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7 ITEMS TO CONSIDER WHEN PLANNING FIRST-IN-HUMAN TRIALS

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Topics

Introduction

A First-in-Human (FIH) clinical trial is a significant milestone in the development of a potential new therapeutic entity in that, as the name suggests, it will be the first opportunity for a pharmaceutical company to evaluate the impact of their New Chemical (or biologic) Entity (NCE) in humans. Typically, FIH trials with compounds that will not be indicated for cancers or some rare non-malignant diseases, are conducted using normal healthy volunteers (NHVs) as trial participants, unless there is some ethical concern (such as known toxicity) in administering the investigational drug to an otherwise healthy population.

During a FIH study, numerous objectives may be included:

- Evaluating safety and tolerance
- Determining pharmacokinetics (PK exposure and dose proportionality)
- Early determination of pharmacologic activity relative to exposure level
  - Based on measured physiologic responses, or
  - Based on "Biomarkers of Response" identified during preclinical testing
- Assessing these 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 indication

For as many objectives that can be accomplished during a FIH trial, there are just as many ways that something can go awry. At this stage of the investigational product's lifecycle, the reason for failure could be as simple as the human participant not responding to the drug in the same manner that was suggested by preclinical testing. This being so, it behooves drug developers to spend a considerable amount of time planning for their First-in-Human clinical trial to ensure that it is designed and conducted in a manner which will ensure the highest probability of successfully achieving its objectives.

As a dedicated Early Phase CRO, WCCT has conducted over 140 FIH trials since 2005 at its clinical pharmacology unit located in Southern California. Drawing from this experience, we have compiled this instructional document in a stepwise approach with our top considerations, strategies, and recommendations when planning for a FIH clinical trial.* Should you have further questions after reading this document, we invite you to reach out to us at mgr@wcct.com for more information.

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

Step 1: Determine the Necessary Regulatory Interactions

When considering a strategy for regulatory interactions and submission, it is paramount to understand that regulatory agencies will place emphasis on the Sponsor's ability to define the uncertainty associated with the treatment being tested during a FIH trial. To the best of their ability, drug developers will need to invest time defining any uncertainties associated with the clinical testing of their compound, as well as identify the potential risks to subject safety that could arise during the trial.

Beyond simply identifying risks, the strategy for proactively addressing those 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 to adapt to data which emerges over the course of the trial itself. These efforts will be supported by the investigational brochure.

In order to identify these potential risks to participant safety, we encourage Sponsors to consider the following questions:

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

When interacting with the FDA, this documentation must be contained within an Investigational New Drug (IND) application. Prior to submitting this application, Sponsors often benefit from scheduled interactions with the FDA (in a Pre-IND meeting) to receive feedback on their plan and incorporate those learnings into their trial design. Investing in such a meeting may reduce the risk of a "clinical hold" being placed on the application due to safety or design concerns, which will delay the conduct of the trial until the concerns have been addressed and the clinical plan updated to satisfy the FDA Reviewer's concerns.

For the purposes of preparation for this Pre-IND meeting, the following information should be readily available:

- A "gap analysis" of available information versus regulatory expectations for management of the Investigational Product (IP)
- A "gap analysis" of available pharmacology support for the intended medical indication versus regulatory expectations for preclinical evidence in support of the intended medical indication
- A "gap analysis" of available toxicology support for the intended medical indication versus regulatory expectations for toxicology necessary to support of the intended early development program
- A detailed study synopsis for the planned FIH study

Step 2: Select the Starting Dose

Imperative to the success of any FIH trial will be determining the dose level at which the trial begins. Sponsors will need to strike a balance between mitigating the risk of toxicity and administering a dose that is 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).

Over the years, several methods for selecting the starting dose have been developed and implemented, dependent upon the therapeutic being evaluated, such as:

- 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

Step 3: Design the Trial

The design of a FIH trial is commonly referred to as a "dose escalation study," where participants will receive increasing doses of the treatment being tested based upon protocol-specified outcomes. The dose is increased once the safety, PK or other protocol-specified requirements have been confirmed by a "Safety Review Committee" or a third-party Independent Data Management Board (IDMB). Most often, both Single-Ascending Dose (SAD) and Multiple-Ascending Dose (MAD) studies are included in the early development program.

Single Ascending Dose (SAD)

In a SAD design, a small group of participants are given a single dose of the treatment and are observed while confined for any clinically relevant adverse events or toxicity. If adverse events are not observed in a pre-determined number of participants, then the dose will be escalated to the next planned higher dose. This dose escalation will continue until a predetermined PK exposure safety level is achieved, or intolerable adverse events are experienced. SAD studies are commonly double-blind and placebo-controlled to determine if the observed adverse events can be attributed to the Investigational Product (IP) without "bias" from the Investigator.

A variation of this exists, in which "sentinel" participants are used as an added safety precaution. Instead of dosing the entire cohort, only two participants are dosed (one given active drug, the other given placebo), and observed for adverse events. If none are observed, the rest of the cohort is then dosed at the same level. If an adverse event is observed, then only two more participants will be dosed and observed for additional adverse events. If observed in these additional two participants, the dosing may be halted. This variation provides a method for drug developers to identify safety issues early on and prevent harm from occurring in as few participants as possible. Sentinel dosing has become standard practice over the past few years.

Multiple Ascending Dose (MAD)

MAD trials usually follow SAD trials and are conducted to further assess the safety, tolerance and PK and PD of the NCE; however, participants within a single cohort will be given multiple doses at pre-specified intervals or at intervals and dose-levels informed by the data generated in the SAD trial. The dose levels and frequency of the doses are most often selected to achieve "therapeutic levels" which will be maintained for several days to enable safety or "activity" parameters to be monitored. It is common for three or more dose levels to be assessed.

During MAD studies, adequate PK sampling is imperative. If samples are collected too infrequently or at incorrect times, the data generated could be of little use to support a Sponsor's objectives. Conversely, sampling too often will increase the burden on study participants and trial personnel without producing significant information. Determining the appropriate PK sampling schedule will often be confirmed by the pharmacokinetic results of the SAD study.

While the MAD study is typically conducted after the completion of the SAD study, significant time

can be saved by conducting these two separate designs under a single study protocol. However, this requires increased levels of planning and more stringent criteria which would allow for the MAD portion of the study to initiate prior to the completion of all the SAD cohorts. Furthermore, the MAD study is typically where new dose levels would be evaluated in "adaptive cohorts." Examples of adaptive modifications could be:

- Sample size adjustment
- Changing the randomization fraction:
  - To favor certain treatments
  - To avoid unfavorable treatments
- Addition of special populations (e.g. patients, post-menopausal women, WOCBP, healthy volunteers with high triglycerides)
- Addition of specific ethnic populations (such as healthy Japanese/Chinese/Korean participants to support global drug development programs)
- Addition or elimination of specific treatment arms

While the incorporation of adaptive cohorts can serve to expand knowledge of the compound's attributes gained during the trial, this design will require restrictive start and stop criteria to ensure the safety of participants.

Step 4: Plan for Subject Safety

Pivotal to the success of any FIH trial is ensuring that there are adequate systems in place for preventing risk throughout the study as well as monitoring subject safety throughout. Due to the fact that the treatment has not yet been studied in humans before, detailed consideration must be given not only to the risks that exist in any early phase trial, but also the risks that can be extrapolated from observations in the preclinical testing phase.

There are many interested parties at this stage. In addition to demonstrating to the FDA that your trial has been properly designed to ensure subject safety in an IND application, Institutional Review Boards (IRBs) will also assess whether subject risk has been minimized, and that the potential risks involved are justifiable in relation to any anticipated benefits. Beyond simply reviewing the protocol, IRBs may also request information related to the approach for trial monitoring, including stopping rules for the study. Furthermore, IRBs may inquire about the establishment of an Independent Data Management Board (IDMB).

<u>Independent Data Management Board (IDMB)</u>
Once proper safeguards have been put into place to mitigate untoward events during trial conduct (related not only to the treatment itself but operational oversight), subject safety must be observed during and after each dose level administration, and data-driven decisions must be made regarding whether to proceed with the trial at a higher dose. Oftentimes, Sponsors may elect to have an IDMB (sometimes referred to as Data Safety Monitoring Board or DSMB) to be responsible for these important trial decisions. When considering an IDMB, you may ask the following questions:

1. When is an IDMB Needed? While all trials require some level of safety monitoring, a formal committee may not be necessary. While the use of an IDMB to provide oversight to your trial is generally a well-accepted practice, they do add a level of administrative complexity to a trial and require additional resources. The decision to use an IDMB should center around the potential risk present to trial participant.

2. What is the responsibility of the IDMB? At a high level, the fundamental responsibility of the

IDMB is to make recommendations to the Sponsor and the PI if the trial should continue, and if so, how it should continue. For the purposes of FIH trials, the primary decision being made is whether the dose level should be escalated. Because this recommendation can impact the safety and health of trial participant, it should be made clearly, both orally and in writing. In order to make this recommendation, the IDMB will review data generated from the trial that are important to determining safety, such as the frequency and severity of adverse events in each treatment arm.

3. Who should be a part of an IDMB? When selecting members of an IDMB, it is important to consider factors such as experience in similar clinical trials as well as service on similar committees (Safety Review Committees, Data Monitoring Committees, Steering Committees, etc.). The members of the IDMB should have no serious conflicts of interest which could bias them toward the success of the trial. Common members of a IDMB are:

a. Scientific consultant (e.g., medical expert in the therapeutic area of interest)
b. Project Manager
c. Clinicians with relevant clinical specialties
d. Medical monitor
e. Biostatistician

4. How do IDMBs operate? Typically, IDMBs operate under written charters that will include well-defined procedures for meetings which allow for a thorough, objective documentation of discussions. This charter may be requested to be reviewed by the FDA and other interested parties. By documenting meeting activities, concerns around biases arising from interim data can be reduced. The charter will:

i. Include a schedule and format of meetings
ii. Describe guidelines for the presentation of data
iii. Outline a list of persons who are permitted to access interim data
iv. Provide a list of who may attend specific sessions of each meeting
v. Specify the methods and frequencies of interim reporting

<u>Protocol-Defined Safety Monitoring Plan</u>

Once the need for an IDMB has been established, the methodology for monitoring subject safety should be developed. An effective Safety Monitoring Plan is imperative to the success of a FIH trial in that it will outline the methods for data collection, the frequency of data review, and provide guidance for how the study should proceed in consideration of the data that has been generated.

In general, the Safety Monitoring Plan should include the following pieces of information to be reviewed or considered:

- 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
- Clinical Laboratory Evaluations
- Physical Examinations
- The occurrence of dose escalation or individual stopping criteria
- Defining the duration of observation, during which time an event must occur in order to be considered related to the investigational product
- Specialty safety examinations, driven by pre-clinical toxicology
- Assessments pertaining to specialized drug administration (e.g. topical, ophthalmic)

The creation and use of a detailed Safety Monitoring Plan will inform the decisions of the of the IDMB or group responsible for reviewing safety-related data generated by the trial in a procedural, repeatable, and auditable manner. In this way, the integrity of the trial data can be scrutinized without any doubt of bias, and interested parties can be certain that dose escalation decisions were made only after taking a holistic view of trial subject safety into account.

Step 5: Identify and Mitigate Potential Risks in Trial Execution

In addition to monitoring subject safety throughout the trial, we advocate that trial Sponsors should have operational plans in place to prevent untoward events from occurring throughout the trial, both related and unrelated to the study drug itself. By doing so, your trial will have the best chance of success and the most complete, accurate data from which to make decisions regarding further clinical development. It would be a disappointment if an otherwise safe trial was put in jeopardy by operational mistakes, delays in recruitment, or other events that could have been avoided.

To this end, we recommend the creation of a Risk Mitigation Plan which considers various trial elements, categorizes them, and gives them a score based on the severity of the risk as well as the potential impact it would have on the study overall should the event occur. Items to consider here, based on prior experience conducting similar trials, would be the probability that the risk occurs and the priority for preventing a specific risk over another, if both cannot be addressed effectively.

There is no single methodology that must be used to create a Risk Mitigation Plan. However, at this stage we would argue that thoroughness is key and there is no such thing as too much detail. Also important is putting in place an objective methodology to assess risk, such that decisions regarding those risks can be understood by all interested parties.

While not an exhaustive list of details to compile, we recommend some basic items such as:

- 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. Some major areas to evaluate when identifying potential risks would be:

- 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)
- Volunteer Recruitment and Retention
  - Stringent I/E criteria
  - Anticipated drop-out rate

- 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

By performing a deep analysis of the potential risks of your FIH trial, and taking steps to remove those risks, you can ensure your trial will be performed in the safest environment possible, eliminating any potential skewing of the data being generated. We encourage Risk Mitigation Plans to be developed collaboratively with other stakeholders such as outsourced partners (e.g. CROs), clinical site staff (such as the Principal Investigator and Project/Clinical Trial Manager), and any others who will have heightened responsibility when it comes to preventing the specific risks present in your trial. The Risk Mitigation Plan is meant to be a dynamic document that can be amended over the course of the trial as new information becomes available, allowing for new risks to be identified and others to be removed as the trial progresses.

Step 6: Recruit, Educate, and Retain Study Participants

FIH trials present an interesting challenge when it comes to volunteer recruitment, mainly because there is no human data on the investigational product and subsequently little information available to respond to a potential volunteer's concerns that may be associated with trial participation. Furthermore, a lack of any derived medical benefits from the Investigational Compound is another factor which contributes to a potential participant's apprehension or unwillingness to participate in a FIH trial.

The average trial participant is unlikely to fully comprehend the ways in which preclinical data generated in animals translates to expected outcomes in humans. Therefore, there is little more than the explanations provided by trial staff at different stages of recruitment to bring potential participants to a level of comfort that would encourage them to participate in the trial. As a result, the education of trial volunteers on the potential risks and safeguards that will be present during their participation should be built in at every stage of recruitment. This will involve an increased focus on providing 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.

Opportunities to educate potential study participants on drug history and study safety measures may include:

1. Subject eligibility interview
2. Subject screening visits
3. Informed Consent administration
4. Study Orientations
5. Periodic study communications between visits

Furthermore, as you may be recruiting research-naïve participants, they will need to be coached on how to successfully fulfill study requirements and remain compliant throughout their participation. Resources such as mobile texts and reminder cards with visit and procedure schedules can go a long

way towards ensuring compliance. 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 subject non-compliance, trial personnel can focus on generating the complete and accurate data that will be necessary to advance the FIH trial.

Step 7: Plan Resources and Execute the Trial

When it comes to executing early phase trial designs, our experience suggests that FIH trials require special consideration when doing resource planning. With the growing complexity of trial designs, and the common inclusion of multiple objectives as well as multiple subject populations, there are many factors to consider when creating a plan for how to staff the project. Below we will outline how common aspects of FIH trials may impact resourcing needs:

Sentinel Dosing

If sentinel dosing is included, factor in a minimum of 1 day (and personnel) to observe the safety in the first two participants at each dose level enrolled before proceeding to the remainder of the cohort. Multiply this factor by however many cohorts will require sentinel dosing.

Drug Interactions

Results from preclinical testing may signal that the metabolism and disposition of the NCE may require that testing is carried out during early clinical testing:

- CYP 450 inducers or inhibitors
- Drug transporter protein studies

Food Effect

Results from preclinical studies or merely the chemical nature of the NCE may require that the timing of administration with meals may impact 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, it is reasonable to expect that subject recruitment timelines will need to be taken into consideration.

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 volunteers and there may be additional evaluations necessary for female volunteers (e.g., pregnancy tests, pap smears, etc.), which may require outside experts to be identified to perform and interpret test results. Expect additional effort required if women of child-bearing potential (WOCBP) will be included.
- **Ethnic populations:** Expect language barriers and other cultural sensitivities which will need to be considered when creating subject-facing materials and assigning staff to manage study participants throughout the trial. Utilizing staff who can speak the same language, and who understand unique cultural sensitivities, will be imperative to ensuring subject understanding and compliance. Another experimental element to consider is whether "matching" criteria will be required between ethnic groups, which may further impact the accrual rate or require additional resources to successfully identify them.
- **Patient cohorts:** The trial may require additional oversight from physicians in that therapeutic

area to confirm subject eligibility or interpret results from laboratory assessments. Furthermore, if study eligibility criteria differ from the standard of care, you will likely need to factor in additional time to identify participant which meet all eligibility requirements.

Conclusion

The above overview for conducting FIH trials is intended to serve as a broad "checklist" for success, and certainly there will be additional details to consider dependent upon the unique nature of the investigational product being evaluated, the intended regulatory and clinical development pathways, and your overall corporate objectives. To further determine what to consider for your FIH trial, we encourage seeking the support of experienced clinical operations personnel who have planned and provided oversight for these types of trials many times in the past. Many Sponsors may even consider outsourcing most or all aspects of trial management.

If executed successfully, a FIH trial can inform various stakeholders at drug development companies and provide a solid foundation of knowledge regarding the safety and exposure of an investigational product at several dose levels within a relatively short period of time. Lastly, the data generated during this time can help identify opportunities to accelerate or enhance a compound's clinical development in the future.

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Our Mission

To achieve our Sponsors' Early Phase clinical objectives of advancing global health. This is accomplished through the development of a scientifically-informed time and budget-sensitive design; and with clinical trial research service execution that delivers high quality data, a superior client experience, and a volunteer-centric approach to care.

To discuss your upcoming clinical development program,
call us at (714) 252-0770 or e-mail us at mgr@wcct.com