Protecting Phase I Subjects
IRB Considerations for Phase I Review of Research
June 5, 2013

Presented by:
Julie Blasingim
Director of Operations, Clinical Pharmacology
About Schulman Associates IRB

- Established in 1983
- US and Canadian boards fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP)
- Superior audit history with FDA—five consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA and OHRP requirements
About Schulman Associates IRB

- Full board meetings **five days a week**
- Dedicated **daily expedited review** of qualifying minimal risk protocols
- **Phase I Board** with streamlined processes tailored to Phase I timelines
- **Oncology Review Board** for all phases of oncology research
- Customized services for **institutions and AMCs**
- Experienced primary points of contact for sponsors, CROs, institutions and sites
About Today’s Presenter

Julie Blasingim, MBA, CIP
Director of Operations, Clinical Pharmacology

- MBA in Leadership
- With Independent (now Schulman) since 2006
- Previous Vice Chair of Phase I Board
- Responsible for direct support of board operations and business operations for clinical pharmacology services
- Certified IRB Professional (CIP) and a member of PRIM&R
Introduction

➢ In this presentation, we’ll discuss:
  • Industry and volunteer Phase I perspectives
  • Measuring risks to healthy volunteers
  • Unique attributes of informed consent
Overview of Phase I Research

**Pre-clinical**

- Animal
- Long-term/short-term
- In-vitro

**Clinical phases**

- Phase I: Pre-clinical
- Phase II: Clinical phases
- Phase III: Healthy volunteers
- Phase IV: Patients

**Healthy volunteers**

- Animal: 20-80
- Long-term/short-term: ~100-300
- In-vitro: 0.5-1 year
- Safety: 1000-5000
- Effectiveness: Varies
- Long-term: 2-3 years
- Safety and Effectiveness: 3-4 years
- Post-market: 1-2 years

**Patients**

- IND
- NDA
Overview of Phase I Research

**Pre-clinical**

- **Healthy volunteers**
  - Animal: 20-80
  - Safety: .5-1 year

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**Clinical phases**

- **Phase I**
  - Pre-clinical
  - Healthy volunteers: 20-80
  - Safety: .5-1 year

- **Phase II**
  - Safety: .5-1 year

- **Phase III**
  - Effectiveness: 2-3 years

- **Phase IV**
  - Long-term Safety and Effectiveness: 3-4 years

- **Post-market**
  - NDA: 1-2 years

- **IND**
FDA has 30 days to respond to any issues

PI assurance that no study procedures will be performed. This includes:
  • Screening
  • Advertising
  • Enrollment/Dosing

Sponsor assurance that they will not release investigational product during this time period

Following completion of 30 day wait period, and IRB approval, research can begin

Generic screening and recruitment are permitted
## Overview of Phase I Research

### Pre-clinical
- **Animal**: Long-term/short-term, In-vitro

### Clinical phases
- **Pre-clinical**: IND
- **Phase I**: 20-80 Healthy volunteers, Safety, .5-1 year
- **Phase II**: ~100-300 Healthy volunteers, Effectiveness, 2-3 years
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### Timeline
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  - Long-term Safety and Effectiveness
  - 3-4 years
- Phase IV: Post-market
  - Varies
  - 1-2 years

**Indicators**

- IND
- NDA
Initial studies of new drugs to:
• Gain early evidence of effectiveness
• Obtain sufficient information for planning of Phase II studies
• Determine metabolism and pharmacologic actions
• Determine a safe dosage range
• Identify side effects
• Investigate tolerability
• Determine pharmacokinetics and pharmacodynamics

Often times includes pharmacogenetic testing
Closely monitored, confined environment
May include healthy participants and/or patients
Small group of people (generally 20-80)
Tight timelines
True or False?

Most Phase I research studies extend beyond a typical one year approval period.
True or False?

Most Phase I research studies extend beyond a typical one year approval period.

False
To the Phase I Subject, Phase I Research Is...

- No treatment benefit
- Unknown side effects and tolerability
- Confinement to a research facility
- Several blood draws in a short period of time
- Intense diagnostic testing and monitoring
- Strict entry criteria to determine healthy participants
- Limited enrollment opportunities
- Short duration
- Opportunities to complete multiple studies a year
- Fast-paced from screening to completion
- Financial reimbursement for participation
Types of Studies

**INDUSTRY**

1. Pharmacokinetics (PK)/Pharmacodynamics (PD)
2. First-in-Human (FIH)
3. Single Ascending Dose (SAD)
4. Multiple Ascending Dose (MAD)
5. Renal/Hepatic Impairment
6. Healthy vs. Elderly, Ethnic Sensitivity
7. Drug Interactions
8. Prolonged QTc
9. Bioavailability/Bioequivalence (BA/BE)
10. Food Effect
11. Radiolabeled [14C]

**PHASE I HEALTHY PARTICIPANT**

1. Several blood draws over short period of time
2. Unknown effects in humans, relying on animal data
3. One dose, one confinement, specific dose level may be unknown at screening
4. Sequential doses, often one confinement with subsequent visits, specific dose level may be unknown at screening
5. Limited enrollment for healthy controls. No treatment for renal/hepatic condition
6. One dose, often one confinement. Enrollment constraints based on matches needed.
7. Crossover, more than one confinement, given a marketed drug in combination
8. High dose with extensive cardiac monitoring
9. Crossover, more than one confinement
10. Crossover, more than one confinement with extensive fasting in one period
11. Radioactive material with collection of urine and feces, confinement period is unknown
Changing Phase I Landscape

- Incorporates “adaptive” study design elements
- Increase in Multi-Part Protocols
  - Single Dose – Dose Escalation Study
  - Multiple Dose – Dose Escalation Study
  - Food Effect Study
  - Probe Medication/Interaction
  - May include other Exploratory Objectives
  - Optional/Mandatory sample collection for future unspecified biomarker and genetic research
- Often conducted at more than one research facility
- May include outpatient dosing or enrollment of disease population in FIH studies

Protecting Phase I Subjects

- Consent requires additional clarity on design
- Multiple consents may be required to single out information to a specific group
- Board may require interim data prior to moving to additional parts
Selection of Subjects

- Healthy subjects
  - Used when drug side effects are unknown
  - Allow for less confounding factors
- Patients
  - Used when drug is known or expected to be toxic
  - Difficulty in separating disease-related side effects from adverse reactions
- Often recruited from clinic database of repeat volunteers

Protecting Phase I Subjects

- Entry Criteria
  - Excludes conditions based on expected side effects from nonclinical research or drug class
  - Include robust screening procedures to gauge current health status
  - Selection is fair and without bias, coercion or undue influence
Payment

- Reimbursed for time and participation
- Viewed as a benefit by subjects, NOT by the IRB
- Payments are prorated based on completed visits
- Payment per visits generally ranges from $150-$300 and are typically classified as:
  - Screening
  - Confinement nights
  - Outpatient visits
  - Check-in
  - Discharge

Protecting Phase I Subjects

- Payment is not considered in risk/benefit assessment
- Payment can’t appear pronounced in any way and must be prorated and not cause undue influence or coercion.
Informed consent forms for Phase I research studies are typically shorter than a late stage informed consent form.
True or False?

Informed consent forms for Phase I research studies are typically shorter than a late stage informed consent form.

True
Purpose is not for treatment.
Alternative is to not participate.
Reasonably foreseeable risks → nonclinical risks in the IC.
Unknown/unforeseeable side effects is key.
  - Some toxicities noted in nonclinical studies translate into adverse events noted in humans, while some do not.
  - Some toxicities in nonclinical studies while they may translate to humans, they may not translate to the “healthy” human.
  - Certain subjective adverse events or hypersensitivity reactions cannot be assessed in nonclinical testing.
  - Additional safety procedures in the event of side effects needs to be noted.
Studies may require more frequent revisions as new human data becomes available.
Dose escalation studies may not have the specific dose level being given, rather a range, or a no higher dose specified will be administered.
Multiple consents for one study (e.g., main study, pharmacogenetics, biobanking).
ClinicalTrial.gov element often does not apply.
TeGenero developed a new immunosuppressant drug
FIH study was conducted in London, March 2006
Eight research participants (2 placebo: 6 active)
Drug was administered IV with about 10 minutes between dosing of the next participant
Minutes after dosing, all active participants receiving drug experienced severe side effects (severe cytokine release syndrome) and were hospitalized
Medicines and Healthcare Products Regulatory Agency (MHRA) found no deficiencies in trial procedure or in manufacturing of the drug
MHRA concluded that the most likely cause of the reaction in trial subjects was an unpredicted biological action of the drug in humans
First in Human Case Study – Lessons Learned

- Pre-clinical animal and in vitro data must be carefully considered to assess possible side effects and hypersensitivities.
- Sufficient *in-vitro* studies must be conducted prior to initiation of human trials.
- When a new drug involves a risky mode of action, a greater than 10-fold safety factor may be needed in first in human trials.
- In first in human studies, investigators must expect the unexpected and have appropriate safeguards in place.
- Investigators should have a plan for theoretical risks.
- Sentinel dosing design with sufficient time between dosing provides safer measures for first in human studies.
Safety Measures

- FIH: Sentinel dosing (2 subjects followed by remainder of group)
- SAD/MAD:
  - Dose escalation criteria and stopping criteria is specific and appropriate.
  - Dose increments are appropriate.
  - Amount of information and follow up before each dose escalation that is available and reviewed is appropriate
  - Number of subjects at each dose is appropriate
- Crossover: Adequate period of observation between dosing to observe and interpret adverse reactions.
Measuring Risk

Board Considerations

- Do nonclinical studies provide sufficient safety support for the proposed clinical trials?
- No Observed Adverse Effect Levels (NOAEL): The highest dose tested in animal species that does not produce a significant increase in adverse effects compared to control group. Much lower than expected therapeutic level.
- Human Equivalent Dose (HED): Converts animal dose to human dose (mg/kg)
- Estimating the Maximum Safe Starting Dose in Initial Clinical Trials: The safety factor provides a margin of safety for protection of human subjects receiving the initial clinical dose (default safety factor is usually 10)
In-house Monitoring

Protecting Phase I Subjects During Confinement

- Crash cart with appropriate rescue medications
- Close proximity to hospital
- Staff trained in emergency medical care (i.e., ACLS certified staff)
- 24-hour medical monitoring
- Ability to obtain basic safety lab results in a timely manner
- Telemetry or other continuous cardiac monitoring
Challenges in Phase I

- Retaining participants without coercion
- Participants traveling cross country
- Participants attempting to participate in multiple studies
- Fast-paced trials
- Determining “healthy” and appropriate for inclusion
- Adaptive study designs
Conclusion

- Additional safeguards and consideration are needed when minimizing risks in Phase I research.
- Dosing subjects requires a thoughtful and minimalistic approach.
- Researchers conducting Phase I research need to have proper equipment and qualified staff to monitor safety.
- Selection of subjects is critical to minimizing risks.
- Payment for participation must be carefully considered, but not when determining risk/benefit ratio.
- Elements of Informed Consent are addressed differently than other stages.
- Informed Consent requires continuous updates as new information becomes available.
Resources

http://prsinfo.clinicaltrials.gov/definitions.html#StudyPhase

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm121345.htm

http://clinicaltrials.gov/ct2/help/glossary/phase


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964774/
Schulman Phase I Services

- Extensive experience in all Phase I study reviews
- One week turnaround times from submission to receipt including approved IC
- Rush Review (approx. 24-36 hour turnaround post review)
- Collaborative approach to resolving IRB concerns in real-time
- Pre-IRB screening process that identifies possible concerns and discrepancies in submission material allowing clients the opportunity to clarify prior to IRB review
- Template IC collaborative development to streamline review process
- Draft IC services with a turnaround of 48-72 hours
- Single point-of-contact that manages each submission from start to finish

For more information on Schulman Phase I services, please contact Bette Bayne, Director of Phase I Business Development (bbayne@sairb.com)
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