IRB and REGULATORY DOCUMENTATION

Presented by:

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Introduction

This seminar is intended to help CTN affiliated research staff improve IRB communications through an increased understanding of the principles behind IRB expectations and regulatory requirements. Site regulatory requirements will also be discussed.

Questions and comments are welcome!
Simply press *1 on your telephone.

Introductory Polling Questions

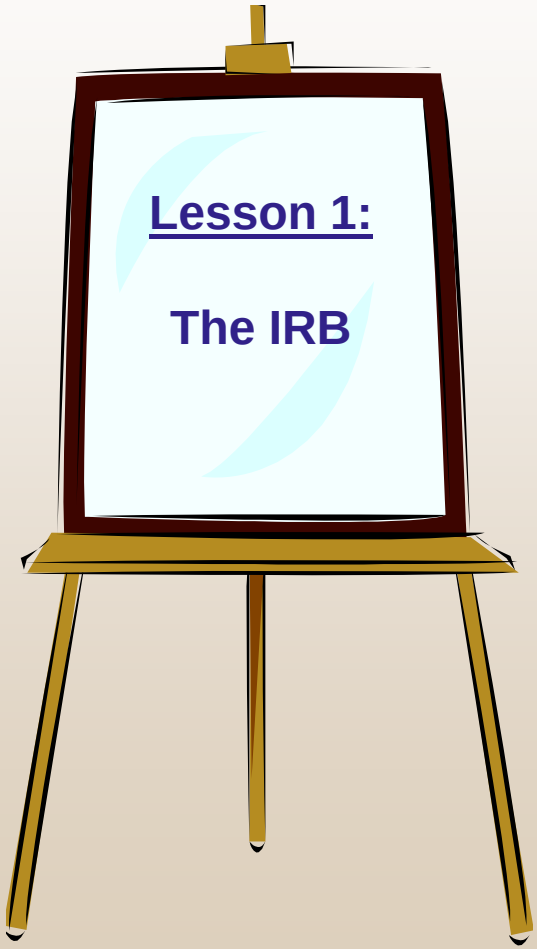
Questions and comments are welcome!
Simply press *1 on your telephone.

Training Outline

- Lesson 1: Institutional Review Board (IRB)
  - Role of an IRB
  - Expectations for IRB submissions for approval
- Lesson 2: Regulatory Documentation
  - Regulatory requirements
  - Clarification on accurate regulatory document completion

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board



Questions and comments are welcome!
Simply press *1 on your telephone.


HOW THE IRB MEMBERS SEE THEMSELVES:
THE BELMONT REPORT
45 CFR 46
APPROVED
SPONSOR
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Don Mayne

Lesson 1: Institutional Review Board

Investigators may see the IRB differently…

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

"The panels, known as Institutional Review Boards, are required at all institutions that receive research money from any one of 17 federal agencies and are charged with signing off in advance on almost all studies that involve a living person, whether a former president of the United States or your own grandmother. This results, critics say, in unnecessary and sometimes absurd demands."

As Ethics Panels Expand Grip, No Field Is Off Limits
Patricia Cohen, February 28, 2007

Lesson 1: Institutional Review Board

What's An IRB?

- Protects the rights and welfare of human subjects
- Institutions engaged in research involving human subjects must establish an IRB to review and approve the research

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- The Composition of the IRB
  - At lease five members, with diverse backgrounds to promote complete and adequate review of research
  - Member of both sexes
  - At least one member whose primary concerns are in the scientific area
  - At least one member whose primary concerns are in nonscientific areas.

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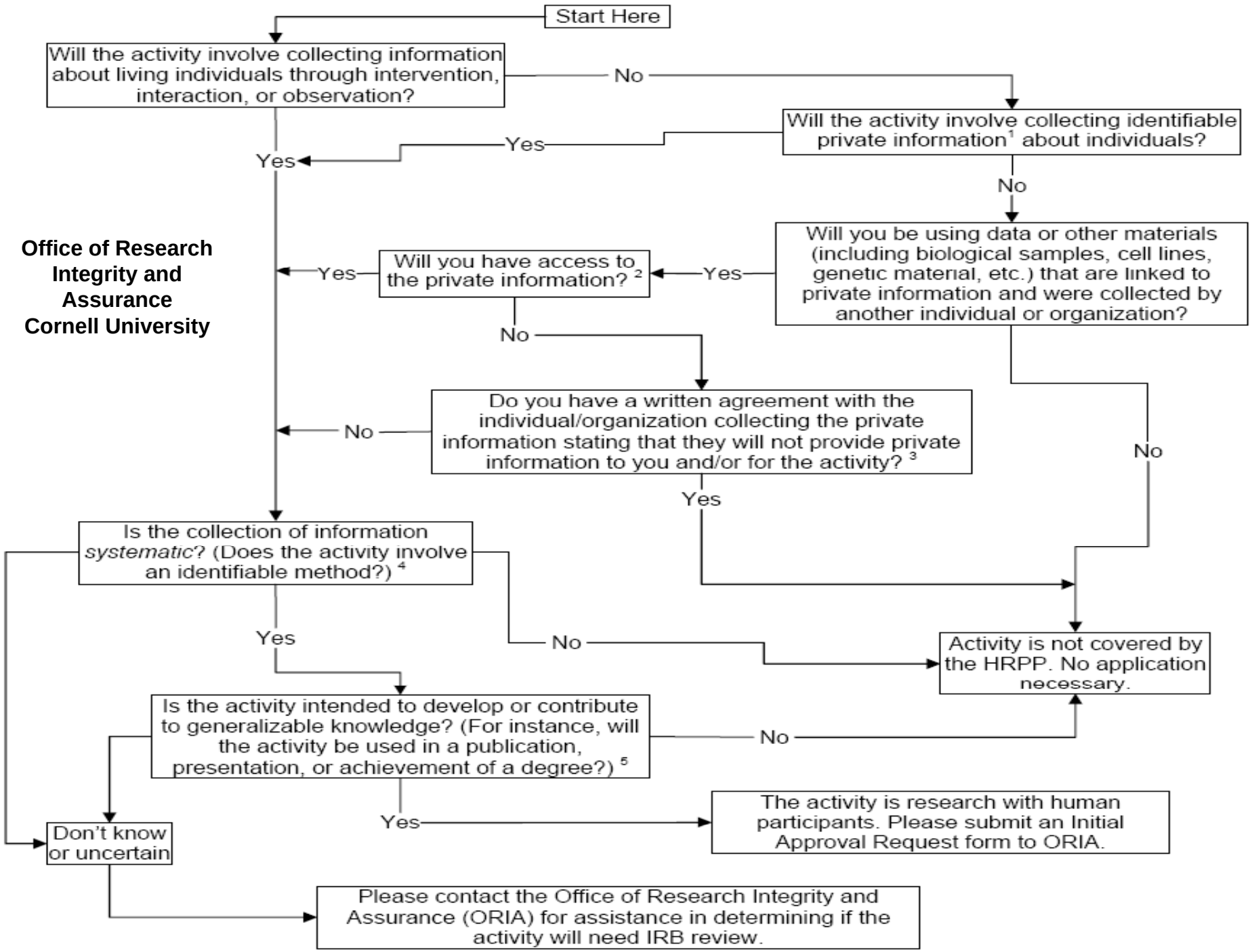

Office of Research Integrity and Assurance
Cornell University

Lesson 1: Institutional Review Board

- Central IRB vs. Local IRB
  - Advantages of each
  - Local IRB must relinquish oversight responsibilities to the Central IRB

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

"Wide variation in standards applied to review and approval of IRB applications. The study was designed to be qualified under U.S. government regulations for expedited review."

Impact of Institutional Review Board Practice Variation on Observational Health Services Research Lee A. Green, Julie C. Lowery, Christine P. Kowalski, and Leon Wyszewianski; Health Services Research 41:1 (February 2006)

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

"Conclusions Several features of the IRB system as currently configured impose costly burdens of administrative activity and delay on observational health services research studies, and paradoxically decrease protection of human subjects. Central review with local opt-out, cooperative review, or a system of peer review could reduce costs and improve protection of human subjects."

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Lesson 1: Institutional Review Board

- Working with Multiple IRBs
  - In studies that require multiple IRB reviews for a given site (e.g. within CTP and RRTC IRBs) the problems of workload and time pressure are amplified
  - Study sites requiring multiple IRB reviews may also be required to reconcile findings from IRB's review

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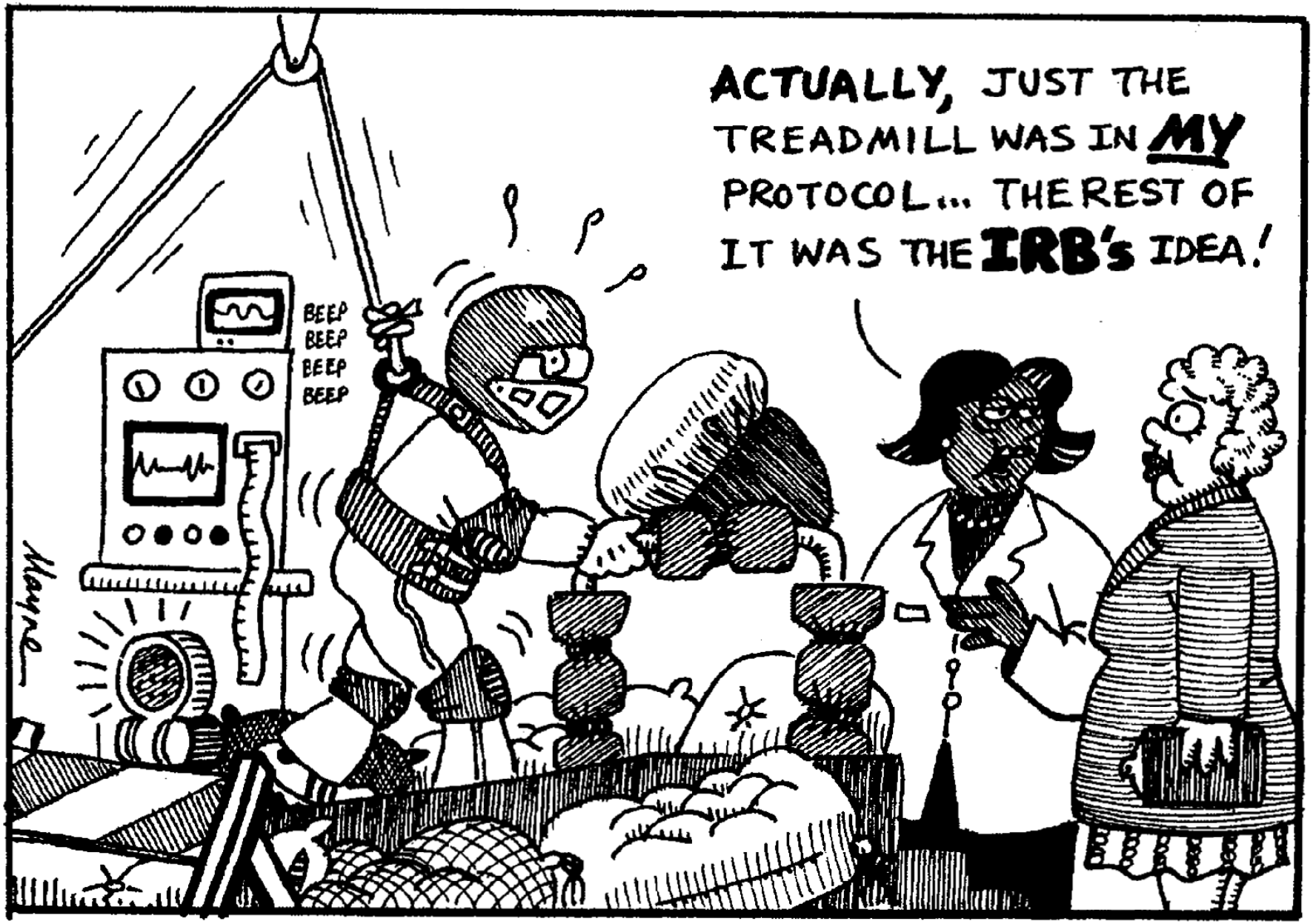


Lesson 1: Institutional Review Board

- The Requirements of the IRB (1)
  - Identify and assess potential risks and anticipated benefits of the research.
  - Determine that risks are minimized
  - Review the research design
  - Ensure the safeguards for the selection of human subjects

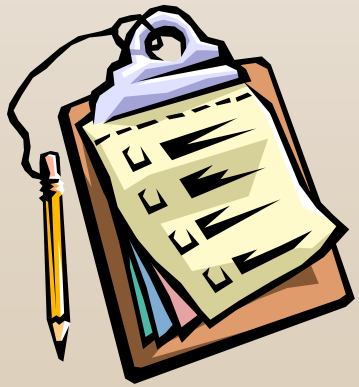
Lesson 1: Institutional Review Board

- The Requirements of the IRB (2)
  - Ensure that all information collected during the research is monitored and does not invade subject's privacy and confidentiality
  - Review the informed consent process
  - Assess the qualifications of the principal investigator

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- IRBs base their reviews on…
  - Codes of research ethics and Federal regulations
  - Relevant guidance documents from OHRP/FDA
  - Institutional policies
  - IRB policies/procedures
  - Rely on expertise from board members



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Lesson 1: Institutional Review Board

- The Authority of the IRB
  - Approve Research
  - Disapprove Research
  - Modify Research
  - Conduct continuing reviews
  - Observe/Verify Changes
  - Suspend or terminate approval
  - Observe consent process and research procedures

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Polling Questions

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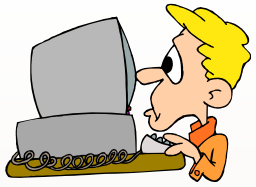

Polling Answers

- True or False? The IRB's job is to make sure that all risks to study participants are eliminated.
  - *Answer: False*
- True or False? IRBs use the same guidance in reviewing research from one institution to the other.
  - *Answer: True*
- True or False? IRBs must modify research before an application is approved.
  - *Answer: False*

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- Types of Submissions
  - Initial Review
  - Continuing Review
  - Amendments or Modifications
  - Reports

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- Responsibilities of Principal Investigator
  - Provide complete description of the proposed research (protocol),
  - Supply samples of the Informed Consent documents must be included with protocol
  - Provide all research recruitment materials (brochures, radio and/or television advertisements)

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- Responsibilities of Principal Investigator (2)
  - Submit study safety information (Adverse Events and Serious Adverse Events)
  - Report progress of the research no less than once per year
  - Obtain informed consent before human subjects are involved in research
  - Comply with all IRB decisions, conditions, and requirements

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- The CTN and Behavioral Research Issues
  - We often think of research as medical, however, due to the sensitive nature of substance abuse and NIDA research, we must look closely at the following issues when applying federal laws/regulations:
  - Psychological/Social Risks
  - Deception
  - Vulnerable Subjects
  - Privacy and Confidentiality
  - Study Methods
  - Quality of Life Issues

Lesson 1: Institutional Review Board

- Some final thoughts to consider…
  - IRBs are required to have representation from a scientist, but no scientist understands all types of science
  - Some studies may be reviewed by non-scientists, or by scientists from different fields than the investigator
  - In cutting-edge research the IRB will always be at a disadvantage in understanding the research they are reviewing

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- Strategies for IRB Submissions (1)
  - If the nature of the research is known to be complex, talk with the IRB BEFORE initial submission
  - If after initial review more questions are raised or the IRB defers action, talk with the IRB before the subsequent submission

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- Strategies for IRB Submissions (2)
  - The information that the IRB is approving should be unambiguous and concise
    - USE LAY LANGUAGE
    - Clearly describe how your procedures will work
  - Submit all documents requiring approval together in one packet
    - Keep similar research elements together

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 1: Institutional Review Board

- Lead node efforts to facilitate IRB review
  - Start early in obtaining IRB approval
  - Determine the level or review burden participating sites will have during the site selection process
  - Work with NIDA and make them aware of progress in seeking IRB approval

Questions and comments are welcome!
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Lesson 1: Institutional Review Board

BOTTOM LINE QUESTION:

Which would you rather do…. Spend two hours clarifying your procedures for submission OR spend two months clarifying procedures with IRB as a result of that time not spent?

Questions and comments are welcome!
Simply press *1 on your telephone.

Polling Questions

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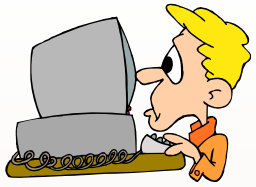

Polling Answers

- True or False? Behavioral are reviewed less stringently by IRBs because they have less risk to participants.
  - *Answer: False*
- True or False? IRBs must staff review committees with scientists in all areas of research.
  - *Answer: False*
- True or False? Corresponding with the IRB before a submission will bias the review.
  - *Answer: False*

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

- Required regulatory documents
- Copy to EMMES to maintain the CCC regulatory files
- Copy in the site regulatory binder
  - Some documents are only in the site binder

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

- Site Binder & Submitted to the CCC
  - Investigator Agreement
    - CV's for each investigator listed on the Investigator's Agreement
    - Appropriate licenses for everyone listed on the Investigator Agreement per local regulations
  - Financial disclosure certifications
    - For everyone listed on the Investigator Agreement
  - IRB Protocol Approval
  - IRB Consent Approval
  - Other IRB Approvals (e.g. Advertising materials)
  - Federal Wide Assurance Number and Expiration Date
  - Signature Sheet and Delegation of Responsibility Log
    - Updated when staff changes occur
  - Protocol Signature Page
  - Certifications for Human Subject Protection Training
  - Clinical laboratory certification and normal ranges

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

- Not forwarded to the CCC but required in site binder:
  - Site Visit/Monitoring Log
  - Current and all previous (if necessary) copies of the IRB approved protocol
  - Shipping Records (for study supplies)
  - Staff Training certificates/documents
  - Waivers for any protocol procedures/items IRB will not approve
  - IRB Roster (if available)
  - Safety reports from this site
  - SAE summaries from other participating sites
  - Other documentation per protocol

Lesson 2: Regulatory Documentation

- Regulatory documents with specific instructions:
  - Investigator Agreement
  - Financial Disclosure
  - Protocol Signature Page
  - CV's
  - Signature Sheet and Delegation of Responsibility Log

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

- Investigator Agreement

  - Used in lieu of the FDA Form 1572
  - Template from the CCC should be completed
    - Send original to the CCC
    - Keep a copy at the site
  - Any time the information on the form changes, a new copy must be submitted to the CCC

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

- Investigator's Agreement and FDA Form 1572
  - Investigator's Agreement required for non-IND clinical research
  - The FDA Form 1572 is required for clinical research involving new investigational drugs

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

- NIDA CTN Investigator Agreement (IA)
  - Specific Instructions

Questions and comments are welcome!
Simply press *1 on your telephone.

NIDA-NDAT CTN Clinical Coordinating Center (CCC) **Investigator Agreement for NON-IND Studies**	Version 3.0 / February 2008 **Note:** Investigators participating in a CTN research study must submit a completed, signed/dated Investigator Agreement to the NIDA-NDAT Clinical Coordinating Center (CCC).

1. Name and Address of Investigator who is the responsible leader of the research team.

2. Education, Training, and Experience that qualifies the investigator as an expert in the field of this clinical investigation. One of the following is attached

   ☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. Name and Address of all facilities where activities will be conducted in support of the study.

4. Name and Address of all clinical laboratory facilities to be used in the study.

5. Name and Address of the Institutional Review Board (IRB) that is responsible for review and approval of the study.

6. Names of Sub-investigator(s) (e.g. key research staff) who will be assisting with the conduct of the study.

7. Education, Training, and Experience that qualifies the Sub-investigator(s) as expert(s) in the field of this clinical investigation. One of the following is attached

   ☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

8. Name and study number of the protocol(s) to be conducted by the investigator.

9. Commitments:

- I agree to conduct this study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the Lead Node, NIDA-NDAT CCC, and my institutional review board (IRB), except when necessary to protect the safety, rights or welfare of research participants.
- I agree to personally conduct or supervise the described study.
- I agree to inform research participants that the interventions are investigational.
- I will ensure that federal, state, and local requirements for obtaining informed consent and IRB review and approval are met.
- I agree to report to the Lead Node, NIDA-NDAT CCC, and my IRB all serious adverse experiences in accordance with the protocol and federal, state, and local requirements, as applicable.
- I will ensure that all research staff assisting in the conduct of the study are informed of their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with federal, state, and local requirements and to make those records available for inspection according to federal, state, and local requirements.
- I will ensure that an IRB that complies with federal, state, and local requirements will be responsible for the initial and continuing review and approval of the study. 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 research participants.
- I agree to comply with all requirements regarding obligations of clinical investigators and all other pertinent federal, state, and local requirements.

Instructions for completing Investigator Agreement Form

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae documents as described, in sections 2 and 7.
3. Sign and date below.
4. Provide addresses for all locations where study activities are conducted, including pharmacies.
5. Forward ORIGINAL completed form and attachments(s) to NIDA-NDAT CCC. Forward a COPY of the completed form and attachments(s) to the Lead Node. Retain a COPY of the completed form and attachments(s) at the Community Treatment Program (CTP).
6. Revise this form as and when investigators and Sub-Investigators are added/ removed from the study or a change to study facility is made.

10. Signature of Investigator:	Date:

Lesson 2: Regulatory Documentation

- Investigator Agreement (IA)
  - Box 1
  - Name and address of site PI
  - Person directly responsible for overseeing site study conduct
  - PI on the IA will be at the site seeing participants and overseeing and directly responsible for research staff activities
  - Responsible for signing all other documents committing the site to study activities

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

(continued)

- Investigator Agreement (IA)
  - Box 2
  - Name and address of the physical facility in which the study activities will be conducted
  - May be the same or a different address than in Box 1
  - Multiple locations must list each location

Lesson 2: Regulatory Documentation

(continued)

- Investigator Agreement (IA)
  - Box 4
    - Names of sub investigators
    - Key personnel assisting in study oversight, sharing responsibility for conduct of the study
    - Involved in decision making regarding study conduct – all staff should not be listed
  - Box 7
    - Signature should match name in Box 1

Lesson 2: Regulatory Documentation

- Financial Disclosure
  - Each investigator/sub-investigator listed on the Investigator Agreement must complete the financial Disclosure form provided by the CCC
  - Principal Investigator on Financial Disclosure is the person listed in box 1 of the IA
  - Required name and signature at the bottom = investigator/sub-investigator whose information is being disclosed

Questions and comments are welcome!
Simply press *1 on your telephone.

NIDA-Clinical Coordinating Center (CCC)

Disclosure of Financial Interests Related to Sponsored Research

Protocol Number Title: [insert protocol title]

Sponsor of the Study: NIDA Node/CTP: [insert node/CTP]

Principal Investigator: [insert investigator's name]

As a clinical investigator in the above study, I certify the accuracy of the following disclosures as required under 21 CFR Part 54, with the understanding that I am certifying not only for myself, but also for my spouse and for each dependent child of mine. I agree to maintain detailed supporting documentation about my financial interests in this study, including any interests in the product itself, its manufacturer and any parent companies, to update this information when necessary, and to provided sufficient accurate information to the study Sponsor upon request.

Please mark the applicable box for each item:

No	Yes	
☐	☐	I have entered into a financial arrangement with the study Sponsor, whereby the value of the compensation or an equity interest could be affected by the outcome of the study, or the compensation is tied to sales of the product, such as royalty interest. [21 CFR 54.4(a)(3)(i)]
☐	☐	I have or will receive significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, a retainer for ongoing consultation, or honoraria during the time of the study and for 1 year following the completion of the study. [21 CFR 54.4(a)(3)(ii)] This is defined as payments made to my institution or me to support activities that have a monetary value or more than $25,000. ***This does not include the costs of conducting the clinical study or other clinical studies.***
☐	☐	I have a proprietary interest in the tested product, meaning property or other financial interest including, but not limited to, a patent, trademark, copyright or licensing agreement. [21 CFR 54.4(a)(3)(iii)]
☐	☐	I have a significant equity interest in the Sponsor of this study. [21 CFR 54.4(a)(3)(iv)] This would include any ownership interest, stock options, or other financial interest that cannot be readily determined through reference to public prices (like a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000, during the study or within 1 year after the study is completed.

Note: For the purposes of this regulation, a clinical investigator means a listed or identified investigator or subinvestigator who actually conducts and take responsibility for an investigation, i.e., under whose immediate direction the test article is administered or dispensed to a subject or who is directly involved in the evaluation of research subjects. It should be noted that hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data are not meant to be included under the definition of clinical investigator.

For FDA guidance, see http://www.fda.gov/oc/guidance/financialdis.html

_____ _____

Signature of Investigator Date

_____

Printed/typed name of Investigator

Lesson 2: Regulatory Documentation

- Protocol Signature Page
  - All investigators/sub-investigators listed on the site's Investigator Agreement must sign the protocol signature page for the IRB approved version of the protocol under which the site conducts study procedures

Lesson 2: Regulatory Documentation

- CV's
  - Each investigator/sub-investigator listed on the Investigator Agreement must submit a CV current within two years of the start of the study and should be kept current within two years of the required CV signature date until study end

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

- Signature Sheet and Delegation of Responsibility Log
  - Header
  - Research Personnel
  - Protocol PI signature and date

Questions and comments are welcome!
Simply press *1 on your telephone.

Signature Sheet and Delegation of Responsibilities Log

Study Start Date:	**Page: ____ of ____**
Protocol: NIDA-CTN-	**Sponsor: National Institutes on Drug Abuse**
Protocol PI:	**Lead Node:**
Node: /Site(s):	**Indicate delegated duties by checking the appropriate boxes**

Research Personnel Printed Name/ Signature & Initials	Staff ID #	Role in Study	Dates of Study Involvement		Consent	Study Oversight	CRFs	Study Co-ordination	Study Assess-ments	Study Inter-vention	*Other: Specify
			Start	End							
					☐	☐	☐	☐	☐	☐	☐
					☐	☐	☐	☐	☐	☐	☐
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					☐	☐	☐	☐	☐	☐	☐

I verify the delegation of duties listed above

Protocol PI Signature/Date:_____

Signature required prior to CTP initiation

I verify that this log is complete and accurate

Protocol PI Signature/Date:_____

Signature required at study close-out

PLEASE MAINTAIN THIS LIST WITH YOUR STUDY FILES (see reverse side for instruction on document completion) Version 5a, 2/9/04

Questions and comments are welcome!
Simply press *1 on your telephone.

Lesson 2: Regulatory Documentation

- Header: Signature Sheet and Delegation of Responsibility Log
  - Study Start Date: Date of Endorsement from NIDA
  - Protocol
    - Include title of protocol and CTN Protocol number
  - Protocol PI
    - Name of the Investigator on record with the local IRB
  - Node: Name of node and/or node number

Lesson 2: Regulatory Documentation

(continued)

- Signature Sheet Header
  - Site: Name of site and/or site number
  - Page __ of __
    - First blank should indicate the page number, the second blank should not be completed until the study is closed out
  - Sponsor
    - National Institute on Drug Abuse
  - Lead Node
    - Name of the Node that is leading the study (usually where the lead investigator is)

Lesson 2: Regulatory Documentation

- Research Personnel: Signature Sheet and Delegation of Responsibility Log *(continued)*
  - List site staff conducting the study. Staff who do not interact with participants, regulatory documents or the data (accounting or business office personnel) should not be included on this document
  - Printed name
    - Top line, should be printed first and last name, letters after name, such as PhD, RN, etc, are not necessary, but are okay
  - Staff ID#
    - All staff members should be assigned an ID # by the Data and Statistical Center; it is usually a five-digit number

Lesson 2: Regulatory Documentation

- Research Personnel: Signature Sheet and Delegation of Responsibility Log *(continued)*
- Role in Study
  - Roles may be written out or abbreviated (e.g., medical clinician or MC, Research Associate or RA, Study Physician or SP, etc.).
  - Dates of Study Involvement:
    - Start date should be study start date or after - the end date should be completed when a staff member discontinues involvement in the study; when the study is closed out at the site, an end date should be filled in for all staff.
  - Boxes for Study Duties
    - Check off all boxes that represent tasks delegated by the Site PI to each individual, respectively

Lesson 2: Regulatory Documentation

- Protocol PI Signature and Date: Signature Sheet and Delegation of Responsibility Log
  - Signed and dated by Protocol PI on the line on the bottom left of the document prior to study initiation
  - The Similar line on the right should be signed and dated at the end of the study, and not before then

Lesson 2: Regulatory Documentation

- What do monitors look for?
  - Expiration dates
  - Updated FWA
    - Sometimes renewed prior to expiration
  - HSP training certificates
    - Current and past staff
  - Regulatory binder organization
    - CCC can offer advisement

Questions and comments are welcome!
Simply press *1 on your telephone.

Polling Questions

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Polling Answers

- Financial disclosure documents are required for all staff on the signature sheet and delegation of responsibility log.
  - False
    - Required for staff listed on the IA
- Some regulatory documents are only kept at the site and not sent to the CCC.
  - True
- What will happen if you use white out on a regulatory document or if you do not follow document completion directions, etc...
  - The document will be returned for resubmission

Questions and comments are welcome!
Simply press *1 on your telephone.

Summary of Training

- Lesson 1: Institutional Review Board (IRB)
  - Role of an IRB
  - Expectations for IRB submissions for approval
- Lesson 2: Regulatory Documentation
  - Regulatory requirements
  - Clarification on accurate regulatory document completion

Questions and comments are welcome!
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Handouts/Resources

- CCC Monitor's Regulatory documentation checklist
- Investigator Agreement template
- Financial disclosure template
- Signature Sheet and Delegation of Responsibility Log

Questions and comments are welcome!
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