

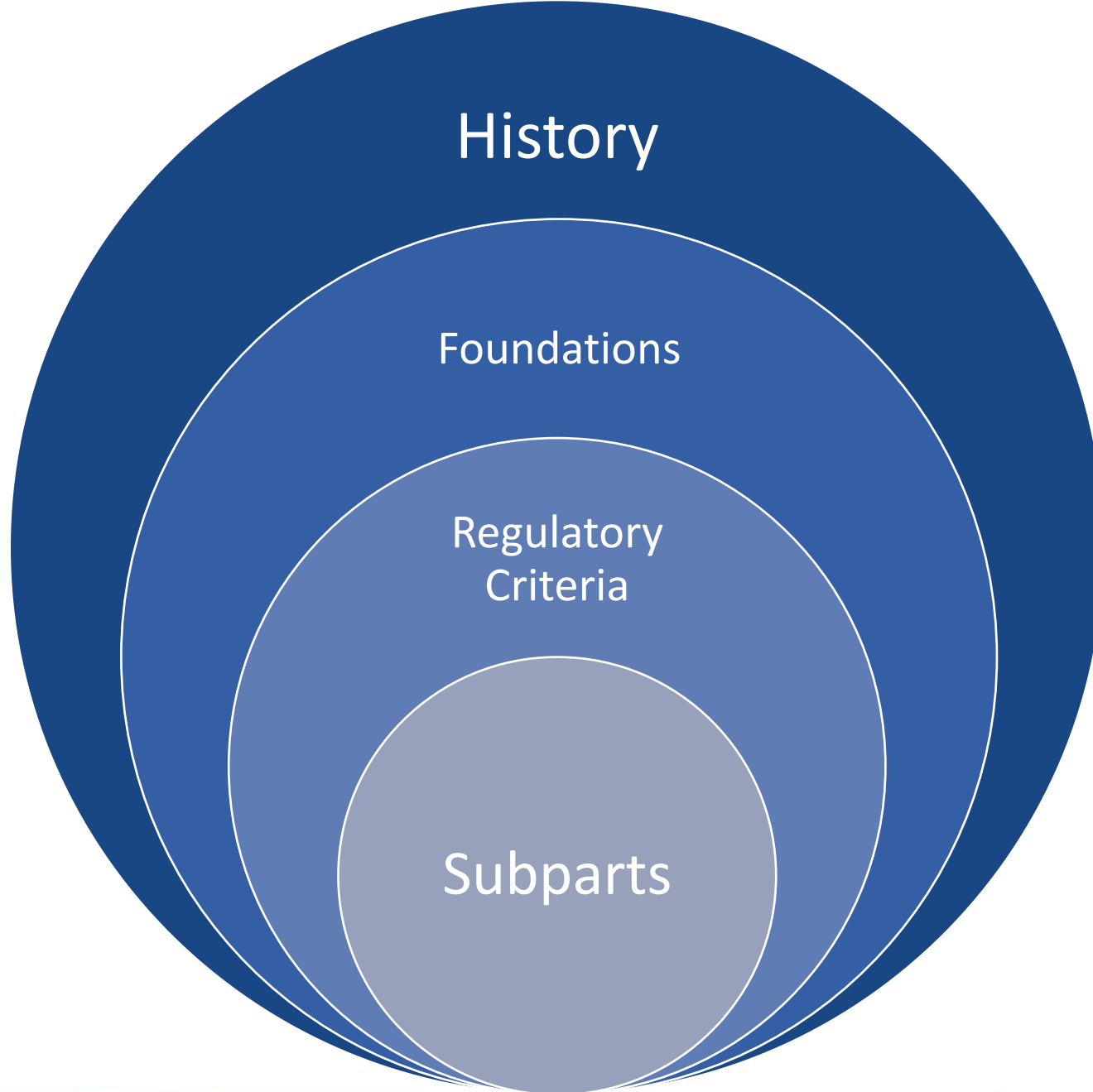
# IRB 101

Columbia University  
Human Research Protection Office

July 25, 2019

# Agenda

- Research ethics history
- Discuss core concepts to provide a fundamental knowledge of Human Research Protection:
- IRB foundations and terminology
- IRB review criteria and tips for submission
- Informed consent requirements
- Special requirements for vulnerable populations
- IRB reliance



# IRB 101

## Research Ethics History

# Objectives

- Provide an overview of the events that have led to the system of protections that are currently in place to protect individuals who volunteer for research.
- Summarize the applicable regulations for the protection of human subjects.

# Pre-20th Century

- Medical practice developed from medical research
- No formal, widely-accepted codes
- No consideration for rights of participants
- Paternalistic
- Reliance on morals, ethical principles of culture
- Hippocratic Oath



# 20<sup>th</sup> Century Cases Covered:



**Yellow Fever Experiment**



**Tuskegee**



**Nazi Experiments**



**Fernald Radiation**



**Thalidomide Drug Trial**



**Willowbrook School**



**Milgram Obedience**



# Walter Reed (1900)

- United States Army Yellow Fever Commission
- Yellow Fever experiments
  - Major Walter Reed
  - Conducted experiments outside of Havana
  - Proved that the mosquito transmits Yellow Fever
  - One of the first documented, systematic uses of informed consent in research



# Yellow Fever Consent Elements

- **Autonomy (respect for persons):** “gives his consent...for the reasons and under the conditions...”
- **Voluntary Participation:** “being in the enjoyment and exercise of his own free will”
- **Risks:** “In case of the development of yellow fever in him, that he endangers his life to a certain extent.”
- **Benefits:** “He will receive from the said commissioner the greatest care and the most skillful medical service.”
- **Compensation:** “he will receive the sum of \$100 in American gold.”
- **Study withdrawal conditions:** “The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.”

# Links

- <http://exhibits.hsl.virginia.edu/yellowfever/>
- <https://schaechter.asmblog.org/.a/6a00d8341c5e1453ef0128762417ec970c-popup>
- <https://www.cdc.gov/tuskegee/timeline.htm>
- <https://encyclopedia.ushmm.org/content/en/article/nazi-medical-experiments>
- [https://bioethicsarchive.georgetown.edu/achre/final/chapter7\\_5.htm#ITHALIDOMIDE](https://bioethicsarchive.georgetown.edu/achre/final/chapter7_5.htm#ITHALIDOMIDE)
- [https://science.education.nih.gov/supplements/webversions/bioethics/guide/pdf/master\\_5-4.pdf](https://science.education.nih.gov/supplements/webversions/bioethics/guide/pdf/master_5-4.pdf)

# PHS Study of Syphilis (1932-1972)

- 1932 Natural history study; justify treatment programs
- 600 black men
  - 399 with syphilis
  - 201 controls
- Conducted without the patients' informed consent.
- Deception: Told had “bad blood”
- Participants did not receive proper treatment needed to cure their illness.
- Participants received free medical exams, free meals, and burial insurance.
- Although originally projected to last 6 months, the study actually went on for 40 years.

# What went wrong?

1932-34

- Study begins; Paper published on health effects of untreated disease

1936

- Criticism of study; Local physicians asked to not treat men

1940-45

- Men hindered from getting treatment; Penicillin treatment

1968-69

- Ethical concerns raised; CDC garners support from AMA

1972

- Exposed; Study stops

# Nazi Prisoner Experimentation (1939-1944)

- ~ 70 morally abhorrent experiments conduct by Third Reich in concentration camps
- Research categories:
  - Survival and rescue of German troops;
  - Testing of medical procedures and pharmaceuticals; and
  - Experiments that sought to confirm Nazi racial ideology.
- Experiment conditions/methodologies included:
  - High Altitude
  - Freezing
  - Testing of sulfanilamide & poison
  - Twin experimentation

# Nuremburg Trials (1945-1946)

- Prosecutors and defense attorneys according to British and American law
- In every single instance appearing in the record, subjects were used who did not consent to the experiments; no free will to withdraw
- Extreme pain, suffering
- Torture: Mutilation, permanent injury, death

# Nuremburg Trials (1945-1946)

- 24 Nazis tried
- 12 sentenced to death
- 2 died before trial complete
- 3 acquitted
- All others given prison terms ranging from 10-20 yrs



# Nuremburg Code (1947)

The infographic is set against a dark blue background with white text and icons. At the top left, the title 'THE NUREMBERG CODE' is displayed in large white letters. Below it is a white icon of a scale of justice. To the right, a text box states: 'NAZI DOCTORS WERE CONVICTED OF WAR CRIMES INVOLVING HUMAN EXPERIMENTS ON CONCENTRATION CAMP PRISONERS.' Below this, four white circles represent the judges, positioned above a white rectangular box. A dotted line connects the scale icon to the text box. On the left side, a white feather icon is positioned next to the text: 'THE VOLUNTARY CONSENT OF THE HUMAN SUBJECT IS ABSOLUTELY ESSENTIAL...'. Below this, another text box says: 'THE CODE WAS AN ATTEMPT AT ESTABLISHING CLEAR RULES ABOUT WHAT WAS LEGAL AND WHAT WASN'T WHEN CARRYING OUT HUMAN EXPERIMENTS.' In the center, a white silhouette of a scientist in a lab coat holds a test tube and a flask. To the right of the scientist, a text box says: 'THE CODE CONSISTS OF 10 POINTS, THESE INCLUDE:'. Below this is a bulleted list of four points. At the bottom, the text reads: 'INSTITUTE ON ETHICS & POLICY FOR INNOVATION: GLOBAL HEALTH FACT OF THE WEEK'. The IEP logo is in the bottom right corner. A vertical source URL is on the far right edge.

## THE NUREMBERG CODE

NAZI DOCTORS WERE CONVICTED OF **WAR CRIMES INVOLVING HUMAN EXPERIMENTS** ON CONCENTRATION CAMP PRISONERS.

FOLLOWING **THE NUREMBERG TRIALS** THE CODE WAS INTRODUCED IN AUGUST, 1947.

**THE VOLUNTARY CONSENT OF THE HUMAN SUBJECT IS ABSOLUTELY ESSENTIAL . . .**

THE CODE WAS AN **ATTEMPT** AT ESTABLISHING CLEAR RULES ABOUT **WHAT WAS LEGAL** AND **WHAT WASN'T** WHEN CARRYING OUT **HUMAN EXPERIMENTS**.

THE CODE CONSISTS OF **10 POINTS**, THESE INCLUDE :

- INFORMED CONSENT
- BENEFITS MUST OUTWEIGH RISKS
- PARTICIPANTS' UNDERSTANDING OF POSSIBLE RISKS
- HOW EXPERIMENTS MUST BE RUN

INSTITUTE ON ETHICS & POLICY FOR INNOVATION:  
**GLOBAL HEALTH FACT OF THE WEEK**

Source: <http://broughttolife.sciencemuseum.org.uk/broughttolife/techniques/nurembergcode>

Credit: <https://twitter.com/hashtag/ghfactoftheweek>

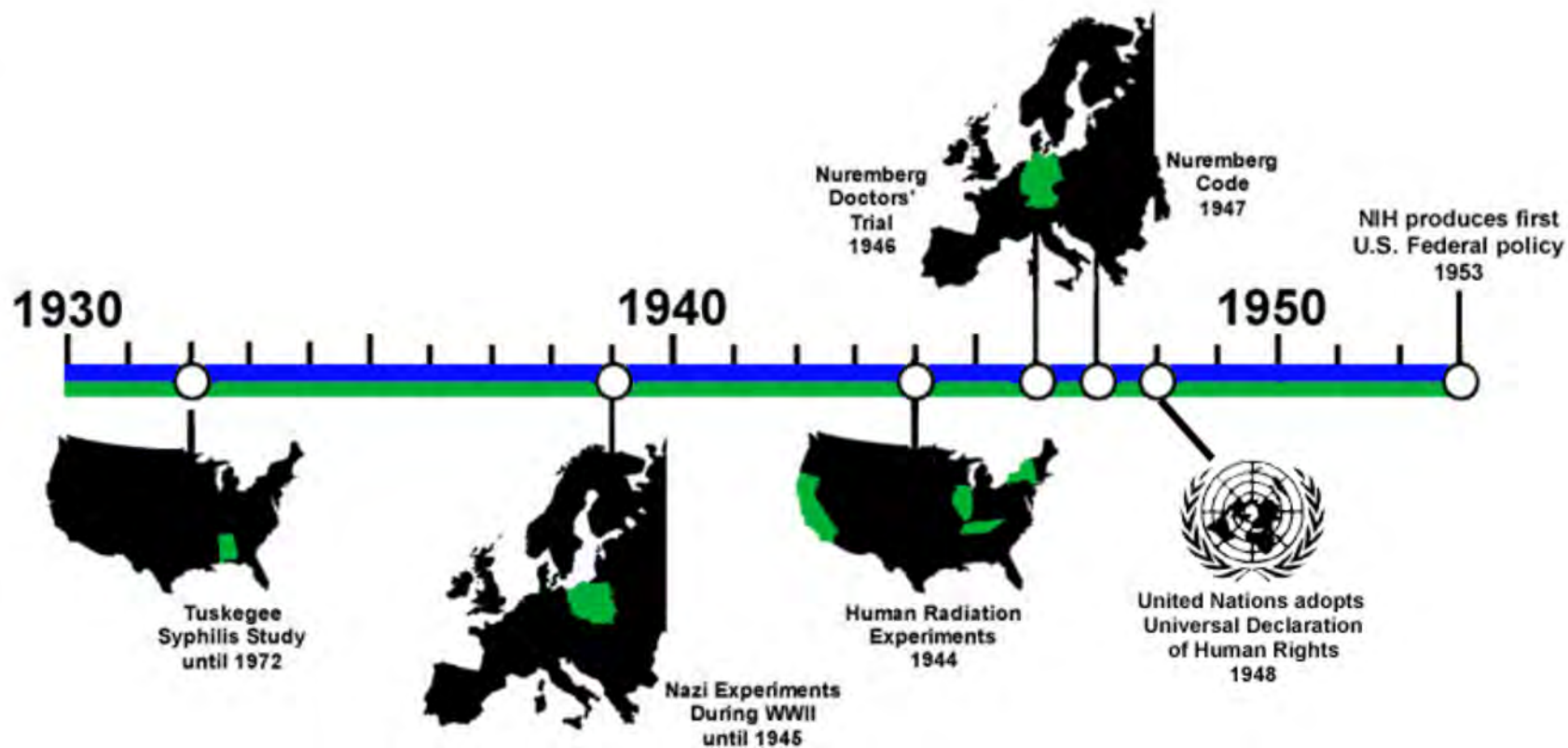


# Declaration of Helsinki (1949)

- Followed Nuremberg Code (1947)
- Developed by World Medical Association for Medical community re: Human Experimentation
- Set of ethical principles
  - Well-being of participant takes precedent
  - Consent should be in writing
  - Use caution if there is a dependent relationship between researcher and participant
  - Limit use of placebo
  - Greater access to benefit
  - Monitoring of special populations

# Rise of Ethical Codes

- 1947: Nuremberg Code
- 1949: Declaration of Helsinki



# Fernald School (1946, 1950-53)

- Massachusetts Institute of Technology researchers & Fernald staff members
  - Exposed 17 students to radioactive iron in first study (1946)
  - Exposed 57 subjects to radioactive calcium in second study (1950 - 1953)
- Consent
  - Misleading information implied benefit
  - No mention of radioisotopes
  - Coercive

# Thalidomide (Late 1950 - Early 1960s)

- Approved in Europe as sedative
- Not approved in U.S.
- Samples provided to U.S. physicians paid to study safety and efficacy
- Given to pregnant women which resulted in babies with malformed limbs and other conditions



# FDA Amendments & Regulation

1962 Amendments to U.S. Food, Drug and Cosmetic Act  
(Kefauver-Harris Amendments)

- Established a framework that required drug manufacturers to prove scientifically that a medication was not only safe, but effective
- Monitoring of pharmaceutical advertising

# Willowbrook (1956-72)

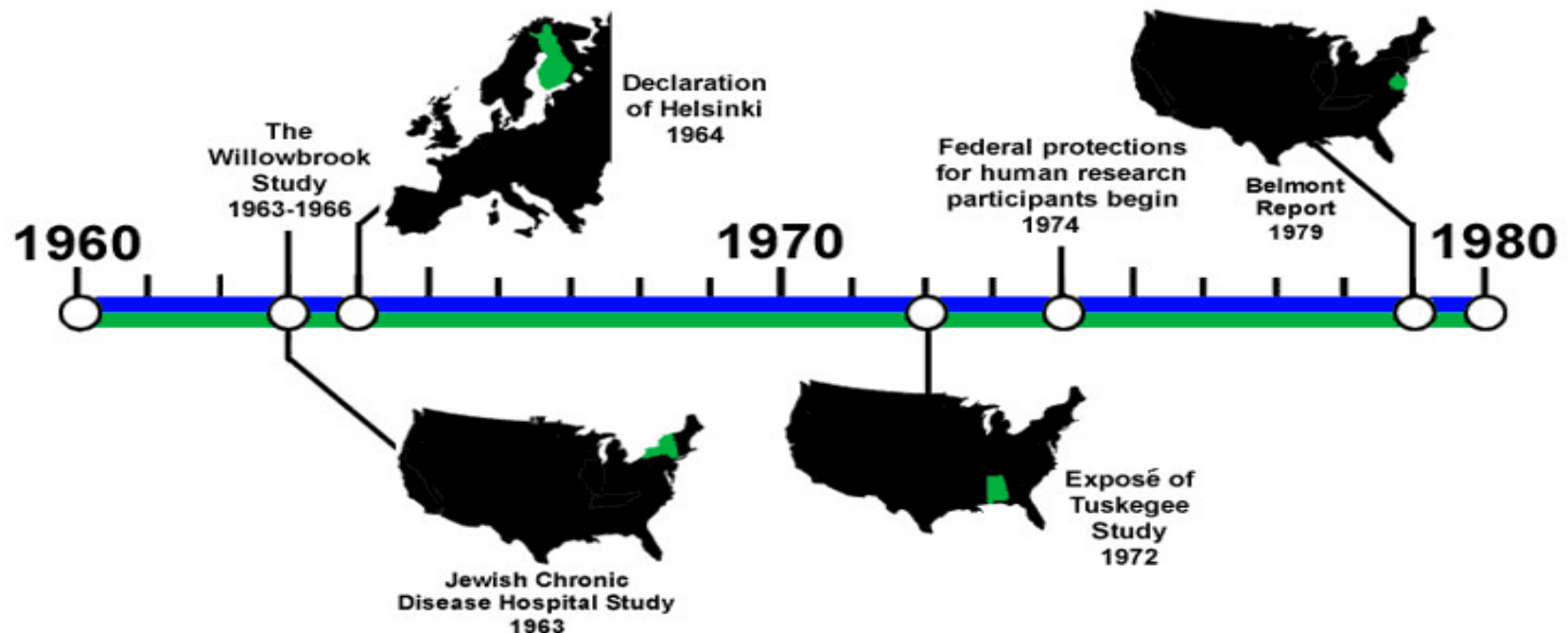
- New York University researchers
- Willowbrook State School, located on Staten Island
- Residents were injected with a mild form of hepatitis serum
- The researchers hoped to find a treatment for the virus by studying the disease in its earliest stages

# Milgram Obedience Study (1961)

- Behavioral Research
- Recruitment by newspaper ad:
  - \$4.50 for one hour's work
  - Psychology experiment investigating **learning and memory** (Deception)
- Individuals gave what appeared to be real electric shocks to another person
- Post-experiment interview

# Rise of a Regulatory Framework

- 1962: Kefauver-Harris Amendment
- 1966: Policies for the Protection of Human Subjects issued
- 1974: National Research Act passed
- 1979: Belmont Report issued





# Regulatory Framework

- 1966 NIH Policies for the Protection of Human Subjects issued
  - Established the IRB as one mechanism through which human subjects would be protected.
- 1974 National Research Act passed (raised NIH policy to regulation)
  - Required regulations for protection of human subjects
    - Informed consent
    - Institutional Review Boards
  - Created National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

# Regulatory Framework

- 1979 Belmont Report published by National Commission
- Respect for persons (informed consent)
- Beneficence (minimize risk, evaluate risk/benefit ratio)
- Justice (selection of subjects)

## *Guiding Principles for Modern Research*

# Regulatory Framework

- Codified as 45 CFR 46
  - Effective 1/16/81; revised 3/4/83; 6/18/91; 1/21/2018
  - 1991 revision involved adoption of Federal Policy for Protection of HS – “Common Rule” (Subpart A) – by 16 agencies
  - Subparts B,C,D adopted 1978, 1978, 1983 respectively
  - Subpart A revised in 2018 (2018 Requirements)
- FDA regulations codified at 21 CFR 50 (1980), 56 (1981)
  - Regulations for drugs, devices, biologics

# 2018 Requirements

- “Revised Common Rule”
  - “2018 Requirements”, “2018 Rule”, “Revised Common Rule”
- DHHS and 19 other federal departments and agencies (not FDA)

## 2018 Requirements *(continued)*

- Significant changes include:
  - Definitions (e.g., research, human subject, identifiable biospecimens, identifiable private information)
  - New requirements for the content of informed consent documents
  - Establishes new exempt categories
  - Revises IRB review criteria
  - Removes the requirement for continuing review of ongoing research for certain studies
  - Allows the use of broad consent

# Differences between DHHS and FDA Regulations

- FDA has not yet signed on to 2018 Requirements
- Comparison of FDA and DHHS Human Subject Protection Regulations (prior to 2018 Req):
  - <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/educationalmaterials/ucm112910.htm#>
- Consult with IRB staff if uncertain about which regulations apply.

# Relevant Regulations

## Code of Federal Regulations

- Title 21, Parts 50, 56, 312, 812
  - Applicable to research that involves testing of FDA regulated drugs, devices, biologics
  - <http://www.fda.gov/oc/ohrt/irbs/>
- Title 45, Part 46 (45 CFR 46)
  - As written, applies to research conducted or supported by federal funds
  - OHRP
  - Belmont Report
  - <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

# Questions?





# IRB 101

## IRB Basics

# Objectives

- Brief introduction to HRPO & IRBs
- Scope of IRB authority
- Review pathways
- Terminology
- Rascal electronic system
- Noncompliance

# Human Research Protection Office

- Component of Office of Executive Vice President for Research
- Purview = All Columbia campuses
- Mission: Protection of subjects in Columbia research
- Primary functions
  - Provide regulatory and administrative support to Columbia IRBs
  - Provide education and training for researchers
  - Maintain accreditation (Association for Accreditation of Human Research Protection Programs)
  - Conduct for cause and routine audits

# Institutional Review Boards (IRBs)

- 7 IRBs at Columbia (6 at CUMC; 1 at CU-MS)
  - Each is scheduled to meet twice per month
  - 2000+ new studies per year
  - 6000+ active studies (approximately)
- Diverse membership
  - Scientific, nonscientific, affiliated, non-affiliated
  - Full/regular and alternate members
- Balance = Quality and timeliness of reviews

# Assurance of Compliance

- Contract (i.e., Federalwide Assurance, FWA) between DHHS (through OHRP) and institution
- Varies by institution
- Can extend protections defined in 45 CFR 46 to all research conducted under aegis of the institution, regardless of funding source, or lack thereof
  - At this time CU extends regulations to all research, regardless of funding

# Functions of the IRB

- Individual Boards:
  - Initial Protocol Review
  - Review of modifications
  - Review of Unanticipated Problem Reports
  - Continuing Review
  - Review of protocol deviations/violations
  - Serving as Single IRB (sIRB)
- Human Research Protection Program:
  - Education, monitoring, efficient review
  - Address allegations of noncompliance

# How do IRBs review research?

- 45 FR 46 Subpart A defines IRB Authority
- Assess research based on:
  - Federal definitions and
  - Regulatory criteria
    - Approval
    - Informed Consent
- 4 pathways for review under DHHS
- Additional protections for vulnerable populations:  
Subparts B-D

# Definition of Human Subjects Research (45 CFR 46)

- **Research** means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
- The following activities are deemed not to be research:
  - 1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.



## And also.....

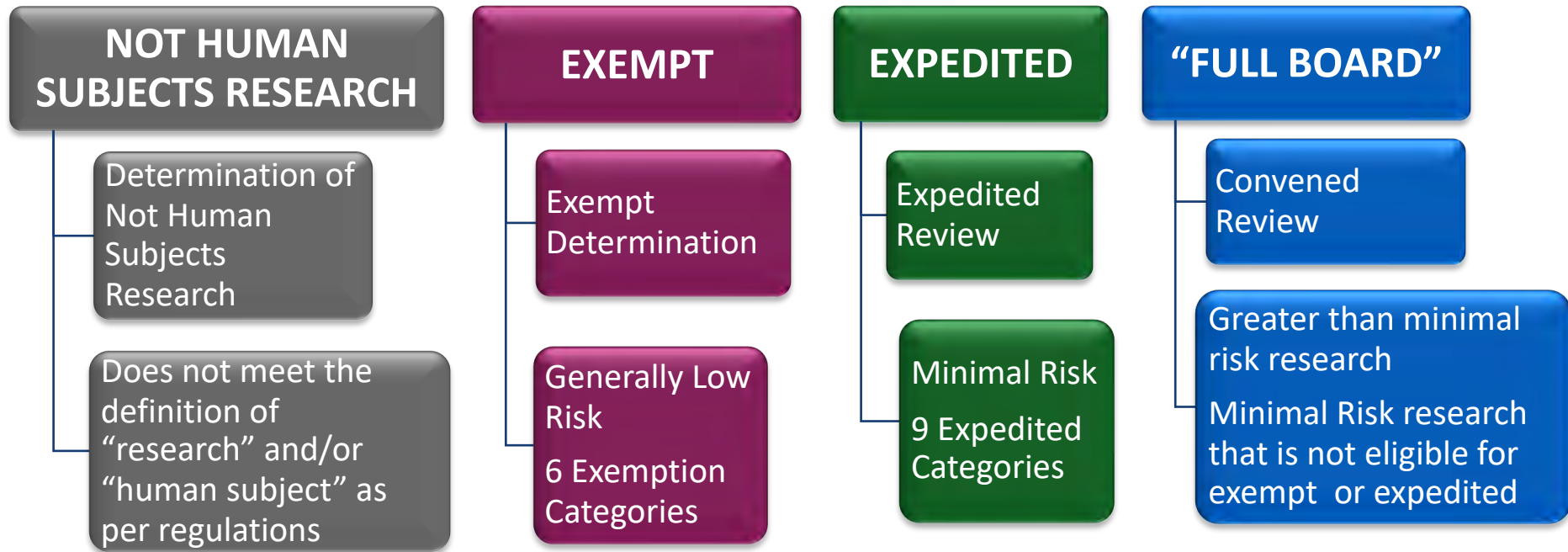
- 2) Public health surveillance activities
- 3) Certain activities authorized by law or court order solely for criminal justice or criminal investigative purposes
- 4) Certain activities in support of intelligence, homeland security, defense, or other national security missions

## Definitions (continued)

- **Human subject** means a living individual about whom an investigator (whether professional or student) conducting research obtains:
  - 1) Information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes, or generates identifiable private information; or
  - 2) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

# Regulatory Pathways

All research projects are categorized based on the level of risks introduced to human subjects and whether they meet the qualifications under specific categories established by the federal regulations at 45 CFR 46.



# Research Method/Procedure Examples

- Interviews
- Questionnaires/Surveys
- Focus Groups
- Observations
- Records Reviews (medical, school, etc)
- Tests/Tasks
- Medical procedures (fMRI)
- Blood draws, genetic tests, saliva samples
- Secondary Data Analysis

## IRB submission also required when...

- Student activities that are not research but present > minimal risk to participants
- Genetic Testing (NYS 79-I definition) using anonymous human biological samples
- Research involving deidentified data from a repository and/or dataset that requires IRB approval (e.g. Framingham heart study data from dbGaP)
- Research involving data for which the provider requires compliance with strict security requirements (e.g. FISMA requirements or CMS data)

# Rascal Electronic System

Electronic system for management and documentation of:

- IRB submissions
- IACUC submissions
- Hazardous materials appendices
- Conflict of interest
- Proposal tracking
- Training
- Stipulated reviews
- HIPAA

# Rascal Terminology

- Event = type of Rascal submission, e.g., Protocol, Renewal, Modification, Unanticipated Problem, Closure
- Protocol = initial Event submitted in Rascal including all information; also, the narrative description of the research.
- Principal Investigator = individual responsible for the conduct of the research
- Engaged personnel = individuals engaged in human subjects research
- Non-engaged personnel = individuals not engaged in human subjects research

# Engagement

- In general, an institution is considered *engaged* in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain:
  - (1) data about the subjects of the research through intervention or interaction with them;
  - (2) identifiable private information about the subjects of the research; or
  - (3) the informed consent of human subjects for the research.

<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html>



# Regulatory Compliance

- “Compliance” = adherence to requirements of applicable federal regulations, state laws, and policies, GCP (e.g., ICH E6 guidelines), sponsors and IRB determinations
- Compliance Oversight Team: for cause and routine audits
- Cost of noncompliance can be significant
- Awareness of requirements (we can help!)
- PI is responsible for conduct of study
  - Can delegate tasks but not responsibility
  - Must ensure documentation as well as appropriate conduct

# Potential Costs of Noncompliance

- Suspension or termination of IRB approval for research
- Delays in recruitment or other study procedures
- Requirements for training or re-training
- Reporting to department and institutional officials
- Reporting to federal oversight agencies and sponsors
- Restrictions on research participation
- Loss of funding
- Negative effect on future funding opportunities

## Helpful links:

- IRB website: <http://research.columbia.edu/irb>
- IRB Policies and Guidance Documents:  
<https://research.columbia.edu/content/human-research-policy-guide>
- Protocol and Consent Form Resources:  
<https://research.columbia.edu/content/irb-protocol-resources>
- Staff Directory:  
<https://research.columbia.edu/content/hrpoirbs-directory>
- Meeting Schedule:  
<https://research.columbia.edu/content/about-hrpoirbs>

# Questions?



# IRB 101

## IRB Criteria for Approval

# Objectives

- Explain IRB requirements for approval;
- Discuss routing of protocols for review;
- Tips for Rascal submission.

# IRB Criteria for Approval

- Foundation for IRB review
- IRB must determine that all of the requirements are satisfied.
  - If not, and there was convened review, Event is either PENDED to Chair (Rascal status “Pending”) or RETURNED to Committee (Rascal status “Returned”)
  - If not, for other than convened review, Event is Returned
- Considered for most events
- Regulations:
  - 45 CFR 46.111 (DHHS)
  - 21 CFR 56.111 (FDA)

# IRB Criteria for Approval

#1	Risks to subjects are minimized
#2	Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
#3	Selection of subjects is equitable
#4	Informed consent will be sought from each prospective subject or the subject's legally authorized representative
#5	Informed consent will be appropriately documented or appropriately waived
#6	When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
#7	When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data
#8	For purposes of conducting the limited IRB review; adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

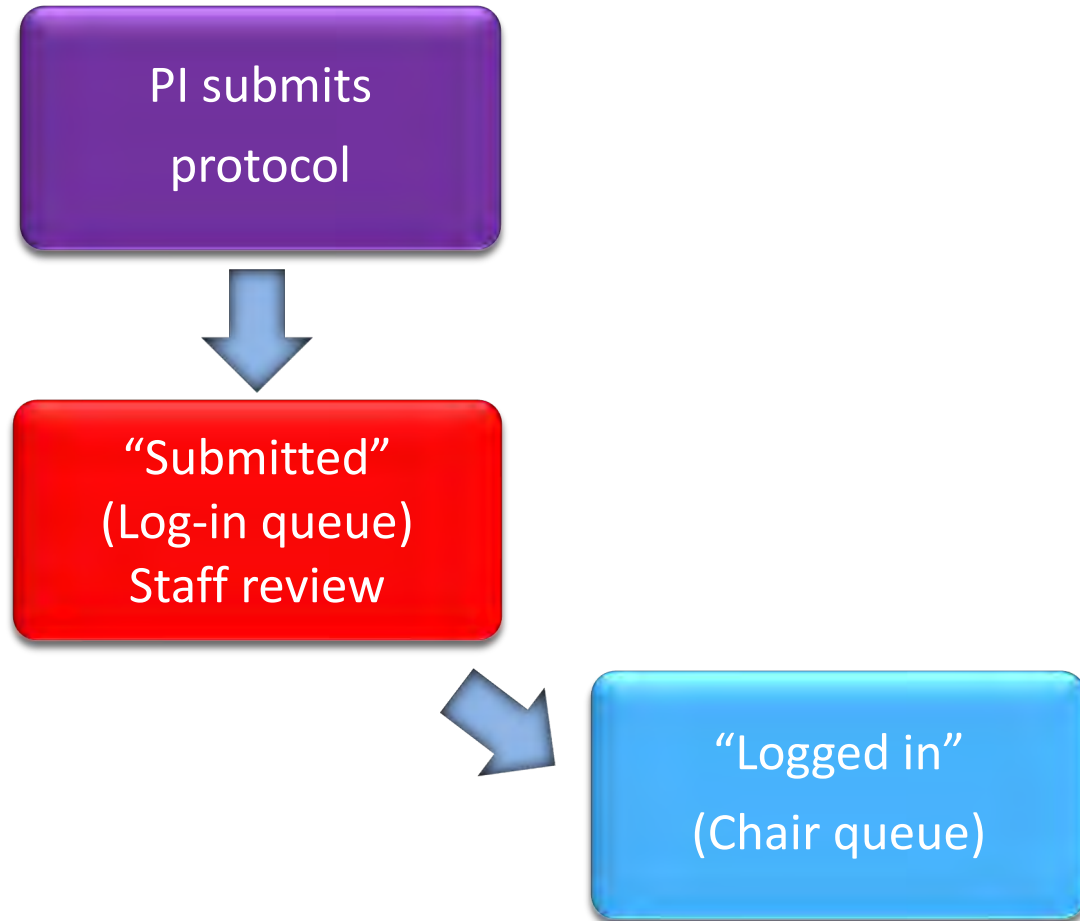


# IRB Criteria Applied for Specific Events:

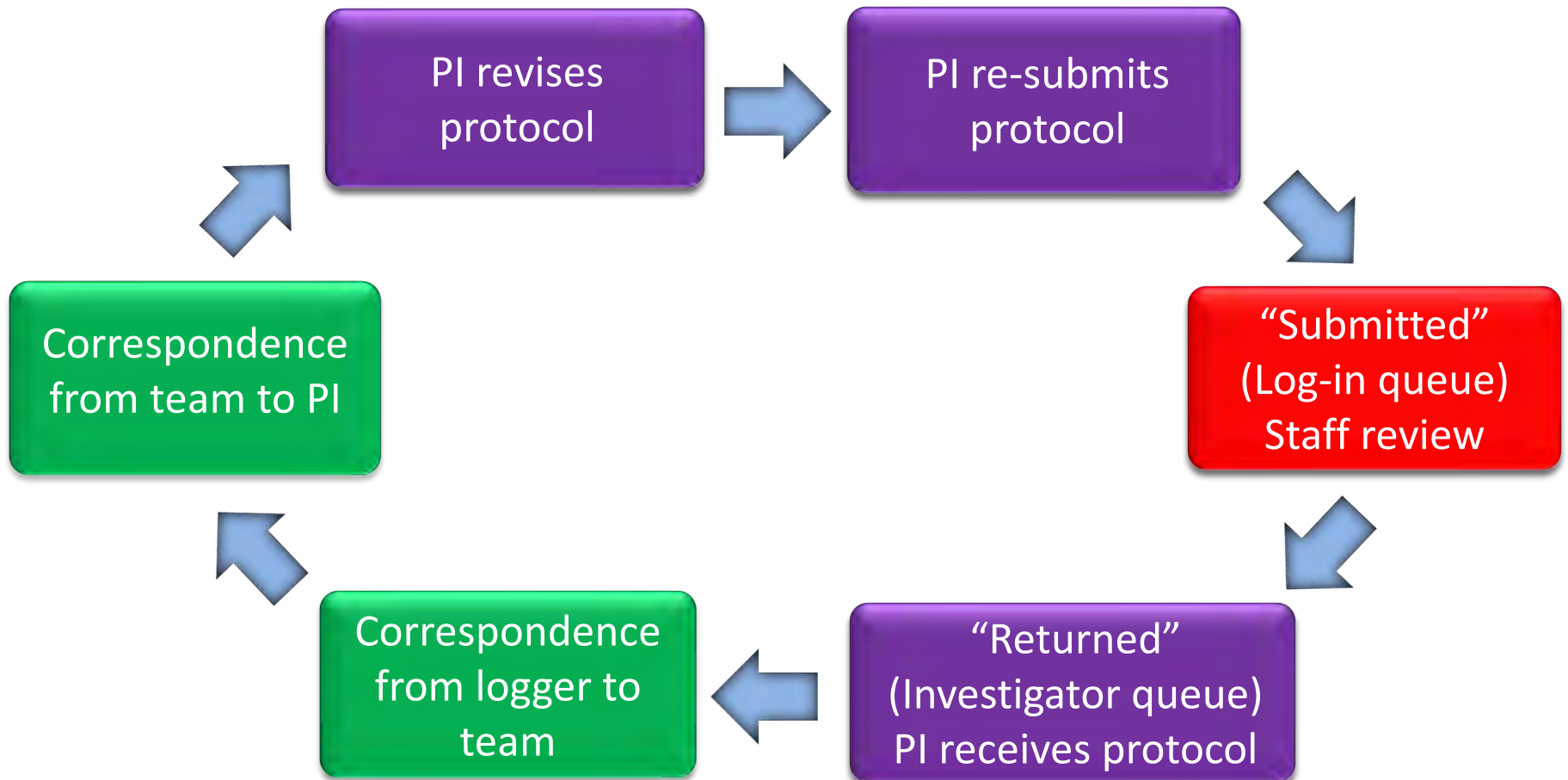
- New Protocol
- Modification
- Continuing Review
- Unanticipated Problems

Administrative staff use checklists  
or templates for review

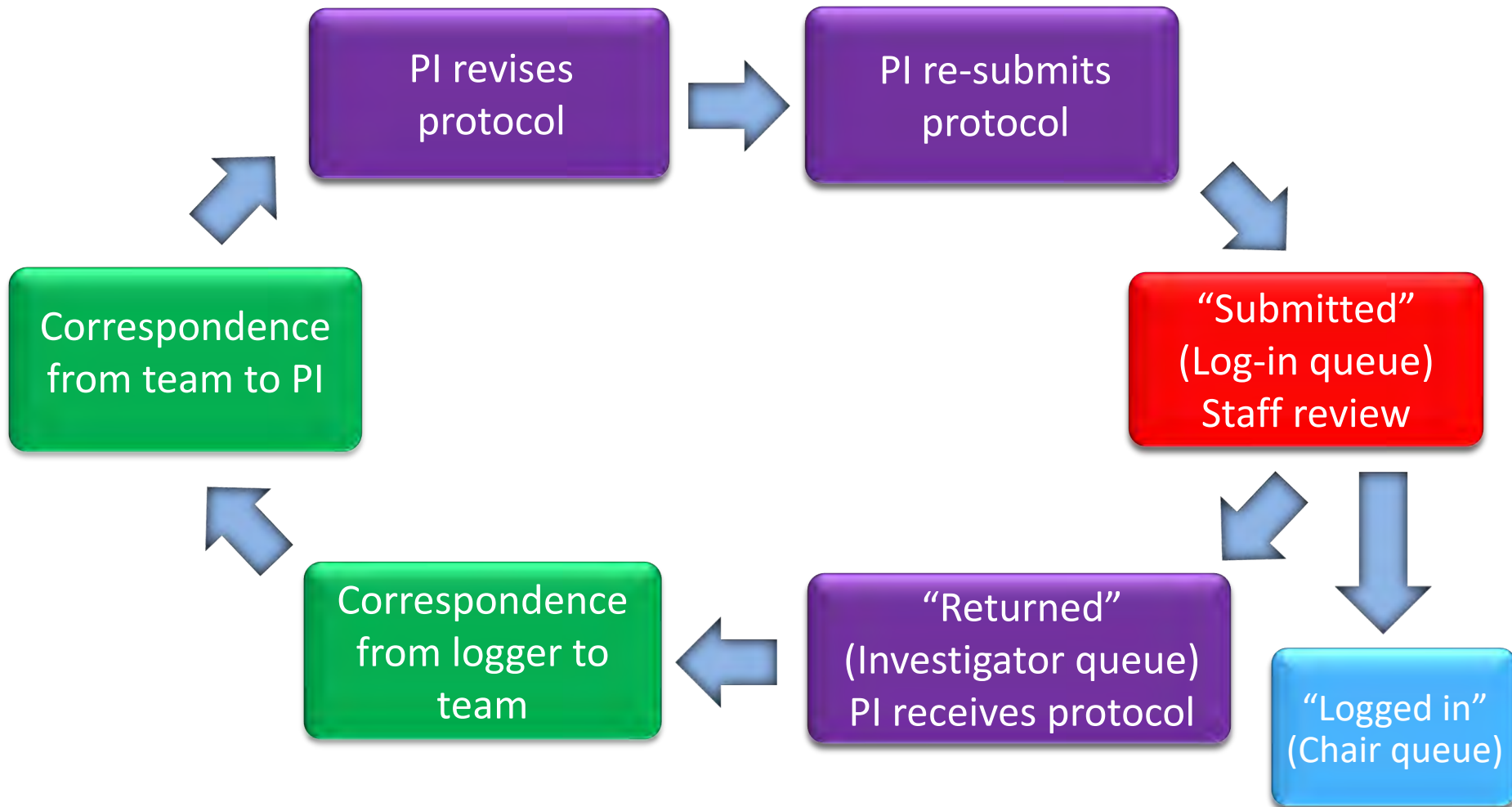
# New Protocol Pathway (Ideal)



# New Protocol Pathway (Common)



# New Protocol Pathway (Common)



# Principal Investigator

- Officer of research with a full-time appointment as
  - Senior research scientist/scholar
  - Research scientist/scholar

Officer of instruction with a full-time appointment in the rank of

- Professor,
- Associate professor,
- Assistant professor, or
- Instructor

- Students cannot serve a PI
- PI must monitor research and sign off on every submission
- Student must keep the PI fully informed of the status of the project

## Rascal Tip (Clarity)

- Describe clearly and accurately what will be done at this site or under the direction of a Columbia investigator;
- Identify related procedures that will be or have been done elsewhere or previously;
- Provide clear descriptions of relationships;
- Accurately describe funding mechanisms;
- Consistently and precisely describe data collection.



# Continuing Review (Renewals)

- IRBs make all approval criteria determinations for the next approval year;
- Assess changes in the research;
- Evaluate publications and information in the literature.
- **Common Return Criteria**
  - Clean copies of consent documents or study; instruments not attached;
  - Enrollment information not provided;
  - Documents or fields not updated;
  - Conditions of previous approval not satisfied;
  - All required attachments not provided.

# Continuing Review (CR) – 2018 Requirements

- Eligible studies for elimination of CR are those that:
  - Were reviewed by an expedited review process, unless the reviewer justifies why CR would enhance protection of subjects
  - Have progressed to the point that they involve only data analysis or “accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care”
- A brief progress report that will be reviewed administratively will be required. Reasons for this include the need to:
  - Account for active research
  - Track recruitment
  - Update personnel
  - Facilitate study-specific COI disclosures



# Modifications

- IRBs assess changes in the research;
- Assess if criteria for approval are still satisfied or must be reevaluated.
- **Common Return Criteria**
  - Clear explanation of changes not provided;
  - Description of modification does not match changes in documentation;
  - Changes are described but not incorporated;
  - Supporting documentation not attached.

# Rascal Tip (Review Attachments)

- Archive superseded documents;
- Review content of attachments for currency, accuracy, outdated approval stamps, and inclusion of new requirements;
- Review correspondence from previous approval.



# Violations & Deviations

- **Deviation:** A divergence to address a temporary situation that is identified by the research team **and approved by the IRB before implementation.**
- **Violation:** A divergence implemented **without prospective approval by the IRB** and was not implemented to avoid or minimize imminent harm
  - **Major Violation:** Violates rights and welfare of subjects, negatively affects the integrity of the study or results in the need for a change to the protocol or consent document(s).
    - Report promptly via modification module, generally within one week (**5 business days**)
  - **Minor Violation:** Violations that are not UPs and do not meet the criteria to be considered major violations.
    - Report at time of continuing review (renewal) or via modification if continuing review is not required.
    - Report via list or log that includes all UPs, deviations, and violations.

# Unanticipated Problems

- IRBs evaluates if event meets criteria:
  - unexpected (in terms of nature, severity, or frequency);
  - related or possibly related to participation in the research; and
  - suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
- **Some violations can also be UPs, as can some AEs**

# Closures

- IRBs assess the reason for closure;
- Ensures research procedures, including data analysis, are complete.

Once a study is closed in Rascal, the researchers **can no longer make changes to the protocol**

# Rascal Tips (File Naming & Correspondence)

- Name files logically for administrative review & for your use;
- Communicate with the reviewer by Rascal correspondence or another method:
  - Cover letter with initial submission;
  - Correspondence or attached “response” with resubmissions;
  - Attach letter to explain unusual or complex collaborations, centers, affiliations, procedures, etc.



# Questions?



# IRB 101

## Requirements for Informed Consent



# Objectives

- Discuss General Requirements for Consent
  - Basic Elements of Consent
  - Additional Elements of Consent
  - Criteria for Waiver or Alteration of Consent
  - Criteria for Waiver of Documentation of Consent
- Posting of Clinical Trial Consent Forms

# Informed Consent: General Requirements

- Obtain legally effective informed consent of the **subject** or the subject's **legally authorized representative**.
- Seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative **sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.**

## Informed Consent General Requirements *(continued)*

- Information given must be in language understandable to the subject or the legally authorized representative.
- Must be provided with information that a **reasonable person would want to have in order to make an informed decision about whether to participate,** and an opportunity to discuss that information.

# Informed Consent General Requirements *(continued)*

- Concise and focused presentation of **key information** to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research.
  - Organized and presented in a way that facilitates comprehension.
  - Include sufficient detail; no lists of isolated facts.

# Broad Consent

- One time consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.
- Specific consent elements required.
- Refusal of broad consent eliminates future waiver by IRB.

**No plans to implement broad consent at this time**

## Informed Consent: General Requirements *(continued)*

- No exculpatory language where one is made to waive or appear to waive any legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence
  - **Exculpatory:** *By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.*
  - **Acceptable:** *By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the research described above.*

# Basic Elements of Consent

#1	The involves research; explanation of the purposes, duration of participation, procedures to be followed, and identification experimental procedures.
#2	Reasonably foreseeable risks or discomforts to the subject.
#3	Benefits to the subject or to others expected from the research.
#4	Alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
#5	The extent, if any, to which confidentiality of records identifying the subject will be maintained.
#6	> Minimal Risk: Compensation and whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
#7	Whom to contact for answers to pertinent questions.
#8	Participation is voluntary.
#9	Coded data/specimens may be used for future research without additional informed consent OR information or biospecimens, even if identifiers are removed, <u>will not</u> be used or distributed for future research studies.

# Additional Elements of Consent

#1	The treatment or procedure may involve unforeseeable risks to subject (or fetus).
#2	Reasons for termination of the subject's participation.
#3	Additional costs to the subject.
#4	Alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
#5	Consequences of withdrawal and procedures to terminate.
#6	Significant new findings that may affect a subject's willingness to continue will be communicated.
#7	Number of subjects.
#8	Specimens may be used for commercial profit & if the subject will/will not share in profit
#9	If clinically relevant research results will be returned & if so, under what conditions
#10	If the research will include WGS



# Consent Templates

- Rascal Consent Form Generator
- Minimal Risk Consent Templates

Each template or module has suggested language for each element to easily satisfy all criteria

# Posting of Clinical Trial Consent Forms

- For each clinical trial conducted or supported by a Federal department or agency that has signed on to the Common Rule, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.
  - ClinicalTrials.gov; and
  - A docket folder on Regulations.gov (Docket ID: HHS-OPHS-2018-0021).
- Guidance will be provided soon

# Waiver of Consent

In order for an IRB to waive or alter consent, the IRB must find and document the:

#1	Research involves no more than minimal risk
#2	Research could not practicably be carried out without the waiver or alteration.
#3	If using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such identifiable information.
#4	The waiver or alteration will not adversely affect the rights and welfare of the subjects
#5	Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

# Waiver of Documentation of Consent

An IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds any of the following:

<b>#1</b>	<b>The only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality.</b>
<b>#2</b>	<b>The research presents &lt; minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.</b>
<b>#3</b>	<b>If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.</b>

## Waiver of Documentation of Consent *(continued)*

- In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or legally authorized representatives with a **written statement** regarding the research.
  - Information Sheet
- In addition, the research record/consent process note must **document that elements of consent were presented orally to the subject, and that key information was presented first.**

# Questions?



# IRB 101

## Vulnerable Populations

# Objectives

- Discuss the different vulnerable populations
  - Subpart B
  - Subpart C
  - Subpart D
- IRB Review requirements
- Consent requirements



# Regulations

- **Vulnerable Population:** Individuals who may be at increased susceptibility to coercion and/or undue influence
- DHHS regulations refer to five vulnerable populations
  - Children;
  - Prisoners;
  - Individuals with impaired decision making capacity; and
  - Economically or educationally disadvantaged persons.
- Subparts C, D of 45 CFR 46
  - Subpart B provides protection for pregnant women, fetuses and neonates

Vulnerable Population:	Regulatory Safeguard:
<b>Pregnant Women/Fetuses/Neonates</b>	<b>Subpart B</b>
Prisoners	Subpart C
Children/Minors	Subpart D

Institutional Guidance/Policies address additional groups:

- 1) Individuals with impaired decision making capacity and
- 2) Economically or educationally disadvantaged persons

# Subpart B: Pregnant Women/Fetuses/Neonates

- Applies to all research involving:
  - pregnant women,
  - human fetuses,
  - neonates of uncertain viability, or
  - nonviable neonates
- Duty of IRB: Review and approve only research which satisfies the conditions of this subpart

# IRB Review – Subpart B Conditions

a	Preclinical studies (pregnant animals) and clinical studies (including nonpregnant women) have been conducted and provide data to assess potential risks to pregnant women and fetuses.
b	Risk to the fetus is caused by interventions/procedures that have direct benefit for the woman or the fetus; If no such prospect of benefit, the risk to the fetus is not > minimal & purpose is the development of important biomedical knowledge which cannot be obtained by any other means.
c	Any risk is the least possible for achieving the objectives of the research.
d	<u>Mother's consent</u> required when: Research holds out the prospect of direct benefit to the pregnant woman, to both the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus.
e	Mother's & Father's consent required when: Research holds out the prospect of direct benefit <u>solely to the fetus</u> .
f	Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.

## IRB Review – Subpart B Conditions *(continued)*

g	For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part.
h	No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
i	Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
j	Individuals engaged in the research will have no part in determining the viability of a neonate.

**Specific requirements for research involving neonates - §46.205**

*Contact the HRPO for more information*

Vulnerable Population:	Regulatory Safeguard:
Pregnant Women/Fetuses/Neonates	Subpart B
<b>Prisoners</b>	<b>Subpart C</b>
Children/Minors	Subpart D

## Subpart C: Prisoners in Research

- Prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research.
- Purpose is to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.
- Applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

## Subpart C: Prisoners in Research

- *Prisoner* - any individual involuntarily confined or detained in a penal institution, including:
  - Individuals sentenced to such an institution under a criminal or civil statute;
  - Individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution; and
  - Individuals detained pending arraignment, trial, or sentencing.
- In other words...
  - A resident of a drug rehabilitation center who is in treatment as an alternative to jail would qualify as a “prisoner”.
  - Children in juvenile detention halls qualify as prisoners.



## Subpart C: IRB Composition

- A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
- At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity
  - **Prisoner Advocate**

# IRB Review of Prisoners in Research

- For research funded by DHHS, the institution must certify 7 findings to the Secretary that the required findings under Subpart C have been made.
- What is a subject becomes temporarily incarcerated while enrolled?
  - If the temporary incarceration has no effect on the study, he/she may remain enrolled as a study participant.
  - Remove the individual if he/she becomes permanently detained or involuntarily confined unless the study is re-reviewed under Subpart C.

*Consult with the HRPO*

Vulnerable Population:	Regulatory Safeguard:
Pregnant Women/Fetuses/Neonates	Subpart B
Prisoners	Subpart C
<b>Children/Minors</b>	<b>Subpart D</b>

**Children:** Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

## Subpart D: Children in Research – Definitions

- **Assent:** A child's affirmative agreement to participate in research.
- **Permission:** Agreement of parent(s) or guardian to the participation of their child or ward in research.
  - **Parent:** A child's biological or adoptive parent.
  - **Guardian:** An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

## Subpart D: Children in Research

When children or minors will be subjects, the IRB must determine one of 4 categories of research:

Category	Risk Level & Proposed benefit	Consent Requirements
§46.404/§50.51	No Greater than Minimal	One parent/guardian
§46.405 /§50.52	Greater than Minimal with prospective of direct benefit	One parent/guardian
§46.406 /§50.53	Greater than Minimal (minor increase over minimal risk) but no prospect of direct benefit	Both parents/guardians
§46.407 /§50.54	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.	Both parents/guardians

# Minimal Risk & Greater than Minimal Risk:

- Minimal Risk examples:
  - Survey or interview questions
  - Medical history review/record review
  - Non-invasive physical measurements
  - Blood draw (considering amount of blood drawn, age, weight and health of the child) – in general no more than 50 ml in an 8 week period
- > Minimal Risk examples:
  - Investigational drug for children with SMA
  - Randomization of children to one of two surgical approaches for club foot

## Greater than Minimal Risk no Benefit

When risks of the research are greater than minimal and there is no prospect of benefit, the IRB may approve such research if:

- The risk is a **minor increase over minimal risk**;
- The intervention or procedure are reasonably commensurate with actual or expected medical, dental, psychological, social or educational situations; and,
- Research is likely to yield generalizable knowledge about the subjects' disorder or condition
- Example:
  - Punch Biopsy >3mm from healthy children as controls

# Research Not Otherwise Approvable

When research is not otherwise approvable under the previous categories, and IRB may consider approval under 45CFR46.406 if:

- The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
- **The Secretary (DHHS) reviews the research and finds it approvable.**



# Consent/Assent Requirements

Applies to children 7 and older who are capable of assenting

- Common Assent Determinations Made by IRBs:
  - Ages 7 through 11: Written or verbal
  - Ages 12 through 17: Written
- A separate age appropriate assent can be provided or the child can co-sign the parental consent.

# Waiver of Assent

- In determining whether children are capable of assenting, the IRB takes into account:
  - Age;
  - Maturity; and
  - Psychological state of the children involved.
- Assent may be waived if the IRB determines:
  - Capacity limited such that they cannot reasonably be consulted;
  - Research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research; or
  - Research is consistent with waiver of consent under 45CFR46.116, even if children are capable of providing assent.

# Waiver of Parental Permission

- Parental permission may be waived if the IRB determines:
  - The research is designed for conditions or a population for which parental or guardian permission is not a reasonable requirement to protect the subjects
  - An appropriate mechanism for protecting the children who will participate as subjects in the research must be substituted
  - Waiver must be consistent with Federal, state or local law.
- Example when waiver of parental permission may not be appropriate:
  - When conducting research in schools where Federal Law (FERPA) requires consent of parents

# Research with Other Vulnerable Individuals

- When inclusion of subjects with a specific vulnerability is proposed:
  - Justify selection of this group;
  - Include plans for additional protections relative to vulnerability;
  - If status is variable, include plans for periodic assessment;
  - Clearly describe any special consent procedures;
  - Provide local or expert documentation, as applicable.

# IRB Submission Tips:

If your research involves vulnerable subjects:

- Ensure your protocol submission includes adequate information for the IRB to make the determinations required as outlined in the previous slides.
- As always, call the IRB office (contact information for individual staff on website) with any questions.

# References

- DHHS OHRP - Subpart B (Pregnant women, human fetuses and neonates)  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb>
- DHHS OHRP - Subpart C (Prisoners)  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc>
- DHHS OHRP - Subpart D (Children)  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>
- FDA - Subpart D (Children)  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.4>

# Questions?



# IRB 101

## IRB Reliance



# Agenda

- When is reliance needed/warranted?
- Types of reliance agreements
- Process for requesting reliance
- NIH Single IRB Review Policy
- Requirements for single IRB review
- Cooperative Research (Common Rule)

# Reliance Scenarios

- NIH sIRB Review Policy
- DHHS requirements for cooperative research
- Required by consortium or other group
- Other, case by case scenarios

# Word of Caution

- Reliance on another IRB means CU relies on the external IRB to document IRB Criteria for Approval ONLY
- CU review required to confirm local requirements:
  - Conflicts of Interest
  - Training Requirements
  - Local, ethical concerns

 **Rascal submission is ALWAYS required** 

# NIH Single IRB Review Policy for Multi-site Research

- Effective date: January 25, 2018
- Requires sIRB review for:
  - 2 or more domestic sites
  - Conducting the same protocol
  - Non-exempt research
  - Minimal risk (usually expedited review) or > minimal risk (convened review)
- Very few exceptions
  - Training (T), Career (K), Fellowship (F) awards
  - Designated single IRB of record is unable to meet the needs of specific populations
  - Local IRB review is required by federal, tribal, or state laws or regulations
  - Compelling reason
- Policy: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>

# Requirements for grant submission

- Notify HRPO
  - Complete reliance request form
  - HRPO assesses applicability of policy
  - HRPO provides letter of support
- If policy applies
  - sIRB plan
  - Concurrence from all collaborators
  - Proposal for sIRB
  - Estimate of IRB review fees
- In most cases, when CU is applicant, rely on independent IRB to serve as sIRB
  - Provides estimate

# NIH sIRB Review Policy – Quick Reference:

- NIH funded or supported
- Competing grant applications (new, renewal, revision, or resubmission)
- Receipt date on or after January 25, 2018
- Non-exempt research
- Conducted at U.S. domestic sites
- Multi-site research

# Common Rule “2018 Requirements”

- Published January 2017, amended January 2018, effective July 2018 for optional implementation of 3 provisions
- Compliance date for most elements = January 21, 2019
  - Informed consent requirements (e.g., key information)
  - Elimination of continuing review for certain research
  - Requirement to post consent forms for certain research
- Compliance date for single IRB review = January 20, 2020
- 20 agencies (including HHS) intend to follow the revised Common Rule (Subpart A of 45 CFR 46)
  - FDA is not considered a Common Rule agency because its regulations differ from the Common Rule.

**List of Common Rule Departments and Agencies:**

<b>DEPT. OR AGENCY</b>		<b>CFR CITATION (2018 REQUIREMENTS)</b>
1	Department of Homeland Security	6 CFR Part 46
2	Department of Agriculture	7 CFR Part 1c
3	Department of Energy	10 CFR Part 745
4	National Aeronautics and Space Administration	14 CFR Part 1230
5	Department of Commerce	15 CFR Part 27
6	Social Security Administration	20 CFR Part 431
7	Agency for International Development	22 CFR Part 225
8	Department of Housing and Urban Development	24 CFR Part 60
9	Department of Justice	28 CFR Part 46
10	Department of Labor	29 CFR Part 21
11	Department of Defense	32 CFR Part 219
12	Department of Education	34 CFR Part 97
13	Department of Veterans Affairs	38 CFR Part 16
14	Environmental Protection Agency	40 CFR Part 26
15	Department of Health and Human Services	45 CFR Part 46
16	National Science Foundation	45 CFR Part 690
17	Department of Transportation	49 CFR Part 11
18	Office of the Director of National Intelligence	Follows CR because of EO 12333, as amended
19	Central Intelligence Agency	Follows CR because of EO 12333, as amended
20	Consumer Product Safety Commission	16 CFR Part 1028



# sIRB Requirement

- “Cooperative Research”
  - ...” are those projects covered by this policy that **involve more than one institution**. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy.” 45 CFR 46.114(a)
- IRB to be designated by the funding agency
  - **Any institution located in the United States** that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB **will be identified by the Federal department or agency** supporting or conducting the research or proposed by the lead institution **subject to the acceptance of the Federal department or agency** supporting the research. 45 CFR 46.114(b)

# Exceptions

- 45 CFR 46.114(b)(2)
  - (i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or
  - (ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

# Recent interpretation

- sIRB requirement for cooperative research applies to all new federally funded research approved  $\geq$  January 21, 2019
  - In other words, multisite studies approved *between*
    - January 21, 2019 (compliance date for most Common Rule revisions) and January 20, 2020 (compliance date for sIRB review for cooperative research)
    - ...must be transitioned to sIRB review no later than January 20, 2020
- What we are doing
  - Identifying funded studies that have to transition
    - Will need to contact funding agency with proposal for sIRB
  - Implementing procedures to proactively identify need for sIRB review
    - Will need to be involved at grant application stage
    - Plan to follow NIH criteria (e.g., assessment, sIRB plan, estimate)

# Overview

- January 25, 2018 – NIH Policy for sIRB Review for Multisite research
- January 21, 2019 – Compliance date for most Common Rule provisions (“2018 Requirements”)
- January 20, 2020 – Compliance date for sIRB review requirement for federally funded\* multisite research  
*\*Funded by a Common Rule agency*

# Consortiums or other Groups

- StrokeNet
- Perinatal Research Consortium (PRC)
- NeuroNext

Currently CU serves as the Reviewing IRB for StrokeNet, PRC and others.

CU relied on Partners IRB for regulatory review of NeuroNext research protocols

## Other Case by Case Scenarios

- When another IRB asks to rely on CU for regulatory review or asks CU to rely on their IRB for regulatory review
  - Requires an Institutional Authorization Agreement (IAA)
- When an investigator is not affiliated with an institution that has an IRB or is not participating in research under their home institution's affiliation
  - Requires an Individual Authorization Agreement (IIA)

# Reliance Process

- Submit a reliance request form to the IRB:
  - Addresses:
    - Collaborating sites
    - Research at each site
    - Funding
- HRPO will assess and confirm if we will rely on another IRB for regulatory review or serve as the Reviewing IRB.
- Appropriate agreement executed

**All Reliance scenarios require a submission in Rascal!**

# Questions?





Please complete our Evaluation!

<https://www.surveymonkey.com/r/VLDSSSC>

# Columbia University Irving Medical Center:

- [irboffice@columbia.edu](mailto:irboffice@columbia.edu)
- 212-305-5883

## IRB Liaison Schedule: PH 10 (Irving Institute)

- Monday: 3-4pm
- Wednesday: 10-11am
- Thursday: 10-11am

Open Office Hours: Tuesday 10-11am (154 Haven)

# Columbia University Morningside

- **Morningside Open Walk-In Consultation Hours:**
  - Mondays, 4:00-5:00 pm, School of Social Work, Rm 306
  - Thursdays, 9:00-10:00 am, 405 Schermerhorn
- **Manhattanville Open Walk-In Consultation Hours:**
  - Tuesdays, 10:00-11:00 am, Studebaker Bldg, Rm 320

Or call for an appointment for a different time

212-851-7040

askirb@columbia.edu

- **<https://research.columbia.edu/irb>**