NIH Clinical Trials Requirements, FORMS-E, and the Common Rule: What You Need to Know

November 27, 2017

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KEY CHANGES TO THE COMMON RULE 45 CFR 46

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Effective January 19, 2018

- *Possible* delay in implementation date until January 2019, except:
  - Certain exemptions
  - Elimination of continuing review
  - Eliminating IRB review of grant applications

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What's in a Name?

The Common Rule: Published in **1991** and codified in separate regulations by 15 Federal departments and agencies

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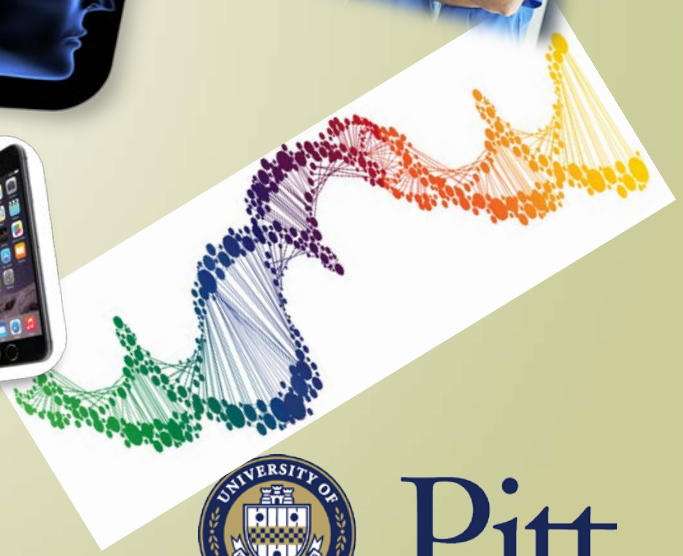
Why change it?

1991

2017



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Research

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. **THERE IS NO CHANGE IN THIS LANGUAGE BUT…**

New: Deems activities not to be research:

(1) Scholarly and journalistic activities that focus directly on the specific individuals about whom the info is collected: oral history, journalism, biography, legal criticism, legal research, and historical scholarship

(2) Public health surveillance activities limited to those conducted, supported, requested, ordered, required or authorized by a public health authority for public health importance (includes "timely situational awareness")

(3) Criminal justice or criminal investigational purposes

(4) Authorized activities in support of intelligence, homeland security, defense or other national security

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Human Subject

Current

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

New

Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

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Unidentifiable today. Identifiable tomorrow.

Identifiable: the identity of the subject is or may readily be ascertained by the investigator or associated with the [information][biospecimen]

Re-examine the meaning of “identifiable private information” and “identifiable biospecimen” within 1 year and then at least every 4 years after

- Addresses advances in technology and science

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CONTINUING REVIEW

Changes to Continuing Review

- Continuing review is being eliminated under the following circumstances
  - Studies approved through an expedited mechanism
  - Studies approved by the Full Board once subject interaction is complete
- Amendments and Reportable Events must still be submitted

Continuing Review – IRB Process

- **Decision made at next review (modification or renewal)**
  - Modifications cannot be submitted for the sole purpose of converting to a “no renewal” status
- **Annual notice to investigator**
  - Generated by system
  - Reminder to submit Modifications, Reportable Events, and Termination Reports

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INFORMED CONSENT

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Changes to Informed Consent

- Additions and changes to the General Requirements for Informed Consent
- Broad Consent
- Posting of consent forms for clinical trials
- Waivers and alterations of informed consent

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General Requirements for Informed Consent

- Reasonable person standard
- Concise and focused presentation of key information
  - Voluntary
  - Summary of research procedures
  - Risks
  - Benefits
- Working group formed to provide guidance

New Elements of Informed Consent

- Notice of future use of identifiable private information or identifiable biospecimens
  - Identifiers might be removed and the de-identified information or biospecimens could be used for future research without additional informed consent,

    or
  - The information or biospecimens will not be used or distributed for future research even if identifiers are removed

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New Elements of Informed Consent

If applicable:

- Biospecimens may result in commercial profit and whether the subjects will share in the profit or not
- Clinically relevant research results will (or will not) be returned to subjects
- Biospecimen research will include whole genome sequencing

Broad Consent

- Optional alternative to traditional informed consent
- Certain new exempt categories (7 and 8) added for administration of Broad Consent
- Used only for "storage, maintenance, and secondary research use of **identifiable** private information or **identifiable** biospecimens…"

- **We will not be implementing "Broad Consent" at this time**
- **Exemptions 7 and 8 will also not be implemented**

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Here's why…

Must be tracked:

- Who was asked
- What were they asked
- Did they say yes or no
- What biospecimens or data were collected under the broad consent
- What did it allow
- What did it limit

If refused:

- May be asked again in the future
- IRB cannot waive informed consent if a person refused broad consent for storage, maintenance and use of private identifiable information and identifiable biospecimens

Exemptions 7 and 8:

7: storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary use under limited IRB review

8: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use if certain criteria are met

Limited IRB Review §111(a)(8): broad consent must be obtained and documented, any changes made to the storage/maintenance of information/specimens must be adequate to protect privacy and confidentiality

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Screening, Recruiting, Determining Eligibility

An IRB may approve a protocol where an investigator will obtain information or biospecimens for screening, recruiting, or determining eligibility without informed consent:

- Information is obtained through oral or written communication with the prospective subject or LAR, or
- The investigator will obtain private identifiable information or identifiable biospecimens by accessing records or stored identifiable specimens

Effectively eliminates the need for the IRB to grant waivers for screening and recruitment, consistent with FDA regulations and HIPAA (preparatory to research)

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Documentation of Informed Consent

- Includes electronic formats as written informed consent. A copy must still be given
- Allows, specifically, consent forms to be read to the subject
- Waiver to obtain a signed informed consent still remains, a 3rd option is included for situations where obtaining written informed consent would be culturally inappropriate

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EXEMPTIONS

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Exemption 1 – Educational Exemption

What's new?

– Now must consider "adverse affects" on student learning of required educational content or on assessment of educators

Exemption 2 – Surveys/Interviews/Educational Tests/Public Observation ONLY

What's new?

- Projects collecting **sensitive** and **identifiable** data may be exempt after "limited IRB review" (for privacy/ confidentiality protections)
- Clarifies that the exemption **does not apply** to projects involving:
  - Interventions
  - Collection of biospecimens
  - Linking to additional personally-identifiable data
  - Children (except for educational tests or some public observations)

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Exemption 3 – Benign Behavioral Interventions

This exemption is completely new

- Limited to research with adults

What is a benign behavioral intervention?

- Brief in duration
- Harmless and painless
- Not physically invasive
- Not likely to have a significant adverse impact on subjects
- Not offensive or embarrassing

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Exemption 3 – Benign Behavioral Interventions

- Information is collected via
  - Verbal or written responses (surveys/interviews)
  - Data entry
  - Observation of subject (including audiovisual recording)
- Does not permit data collection via physical procedures
  - Physical sensors (e.g. blood pressure monitors, EEG, FitBits)
  - Minimally invasive procedures (e.g. blood draw or saliva collection)

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Exemption 3 – Benign Behavioral Interventions

- Must obtain "prospective agreement to the intervention and information collection"
- **No deception**, except where the subject is told that they will be unaware or misled about the nature or purposes of the research and they agree
  - Debriefing still encouraged
- "Limited IRB Review" required for projects collecting sensitive and identifiable data

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Examples

- Solving puzzles under various noise conditions
- Playing an economic game
- Being exposed to stimuli such as color, light or sound (at safe levels)
- Performing cognitive tasks

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Exemption 4 – Secondary Research Uses of Identifiable Private Information or Identifiable Biospecimens

What's new?

- No longer limited to retrospective data review
- Permits secondary use of identifiable protected health information (PHI) (with HIPAA privacy board review)

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Exemption 5 – Research and Demonstration Projects

- No longer limited to federally conducted research; can also be used for federally supports
- Must be posted on a Federal website or other approved location

Exemption 6: Taste and Food Quality Evaluation

This exemption was unchanged

- Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

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SINGLE IRB

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Requirement for Single IRB Review

U.S. institutions engaged in cooperative research must rely upon a single IRB for review

- Reviewing IRB named by the Federal Agency supporting the research or proposed by the lead institution
- May not be required if supporting Federal Agency or agency deems a single IRB inappropriate in a particular context
- Effective January 20, 2020

NOTE: NIH Single IRB requirement is effective January 25, 2018

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NIH Policy

- Expectation that “a single IRB of record will be used in the ethical review of non-exempt human subjects research protocols funded by NIH” that are multi-center
- Scope
  - All domestic sites of NIH-funded multi-site studies
  - Research supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program
  - Does not apply to career development, research training, or fellowship awards

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Authorization and Approval

- Applicant/Offeror must include a plan describing the single IRB of record and a statement that the study sites will adhere to the single IRB policy
  - Letters of support from study sites
  - Letter of support from Human Research Protection Office
- Applicant/Offeror must assure that the single IRB is “qualified to serve”

VERY IMPORTANT: Please don’t commit the Pitt IRB to serve in this capacity without speaking to us first

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Review Costs

- The primary activity of IRB review of the research protocol and template consent are covered by the grant's indirect costs.
- "Secondary" activities can be charged as direct costs with appropriate justification.
  - Includes site-specific considerations for all of the participating sites.
- Contact HRPO when formulating budget

Requesting Use of a Single IRB

- Contact us early in the process
  - letter of support in RFAs if requested
- Request forms under A-Z guidance
- Submit to irb.reliance@pitt.edu
- Approval by Institutional Official
- Execution of agreement
  - SMART IRB
  - IRBChoice

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Pitt as Reviewing IRB

- Normal submission through OSIRIS
- We will work with relying sites to negotiate agreement
- Relying sites supply “local context” information
- Our IRB issues a template consent for all sites
  - Consents will be watermarked once local required language is inserted

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PI/Research Team Responsibilities

- Assisting IRB with obtaining contact information from local IRBs
- Presenting study to all sites and addressing any issues identified
- Submitting study into OSIRIS
  - Complete workflow not yet developed
  - Site PI/study team will need access to system
- Following provisions of agreement

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Outside institution is Reviewing IRB

- A registration application is submitted through OSIRIS
- Research cannot begin until acknowledgement issued
- Only limited information is submitted to Pitt IRB
  - Time of continuing review
  - If the PI changes
  - If any procedure related to an ancillary review changes
  - If the Reviewing IRB makes a determination of serious or continuing non-compliance or an unanticipated risk to subjects or others

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PI/Research Team Responsibilities

- Complying with the reviewing IRB's policies and procedures
- Registering through OSIRIS
  - Ensures completion of other institutional requirements
  - Allows tracking of approved studies at institution
- Maintaining a current and accurate protocol file
  - Including correspondence from reviewing IRB
- Submit Reportable Events to reviewing IRB

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QUESTIONS?

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NIH Policy Changes

Good Clinical Practice (GCP) Training

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NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site | Saved Studies (0)

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 258,784 research studies in all 50 states and in 201 countries.

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.

Search (all fields optional)

Condition / Disease: e.g. breast cancer

Other Terms: e.g., NCT number, drug name, investigator name

Country:

Find a study to participate in | Search all studies

Advanced Search

Help | Studies by Topic | Studies on Map | Glossary

Patients and Families

Search for actively recruiting studies that you may be able to participate in or learn about new treatments that are being considered.

Researchers

Search the database to stay up to date on developments in your field, find collaborators, and identify unmet needs.

Learn more

Study Record Managers

Learn about registering studies and about submitting their results after study completion.

Learn more

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Policy & Compliance

- NIH Grants Policy Statement
- Notices of Policy Changes
- Compliance & Oversight

Select Policy Topics

- Animal Welfare
- Application Submission Policies
- Clinical Trial Requirements
  - Clinical Trial Definition
  - Why the Changes
  - Good Clinical Practice
  - Specific Funding Opportunities
  - New Form
  - Single IRB Policy
  - Protocol Template
  - Registration and Reporting
- NIH Funding Strategies
- Human Subjects Research

Clinical Trial Requirements for Grants and Contracts

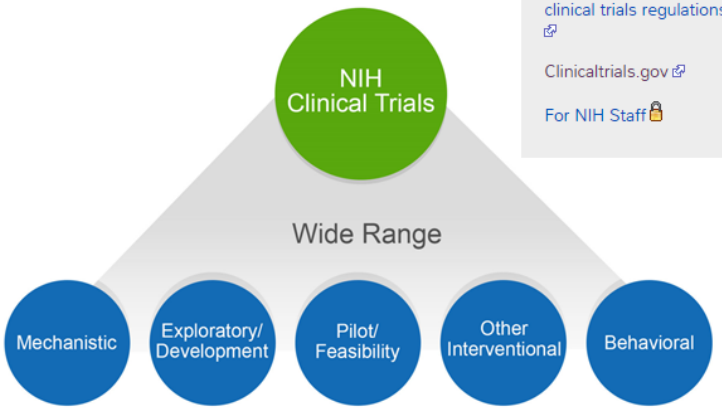
NIH is launching a series of initiatives that are rolling out in 2017-2018 to enhance the accountability and transparency of clinical research. These initiatives target key points along the whole clinical trial lifecycle from concept to results reporting. Learn more about these changes and how they will affect your research.

NIH Definition of a Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. Learn more

Your human subjects study may meet the NIH definition of a clinical trial.

FIND OUT HERE



Related Resources

- FAQs
- Training Resources
- Important Terms
- Research Involving Human Subjects
- ClinRegs: international clinical trials regulations
- Clinicaltrials.gov
- For NIH Staff

NIH Definition of a Clinical Trial

- A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

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Intervention

- **A manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.**

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Interventions include:

- Drugs, devices, biologics and procedures
- Delivery systems
- Strategies to change health-related behavior
- Treatment, prevention and diagnostic strategies

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A health related biomedical or behavioral outcome

- Physiological or biological parameters
- Psychological or neurodevelopmental parameters
- Disease processes
- Health-related behaviors
- Quality of life

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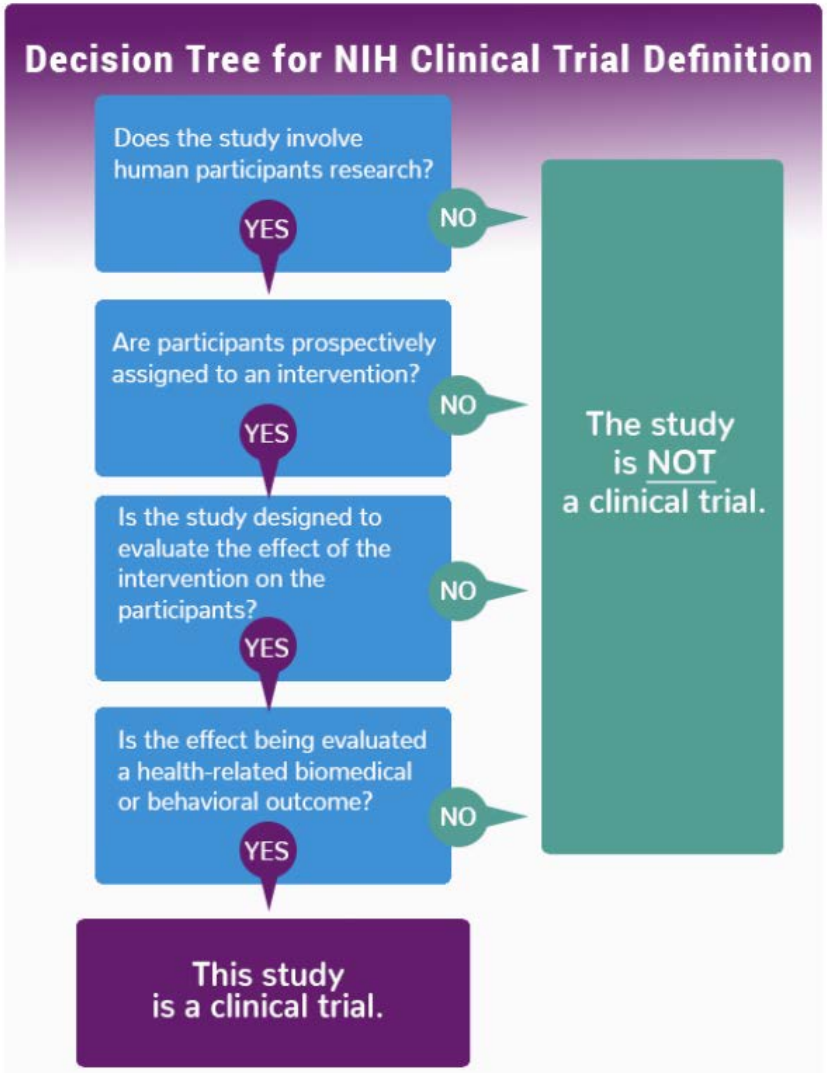
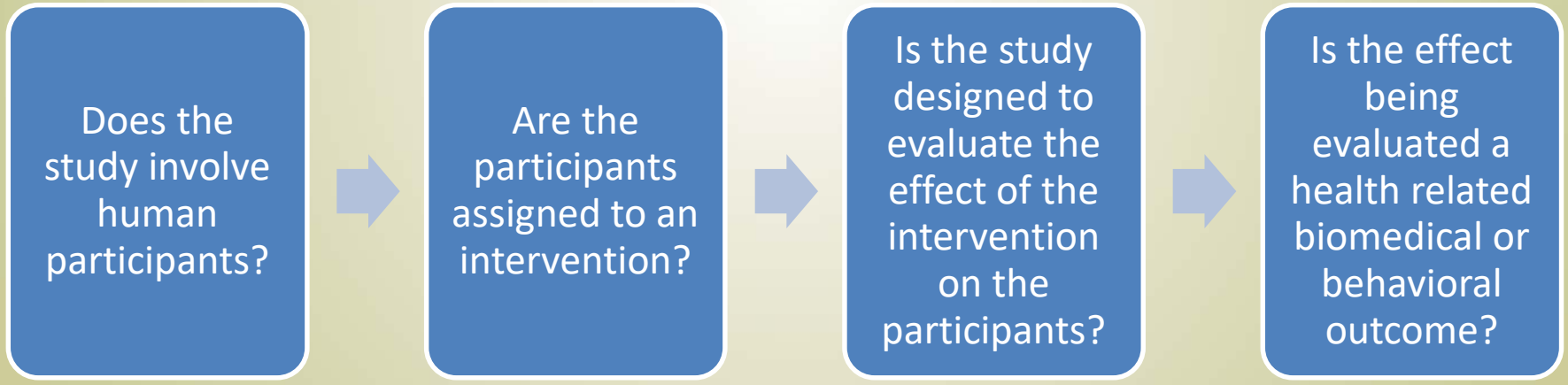

Decision Tree for NIH Clinical Trial Definition
Does the study involve human participants research?
YES
NO
Are participants prospectively assigned to an intervention?
YES
NO
Is the study designed to evaluate the effect of the intervention on the participants?
YES
NO
Is the effect being evaluated a health-related biomedical or behavioral outcome?
YES
NO
The study is NOT a clinical trial.
This study is a clinical trial.

The study involves the recruitment of research participants with disease x to receive an investigational drug. It is designed to assess whether there is a change in disease progression compared to baseline. There is no concurrent control in this study.



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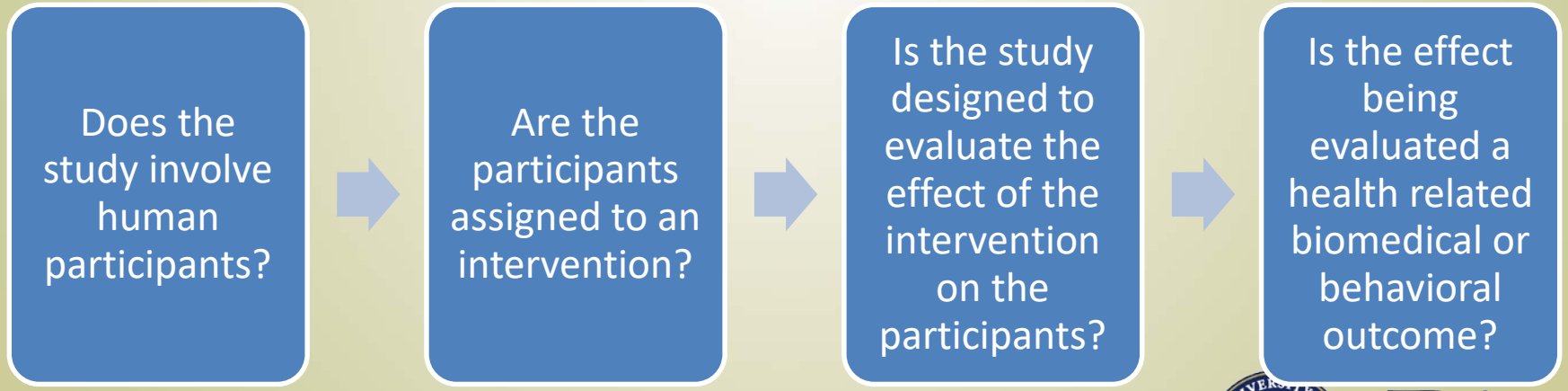
The study involves the recruitment of healthy controls who will be randomized to different durations of sleep deprivation (including no sleep deprivation as a control) and who will have stress hormones levels measured. It is designed to determine whether the levels of stress hormones in blood rise in response to different durations of sleep deprivation.



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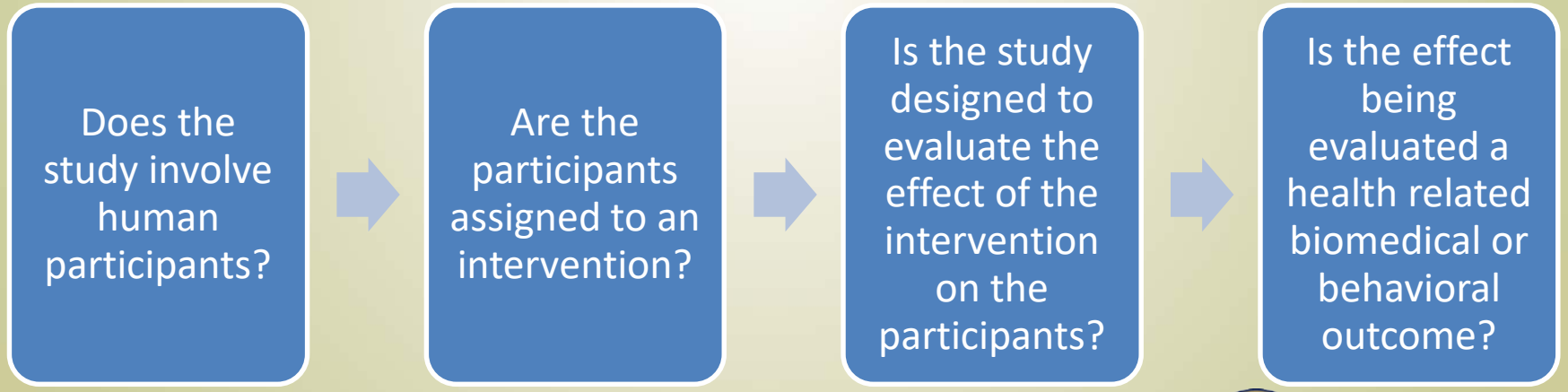
The study involves the recruitment of healthy controls volunteers to test a new behavioral intervention. It is designed to evaluate the acceptability of the intervention. The outcome is acceptability, not efficacy, of the intervention to the target providers and their patients.



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References and Useful Links

NIH Clinical Trial Requirements: https://grants.nih.gov/policy/clinical-trials.htm

NIH Clinical Trial Case Studies: https://grants.nih.gov/policy/clinical-trials/case-studies.htm

NIH Good Clinical Practice Training: https://grants.nih.gov/policy/clinical-trials/good-clinical-training.htm

Clinical Trials.gov: https://clinicaltrials.gov/

NIH Extramural Nexus: ExtramuralNexus@mail.nih.gov

Research Conduct and Compliance Events: http://www.rcco.pitt.edu/events

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Clinical Trial-Specific Funding Opportunity Announcements

- NIH applications/proposals involving clinical trials with **due dates on or after January 25, 2018** must be submitted to an FOA that explicitly states it will accept clinical trials.
- "Parent R01 Clinical Trial Required" and "Parent R21 Clinical Trial Required" FOAs will be published November 2017
- Some NIH Institutes and Centers may publish separate FOAs

https://grants.nih.gov/policy/clinical-trials/specific-funding-opportunities.htm

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Specific Clinical-Trial Review Criteria

- New review criteria questions for clinical trials that focus on rationale, study design, and include considerations for mechanistic studies
- Ensures key clinical-trial information is included in application, and that reviewers considering it.
- New review criteria questions will be in Section V. Application Review Information for FOAs that accept clinical trials

https://grants.nih.gov/policy/clinical-trials/specific-funding-opportunities.htm

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New NIH FORMS-E

- In effect for NIH applications due on or after **January 25, 2018**
- Most significant change is the new Human Subjects and Clinical Trial Information form
- Aligns with ClinicalTrials.gov (where possible) and positions the NIH for future data exchange with ClinicalTrials.gov

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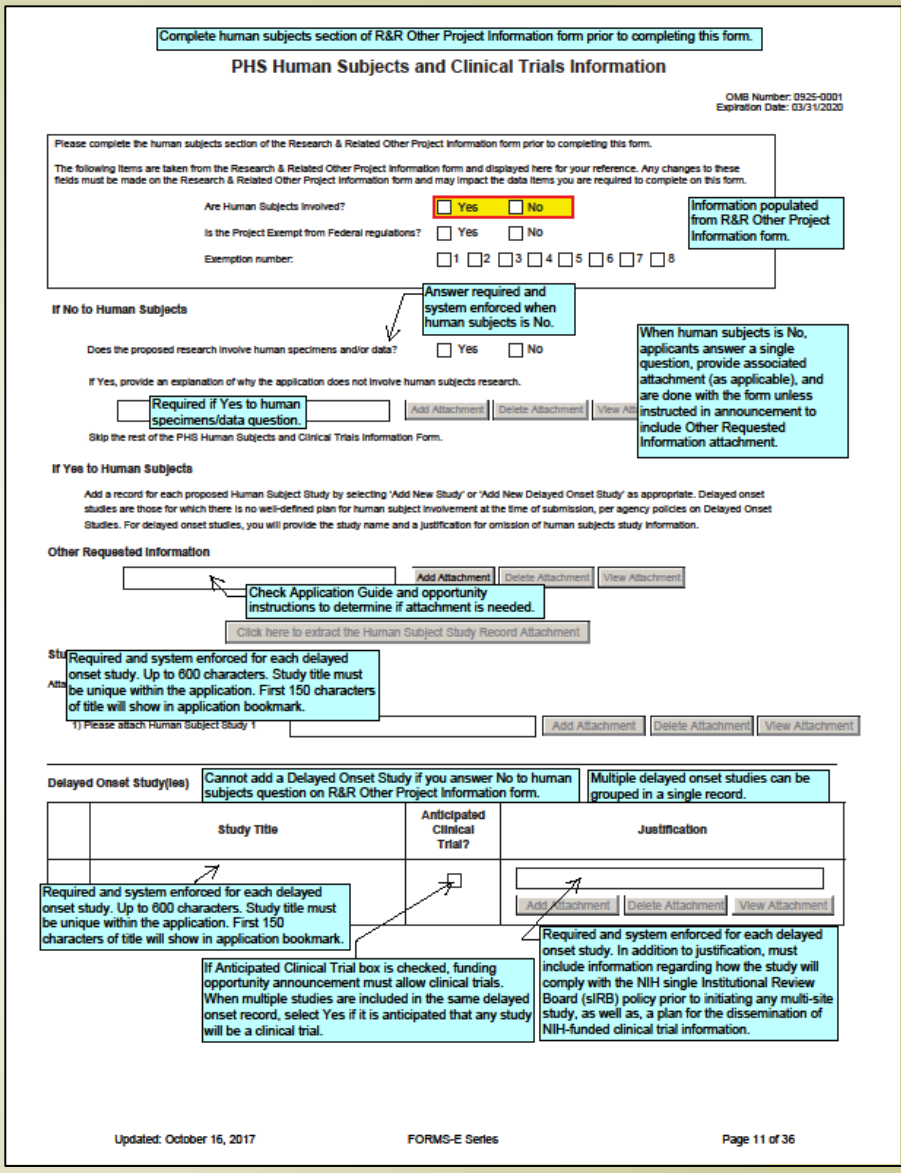
FORMS-E Application Package: Human Subjects and Clinical Trials Information (page 1 of 4)



Video tour of new form:
https://www.youtube.com/watch?v=nz9NWFhYOG8&list=PLOEUwSnjvqBJeHcb4yai7_fDnFZFPEmQK&index=1

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Clinical & Translational Science Institute (CTSI)

When you have questions about research, such as questions about changes to the forms described, CTSI can help.

- **CTSI helps:**
  - UPMC and Pitt faculty, staff, coordinators, investigators, students, residents, fellows, and others
- **CTSI assists with:**
  - Protocol development, implementation questions, recruitment assistance, understanding of funding opportunities, brainstorming, and more
  - Regulatory/research questions, statistical support, education/training, and more
- **CTSI collaborates with:**
  - Human Research Protections Office (HRPO), the Office of Sponsored Programs and others to ensure researchers are provided with guidance.

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Clinical & Translational Science Institute (CTSI)

CTSI Facilitators can assist with questions about and assistance needed for research projects:

RESEARCH FACILITATORS

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