Role of Academic Investigators in Drug Development

Howard Lee, MD, PhD

Associate Adjunct Professor
Director, Center for Drug
Terminology

- Sponsor
- Investigator
- Sponsor-investigator

21 CFR Parts 312(b), 312.3(b), 312.50, & 312.60
Sponsor

- Anyone that takes responsibility for and initiates a clinical study
- An individual, company, institution, or organization
Investigator

- The one who *conducts* a study
  - Under the direction, the study drug is administered and dispensed
- If a team is involved
  - The leader becomes the investigator
  - Other team members are sub-investigators
Sponsor-Investigator

- An individual who both *initiates* and *conducts* a study
- Must follow the requirements pertaining to
  - A sponsor
  - An investigator
Dr. Research wants to study drug *ItWorks*, manufactured and sold by *WeSell*. The company sponsors clinical supplies for the study (i.e., study drugs for free).

*Who is the sponsor?*
Drug Development: Options for Academic Investigators

- A pharmaceutical firm (i.e., sponsor) initiates and approaches an investigator for help
- An investigator initiates and conducts a drug study (i.e., sponsor-investigator)
- Mixed
## Which Option Suits Me Best?

<table>
<thead>
<tr>
<th>Serve as</th>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>Investigator only</td>
<td>- Don’t bother details</td>
<td>- Less flexible</td>
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<tr>
<td></td>
<td>- No worry about funding</td>
<td>- Less intriguing</td>
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<tr>
<td>Sponsor-Investigator</td>
<td>- More flexible</td>
<td>- Sole responsibility</td>
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<td></td>
<td>- Scientifically more interesting</td>
<td>- Resources limited</td>
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<td>- Funding may be an issue</td>
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The Most Frequently Asked Question for Sponsor-Investigators

Does my study need an IND?
## Typical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Need IND?</th>
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<tbody>
<tr>
<td>Unapproved drug</td>
<td>Yes.</td>
</tr>
<tr>
<td>Approved drug, but for unapproved use</td>
<td>Depends.</td>
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</tbody>
</table>
Approved Drug for Unapproved Use

- If no ‘research’ component involved, IND is NOT required
  - Prescribed the drug as part of *regular medical care* with no problem

- What if you want to formally ‘study’ it?
  - Have tried the drug in a few patients as part of standard care, and you’ve now gotten promising results
No IND If ALL Conditions Are Met

- No intention to support FDA approval of a new indication or significant change in the labeling
- No intention to support a change in advertising
- In compliance with IRB and informed consent requirements
- In compliance with promotion and charging for investigational drugs

21 CFR 312.2(b)(1)
Wait! We’re Not There Yet

- The investigation does NOT involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
Significantly Increase the Risks

- New dose
- New route of administration
- New or unstudied population (i.e., pediatric patients)
- New regimen (i.e., schedule)
- New combination
- New formulation
Increased Risks for Cancer Drugs

- IND may be exempted if
  - Investigators and their IRBs determine that, based on the scientific literature and generally known clinical experience, there is no *significant increase in the risk associated with use of the drug product*.

- Translation
  - Check the literature for the new dose, route, or schedule of administration, or a new combination of marketed drugs
  - If no safety data found, probably need an IND

*Guidance for Industry, IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer, FDA, 2004*
Still Not Sure or Want a Second Opinion?

Contact at FDA:

Drugs: Barry Poole (301) 827-4570
Biologics: Robert Yetter (301) 827-0373
Devices: IDE Staff (301) 594-1190
Foods: David Hattan (202) 418-3126

Call, and then submit a written request (FAX or e-mail)

Modified from Constance Lewin, MD, CDER, FDA, 2003
What to File?

- Cover sheet
- FDA Form 1571
- Table of contents
- Introductory statement and general investigational plan
- Clinical protocol
- Chemistry, manufacturing and control (CMC) information
- Pharmacology and toxicology information (i.e., preclinical animal experiments)
- Previous human experience
- Form FDA 1572 (statement of investigator, one for each)
- Additional Information (e.g., IRB approval, informed consent form, etc.)
Post IND Filing

- FDA will respond within 30 days of filing
- 3 possible responses
  - FDA silent for 30 days (i.e., IND approved)
  - FDA may request more data (i.e., Clinical Hold)
  - FDA may exempt IND (i.e., IND exempt)
IND Approved or Exempt

Great, but this is not the end of the story!

Responsibility of a Sponsor-Investigator

- Conduct the study according to the approved protocol
- Personally conduct or supervise the study
- Assure that all associates are informed of their obligations
- Obtain informed consent of each subject
- Select a qualified clinical monitor
- Monitor the progress of the clinical study and document the monitoring activities
- Prepare and maintain adequate and accurate case records on each subject in the study
- Maintain written records showing receipt and disposition of the drug
- Inform the FDA of significant adverse events
Do You Want Me to Continue?

- Review and evaluate the evidence relating to the safety and effectiveness of the drug and submit
- Reports to the FDA (periodic)
- Secure compliance by all investigators or terminate their involvement
- Retain the records and reports for two years after the FDA has been notified the study has been completed or discontinued
- Assure no conflict of interest
- Assure initial and continuing approval of the study by the IRB
- Submit annual reports of the progress of the study to the FDA
- Submit, upon completion of the study, a final report to the FDA
- Permit inspection of the study records and reports by the FDA
You Still Want to Become a Sponsor-Investigator

- DTRCS may help you in several areas
  - To determine if IND is required
  - To review an IND package
  - To help investigators make important drug development decisions
  - To connect investigators with expert drug developers (fees may be assessed)
Other Consultation Services

- General drug development
- Regulatory road map
- Regulatory decision
- Project management
- IMPACT
Integrated Model-based Pharmacometric Analysis of Clinical Trials (IMPACT)

Howard Lee, MD, PhD
Adjunct Associate Professor
Director, Center for Drug Development Science
Department of Biopharmaceutical Sciences
School of Pharmacy
University of California San Francisco
What is IMPACT?

- Advanced *design* and *data analysis* services for studies of:
  - Pharmacokinetics (PK)
  - Pharmacodynamics (PD)
  - Clinical pharmacology
  - Mechanism of pharmacological action
  - Proof of concept (POC)
  - Translational, exploratory, learning or confirming studies of a preventive, therapeutic, and diagnostic agent
What Makes IMPACT Unique?

- Needs to be addressed
  - Cutting-edge PK and PD approaches
  - Limited practical knowledge for PK and PD

- Approaches
  - Design optimization, modeling, and simulation
  - Mechanism based

- Clients
  - UCSF clinical and translational investigators
  - Outside collaborators
IMPACT: Specific Services

- Design of a translational and clinical study
- Advanced pharmacometric modeling and simulations
- Conventional PK, PD, PK-PD analysis
- Training and education
- Resources and services for use of advanced pharmacometric software
  - WinNonlin, NONMEM, PC-BUG, TrialSimulator, WinPort
IMPACT: Compensation

- Collaboration-based (preferred)
  - To participate in a research project at any stage
    - Grant writing, protocol design, development of a pharmacometric data analysis plan
  - Support for salary of personnel, travel, equipment, license maintenance fee

- Fee-for-service-based (also welcomed)
  - Tailored research services
    - *ad hoc* consultation, full range data analysis project
Need More Information?

- Contact Julie Nelson
  - E-mail: Julie.Nelson@ucsf.edu
  - Phone: 202-785-5450
  - Fax: 202-822-5040

- [http://cdds.ucsf.edu/cdds_ps/](http://cdds.ucsf.edu/cdds_ps/)

- Link available at CTSI web site
The ACDRS is a nonprofit educational course established in 2006 by the Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco (UCSF) and the Center for Drug Development Science (CDDS). UCSF working with the FDA, professional societies, a network of universities, a network of pharmaceutical, biotechnology and device companies, and with the European Course in Pharmaceutical Medicine (ECPM), University of Basel, Switzerland. ACDRS is managed by an Executive Office and collaborates with a science-driven and highly experienced international faculty with a network of experts in pharmaceutical medicine and medical product development science.

ACDRS (Inaugural) Cycle 1 (Washington, DC)*
Session 1: September 10-13, 2007
Session 2: January 7-10, 2008
Session 3: May 12-15, 2008
Session 4: September 8-11, 2008
Session 5: January 12-15, 2009
Session 6: May 11-13, 2009
Examination: May 14, 2009

*A Parallel ACDRS cycle will be started in the San Francisco Bay Area in the Fall 2008.
ACDRS: Mission and Vision

- Modernization of development and regulation of medical products via
  - Certified, comprehensive instruction
  - Integration of cutting-edge concepts
  - Best practices in medical product development and regulatory sciences
ACDRS: 6 Sessions in 2 Years

- The Pharmaceutical Development Enterprise: Current and Future Perspectives
- Learning Trials: From Discovery to FIH
- Learning and Confirming Trials: Finding and Confirming the Right Dose
- Confirming Trials: Methodology and Biostatistics
- Global Registration and Approval Process
- Integrated Product Development and Project Management
ACDRS: The Launch

- East and West coasts
  - Washington DC in September 2007
    - CDDS, FDA
  - San Francisco in September 2008
    - UCSF Mission Bay Campus