

Regulatory Obligations for Investigator-Sponsored Research: An FDA Perspective

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Agenda

IND sponsor responsibilities
IND recordkeeping requirements
Investigator-Sponsored Trials
Paradigms for submitting IND/IDEs to FDA
 How these choices impact the investigator &
 institution
Suggestions for successful research
FDA inspects investigator-sponsored research
Types of violations found during inspections

Legal Framework for Requiring INDs and IDEs

Laws require that FDA OK certain products
before they can be shipped in interstate
commerce.

An IND must be in effect, and an IDE must be
approved to allow unapproved drugs/devices
to move in interstate commerce in order to
be studied.

FDA Expectations for INDs

FDA objectives for reviewing an IND are to assure the
safety and rights of subjects in all phases of the
research,

And in phase 2 and 3, to help assure that the quality of
the scientific evaluation is adequate to permit
evaluation of the drug's effectiveness and safety.

21 CFR 312.22(a)

The sponsor requirements to select qualified investigators, ensure
protocol compliance, document, report, and monitor are based
on these objectives.

What is an IND?

Investigational New Drug Application
A formal submission with defined structure and
content
Provides an exemption from restrictions on
interstate commerce of shipment of an unapproved
new drug
21 USC 355

21 CFR 312 outlines requirements
§ 312.23 IND Content and Format
§ 312.42 Clinical Holds
§ 312.50 – 312.69 Responsibilities of Sponsors /
Investigators

Responsibilities of IND Sponsors

21 CFR §§ 312.50 – 312.59

- Keep the IND current
- Select qualified investigators
- Provide all investigators with sufficient information to
conduct the investigation
- Control the drug
- Prepare and maintain records
- Inform FDA & investigators of SAE's or newly
identified risks to subjects.
- Monitor the ongoing investigations

Sponsor

- An individual, company, or institution who takes responsibility for and initiates a clinical investigation.
- Investigator-sponsored research may involve other sites.

Responsibilities of Investigators

21 CFR 312.60-312.69

Perform investigation consistent with protocols

Ensure safety and welfare of subjects under care

Obtain IRB approval for investigations

Promptly report any adverse events to Sponsor

Maintain adequate records

Sponsor-Investigator

- An individual who both initiates and conducts an investigation.
- The term refers only to an individual. A sponsor-investigator does not involve other sites.
- Must comply with the requirements of both an investigator and a sponsor.

FDA Expectations for Sponsor-Investigators

FDA regulations (21 CFR 312 or 812, 50, 54, and 56) apply to ALL sponsors and clinical investigators.

EXCEPT sponsor-investigators do not need to submit an investigator brochure to the IND. An investigator brochure is required when other sites are involved.

Sponsors Must Monitor the Investigation

To verify that:

- The rights, safety, and welfare of human subjects are protected
- The reported clinical data are accurate, complete (“adequate and accurate”)
- The conduct of the trial is in compliance with the protocol and regulations

Sponsors must correct problems or terminate a site's participation, and report terminations

Monitoring is **NOT** Optional

- Required by FDA regulation 21 CFR
 - 312.50 Responsibilities of sponsors
 - 312.53(d) Selecting monitors
 - 812.25(e) Monitoring procedures
- Recommendations in guidance documents
 - FDA: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (Draft Guidance)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm269919.pdf>
 - ICH: E6 Good Clinical Practice
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>



IND Sponsors Must Train Sites and Monitor

- Investigators sponsoring research often do not train or monitor the participating sites
 - Assumptions that colleagues don't need training?
 - Or that this isn't "really" research?
- Monitoring is often not planned for in investigator-sponsored research.
 - Logistics? Cost? Ignorance of the requirement?
- How will you select a qualified monitor?

Monitoring may be delegated to a contract research organization

For drugs, sponsor may transfer responsibility to contractors 21 CFR 312.52

21 CFR 812 is silent regarding contracting for device sponsors, who remain responsible for contractors' actions

CDER INDs With Activity During 2010

	CDER	%
Commercial	5,834	59.8
Research	3,890	39.9
Unknown	26	0.3
Total	9,750	

Profile of CBER Active IND/IDE Sponsors

As of 10/5/11

	#	%
Total	1,952*	
Commercial	768	39
Individual	665	34
Government (NIH, CDC,...)	200	10
Hospital/Medical Center/University	185	9
Zoo	62	3
Military	48	2
"Other" (COGs, nonprofits...)	24	1

*About 10% are on clinical hold or partial hold.
Includes single patient and emergency INDs still open.

Profile of CBER INDs/IDEs Sponsored by Individuals

	Total	665*
Cell and Gene therapies	411	
Vaccines	115	
Hematologic	53	
Devices	41	
Allergens	43	
Blood bank/source plasma	2	

*About 10% are on clinical hold or partial hold.
Includes single patient and emergency INDs still open.

Many Investigators Sponsor
More than One IND

# IND/IDEs sponsored by an individual	Count of individuals
1	358
2	58
3	19
4-5	14
6-7	4
13	1
15	1
17	1

Profile of CBER Non-Commercial INDs
No matter who is designated as the IND contact, the sponsor is responsible

Sponsor	IND Contact
Individual	Individual
Individual	Research Office
Individual	Staff member (i.e., fellow, nurse)
Individual	Contractor
Contractor	Clinical investigator
"Program"	Clinical investigator
Staff member (fellow, nurse)	Clinical investigator
Institution	Research Office staff

Some institutions are inconsistent in how they identify sponsors— sometimes the institution, sometimes the individual

For example – 3 INDs list CI as sponsor, 3 list the institution.

Institutions also vary greatly as to how involved an Office of Research may be.

Historical Perspective

High-profile problems have impacted how academic medical centers oversee INDs and sponsor-investigators.

Other institutions reviewed their practices and implemented changes after high-profile cases.

The Clinical Investigator Conducts the Investigation
Form FDA-1572

COMMITMENTS:

- I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation(s).
- I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
- I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

Separating Investigator and
Sponsor Responsibilities

Clinical Investigator

- Submits protocols to the IRB
- Submits progress reports to the sponsor
- Reports adverse events to the IRB and sponsor

Sponsor

- Submits protocols to FDA in the IND
- Reports progress to FDA in the IND
- Reports adverse events to FDA in the IND

Suggestions for Sponsors - BEFORE -

Understand what you are responsible for... and get training as needed.

Request a pre-IND meeting with FDA, and listen to the advice. (5/25/01 Guidance)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070568.pdf>

Seek advice for maintaining your IND. Ask for help and ask questions.

Document duties delegated to others.

Suggestions for Sponsors - BEFORE -

Prepare a detailed protocol.

("I'm the expert. I wrote the protocol -- I know what I meant to do.") no! no! no!

Develop plans for monitoring.

What are the critical activities? How often?
Which activities? Who will monitor?

Don't take on satellite sites you cannot directly supervise

How & how often will you collect the data from the sites?

Suggestions for Sponsors - BEFORE -

Develop case report forms or checklists to make sure all required activities are performed.

Screening, study visits, follow-up

Don't overextend to many concurrent projects.

Train study staff before the study starts....and train replacements when staff leave.

Develop plan for organizing records.

Suggestions for Sponsors - DURING -

Call FDA as needed to consult about trial or product issues

Perform monitoring during critical activities. Make sure replacement staff at sites are trained

Amend the protocol when needed – and submit to your IRB, the clinical investigators, and FDA.

("I decided I didn't need to do those tests.") no! no!

Verify that delegated duties are performed.

Suggestions for Sponsors - DURING -

Keep up with data as the trial progresses

Track dates when your IND annual reports are due.

Correct small problems before they grow.

Train your/sponsor's replacement staff.

Report adverse events to the IND/IDE

Suggestions for Sponsors - AFTER -

Organize the study records ---

- So non-study staff can find them
- To show what a good job you did
- To fulfill record retention requirements
- For possible FDA inspection

(may be years later - depending on the sponsor and phase of the research)

- For possible transfer for further development
- Remember to notify FDA of status changes (withdraw, inactivate) so your IND/IDE is current.

FDA Inspects Investigator-Sponsored Trials

Most of these inspections are **DIRECTED**:

- * complaints (subjects, staff, IRBs)
- * requests from FDA reviewers
- * FDA District-initiated (news reports)

FDA Surveillance inspections of ongoing studies of drugs and devices.

Significant Sponsor Violations

Clinicians used unapproved product without IND

Sponsor shipped product to sites not named in IND (failure to maintain IND, lack of Form 1572)

Failed to monitor progress of study / did not obtain information from sites

Failed to report adverse events to FDA under the IND

MOST COMMON Clinical Investigator Violations

Failed to follow protocol requirements
Inadequate case histories
Discrepancies between source records and CRF
Inadequate drug/device accountability records
Enrolled ineligible subjects

You should be looking for these problems during monitoring!

MOST COMMON Clinical Investigator Violations

Failure to retain records
Failure to notify the IRB of adverse events
Lack of supporting raw data for CRF entries
Failure to list all subinvestigators on Form FDA 1572
Inadequate informed consent form
Failure to report adverse events to the sponsor

You should be looking for these problems during monitoring!

MOST SIGNIFICANT Clinical Investigator Violations

- Enrolled ineligible subjects
- Enrollment exceeded protocol or IRB limit
- Did not conduct required evaluations
- (related to safety assessments)
- Violated clinical hold
- Submitted false information to the sponsor
- Use of drug/device before submission of IND/IDE

These are significant because they:

- place subjects at added risk
- bypass the good clinical practice framework
- violate regulations and laws

Contact Information

<http://www.fda.gov/BiologicsBloodVaccines/default.htm>

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)

Email: ocod@fda.hhs.gov

Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch (MATTB)

Email: industry.biologics@fda.gov

Phone: 301-827-4081

Follow us on Twitter

<https://www.twitter.com/fdacber>

Further Resources

Website regarding CBER IND/IDE process:
<http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/default.htm>

**Accompanying Web Seminar Series from
CBER's Office of Cellular, Tissue, and Gene
Therapies**

Contacts to Find Out if the Research Needs an IND or IDE

Drugs - CDER Division of Drug Information
888-463-6332 301-796-3400
druginfo@fda.hhs.gov

Biologics – CBER Manufacturer's Assistance
800-835-4709 301-827-1800
Industry.Biologics@fda.hhs.gov

Devices – CDRH Manufacturer's Assistance
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