Research Regulatory Reform Review or "May You Live in Interesting Times"

Adrienne Meyer, MPA, CIP

Assistant Director for Researcher Support

UW Human Subjects Division

ITHS | Institute of Translational Health Sciences

ACCELERATING RESEARCH. IMPROVING HEALTH.

Learning Objectives

By the end of this session, you will be able to:

- Recognize several key regulatory changes that have an impact on clinical trial research management.
- Explain how regulatory changes impact certain types of research studies.
- Recognize how to coordinate an approach to the regulatory changes as well as how to apply those changes into your clinical research.
- Review the resources available when managing regulatory aspects of research.

Increased Pressure for Return on Investment

"As part of its mission, NIH is responsible for exercising good stewardship of its multi-billion dollar public investment in clinical trials. The outcomes of these trials are vital for improving public health and advancing science, as they are used to identify the effects of medications and other healthcare interventions on people, some with life-threatening illnesses and conditions."

GAO Highlights

Highlights of GAO-16-304, a report to congressional committees

Why GAO Did This Study

In fiscal year 2014, NIH spent nearly $3.2 billion on clinical trials as part of its research activities. NIH's OD oversees the operations of 27 ICs to ensure that NIH's research portfolio is balanced, not unnecessarily duplicative, and utilizes cross-cutting research. In 2010, IOM made recommendations for clinical trials supported by NCI, one of NIH's ICs. In 2012, NIH was directed to conduct a review of the applicability of IOM's recommendations across all NIH ICs that conduct clinical trials.

A Joint Explanatory Statement accompanying a 2015 appropriations act included a provision for GAO to review how NIH applied the IOM recommendations. This report examines (1) the steps that NIH took, if any, to apply the IOM recommendations across its ICs other than the NCI, and (2) the extent to which NIH's OD uses data to oversee clinical trial activity across the ICs. GAO reviewed NIH documentation on the applicability of the IOM recommendations, data the OD uses to oversee clinical trial activity, and its process for using such data. GAO compared these to federal standards for internal control. GAO also interviewed NIH and IC officials, IOM officials, and stakeholders, such as a group representing researchers.

What GAO Recommends

GAO recommends that the NIH OD (1) finalize data on clinical trial activity that the OD needs to collect from ICs, and (2) establish and implement a process for using those data. HHS concurred with the recommendations.

View GAO-16-304. For more information, contact Linda Kohn at (202) 512-7114 or kohnl@gao.gov.

March 2016

NATIONAL INSTITUTES OF HEALTH

Additional Data Would Enhance the Stewardship of Clinical Trials across the Agency

What GAO Found

Although the National Institutes of Health (NIH) assessed the applicability of recommendations made by the Institute of Medicine (IOM) in 2010 to improve clinical trials—studies involving human subjects that test the effects of interventions on health-related outcomes—within one of its Institutes and Centers (IC), NIH did not apply the recommendations across its ICs. In response to a conference report provision that it review the applicability of the IOM recommendations across its ICs, NIH administered a survey to all 24 of the ICs that fund clinical trials and presented the findings at a leadership forum and in a report to Congress. These findings showed that over half of the ICs surveyed indicated that the majority of the recommendations were applicable. NIH decided not to apply the recommendations across its ICs because more analysis was needed before proposing any NIH-wide recommendations, given the variation across ICs. Officials explained that the IOM recommendations were designed for one program within the National Cancer Institute (NCI) and that most ICs do not support clinical trial networks that operate with the size and volume of the program, thus making the recommendations more pertinent to NCI. Leaders from NIH and the ICs indicated that more analysis was needed to account for the ICs' portfolios and management activities. As a result, NIH developed its own recommendations that aimed to enhance its stewardship of clinical trials, including several to improve data collection across the ICs. For example, its recommendation to improve monitoring systems, tools, and processes could assist NIH in identifying additional data that could be collected across the ICs.

NIH's Office of the Director (OD) reviews some data on clinical trial activity across NIH but has not finalized what additional data it needs or established a process for using these data to enhance its stewardship of clinical trials, as intended by NIH's own recommendations. The OD only reviews two types of data related to clinical trial activity on a regular basis: financial data and data on the inclusion of minorities and women. Beyond these data, OD officials review other data from the ICs on clinical trial activity if there is a specific inquiry. Officials from the OD acknowledged that they do not regularly review much data specifically related to clinical trial activity, but they are considering reviewing additional data collected from the ICs to inform the OD's stewardship of clinical trial activity across NIH. However, the OD has not finalized what data it needs from the ICs. In addition, the OD has not established a process that specifies how and when the OD will use the additional data it decides to review. As a result, it is unclear how often the OD will review the data, for what purpose, and what the product of its analysis will be. *Federal Standards for Internal Control* state that agencies need operational and financial data to determine whether they are meeting their goals for effective and efficient use of resources. Given that ICs oversee specific clinical trials, the OD may not need the same data or level of detail collected by ICs. However, until the OD determines which additional data it will review and the process it will use to review these data, NIH is limited in its ability to make data-driven decisions regarding the use of its roughly $3 billion annual investment in clinical trials.

United States Government Accountability Office

Increased Pressure for Results Reporting

"Under the law, it says you must report. If you don't report, the law says you shouldn't get funding," Biden said, citing a STAT investigation that found widespread reporting lapses. "I'm going to find out if it's true" that the research centers aren't reporting the results, Biden said — "and if it's true, I'm going to cut funding. That's a promise."

Increased Pressure for Reducing Administrative Burden

"42% of the time spent by an average PI on a federally funded research project was reported to be expended on administrative tasks related to that project rather than on research. [This] reflects the cumulative effect of the many administrative burdens imposed by different funding agencies, different offices within agencies, auditing and accrediting agencies, and academic institutions."

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2887040/

Increased Pressure for Subject Protections

"I've talked to other still-anonymous donors with strikingly similar experiences. Like the Lacks family, they're proud they helped science. They believe tissue research is important, but they wish they'd been asked permission from the start, to avoid difficulties that followed: the shock of learning they were part of research, debates over who controlled samples, questions over profits."

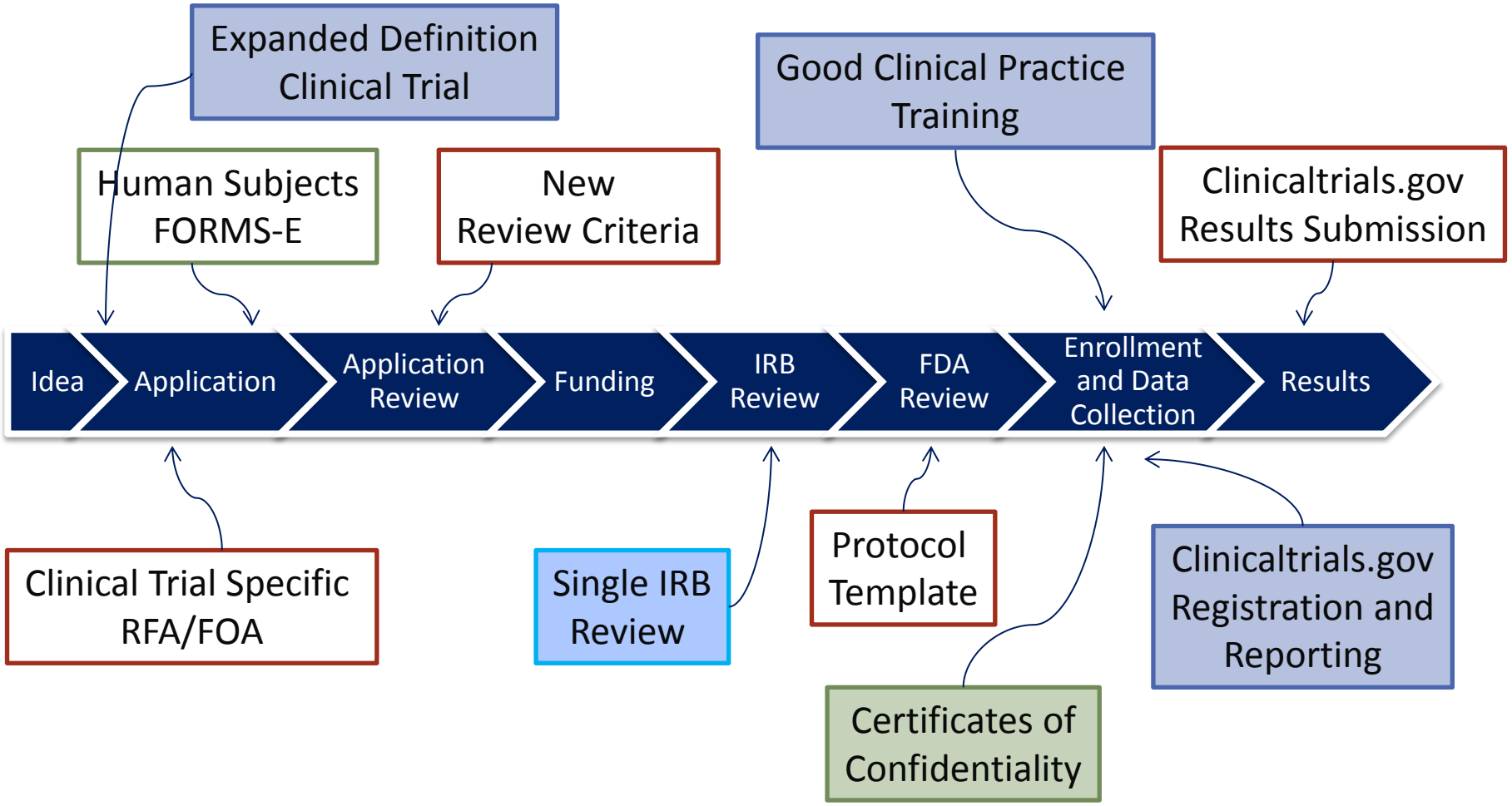
~Rebecca Skloot

Source: https://www.nytimes.com/2015/12/30/opinion/your-cells-their-research-your-permission.html

Two Major Reforms

- NIH Research Stewardship Reforms
- 2019 Revised Federal Common Rule

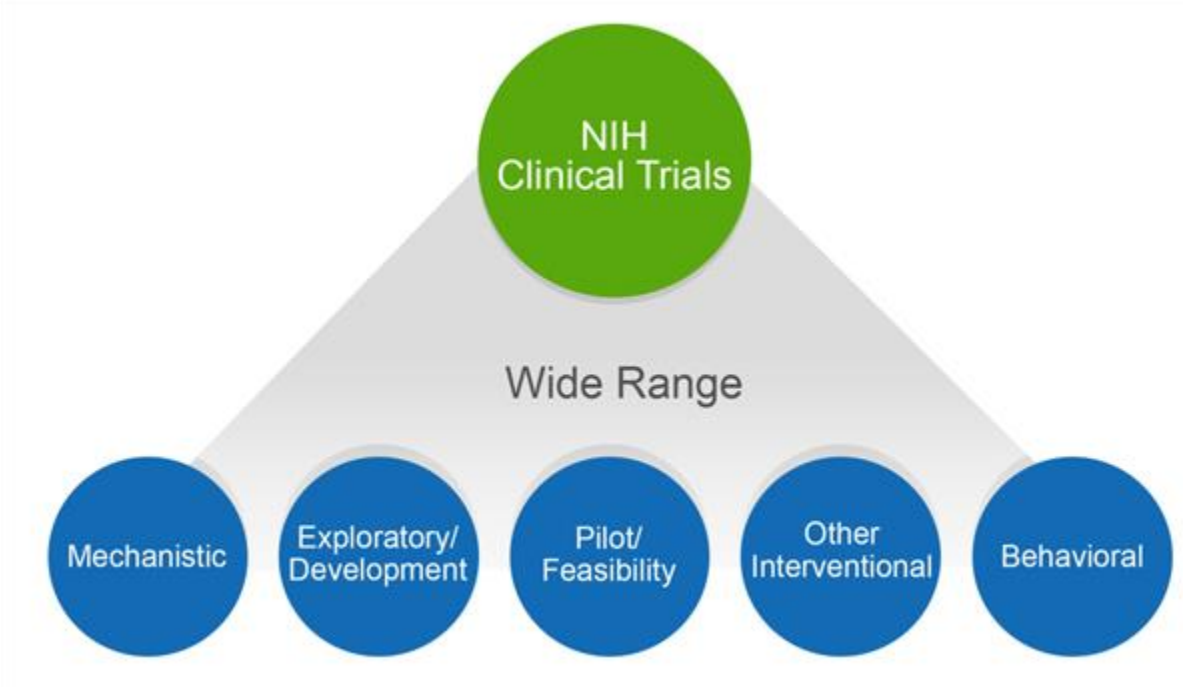
NIH Research Stewardship Reforms



#1

Expansion of the types of studies that are considered "clinical trials" under NIH's existing definition

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.



An "intervention" is defined as 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. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

A "health-related biomedical or behavioral outcome" is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

The study involves the recruitment of patients prior to brain surgery. While an fMRI is performed, half of the volunteers will be randomly assigned to perform a language listening task, and half will be assigned to perform a language generation task. Brain function maps will be used by surgeons to identify language areas for surgical planning. The investigators will compare post-operative language function in the two groups.

- **Does the study involve human participants?** Yes, the participants are patients enrolled prior to brain surgery.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to an intervention, a language listening task or a language generation task during pre-operative fMRI brain function mapping.
- **Is the study designed to evaluate the effect of the intervention on the participants** Yes, the study is designed to compare the impact of different methods of brain function mapping on post-operative language function.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, post-surgery language function is a health-related outcome.

✓ **This study is a clinical trial.**

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

- **Does the study involve human participants?** Yes, the healthy volunteers are human participants.
- **Are the participants prospectively assigned to an intervention?** Yes, the participants are prospectively assigned to an intervention, different durations of sleep deprivation followed by a blood draw.
- **Is the study designed to evaluate the effect of the intervention on the participants?** Yes, the study is designed to measure the effect of different durations of sleep deprivation on stress hormone levels.
- **Is the effect being evaluated a health-related biomedical or behavioral outcome?** Yes, the effect being evaluated, stress hormone levels, is a health-related biomedical outcome.

✓ **This study is a clinical trial.**

The study involves the recruitment of healthy volunteers and mild cognitive impairment patients who are administered a series of standard cognitive tasks while undergoing a brain scan or imaging procedure (e.g., fMRI). The purpose of administering these standard cognitive tasks (or behavioral tasks or presentation of stimuli) is to assess brain activity under standardized laboratory conditions and compare this activity between healthy individuals and mild cognitive impairment groups.

- **Does the study involve human participants?** Yes, the healthy volunteers and individuals with mild cognitive impairment are human participants.
- **Are the participants prospectively assigned to an intervention?** No, not in this context. The standard cognitive tasks and the fMRI are being performed to measure and describe brain activity, but not to modify it.

X This study is not a clinical trial.

#2

Single IRB Review for Multi-site Research

What Does This Mean for Researchers?

- NIH proposals must include:
  - A plan for single IRB review
    - Name of the single IRB
    - That all sites have agreed to rely on the single IRB
    - Communication plan
    - Documentation plan
    - Requests for exceptions
  - Budget for IRB fees if they are charged
  - Budget for staff who will coordinate this review if needed
- The lead site will have much more responsibility for coordinating IRB review
- Participating sites may have less responsibility for IRB review

From Many IRBs to a Single IRB

	New NIH policy **NIH-funded studies**
When does it take effect?	Most submissions for new funding **received by NIH** on or after January 25, 2018
To what does it apply?	All multi-site studies conducting the **same protocol** at each site
Are there exceptions?	• Foreign sites • Policy/law requires local IRB review: tribal, Veteran's Affairs • K and T awards

SMART IRB

1. Master Reliance Agreement
   - Eliminates the need to negotiate and sign reliance agreements for each study
   - Enables reliance decision on a study-by-study basis
   - Clearly defines roles and responsibilities for each institution
2. Online Reliance System (optional)
   - Request, track, and document reliance arrangements on a study-by-study basis
3. SOPs and resources (optional)
   - Documents to help IRBs and researchers develop processes and procedures for using SMART IRB Agreement

TRIAL INNOVATION NETWORK

New, collaborative initiative within the NIH Clinical and Translational Sciences Awards (CTSA) Program

3 Organizational Partners→

50+ CTSA Program Hubs

ITHS | Institute of Translational Health Sciences
Accelerating Research. Improving Health.

3 Trial Innovation Centers (TICs)
Duke/Vanderbilt
University of Utah
Johns Hopkins/Tufts

Recruitment Innovation Center (RIC)
Vanderbilt

What is HSD Doing?

UW IRBs will **not** serve as the single IRB for the first two years of the NIH mandate.

If UW is the lead site, we will work with the PI to identify an appropriate IRB

- May be private, such as WIRB, Advarra, BRANY, etc.
- May be another site for the study
- May be an IRB identified by NIH
- May be a TIN IRB

NEW REQUIREMENT

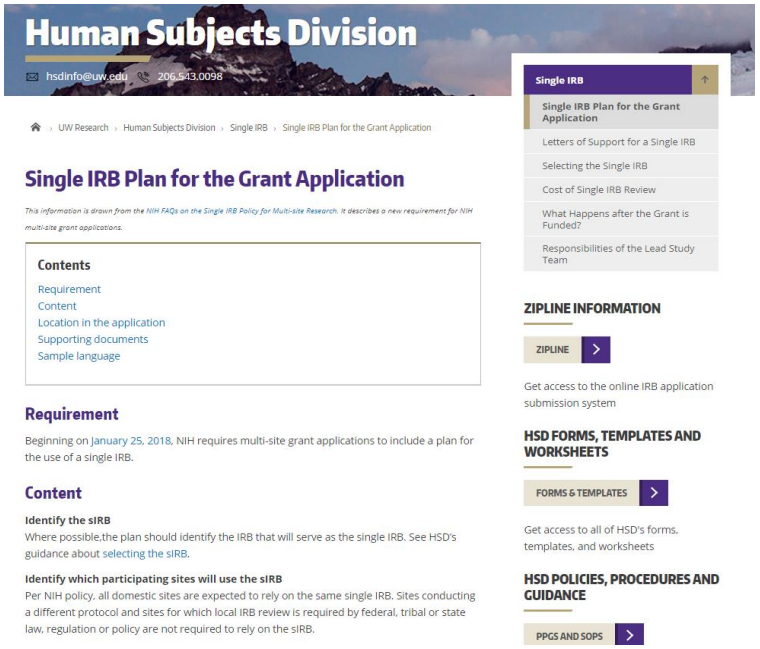
All UW studies (lead or site) proposing to use a single IRB under the NIH policy must obtain a letter of support from HSD before the grant is submitted to NIH.

WHY?

We want to make sure that the IRB selected is one that we can agree to rely on.

What is HSD doing?

- New single IRB webpages
  - Template language for grants
  - Template letters of support
  - Sample job description for staff member at lead site that will coordinate IRB submissions
  - Lots of resources and instructions
- Expansion of Reliance Team
- Establishing new reliance agreements with other IRBs (e.g. Advarra)
- Establishing new processes to support researchers and facilitate review by other IRBs
- Revising Cooperative Agreements with regional partners to better clarify roles and responsibilities.



#3

Clinicaltrials.gov reporting requirements for clinical trials

Registration and Reporting

- Initial registration
  - No later than 21 days after enrollment of the first subject.
- Interim updates
  - The record must be updated at least once a year (even if nothing has changed) until final results are reported. Certain types of changes must be reported within 30 days.
- Results reporting
  - No later than one year after the trial's primary completion date. For information about exceptions, see How to Report Clinical Trial Results.
- Correction of errors
  - Within 15 days for registration information
  - Within 25 days for results information

What is HSD doing?

- All incoming applications are assessed for status as applicable clinical trial
- HSD staff will contact the PI to confirm registration and to provide basic assistance
- Studies will be assessed at year 1 continuing review (status report) for registration
  - If not registered, IRB will be informed and IRB approval may be put on hold or have conditions
- Significant information about registration and reporting requirements are is on the HSD website

#4

Good Clinical Practice (GCP) Training is Required for Clinical Trial Investigators and Staff

Good Clinical Practice Training

- Clinical trial investigators
  - Individuals responsible for the conduct of the clinical trial at a trial site
- Clinical trial staff
  - Individuals responsible for study coordination, data collection and data management

What is HSD Doing?

› UW Research › Human Subjects Division › HSD Training and Education › HSD Required Training › Good Clinical Practice Training

Good Clinical Practice Training

Researchers working in behavioral or biomedical clinical research must sometimes complete training in Good Clinical Practice (GCP) in order to meet the requirements of the organizations they are affiliated with, funding agencies, or study sponsors. GCP training educates researchers on the fundamental principles of conducting high quality clinical trials.

University of Washington Requirements

The UW and HSD do not currently require that researchers complete GCP training.

HSD Required Training

- Human Subjects Protections Training
- **Good Clinical Practice Training**
- Web Based CITI Training
- Documenting and Tracking Training

ZIPLINE INFORMATION

ZIPLINE

Get access to the online IRB application submission system

#5

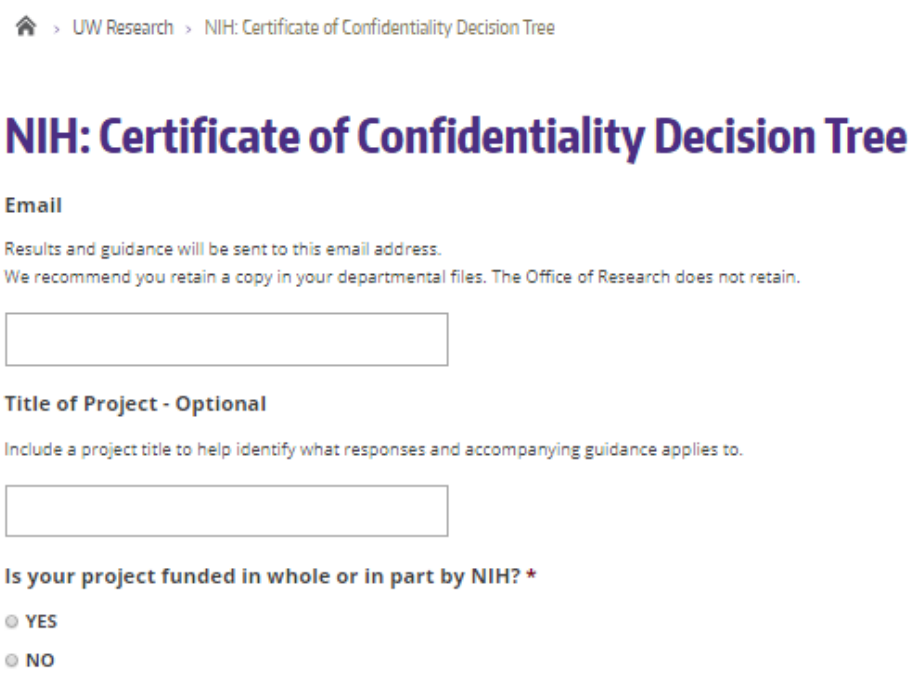
Federal Certificate of Confidentiality Issued for all Human Subjects Research

Certificate of Confidentiality

- Allows researchers to refuse to disclose name or any information, documents or biospecimens containing identifiable information about the research subjects. The Certificate specifically prohibits disclosure of the information in response to legal demands, such as a subpoena, Public Records request, or Freedom of Information Act (FOIA) request.

What is HSD Doing?

- Enhanced guidance on website about CoC's
- Provide documentation about CoC requirements with each study approval



Revised Federal Common Rule

- Initial effective and compliance date was January 2018
- On hold by the Trump administration for one year
- Delayed once to July 2018
- Will now go into effect on January 21st, 2019

Revised Common Rule

Long anticipated changes to the federal regulation that applies to all federally-funded research

- New consent requirements
  - Information about the identifiability and future use of specimens and data
  - "Key Information" section to assist subjects in understanding whether or not to participate in the study
  - Consent forms for clinical trials must be uploaded to a government website
- New exemption categories
  - Benign behavioral interventions
  - Secondary use of data/specimens when certain criteria are met
- No more continuing review (status reports) for minimal risk research
- Other minor changes to reduce the work on IRBs
- **Requirement** for a single IRB to review all cooperative research goes into effect in January 2020.

What is HSD Doing?

Revised Common Rule

A frequently updated webpage for all information and resources related to the pending revision of the Common Rule on January 21, 2019.

The **Common Rule** is the informal name given to a set of human subjects regulations that was developed in the 1970s. It was adopted by almost all federal agencies that fund human subjects research – in other words, it is the set of regulations that they all have in common. The Common Rule describes responsibilities and requirements for Institutional Review Boards (IRBs), researchers, and the researcher's institution. Most academic institutions (including the UW) apply the Common Rule regulations to all human subjects research, even if the research is not funded by a federal agency. It is being revised, effective January 21, 2019.

Revised Common Rule Timeline