MEET THE INSTITUTE OF TRANSLATIONAL HEALTH SCIENCES

ITHS | Institute of Translational Health Sciences

Accelerating Research. Improving Health.

Overview

Our Focus

- Speeding science to the clinic for the benefit of patients and communities throughout WWAMI
- We promote the translation of scientific discovery to practice by:
  - ❑ Fostering innovative research
  - ❑ Cultivating multi-disciplinary research partnerships
  - ❑ Ensuring a pipeline of next-generation researchers through robust education and career development programs

Who We Are

Key Statistics:

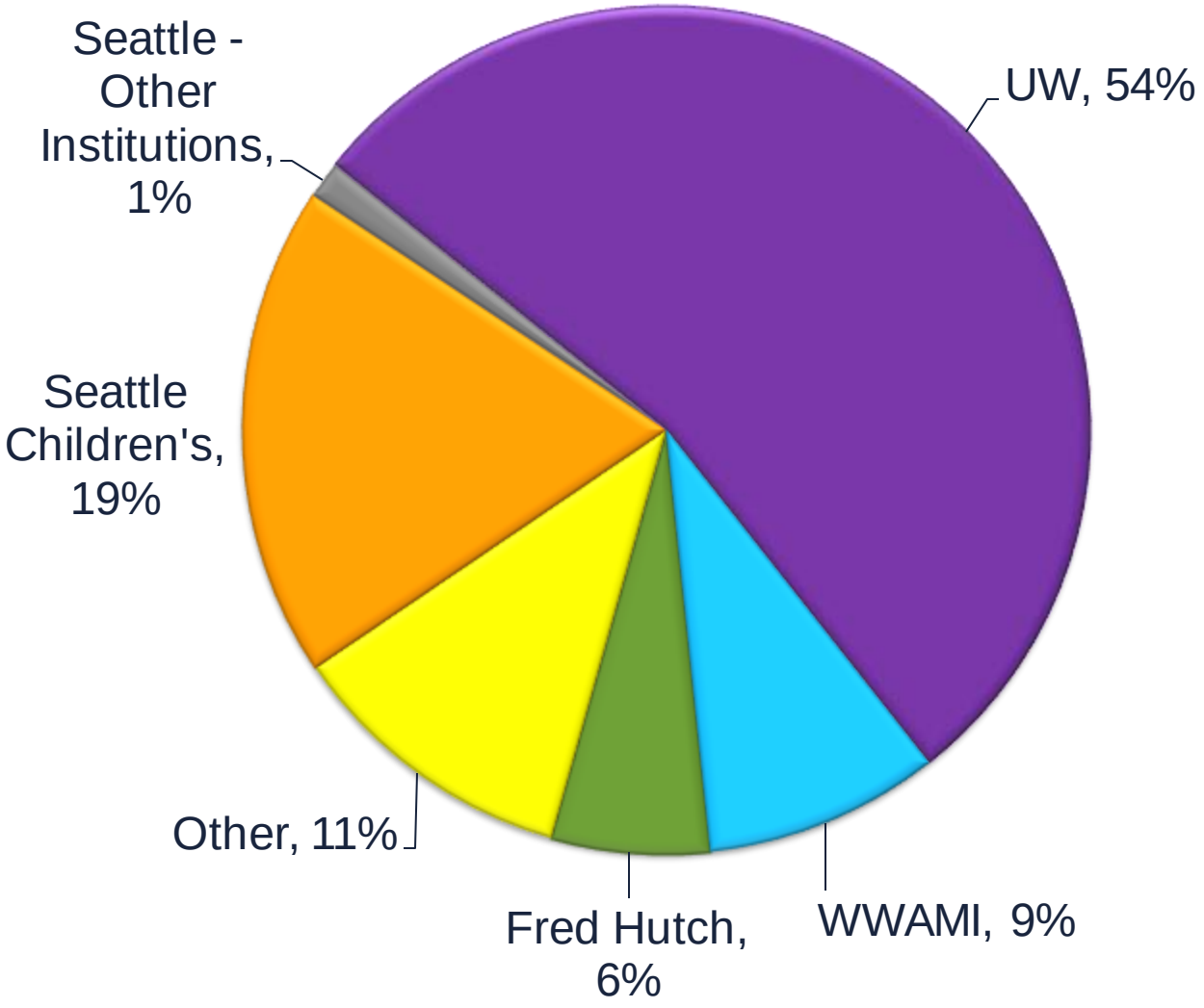
- One of 62 NIH-funded CTSA sites nationally
- Approximately 160 faculty and staff from across all health science disciplines

Funding:

- Approximately $17 million/year
- Primary source is NCATS
- Additional funding from institutional support and program income

Our Partners:

Who We Support



- ~1,800 unique investigators last year
- Junior and senior researchers
- Administrators and staff
- Community members
- Pre- and post-docs

What We've Helped Accomplish

Accomplishments supported since 2007

- Worked with more than 6,500 researchers from nearly 200 institutions across the five-state WWAMI region
- Helped realize more than $585 million in federal grant funding
- Helped realize publication of more than 1,800 articles

MANAGEMENT OF INVESTIGATOR-SPONSORED INDs

January 21, 2016

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Objectives

- Understand the differences between FDA regulations for sponsors versus investigators under 21 CFR Part 312
- Review the three most common scenarios for investigator-sponsored INDs in academic research settings
- Discuss procedures and documentation requirements to ensure that sponsor-investigators meet their regulatory obligations for these three scenarios

Regulations 21 CFR Part 312

- Code of Federal Regulations (CFR): collection of the rules published by U.S. Government departments and agencies
  - Fifty titles represent general areas subject to federal regulation
- Title 21 of the CFR: Food and Drug Administration (FDA) rules
  - 21 CFR Part 312: Investigational New Drug Application (broad set of regulations applying to IND activities)
  - 21 CFR Part 312 Subpart B: Investigational New Drug Application (IND) (submitting and maintaining an active IND file)
  - 21 CFR Part 312 Subpart D: Responsibilities of Sponsors and Investigators

Definitions (21 CFR 312.3)

- Investigational new drug: a new drug or biological drug that is used in a clinical investigation.
  - does not have FDA approval for marketing
- Clinical investigation: experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.
  - any use of a drug except a marketed drug used in the course of medical practice.

Definitions (21 CFR 312.3) - cont.

- Investigator: individual who actually conducts a clinical investigation. [Principal Investigator]
  - drug is used under the investigator's direction
  - "responsible leader" of a team of individuals
- Sponsor: person who takes responsibility for and initiates a clinical investigation.
- Sponsor-Investigator: individual who both initiates and conducts an investigation.

Sponsor vs. Investigator Responsibilities

SPONSOR	INVESTIGATOR
Submit and maintain an effective IND	Oversee study conduct
Investigator selection; informing investigators	Safety Review and Reporting
Monitor investigations	Report Study Activity
Safety Review and Reporting	Control of Investigational Product
Report IND activity	Recordkeeping and Data
Investigational Product Accountability	Permit FDA Inspection
Recordkeeping and Data	
Permit FDA Inspection	

Sponsor vs. Investigator Responsibilities

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Submit and maintain an effective IND

- Submit IND application including necessary elements described in 21 CFR 312.23, including:
  - product information (characterization, manufacture, prior testing, investigator's brochure as required)
  - investigator information
  - protocol information
- IND is in effect
  - 30 days after FDA receives application, unless FDA places clinical hold, or
  - on earlier notification by FDA
- Maintain IND by submitting protocol amendments, safety information, annual reports, and information amendments as required by regulations

Sponsor vs. Investigator Responsibilities

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Investigator selection; informing investigators

- Select investigators qualified by training and experience
- Obtain Form FDA 1572 and financial disclosure information
- Give each participating investigator an investigator brochure, except individual Sponsor-Investigator
- Provide investigators with necessary information to conduct study

Sponsor vs. Investigator Responsibilities

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Oversee study conduct

- Personally conduct or supervise study
- Select qualified sub-investigators and staff
- Assure initial and continuing IRB review/approval
- Obtain informed consent
- Protect subjects' rights, safety, and welfare
- Ensure compliance with protocol, investigator statement (1572), and regulations

Sponsor vs. Investigator Responsibilities

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Monitor investigations

- Select monitors qualified by training and experience
- Monitor the progress of all clinical investigations under the IND
- Ensure investigation is conducted in accordance with protocol, investigator statement (1572), and regulations
- Secure compliance or discontinue investigator participation if non-compliance is identified

Sponsor vs. Investigator Responsibilities

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Safety Review and Reporting

Sponsor:

- Review drug safety and efficacy data as it is received
- Notify FDA of new safety/risk information
- Notify investigators of new safety/risk information
- Discontinue study if investigational product presents unreasonable and significant risk to subjects

Investigator:

- Notify sponsor of all SAEs and other adverse events as required by protocol
- Notify IRB of SAEs, unanticipated risks, and noncompliance as required by IRB policies

Sponsor vs. Investigator Responsibilities

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Report IND Activity

- Report to FDA on all protocols and study sites under IND
- Submit protocol changes that significantly affect subject safety, scope of investigation, or scientific quality of the study
- Submit new protocols or new investigators
- Submit IND safety reports and other safety information reflecting all use of investigational product
- Submit annual reports including progress of investigations at all study sites

Sponsor vs. Investigator Responsibilities

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Report Study Activity

- Provide sponsor with progress reports, safety reports, final report, and financial disclosure information
- Notify sponsor and IRB of any changes to research activity

Sponsor vs. Investigator Responsibilities

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Investigational Product Accountability

- Provide investigational product only to participating investigators
- Assure return of unused investigational product, or authorize alternative disposition
- Maintain records of product receipt, shipment, other disposition
  - Must include: investigator name, date, quantity, and batch/code identifier for each shipment.
- Retain reserve samples and reference standards as appropriate

Sponsor vs. Investigator Responsibilities

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Control of Investigational Product

- Administer product only to subjects under supervision of
  (1) investigator, or
  (2) a sub-investigator responsible to the investigator
- Supply product only to individuals authorized to receive it
- Maintain records of product receipt, subject use, and return or other disposition

Sponsor vs. Investigator Responsibilities

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Recordkeeping and Data

Sponsor:

- Maintain records of product receipt/shipment/disposition and investigator financial interests
- Retain “records and reports required by this part” (i.e., Part 312) at least 2 years after final marketing approval or discontinuation of shipment/delivery of product and notification of FDA.

Investigator:

- Maintain records of product disposition
- Maintain case histories: CRFs, ICFs, medical records
- Retain records at least 2 years after final marketing approval or discontinuation of shipment/delivery of product and notification of FDA.

RETENTION PERIOD FOR BOTH: INSTITUTIONAL, STATE, OR OTHER REQUIREMENTS MAY APPLY

Sponsor vs. Investigator Responsibilities

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Permit FDA Inspection

Common IND Scenarios in Academia

- Sponsor-Investigator
- Sponsor plus Principal Investigator at same institution
- Sponsor plus Principal Investigators at multiple institutions

Sponsor-Investigator

- Dr. Jekyll holds an IND.
- Dr. Jekyll is Principal Investigator of the protocol conducted under that IND.
- Dr. Jekyll is a “true” Sponsor-Investigator who both initiates and conducts a study. She must fulfill all sponsor and investigator obligations described under 21 CFR 312, except providing an investigator’s brochure.
- Challenges in this scenario may include “merging” of responsibilities and documentation associated with the two roles.

Sponsor plus Investigator

- Dr. Watson holds an IND.
- Dr. Moreau, a colleague at the same institution, is Principal Investigator of the protocol conducted under Dr. Watson's IND.
- Dr. Watson must fulfill all sponsor obligations described under 21 CFR 312
- Dr. Moreau must fulfill all investigator obligations described under 21 CFR 312
- Challenges in this scenario may include informal sponsor/investigator interactions that are not well documented, and institutional hierarchies or structures that do not align with respective roles of sponsor and investigator.

Sponsor plus multiple Investigators

- Dr. Zhivago holds an IND and is Principal Investigator of the protocol under that IND at his own institution.
- Dr. Frankenstein and Dr. No, two researchers at separate academic research centers, are Principal Investigators of the protocol under Dr. Zhivago's IND at their respective institutions.
- Dr. Zhivago must fulfill all sponsor obligations described under 21 CFR 312.
- Dr. Zhivago, Dr. Frankenstein, and Dr. No must fulfill all investigator obligations described under 21 CFR 312.
- Challenges in this scenario may include having sufficient resources to structure and oversee a multi-site study.

Sponsor Responsibility Workgroups

- Safety Review and Reporting
- Monitoring
- Selecting and Informing Investigators
- Reporting IND Activity
- Investigational Product Accountability

Exercise: Safety Review and Reporting

Sponsor responsibilities for safety review and reporting include:

- Review drug safety and efficacy data as it is received
- Notify FDA of new safety/risk information
- Notify investigators of new safety/risk information
- Discontinue study if investigational product presents unreasonable and significant risk to subjects

Safety Review and Reporting: Case 1

Dr. Jekyll (Sponsor-Investigator) determines that an adverse event is serious, unexpected, and related to the study drug.

Recommendations include:

- process and documentation for review/assessment of individual AEs
- process and documentation for review/assessment of cumulative AEs (line listings)
- process for preparation and submission of IND Safety Reports
- documentation of all correspondence with FDA
- understanding of IND reporting requirements vs. IRB requirements
- Sponsor-Investigator always named on 1571 as responsible for safety oversight

Safety Review and Reporting: Case 2

Dr. Moreau (Investigator conducting a clinical trial under Dr. Watson's IND) determines that an adverse event is serious, unexpected, and related to the study drug.

Recommendations for Sponsor include:

- process for prompt Sponsor notification of all SAEs
- documentation of both Investigator's and Sponsor's assessment of SAE
- process for preparation and submission of IND Safety Reports
- documentation of IND Safety Report submitted to Investigator
- documentation of all correspondence with FDA

Safety Review and Reporting: Case 3

Dr. No (one of multiple Investigators conducting a clinical trial under Dr. Zhivago's IND) determines that an adverse event is serious, unexpected, and related to the study drug.

Recommendations in Cases 1 and 2 apply.

Additional recommendations for Sponsor include:

- process/forms for consistent notification by Investigators to Sponsor
- site manual with reporting instructions for Investigators (must include timelines allowing Sponsor to meet FDA requirements)
- process for distribution of IND Safety Reports to all Investigators

Exercise: Monitoring

Sponsor responsibilities for monitoring include:

- Select monitors qualified by training and experience
- Monitor the progress of all clinical investigations under the IND
- Ensure investigation is conducted in accordance with protocol, investigator statement (1572), and regulations
- Secure compliance or discontinue investigator participation if non-compliance is identified

Monitoring: Case 1

A. Dr. Jekyll (Sponsor-Investigator) must arrange protocol monitoring.

B. The monitor discovers that two participants received an incorrect dose of study drug.

Recommendations include:

- qualified monitor <u>independent</u> of research team
- frequency and standards for monitoring (DSMP)
- review of monitoring reports
- documentation of investigation, root cause analysis, corrective and preventative actions (CAPA), FDA reporting as applicable
- Sponsor-Investigator always named on 1571 as responsible for monitoring

Monitoring: Case 2

A. Dr. Watson (Sponsor of an IND under which a colleague at the same institution is conducting a clinical trial) must arrange monitoring.

B. The monitor discovers that two participants received an incorrect dose of study drug.

Recommendations in Case 1 apply.

Additional recommendations include:

- review of Investigator's documentation, reporting, and CAPA as applicable
- may require copy of Investigator's report to IRB or other entities
- may require additional CAPA plan

Monitoring: Case 3

A. Dr. Zhivago (Sponsor of an IND under which Investigators at other institutions are conducting a clinical trial) must arrange protocol monitoring.

B. The monitor discovers that two participants at Dr. No's site received an incorrect dose of study drug.

Recommendations in Cases 1 and 2 apply.

<u>Additional</u> recommendations include:

- more extensive planning and budget for external site monitoring
- may specify additional requirements in protocol or site manual, such as forms for Investigator reporting to Sponsor; required reporting to IRB; etc.

Exercise: Selecting/Informing Investigators

Sponsor responsibilities for selecting and informing investigators include:

- Select investigators qualified by training and experience
- Obtain Form FDA 1572 and financial disclosure information
- Give each participating investigator an investigator brochure, except individual Sponsor-Investigator
- Provide investigators with necessary information to conduct study

Selecting/Informing Investigators: Case 1

A. Dr. Jekyll (Sponsor-Investigator) must be qualified to conduct the study.

B. Dr. Jekyll must have sufficient information to conduct the study.

Recommendations include:

- CV and medical license on file
- Form FDA 1572
- financial disclosure for all individuals named on 1572

Selecting/Informing Investigators: Case 2

A. Dr. Moreau (Investigator) must be qualified to conduct the study.

B. Dr. Watson (Sponsor of the IND under which Dr. Moreau is conducting a clinical trial) must provide Dr. Moreau with sufficient information to conduct the study.

Recommendations include:

- standard for Investigator information to be collected/assessed
- Investigator's CV and medical license on file
- Form FDA 1572 for Investigator; financial disclosure for all individuals on 1572
- Investigator's Brochure
- documented communication regarding protocol changes (must be approved by Sponsor) and new safety information

Selecting/Informing Investigators: Case 3

A. Dr. Frankenstein and Dr. No (Investigators at separate sites who are conducting clinical trials under an IND held by Dr. Zhivago) must be qualified to conduct the study.

B. Dr. Zhivago must provide Investigators with sufficient information to conduct the study.

Recommendations in Cases 1 and 2 apply.

Additional recommendations include:

- process and documentation for Investigator/site qualification
- site manual; standardized CRFs and reporting methods
- documentation of Investigator/site training and ongoing communication (e.g., conference call minutes)
- protocol flexibility to accommodate local standard practices

Exercise: Reporting IND Activity

Sponsor responsibilities for reporting IND activity include:

- Report to FDA on all protocols and study sites under IND
- Submit protocol changes that significantly affect subject safety, scope of investigation, or scientific quality of the study
- Submit new protocols or new investigators
- Submit IND safety reports and other safety information reflecting all use of investigational product
- Submit annual reports including progress of investigations at all study sites

Reporting IND Activity: Case 1

Dr. Jekyll (Sponsor-Investigator) holds an IND that has been in effect for one year. Interim data show an unexpected number of adverse events in one cohort of study participants, so she has determined that dosage of study drug for this cohort must be decreased.

Recommendations include:

- process to track IND “in effect” dates and reporting due dates
- process and documentation for review/assessment of cumulative study data (safety, efficacy, interim results)
- IND annual report to FDA
- protocol amendment submitted to FDA with description of changes and rationale

Reporting IND Activity: Case 2

Dr. Watson (Sponsor) holds an IND that has been in effect for one year. Interim data show an unexpected number of adverse events in one cohort of study participants, so she has determined that dosage of study drug for this cohort must be decreased.

Recommendations from Case 1 apply.

Additional recommendations include:

- process to collect and review data from Dr. Moreau (Investigator conducting clinical trial under Dr. Watson's IND)

Reporting IND Activity: Case 3

Dr. Zhivago (Sponsor) holds an IND that has been in effect for one year. Interim data show an unexpected number of adverse events in one cohort of study participants, so he has determined that dosage of study drug for this cohort must be decreased.

Recommendations from Cases 1 and 2 apply.

Additional recommendations include:

- consistent data collection and submission from all Investigators/sites conducting clinical trials under Dr. Zhivago's IND
- incorporation of data from multiple sites into comprehensive data set(s) for review

Exercise: Investigational Product

Sponsor responsibilities for investigational product include:

- Provide investigational product only to participating investigators
- Assure return of unused investigational product, or authorize alternative disposition
- Maintain records of product receipt, shipment, other disposition

Investigational Product: Case 1

Dr. Jekyll (Sponsor-Investigator) hears these two statements from a participant in a study involving long-term use of an investigational oral drug.

> "I think I took most of my medicine on time, but I dropped a couple of pills on the floor last week and threw them away."
>
> "I'm spending the winter in Arizona. Can you send my medicine to my doctor there?"

Recommendations include:

- drug accountability included in monitoring
- documentation of drug disposition outside of Sponsor's control
- study drug provided only to participating investigators
- NOTE: additional Investigator requirements may apply in this situation but should not be confused with Sponsor obligations.

Investigational Product: Case 2

Dr. Watson holds an IND for a drug that is manufactured and sent to the site by a pharmaceutical company. A company representative asks two questions:

> "Are you sure you sent that expired batch of drug back to us? I thought your pharmacy destroyed it on site."
>
> "A doctor at your site is conducting a different study for us, and his drug shipment got delayed. Can you transfer the drug from your stock to this other study for a patient tomorrow?"

Recommendations include:

- procedure for destruction or disposition of expired drug
- drug accountability logs and shipping records
- chain of custody document
- documented correspondence between manufacturer and Sponsor and between Sponsor and pharmacy

Investigational Product: Case 3

Dr. Zhivago (Sponsor of IND with multicenter study) receives these questions from Investigators at other sites conducting the clinical trial.

> "Most of our sponsors have our pharmacy destroy leftover study drug on-site. Do we really have to send it back to you?"
>
> "Our pharmacy got fifty drug shipments in the last three days, and they're losing track of everything! Can you help them figure it out?"

Recommendations include:

- procedure for destruction or disposition of expired drug
- review of local pharmacy drug destruction SOP
- maintenance of complete shipping records identifying drug product, batch/lot numbers, quantity, etc.
- confirmation of appropriate drug allocation, as needed

Questions:

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