessments pertaining to the specific mechanism of action of the IP, such as eye exams for ophthalmic products or cognitive batteries for CNS drugs

The detailed SMP informs the decisions of the SRC in a procedural, repeatable, and auditable manner. In this way, the integrity of the trial data can be scrutinized without any concern of bias, and interested parties can be certain that dose escalation decisions were made with a holistic view of subject safety at the forefront.

Identify and Mitigate Potential Risks in Trial Conduct

Operational plans should be developed to address any events that may occur during the trial, related and unrelated to the study drug.

A Risk Mitigation Plan (RMP) considers various trial elements, categorizes them, and provides a score based on the severity of the risk as well as the overall impact should the event occur.

There is no single methodology for the creation of a RMP. Thoroughness is key, as well as an objective methodology to assess risk, so that all interested parties can understand how decisions are made.

Typical plans would include:

- Functional area or type of risk
- The personnel or department from which the event would originate
- The type of procedure or assessment associated with the risk
- Steps for prevention
- Contingency plan should the risk occur

Potential risks can be identified in multiple aspects of the trial.

- **Study protocol**
  - Procedures
  - Drug profile
  - Disease information
  - Route of administration
  - Patient demographics (if including patients)
- **Equipment and instrumentation requirements**
  - Laboratory instruments and value ranges
  - Sample storage and processing
  - Investigational product preparation and storage
  - Drug administration devices (e.g., infusion pumps)
  - Need for alternate participants
  - Subject stipend expectations
  - Retention and compliance challenges
  - Population-specific recruitment challenges
- **Staffing needs**
  - Impact of cohort sizes
  - Impact of sentinel dosing
  - Impact of including special populations
  - Availability of personnel with specialized training
- **Participant recruitment and retention**
  - Stringent I/E criteria
  - Anticipated drop-out rate

By performing a deep analysis of the potential risks of a FIH trial, and taking steps to remove those risks, the trial will be performed in the safest environment possible, eliminating any skewing of the generated data. Key stakeholders with responsibility for the identified areas should collaborate in the development of the Plan. The RMP is a dynamic document that can be amended over the course of the trial as new information becomes available, allowing for adaptations and amendments as the trial progresses.

Recruit, Educate, and Retain Study Participants

FIH trials present an interesting challenge when it comes to participant recruitment, mainly due to the lack of human data and information available to respond to subject questions. A lack of any derived medical benefits from the IP is another factor which may negatively impact willingness to participate in a FIH trial.

The education of study subjects on the potential risks and safeguards in place during their participation should be built in at every stage of recruitment. The goal is to provide participants with the background on the drug and how to reasonably interpret results from animal models, as well as the decision-making process for continuing dose escalation. Potential participants must have adequate access to study personnel, physicians, and anyone they need to answer questions prior to and during the study. They should be counseled to consult their primary care physician for guidance prior to joining a trial.

Subjects receive crucial information about the study during the informed consent process, their eligibility interview, their screening visits, study orientations, and throughout the study.

Research-naïve participants are coached on how to successfully fulfill study requirements and remain compliant throughout their participation. Text messages and reminder cards with visit and procedure schedule are utilized to support maximum compliance, among other tools. The fundamental idea is to reduce as much burden as possible from participants and remove any potential barriers to fulfilling their trial obligations. In advance of study start, by taking steps to reduce the occurrence of protocol deviations caused by participant non-compliance, trial personnel can focus on generating the complete and accurate data that will be necessary to advance the FIH trial.

Plan Resources and Conduct the Trial

With the growing complexity of trial designs, and the common inclusion of multiple objectives and/or participant populations, there are many factors to consider when creating a resource plan:

Sentinel Dosing

If sentinel dosing is included, factor in a minimum of one day (and personnel) to observe the safety in the first two participants at each dose level. Multiply this factor by the number of cohorts that requires sentinel dosing.

Drug Interactions

Preclinical testing results may suggest potential drug interactions, and the need for additional evaluations:

- CYP 450 inducers or inhibitors
- Drug transporter protein studies

Human Abuse Potential/Dependence

If preclinical studies or other available data suggests possible abuse potential or dependence concerns, these specialized evaluations can be incorporated into a FIH program.

Cognitive Testing

For CNS-active drugs, cognitive batteries must be considered.

Food Effect

The timing of administration with meals may need to be considered, for its impact on absorption characteristics. Also, local gastrointestinal tolerance may be enhanced by concomitant food administration.

Inclusion of Special Populations

When incorporating special populations (e.g., ethnic groups, age groups, patient arms) into your FIH trial, participant recruitment timelines may need to be adjusted accordingly.

Incorporating a special population may also require the use of smaller cohorts to accommodate for the slower subject accrual rates.

Consider some of the below factors when developing a recruitment plan for a FIH trial incorporating special populations:

- **Gender stratification:** It is generally easier to recruit male participants, and there may be additional evaluations necessary for female participants, or women of child-bearing potential (e.g., pregnancy tests, pap smears), which may require outside experts to perform and interpret test results.
- **Ethnic populations:** Language barriers and other cultural sensitivities will need to be considered when creating subject-facing materials and assigning staff to manage study participants throughout the trial. Ensuring appropriately skilled staff is imperative to ensuring subject understanding and compliance. Another element to consider is whether matching criteria are required between ethnic groups, which may further impact the accrual rate or require additional resources.
- **Patient cohorts:** The trial may require additional oversight from physicians in a therapeutic area to confirm subject eligibility or interpret results from laboratory assessments. Furthermore, if study eligibility criteria differ from the standard of care, additional time to identify participants who meet all eligibility requirements may be required.

Conclusion

The above overview for conducting FIH trials is intended to serve as a broad checklist for success. Certainly, there will be additional details to consider depending on the unique nature of the investigational product, the intended regulatory and clinical development pathways, and your overall corporate objectives.

Altasciences has the in-depth expertise to fully support your FIH trial management. Scientific and regulatory experts, data management and biostatistical experts, and clinical trial monitoring personnel work together with your team to ensure all important elements are being fully addressed. With preclinical, small molecule, and bioanalytical capabilities in-house, we provide a holistic, integrated overview that provides the most efficient, relevant, and robust FIH program for your needs.

A successfully conducted FIH trial provides a solid foundation of knowledge regarding the safety and exposure of an IP, at several dose levels, within a relatively short period of time. The data generated can help identify opportunities to accelerate or enhance a compound's clinical development in the future.

RELATED RESOURCES

Webinar

Comparing CTA Submission (EMA/Health Canada) to IND Applications (FDA) for Phase I Trials

Scientific Support for your Studies

Five Things to Know About Scientific Affairs

The Altascientist

Maximizing Drug Formulation for First-in-Human Trials

Videos

Altasciences' Clinical Video (3 mins)

Quick Chats Series: Short, Relevant Chats with Altasciences' Experts on a Variety of Topics

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