General Considerations for Clinical Trial Design

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Disclosure

- No financial relationships to disclose

Phases of Development: Phase 1

- Includes the initial introduction of an investigational new drug into humans.
- Typically closely monitored and may be conducted in patients or normal volunteer subjects.
- Designed to determine:
  - The metabolism and pharmacologic actions of the drug in humans (Note: the PK considerations are different among drugs, cell therapies, and gene therapies, as discussed elsewhere in this training course).
  - The side effects associated with increasing doses, and, if possible, to gain early evidence of biologic activity and perhaps efficacy.
- Information about the drug's safety profile pharmacokinetics and pharmacological effects is obtained in order to help design subsequent Phase 2 studies.
- The total number of subjects is generally in the range of 20 to 80.

Phases of Development: Phase 2

- Includes the controlled clinical studies conducted to evaluate:
  - Preliminary evidence of efficacy of the drug for a particular indication or indications in patients with the disease or condition under study.
    - The evidence may rely on biomarkers, surrogates, or clinical outcomes
  - The common short-term side effects and risks associated with the drug
- Phase 2 drug studies are typically well controlled, closely monitored, and usually conducted in no more than several hundred subjects.
  - For cell and gene therapies, the size of Phase 2 studies is often limited by practical concerns, but Phase 2 is important for planning subsequent Phase 3 pivotal trials.

Phases of Development: Phase 3

- Expanded controlled and uncontrolled trials (e.g., long-term open-label extensions of controlled trials)
- Performed after preliminary evidence suggesting effectiveness of the drug has been obtained
- Intended to gather sufficient information about efficacy and safety needed:
  - To evaluate the overall benefit-risk relationship of the drug, and
  - To provide an adequate basis for labeling.
- Phase 3 studies usually include from several hundred to several thousand subjects.

Product Development Plan

- A Phase 1 study should be one component of a larger development plan
- Designing a trial that has the potential to effectively test a hypotheses relies on:
  - Knowledge of disease pathophysiology (e.g., if a protein is noted to be expressed at low levels in the disease state, is it merely a marker, is it an adaptive response that may be beneficial, or is it part of the disease pathophysiology?)

Product Development Plan

Designing a trial that has the potential to effectively test a hypotheses also relies on:

- Knowledge of your product
  - What is the pattern of expression, and how does this fit with the scheme for treatment of the disease (e.g., does the time of peak expression correlate with the window for injury in the case of prevention of post-operative ischemia using a vector-delivered transgene?)?
  - For a chronic disease, what is the long-term scheme for treatment if effects are transitory?
    - Is only a single dose required to modify the disease?
    - If multiple dosing is required, how will this be addressed in the development plan?
    - Is multiple dosing even feasible (e.g., tissue trauma due to repeated injection of a small muscle, toxicity, immunogenicity)?

Overview of Required Content of Phase 1 Protocols

- Phase 1 protocols should be directed primarily at providing an outline of the investigation:
  - An estimate of the number of patients to be involved
  - General enrollment criteria, with a detailed description of safety exclusions
  - A description of the dosing plan including duration, dose, or method to be used in determining dose

Phase 1 Protocol Elements

- Background
  - Pre-clinical studies
    - In vitro testing
    - Bench testing (delivery logistics)
    - Animal studies
  - Previous experience from human studies
- Rationale
  - What is the mechanism of action
  - What is the basis for the hypothesis that the proposed treatment will have some activity against the disease?
    - For example, if cell engraftment is felt to be critical, have you assessed whether injected cells are retained in the target tissue for any appreciable amount of time?

Phase 1 Trial Design

- Objectives
  - Phase 1 studies are primarily focused on the evaluation of safety
  - Preliminary evidence of efficacy
    - For cell and gene therapies, the clinical studies should provide some evidence of biological activity of the product.

Study population

- Selection of the study population
  - Depends on pre-clinical and clinical safety and preliminary efficacy data
  - Consider enrolling subjects whose disease falls within a limited range of severity
    - When obtaining preliminary evidence of efficacy, if severity of disease in the study group is too high, it may ultimately be difficult to demonstrate an impact on disease outcome in later trials
    - Results may be confounded by inclusion of multiple subgroups that differ in natural course of disease
    - Later-phase studies may enroll a more general population to address the issue of generalizability
  - Exclude subjects who are at high risk of complications
  - Exclude vulnerable populations if feasible

Dosing

- Dose
  - Starting dose should be selected based on pre-clinical studies
- Dosing Regimen
  - Single dose for first human trial; multiple doses for later Phase 1 trials
  - Usually 1 route of administration per trial
  - Dose escalation should be conservative for first-in-human trial
- Other Considerations
  - Are there issues (e.g., cell clumping) that affect reproducibility of a consistent dose
  - What should be done for subjects for whom collected/expanded cells do not meet lot release criteria (# of cells)

Controls and Blinding

- Control comparator arms
  - None (open-label study)
  - Standard of care comparator
  - Placebo
  - Sham (e.g., catheter-based delivery of cells to the myocardium)
- Blinding
  - Single-blinded (subjects only)
  - Double-blinded (subjects and investigators/assessors)
  - Open-label trial: no blinding

Sample Size

- In general, cohorts should be fairly small (less than 20 subjects in a single cohort)

Enrollment Rate

- Staggered intra-cohort and inter-cohort enrollment of subjects
- Interval between subjects and between cohorts should be determined by the time course of expected and unexpected adverse events, as well as an estimate of the time required to assess these events.
- Once a safety signal arises, the trial can be halted prior to enrollment of subsequent subjects.

Study Period

- Duration of the study should be appropriate for the disease (e.g., studies of acute versus chronic disease have different considerations).
- Duration should also take into account the mechanism of action of the product (e.g., what is the time by which the intervention will be expected to have had a measurable effect?).

Safety Monitoring Plan

- Should take into account product characteristics (e.g., vector biodistribution and potential for insertional mutagenesis; transgene's potential for promotion of cancer) when determining duration of long-term monitoring (see CBER guidance document on gene therapy monitoring)
- Should be based on pre-clinical study data and also on theoretical concerns
- Should be presented as a table of scheduled assessments
- Types of assessments and time points for data collection should be sufficient to capture expected and unexpected adverse events.
- Stopping rules should be strongly considered for all studies under IND, and may be required for higher risk studies.

Endpoints

- Events or outcomes that can be measured to evaluate the safety or efficacy of a treatment
- An efficacy endpoint should be clinically relevant.
- Phase 1 studies often utilize multiple endpoints (it is important to collect as much relevant data as possible, however, an improper analysis of data from multiple endpoints may lead to a misinterpretation of product activity)

Biomarkers in Phase 1 Studies

- Biomarker: “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” (Biomarker Definitions Working Group, 2001, Clin Pharmacol Ther 2001;69:89-95)
  - Use of biomarkers may help in early development (both safety and efficacy).
  - A biomarker is not necessarily a surrogate.

Surrogates in Phase 1 Studies

- Surrogate
  - "A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence." (Biomarker Definitions Working Group, 2001, Clin Pharmacol Ther 2001;69:89-95)
  - May allow for faster collection of data; however that should be weighed against the potential for incorrect assumptions regarding preliminary efficacy
- Examples of biomarkers that are not surrogates for outcome:
  - Left ventricular ejection fraction as a surrogate for mortality in cardiovascular trials
  - Carotid intimal medial thickness as a surrogate for improvement of atherosclerotic disease

Statistical Analysis Plan

- Analysis is exploratory.
- Phase 1 studies are not generally powered to demonstrate statistically significant differences in outcome but can still provide some preliminary evidence of efficacy.
- Pre-specification of the analytical plan improves the interpretability of data.

Common Reasons for Clinical Hold

- 21 CFR 312.42(b)(i): Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury:
  - Risk-benefit ratio unfavorable
  - Eligibility criteria issues
  - Inadequate justification of dosing scheme
    - Insufficient justification for starting dose/volume
      - What may appear to be a safe volume (e.g., intramyocardial injection) administered to a normal organ may not be safe when administered to a diseased organ (e.g., may cause arrhythmias and diastolic dysfunction).
    - Dose escalation not sufficiently conservative for a first-in-human study
  - Inadequate safety monitoring plan
  - Failure to include stopping rules in the protocol

Contact Information

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