Adaptive Phase I Studies: The IRB Perspective
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IRB Member, Schulman IRB
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About Schulman IRB

- Established in 1983
- Superior audit history with FDA—five consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
- Full Board meetings five days a week
- Dedicated daily expedited review of qualifying minimal risk protocols
About Schulman IRB

- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
- Dedicated streamlined processes tailored to **Phase I timelines**
- **Expert oncology IRB members** experienced in all phases of oncology research
  - National IRB for **Cancer MoonShot 2020** initiative
- Customized services for **institutions**
- **Experienced primary points of contact** for sponsors, CROs, institutions and sites
About Schulman IRB

- Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by Provision Research Compliance Services

www.provisionrcs.com
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- Schulman IRB member since 2014
- Previously held leadership positions in Clinical Operations, Drug Safety, Clinical Quality Assurance and Product Development in prescription drug, OTC medicines, device and consumer healthcare fields
  - Was responsible for global, innovative training programs for corporate scientists, building organizational capacity, and shaping organizational culture to embrace diversity and inclusion
- Has served as consultant in early phase drug development and as medical writer/editor
- Also previously worked as hospital pharmacist
- Academic experience includes clinical research, teaching, and clinical practice
- Post-doctoral fellowship in Emergency Medicine and Critical Care Pharmacy
Objectives

- Describe why adaptive Phase I study design is used
- Discuss what the IRB looks for when reviewing adaptive Phase I studies
- Identify best practices for developing informed consent forms for these studies
Adaptive Design
Definition

What Is Adaptive Design?

- An **adaptive design clinical study** is defined as a study that includes a **prospectively** planned **opportunity** for modification of one or more **specified** aspects of the study design and hypotheses based on **analysis** of data (**usually interim data**) from subjects in the study.

Source: [FDA Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics](https://www.fda.gov)
Definition

What Is Adaptive Design?

- Analyses of the accumulating study data are performed at prospectively planned time points within the study, can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing.

Source: [FDA’s Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics](#)
Characteristics of Good Adaptive Design

Design is nothing if it’s not smart.
Characteristics of Good Adaptive Design

- Proactive vs. Reactive
- Does not reduce study integrity
- Provides benefit or enhancement of the overall design strategy
- Typically adaptation is based on data from the study
- Can be carefully (safely) implemented
- Can involve **clinical**, statistical, and/or regulatory aspects of a clinical trial
This Is NOT Good Adaptive Design
Why Use an Adaptive Design?

- Efficiency
- More likely to demonstrate an effect
- More information (e.g., reach MTD, show fuller dose-response curve)
- Speed to decision making
- Cost savings
Cost to Develop New Pharmaceutical Drug Now Exceeds $2.5B

A new report published by the Tufts Center for the Study of Drug Development (CSDD) pegs the cost of developing a prescription drug that gains market approval at $2.6 billion, a 145% increase, correcting for inflation, over the estimate the center made in 2003.

Scientific American November 20, 24, 2014
What Kind of Changes or Adaptations?

- Study eligibility (including subject subsets)
- Treatment arms
- Sample size
- Randomization procedures
- Treatment regimens (dosage, duration)
- Concomitant treatments or activities allowed
- Schedule of events
- Termination of study
- Primary and/or secondary endpoints
- Statistical methods of analysis
Examples of Adaptive Early Phase Studies

- SAD
- SAD to MAD (same or separate cohorts)
- Addition of food effect
- Adding early efficacy/activity/surrogate measures
- Adding patient subgroups
- Add special population subgroups
How Does the IRB Approach Review of an Adaptive Design Study?

- Scientific validity
- Subject safety
- Informed consent
- Site review
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IRB Focus: Scientific Validity in Design

- Are basic good design principles in place?
- Is there a benefit to the adaptive design?
- Is there sound design that will answer the research question(s)?
- Has bias been introduced by the adaptive design?
- Does blinding, where appropriate, remain intact?
- Will the results reflect the target population?
How Does the IRB Approach Review of an Adaptive Design Study?

- Scientific validity
- **Subject safety**
- Informed consent
- Site review
IRB Focus: Subject Safety

- Adequate preclinical data to support the design?
- The right safety measures and monitoring plan in place?
- Adaptive options are clearly and definitely described?
- Well defined safety criteria, stopping rules, maximum doses, etc.?
IRB Focus: Subject Safety

- Dosing schedules
- Sufficient time to assess safety data prior to decision points
- Who will be the decision makers at the decision points?
- How are decisions documented and reported
- Contingency plans if safety issues arise
How Does the IRB Approach Review of an Adaptive Design Study?

- Scientific validity
- Subject safety
- Informed consent
- Site review
IRB Focus: Informed Consent

"You might feel a little prick."
IRB Focus: Informed Consent (IC)

Basic components of informed consent apply:

1. A statement that the study involves research
2. An explanation of the purposes of the research
3. The expected duration of the subject's participation
4. A description of the procedures to be followed
5. Identification of any procedures which are experimental
6. A description of any reasonably foreseeable risks or discomforts to the subject
7. A description of any benefits to the subject or to others which may reasonably be expected from the research
8. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
9. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
10. For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained
11. Research, Rights or Injury: An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
12. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled
IRB Focus: Informed Consent (IC) Considerations

- Level of complexity of the design
- Differences between treatment arms
- Design elements that address safety
- How are treatments assigned
IRB Focus: Informed Consent

- Complexity
  - Break it up when possible
- Include the risk language that relates to their participation
- Communicate boundaries and safeguards
- Treatments assignments
  - Do they have a choice?
How Does the IRB Approach Review of an Adaptive Design Study?

- Scientific validity
- Subject safety
- Informed consent
- Site review
CONSIDERATIONS

- Site expertise
- Experience $\Leftrightarrow$ complexity of design
- Staffing levels and experience
- Facilities and equipment
- Emergency readiness
- Contingency plans
**IRB Focus: Site Review**

**SECTION 1.0: Study Information**

<table>
<thead>
<tr>
<th>1. PI/QI Name:</th>
<th>2. Sponsor:</th>
<th>3. Protocol No.:</th>
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**SECTION 2.0: Investigational Product (IP) Administration**

| 1. What is the anticipated interval of time between IP administration for each subject in a cohort? |
| 2. What is the maximum number of subjects that would receive IP in a given day? |

**SECTION 3.0: Site Staffing**

| 1. How many physicians will be present at the time of IP administration? |
| 2. How long will physician(s) remain on site post IP administration? |
| 3. Describe physician availability off-site (on call): |

| 4. How many non-physician, medically-licensed (e.g., RNs, CNPs, PAs) staff will be on site at the time of IP administration? |
| 5. How long will non-physician, medically-licensed staff remain on site post IP administration? |
| 6. Are non-physician, medically licensed staff ACLS certified and trained to administer emergency medications?  
  □ No □ Yes |
| 7. Does the site have access to hospital emergency response/code team?  
  □ No □ Yes |
| 8. Describe the additional staff members, and their qualifications, that are available during the first 24 hrs. after IP administration: |
SECTION 4.0: Facilities

1. Describe the resuscitative equipment available on site: 

2. Describe the emergency medications available on site: 

3. Does the site have a defibrillator available on site?  
   ☐ No  ☐ Yes  

4. Does the site have equipment and expertise to apply continuous safety monitoring if needed (e.g., telemetry, SaO2 monitoring, continuous vital sign monitoring)?  
   ☐ No  ☐ Yes  >>> Provide a description: 

SECTION 5.0: Additional Information

1. Does the site have an SOP(s) or policy(ies) for medical emergency management?  
   ☐ No  ☐ Yes  >>> Complete a.:  
   a. Has site staff been trained on the SOP(s) or policy(ies) for medical emergency management?  
      ☐ No  ☐ Yes  

2. Provide any additional information for board consideration regarding subject safety processes for your site or practices that will be implemented for this research protocol: 

Conclusions

- Adaptive study design can be a smart and effective strategy with many benefits.
- Added complexity requires close attention during IRB review.
- Impact of adaptive design will be considered during the assessment of scientific merit, subject safety, informed consents and site review.
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