Study Design & IRB Review of Phase I Healthy Clinical Trials

October 2015

fully accredited since 2006
Announcements

More services & faster review for Phase I Healthy studies

- Faster review times
  - Approved consent forms in 5 days
  - Amended consent forms within 2 days

- Unprecedented alternatives in the review of recruitment materials

QuorumReview.com/P1H
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Overview

1. Scope
2. Introduction
3. Case Study
4. The IRB’s Role
5. Advertising & Recruitment
6. Screening
7. Informed Consent
8. Facility Issues
9. Compensation & Reimbursement
10. Trends
Not Covered Today

Phase 1 Oncology
Pediatric Considerations
Preclinical Studies
Phase 2, 3, and 4 Studies
Device Studies
Studies not subject to FDA regulation
Introduction

Who, What, When, Where, Why, and How
Why?

First in Human (FIH)

Metabolism and pharmacologic actions

Side effects associated with increasing doses

Early evidence of effectiveness

Pharmacologic effects to permit design of Phase 2

21 CFR 312.21(a)
### When?

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Clinical</td>
<td>Laboratory</td>
<td>1-2 years</td>
</tr>
<tr>
<td></td>
<td>In vitro / In vivo</td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>1st in human</td>
<td>20-100 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Months – months</td>
</tr>
<tr>
<td>Phase II</td>
<td>Efficacy</td>
<td>Months – 2 years</td>
</tr>
<tr>
<td>Phase III</td>
<td>Confirm results</td>
<td>300-3000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4 years</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Post-marketing</td>
<td>Thousands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Varies</td>
</tr>
</tbody>
</table>
What?

Small molecules (drugs), biologics

New compound, combination of FDA-approved and new product, new formulation or route of administration
Who?

Healthy?

Guinea pig?

Pfizer P1H Studies from 9/2004 – 3/2011

– 88% male

– Median age: 33

– 53% participated in a single study

Where?

Screening

Confinement

Outpatient
### How?

<table>
<thead>
<tr>
<th>Dose escalation – Maximum Tolerated Dose (MTD)</th>
<th>Food Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Single Ascending Dose (SAD)</td>
<td>Bioavailability/ Bioequivalence (BA/BE)</td>
</tr>
<tr>
<td>– Multiple Ascending Dose (MAD)</td>
<td>Drug-Drug Interaction (DDI)</td>
</tr>
</tbody>
</table>

Pharmacokinetics (PK) & Pharmacodynamics (PD)  

QT  

Radiolabeling  

Pharmacogenomics (PGx)
P1H on ClinicalTrials.gov

Total open clinical trials (I – IV)  20,500

Phase 1  5,500

P1H  550

Accessed 9/18/2015
Case Study
Case Study

TGN1412
Risks in P1H Designs

Phase 1 study of TGN1412 in London, 2006
Recruited healthy subjects
Offered £2,000
TGN1412 – Monoclonal antibody intended to treat B cell chronic lymphocytic leukemia & rheumatoid arthritis
2 subjects received placebo, 6 subjects received drug

All 6 subjects in the test arm hospitalized - multiple organ failure
Side effects should have been anticipated?

Subjects dosed in swift succession

- Protocol provided for dosing 2 hours apart, but dosed within 20 minutes
- Outcry lead to industry changes

Criticized for paying subjects more than industry norm (£1,000 per week standard)
Safety in P1H Clinical Trials

$\frac{2}{3}$ Experienced Adverse Events (AEs)

$\frac{3}{4}$ AEs attributed to test product (prior to unblinding)

1% Severe

**TIP:** Make AE determinations prior to unblinding

Emanuel, et al.
The IRB's Role
Risks & Benefits of P1H Trials

Risks must be **minimized**...[b]y using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk....21 CFR 56.111(a)(1) & 45 CFR 46.111(a)(1)

Risks to subjects must be **reasonable** in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result....21 CFR 56.111(a)(2) & 45 CFR 46.111(a)(2)
Minimizing Risks of P1H Trials

Gather more data on the short-term and long-term risks of participation.

Develop strict inclusion/exclusion criteria to ensure subjects are healthy and not vulnerable.

Subjects should not participate in more than one phase 1 trial concurrently.

Minimizing Risk – “Sound Design”

Phase 1 protocols – less detailed, more flexible

Chemistry, Manufacture, and Control (CMC): safety concern or insufficient data to evaluate safety may result in clinical hold

Validation data and established specifications ordinarily not submitted

Statement regarding any prior use in humans
Minimizing Risks – Dosing

Estimating the maximum **safe starting dose**

Dose **increments**

**Number of subjects** at each dose

**Sentinel** dosing

**Dose escalation** and **stopping** criteria

**Crossover** considerations
Genomic-dependent dosing and efficacy
PK/PD effects on known biomarkers can provide proof of concept
PGx factors should be considered, particularly where the threshold between activity and toxicity is narrow
Collection of genetic samples from all participants recommended
Leverage technology platforms
More efficient later-phase design
The following should **NOT** be considered a “benefit” of P1H research

- “Free” medical exams
- Reimbursement for expenses
- Room & board
- Payment/incentives for participation
What are the benefits of P1H research?

Gain in scientific knowledge and the hope that one day you or others will be helped.
P1H research should follow FDA guidance in advertisements:

- Avoid characterizing IP as “treatment”
- Make clear that IP is investigational
- Should not over emphasize payment
- Do not advertise “free medical treatment”

FDA guidance encourages the following content for advertisements:

- Name and address of PI & facility
- Condition studied/purpose of the research
- Summary of inclusion/exclusion criteria
- Brief list of benefits
- Time commitment
- Contact information

Screening

Screening is of critical importance in P1H trials

43% of participants who had participated in more than one clinical trial in the recent past (n=100) failed to disclose concurrent enrollment

“Repeat customers” — avoid enrolling someone who is already in a trial

- Registries (background check databases/services)
- Fingerprinting
- Laboratory tests
- Positive reinforcements
- Exclusion

“Generic” or “general” screening process and consent to build a database of potential participants

Any modification of behavior for research purposes prior to screening requires IRB oversight and informed consent

Waiver of documentation of informed consent and a phone script

Citation: FDA “Screening Tests Prior to Study Enrollment – Information Sheet” (available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm)
Informed Consent

Respect for Persons

Eight Elements of IC

- Purpose is for research
- Reasonably foreseeable risks – nonclinical
- Benefit to others reasonably expected?
- Alternative is not to participate
- Confidentiality
- Compensation/treatment for injury
- Contact information
- Voluntary – decline or discontinue without penalty

21 CFR 50.25
Informed Consent (Cont.)

Additional Elements of Informed Consent

- Unforeseeable risks
- Anticipated circumstances under which participation may be terminated without subject’s consent
- Any additional costs to the subject
- Consequences of a subject’s decision to withdraw and termination procedures
- Update subject as to significant new findings which may relate to the subject’s willingness to continue participation
- The approximate number of subjects involved in the study

ClinicalTrials.gov registration often does not apply

21 CFR 50.25
Informed Consent (Cont.)

Generally shorter IC forms than later-phase counterparts

Multiple consents (e.g., main study, PGx, biobanking)

Specificity - dose escalation studies may not have the specific dose level being given, rather a range or a no higher dose specified

Obtained by health professional?

Delay between consent and other study procedures?
Facility

Qualified PI and study staff

- Trained in emergency medical care (i.e. ACLS certified staff)
- Prior experience with P1H

Emergency preparedness

- Crash cart with appropriate rescue medications
- Close proximity to hospital
- 24-hour medical monitoring
- Ability to obtain basic safety lab results in a timely manner
- Telemetry or other continuous cardiac monitoring

Signage stressing importance of reporting symptoms
Compensation for Participation

Undue influence

Reduce influence by prorating payments

Completion bonuses?

Amount should be appropriate for time/effort and not risk-based

– Consider economics of the region

– Consider population from which recruiting (e.g., homeless, students)

Trends in P1H Clinical Trials

Study design of P1H trials continues to evolve

Sponsors concerned with efficiencies

Studies now may be more complex than in the past:

- Adaptive designs
- Single ascending dose with multi ascending dose design in same trial
- Inclusion of a patient cohort
Summary
Do’s and Don’ts

1. Do make payments based on number of procedures and time involved, not risk.

2. Do not allow dual enrollment or enrollment within 30 days or within certain drug half-life of prior study.

3. Do ask participants about symptoms multiple times per day using non-leading questions (once before dosing).

4. Do determine AEs related to test article prior to unblinding.
Do’s and Don’ts (Cont.)

5. Do consider many fold safety factor when developing dosing plan with risky mode of action

6. Do utilize sentinel dosing

7. Do emphasize importance of reporting symptoms in the IC, without financial penalty for being withdrawn due to AE

8. Do use 2 category classification for safety reporting: (1) did not cause AE and (2) uncertain or caused AE

9. Do monitor participants after discharge for at least 30 days or certain half-life of the study drug
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