IRB 101

Columbia University
Human Research Protection Office

May 9, 2019

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Agenda

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

IRB 101

Foundations

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Objectives

- Human Research Protection Office
- Institutional Review Boards
- Scope of IRB authority
- Terminology
- Rascal electronic system

Facilitate compliance through a better understanding of the IRB review process and requirements

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

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

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

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.

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-l 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

Regulatory Compliance

- “Compliance” = adherence to requirements of applicable federal regulations, state laws, and policies, GCP (e.g., ICH E6 guidelines), sponsors and the IRB
- 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

HRPO is here to help!

- Presentations for staff, department, school
- Consultations (details later)
- Monthly IRB-Investigator meetings
- Staff directory on website
- Consent form templates
- Suggested consent form language
- Workshops

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?

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Research Ethics History

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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

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

20th Century

Walter Reed (1900)

- Yellow Fever experiments
  - 1898: Spanish American War
  - 968 soldiers killed in combat
  - 5000+ died of disease, mostly Yellow Fever
- United States Army Yellow Fever Commission
- 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.”

PHS Study of Syphilis (1932-1972)

- Significant health problem
  - Initially, no intent to deny treatment
- Complete physical exam, medical history taken
  - Followed for 6-8 months without treatment
- New follow-up study started in late 1933
  - New procedures to strengthen scientific validity, control group
  - No information provided about true nature of study: “government doctors” were examining people for “bad blood”
- Penicillin accepted as curative treatment in 1943
  - Not provided
  - Exemption from draft to keep subjects in study

Nazi Prisoner Experimentation (1939-1944)

- Morally abhorrent research conducted by German Scientists on concentration camps prisoners
- Experiment conditions/methodologies included:
  - High Altitude
  - Freezing
  - Sulfanilamide
  - Twin experimentation
  - Poison
  - Among others….

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;…
- In no case was the experimental subject at liberty of his own free choice to withdraw from any experiment. …

Nuremburg Trials (1945-1946)

- All of the experiments were conducted with unnecessary suffering and injury and but very little, if any, precautions were taken to protect or safeguard the human subjects from the possibilities of injury, disability, or death.
- In every one of the experiments the subjects experienced extreme pain or torture, and in most of them they suffered permanent injury, mutilation, or death, either as a direct result of the experiments or because of lack of adequate follow-up care.
- Twenty-four individuals were indicted, along with six Nazi organizations determined to be criminal

Nuremburg Code (1947)

- The results of the research must be useful and unobtainable by other means.
- The study must be rationally based on knowledge of the disease or condition to be studied.
- It must avoid unnecessary suffering.
- The study cannot include death or disabling injury as a foreseeable consequence.
- Its benefits must outweigh its risks.
- The study must use proper facilities to protect participants.
- The study must be conducted by qualified individuals.
- Participants may withdraw from the study if they wish.
- Investigators must be prepared to stop the study should participants die or become disabled as a result of participation.

Declaration of Helsinki (1949)

- Included General Principles
- Risks, Burdens and Benefits
- Vulnerable Groups and Individuals
- Scientific Requirements and Research Protocols
- Research Ethics Committees
- Privacy and Confidentiality
- Informed Consent
- Use of Placebo
- Post Trial Provisions

Declaration of Helsinki (1949)

- Provides basic principles for medical research and reaffirmed the Nuremburg Code
- Expands voluntariness of the Nuremburg Code significantly
- Discusses what human research is and why it is necessary
- Stresses the obligation of the physician to prioritize the participant's health
- Discusses monitoring of special populations

Fernald School (1946,1950-53)

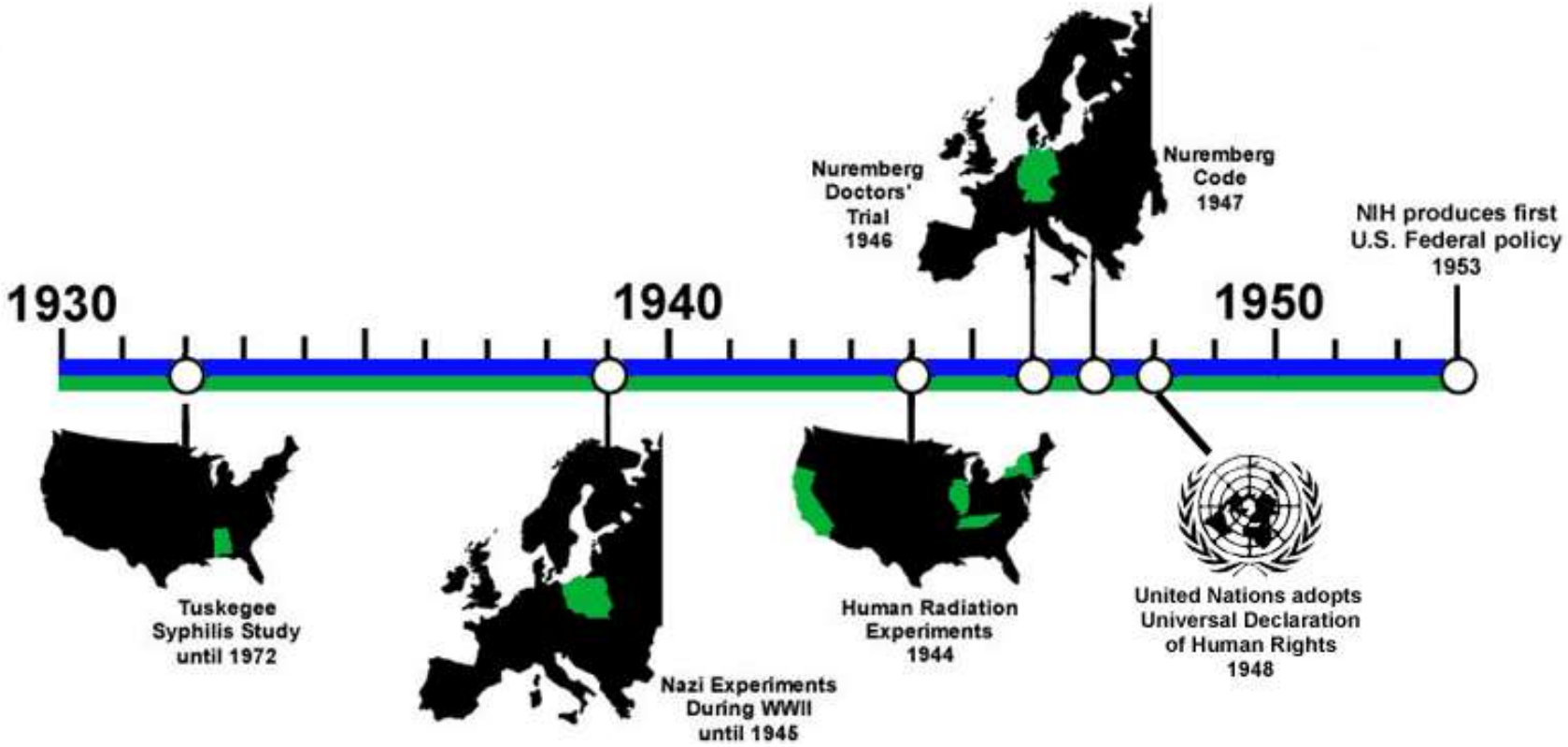
- Massachusetts Institute of Technology researchers and Fernald staff members
- Studies with radioisotopes at the school
- The first study, in 1946, exposed seventeen students to radioactive iron.
- The second study exposed fifty seven subjects to radioactive calcium between 1950 and 1953.

Fernald Radiology Consent Document

- Misleading information implies benefits
- No mention of radioisotopes
- Coercive
- Active consent not required

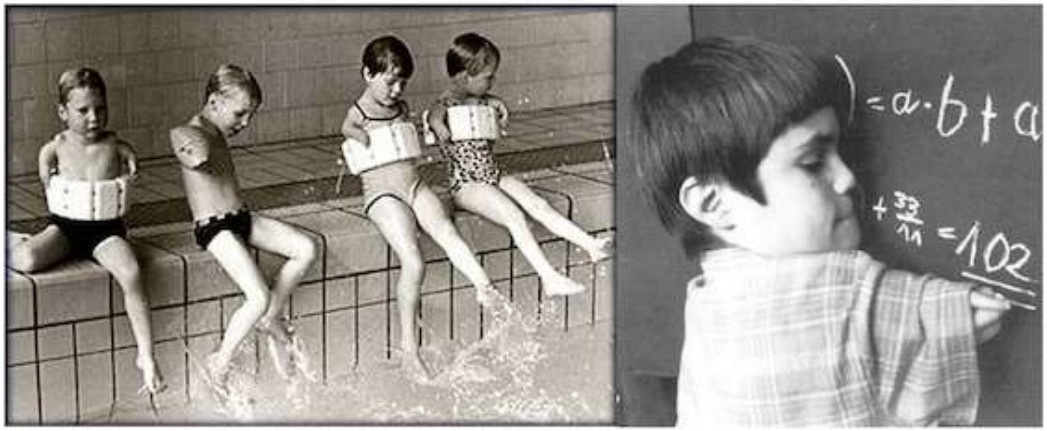
Rise of Ethical Codes

- 1947: Nuremburg Code
- 1949: Declaration of Helsinki



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)

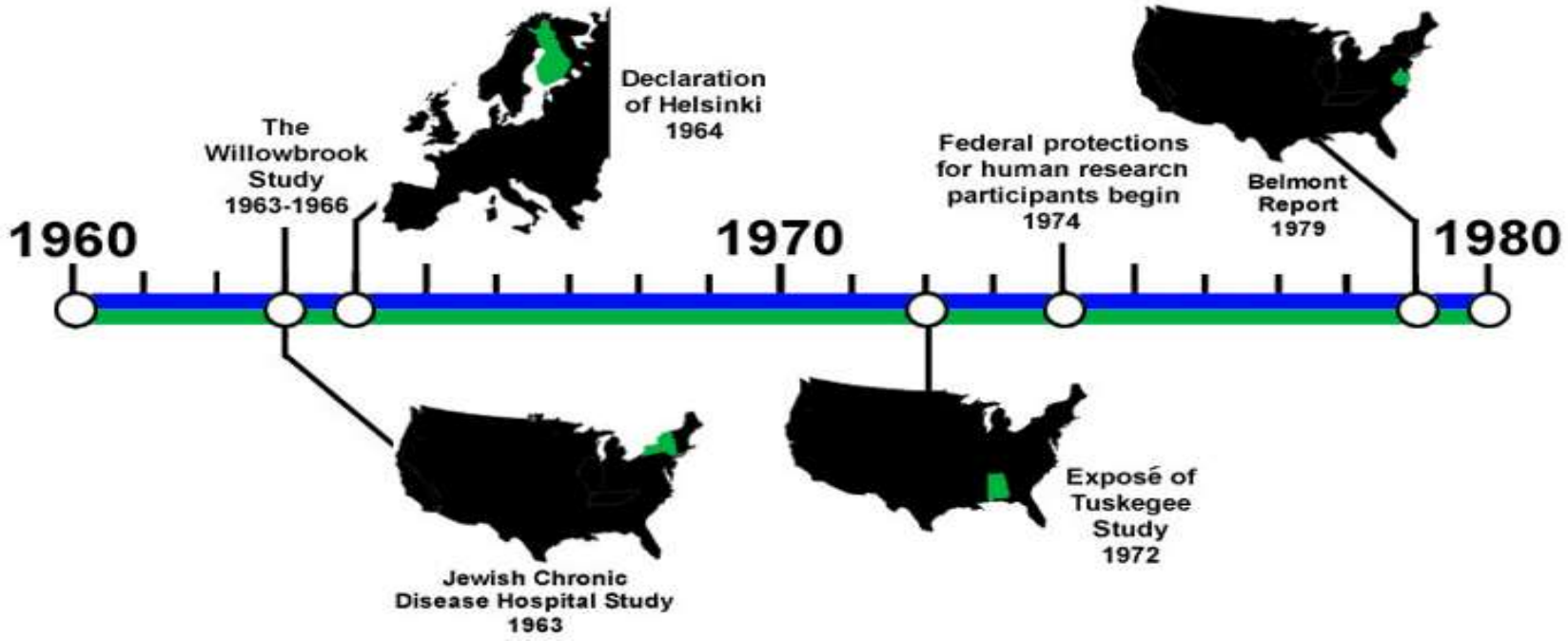
- New York University researchers
- Willowbrook State School, located on Staten Island
- Residents were injected with a mild form of hepatitis serum
- The researchers hoped to find a treatment for the virus by studying the disease in it’s earliest stages

Milgram Obedience Study (1961)

- Recruitment by newspaper ad:
  - $4.50 for one hour's work
  - Psychology experiment investigating learning and memory
- Involved deception
- Individuals were asked to give what appeared to be real electric shocks to another person
- The researchers wished to test how far subjects would follow the orders of an experimenter
- 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 Discussion

- 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 Discussion

- 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 - Then and Now

- Basic regulations governing the protection of human subjects in research supported or conducted by DHHS published in 1974
- Based on the Belmont Report, DHHS revised and expanded its regulations for the protection of human subjects in the late 1970s and early 1980s.

Regulatory Framework - Then and Now *(continued)*

- 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)
  - Additional regulations for drugs, devices, biologics

2018 Requirements

- “Revised Common Rule”
  - “2018 Requirements”, “2018 Rule”, “Revised Common Rule”
- DHHS and 15 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?

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IRB Criteria for Approval

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Objectives

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

IRB Criteria for Approval

- Federal regulations at 45 CFR 46.111 & 21 CFR 56.111 incorporate guidance, codes and ethical reports for research with humans
- In order to protect human participant in research, the IRB must ensure proposed research meets, and in some cases, continues to meet, specific criteria for approval.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

IRB Criterion #1

Risks to subjects are minimized:

(i) by using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk, and

(ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

IRB Criterion #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. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).
- The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

IRB Criterion #3

- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

IRB Criteria #4 - #6

- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, §46.116
- Informed consent will be appropriately documented or appropriately waived in accordance with §46.117.
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

IRB Criterion #7

When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(i) The Secretary of DHHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.

IRB Criterion #8

For purposes of conducting the limited IRB review required by §46.104(d)(7)), the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the following determinations:

> If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

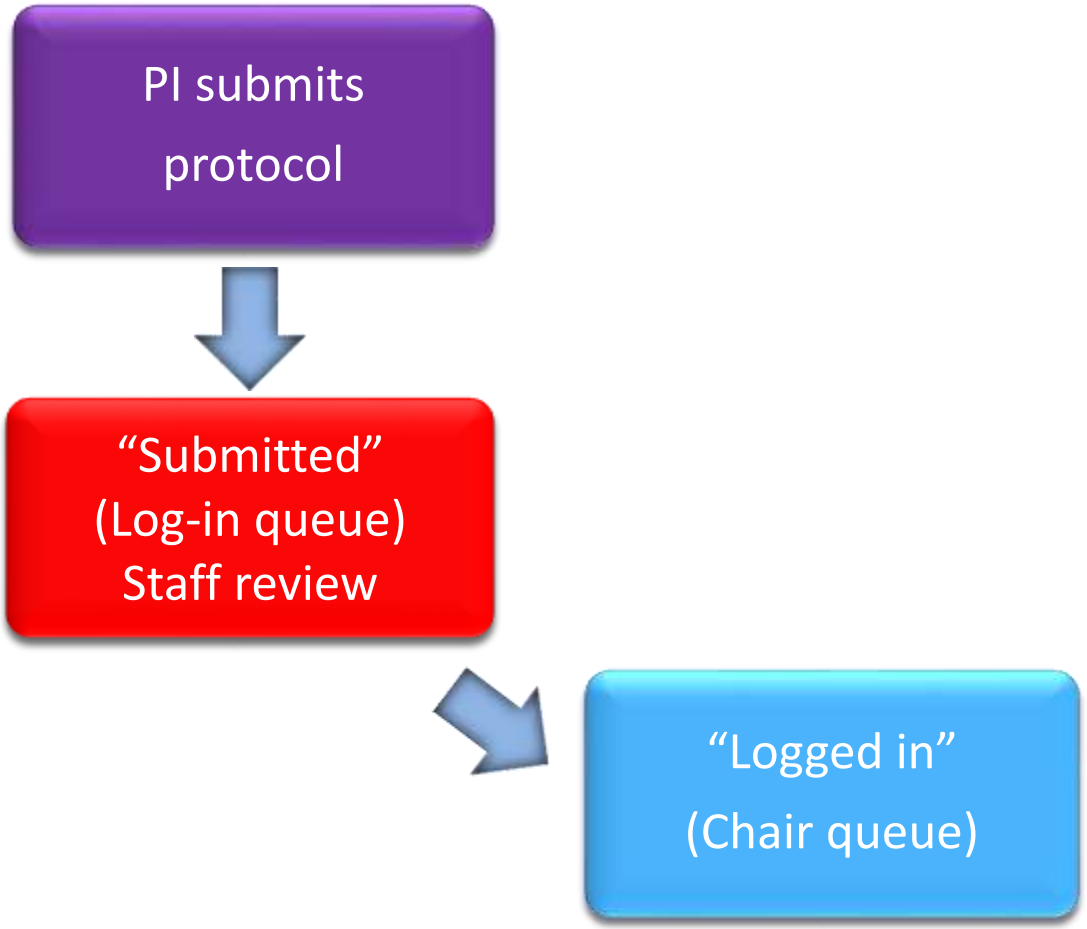
IRB Review of Events

- New Protocols
- Modifications
- Continuing Review
- Unanticipated Problems
- Closures

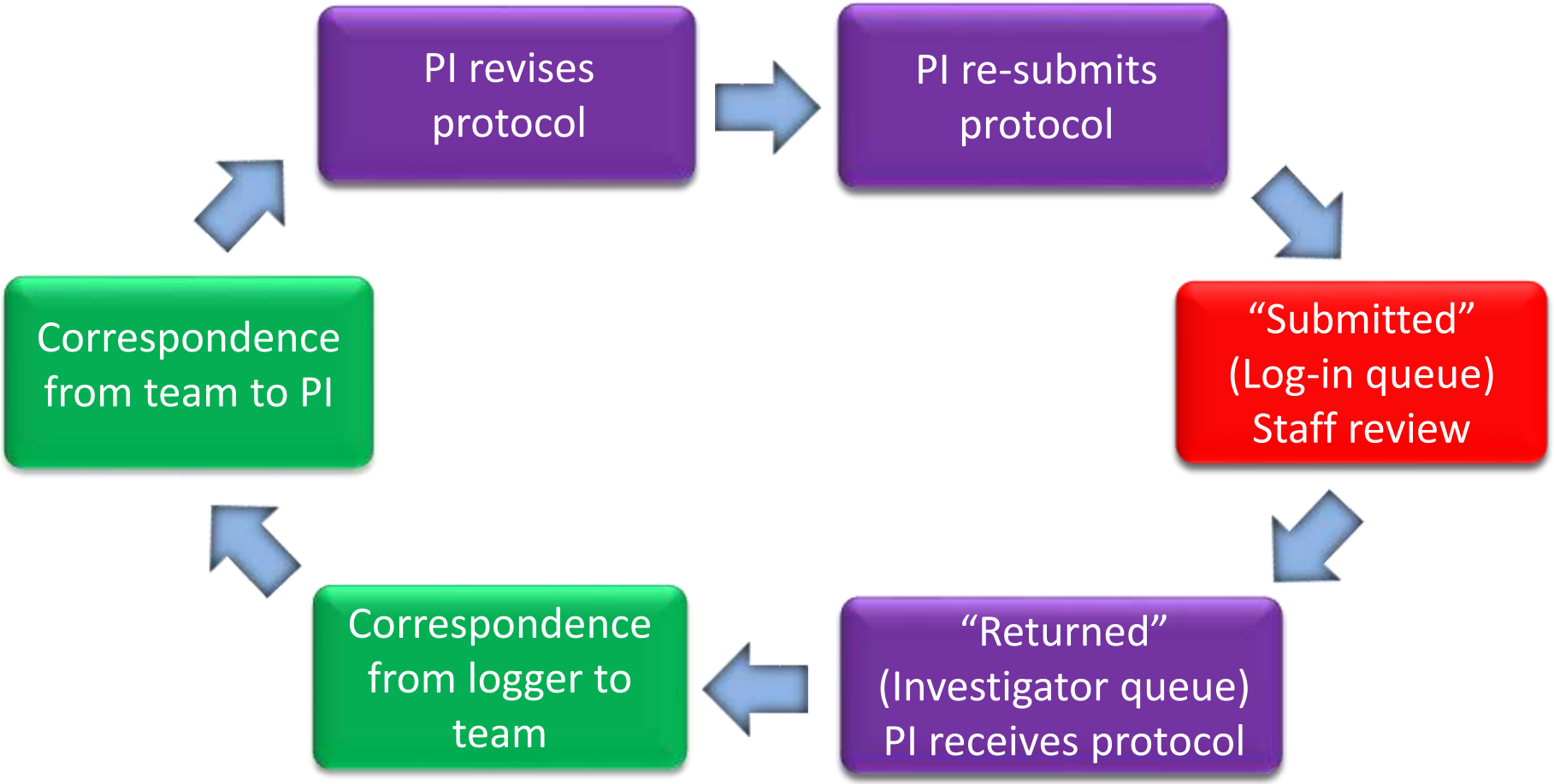
Administrative staff use checklists

or templates for review

New Protocol Pathway (Ideal)



New Protocol Pathway (Common)



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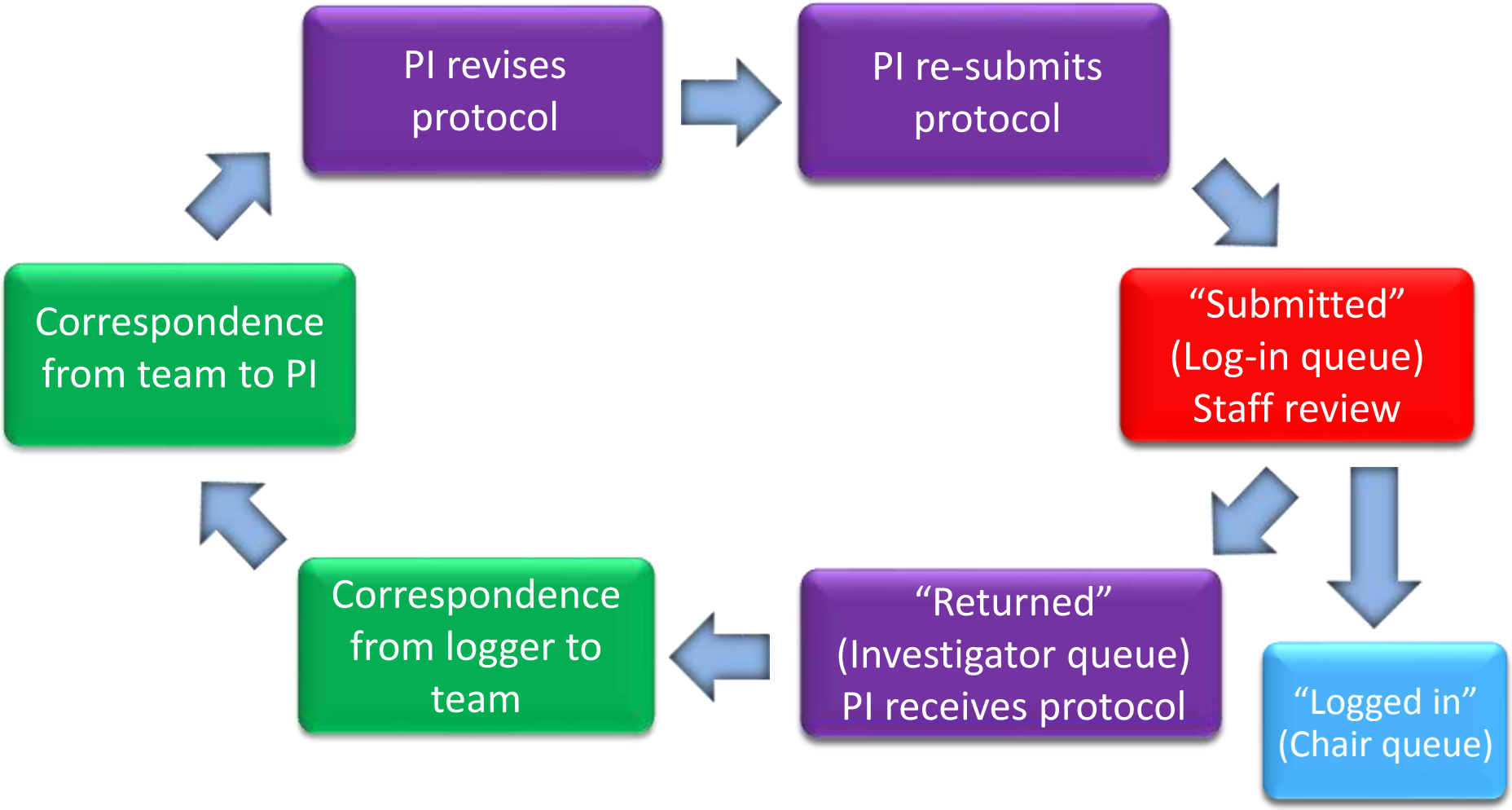


Rascal Tip (Clarity)

- 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 – 2018 Requirements

- Eligible studies 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

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.

Modifications

- IRBs assess changes in the research;
- Assess if criteria for approval are still satisfied or must be reevaluated

- **<u>Common Return Criteria</u>**
  - 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.

Unanticipated Problems

- IRBs assess the event;
- Evaluates if the event meets criteria of an UP:

  Any incident, experience, or outcome that is:

  - 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.

Closures

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

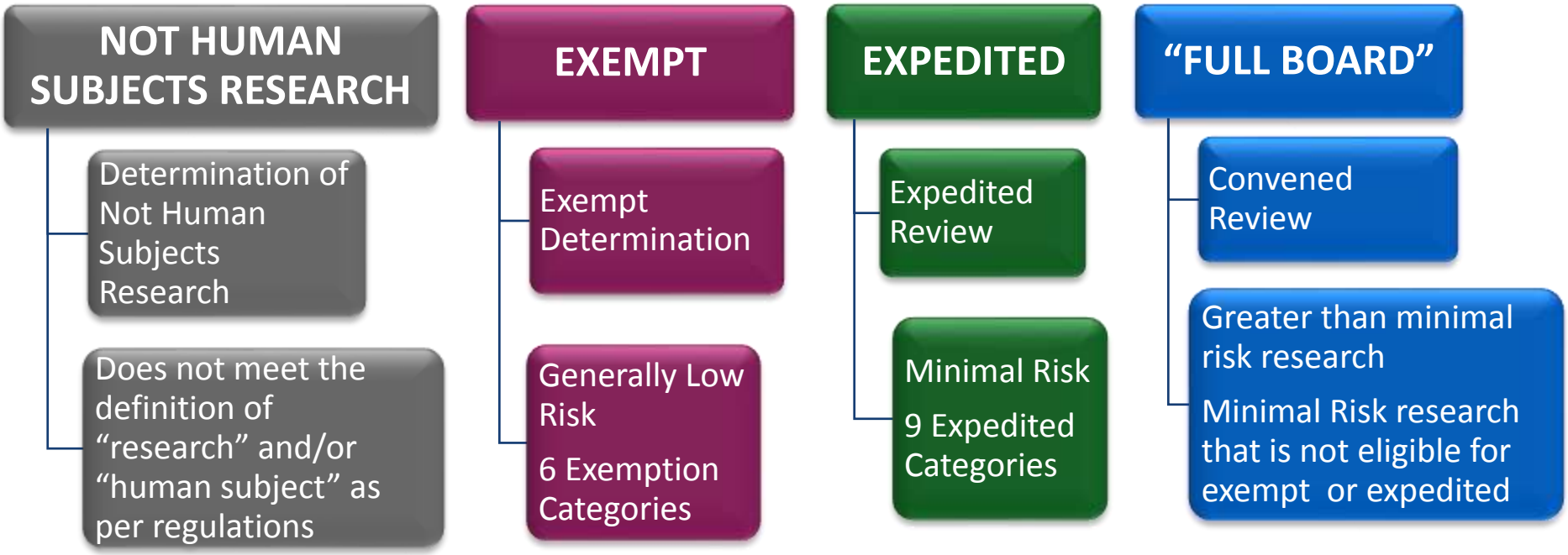
Once a study is closed in Rascal, the Principal Investigator no longer has access to the submission

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.

Levels of IRB Review

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.



Questions?

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Requirements for Consent

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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

1) Before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.
2) An investigator shall 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)*

3) The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.
4) The prospective subject or the legally authorized representative must be provided with the 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)*

5) Except for broad consent obtained in accordance with paragraph (d) of this section:

(i) Informed consent must begin with a concise and focused presentation of the key information that is most likely 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. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

(ii) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

Broad Consent

- One time consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.
- Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or nonresearch purposes) *is permitted as an alternative to the informed consent requirements.
- 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 informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Basic Elements of Consent

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or to others which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

Basic Elements of Consent *(continued)*

- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and

Basic Elements of Consent *(continued)*

One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

1) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
2) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional Elements of Consent

1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;
2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent;
3) Any additional costs to the subject that may result from participation in the research;
4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;

Additional Elements of Consent *(continued)*

6) The approximate number of subjects involved in the study;
7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

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, 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).

Waiver of Consent

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

(i) The research involves no more than minimal risk to the subjects;

(ii) The research could not practicably be carried out without the requested waiver or alteration;

(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

(v) 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:

(i) That 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. Each subject (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

(ii) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or

Waiver of Documentation of Consent *(continued)*

(iii) 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.

Note: *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.*

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

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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:
Pregnant Women/Fetuses/Neonates	**Subpart B**
Prisoners	Subpart C
Children/Minors	Subpart D

Institutional Guidance/Policies address:

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 conducted or supported by the Department of Health and Human Services (DHHS).

- Duty of IRB: In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

IRB Review – Subpart B

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

IRB Review – Subpart B *(continued)*

c) Any risk is the least possible for achieving the objectives of the research;

d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

IRB Review – Subpart B *(continued)*

e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

IRB Review – Subpart B *(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; and

j) Individuals engaged in the research will have no part in determining the viability of a neonate.

Subpart B Consent Requirements:

- If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus and the risk to the fetus is minimal, consent of ONLY the pregnant woman is required.
- If the research holds out the prospect of direct benefit to the fetus only, then the consent of the pregnant woman AND the father must be obtained. The father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.

Vulnerable Population:	Regulatory Safeguard:
Pregnant Women/Fetuses/Neonates	Subpart B
Prisoners	**Subpart C**
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

An Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

a) 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.

b) 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, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

What is Considered Minimal Risk?

Definitions of Minimal Risk:

- Subpart C: “Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.
- Subpart A: Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

IRB Review of Prisoners in Research

- Prisoner representative must participate in IRB review.
- The majority of the Board must have no association with the prison.
- For research funded by DHHS, the institution must certify 7 findings to the Secretary that the required findings under subpart C have been made.
- The research cannot commence until OHRP has approved the research.

IRB Review Requirements (Certification)

- The research under review represents one of the categories of research permissible under §46.306(a)(2);
- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

IRB Review Requirements (Certification)

- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- The information is presented in language which is understandable to the subject population;

IRB Review Requirements (Certification)

- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Approvable Categories of Research w/Prisoners

- Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

Approvable Categories of Research w/Prisoners

Research on conditions particularly affecting prisoners as a class

- *(for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)* provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research.

Approvable Categories of Research w/Prisoners

Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

- In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

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

Subpart D: Children in Research

- Applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.
- Children are 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.
- Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.
- Parent means a child's biological or adoptive parent.
- Guardian means 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

No Greater than Minimal Risk

- The IRB may approve research if it finds that the risks of the research are no more than minimal.
- Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- 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

Greater than Minimal Risk w/Benefit

The IRB may approve research that presents more than minimal risk to children and which:

- Holds out the prospect of direct benefit for the child or
- By a monitoring procedure that is likely to contribute to the child's well being

The IRB must find that the risk is justified by the anticipate benefit, and the risk/benefit ratio is at least favorable to children as available alternatives

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 presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; and,
- The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition.
- Example:
  - Anesthesia administered for research MRI (Correlation Research)

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

- Obtain Assent from Child
- Parental Permission from Parent or Guardian

Per the regulations:

- The IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.
- The IRB shall determine that adequate provisions are made for soliciting the permission of each child's parents or guardian

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:
  - The capability of some or all of the children is so limited that they cannot reasonably be consulted;
  - That the intervention or procedure involved in the 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

Rascal:

Child Involvement

Please refer to the Columbia University IRB policy on research involving children for further information.

RISK/BENEFIT DETERMINATION

'Minimal risk' means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

***Select the option below that best describes your study.**

- ◯ No more than Minimal Risk (45 CFR 46.404/21 CFR 50.51; i.e., 'Section 404')
- ◯ Greater than 'Minimal Risk' with the prospect of direct benefit to the subjects. (45 CFR 46.405/21 CFR 50.52; i.e.,'Section 405')
- ◯ Greater than 'Minimal Risk' with NO prospect of direct benefit to the subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR 46.406/21 CFR 50.53; i.e., 'Section 406')
- ◯ Research not included in one of the above categories but which otherwise presents an opportunity to understand, prevent or alleviate a serious problem affecting the health and welfare of children. (45 CFR 46.407/21 CFR 50.54; i.e., 'Section 407')

WARDS AND FOSTER CHILDREN

***If 'Section 406' or 'Section 407' research was indicated, the inclusion of wards or foster children requires additional information and, if the research will be conducted in New York City (NYC), approval from the NYC Administration for Children's Services (ACS). Please select the appropriate option below.**

- ◯ This research has not been categorized as 45 CFR 46.406 ('Section 406') or 45 CFR 46.407 ('Section 407').
- ◯ This research has been categorized as 45 CFR 46.406 ('Section 406') or 45 CFR 46.407 ('Section 407') but the enrollment of wards or foster children is not anticipated.
- ◯ This research has been categorized as 45 CFR 46.406 or 45 CFR 46.407 and the enrollment of wards and/or foster children is anticipated.

ASSENT OF SUBJECTS

Assent of the child is required except in limited circumstances. The first step in determining whether assent is required and/or appropriate is to assess whether the children who will participate in the study will be capable of providing assent. The next step is to determine, for children who are capable of providing assent, whether assent will be obtained or should be waived.

***Indicate whether the children who will be enrolled in this study will generally be capable of providing assent.**

- ◯ Some or all are expected to be capable of providing assent.
- ◯ None are expected to be capable of assent.

PARENT/GUARDIAN PERMISSION
Permission of parents/guardians of the children is required except in limited circumstances. Permission from one parent/guardian is acceptable for research categorized as Section 404 or Section 405 unless waiver of informed consent is approved or the IRB determines that permission from both parents is warranted.

***Select the parental permission option that applies to your study, and provide the rationale for your response if justification is requested. For most studies, one selection is appropriate, however, if more than one option applies, select all that apply.**

- ☐ The permission of one parent/guardian will be obtained.
- ☐ The permission of both parents/guardians will be obtained. - THIS IS REQUIRED IF YOU HAVE CATEGORIZED YOUR RESEARCH AS 45 CFR 46.406 OR 45 CFR 46.407
- ☐ No parental permission will be obtained because each of the following waiver criteria for waiving parental permission apply (45 CFR 46.408(c)):
- ☐ No parental permission will be obtained because the involvement of children in this research meets the criteria for a complete waiver of consent (45 CFR 46.116(d)), which is requested in the "Recruitment and Informed Consent" section.

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

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Objectives

- Common Terminology
- When is reliance needed/warranted?
- Types of reliance agreements
- Process for requesting reliance

Common Terminology

- **IRB Reliance:** two or more institutions in a multisite or collaborative study agree to rely on one IRB (Reviewing IRB) to review, approve and monitor study procedures at those institutions.
- **Single IRB:** the IRB of record (aka Reviewing IRB), selected on a study-by-study basis, which provides the ethical review for all sites participating in a multi-site study. (NIH FAQ)
- **Central IRB:** the IRB of record that provides the ethical review for all sites participating in more than one multi-site study. The sites are usually in a network, consortium or particular program. (NIH FAQ)

Common Terminology *(continued)*

- **Reviewing IRB:** The IRB that provides review for a human subjects research project, i.e., frequently called the “IRB of record”. When one IRB is reviewing for more than one participating site in a multisite or collaborative research project, the IRB is either a “single IRB” or a “central IRB”. Both “single IRB” and “central IRB” relationships are designed to help streamline IRB review, and the terms are sometimes used interchangeably.
- **Relying Site:** An institution that is participating in human subjects research and has ceded responsibility for IRB review of such research to an IRB that is not affiliated with the institution
- **Local context:** Knowledge of the institution and community environment in which human subjects research will be conducted. (Mayo)

Common Terminology *(continued)*

- **Local requirements:** A component of local context, specifically referring to applicable institutional policies or other requirements, and applicable local, state, or other laws or statutes.
- **Reliance agreement:** a written agreement that establishes the relationship between a Reviewing IRB and one or more site(s) that are distinct from the entity that supports the Reviewing IRB and will be conducting the research under review.
- **IRB Authorization Agreement:** a reliance agreement (see definition). The sample reliance agreement posted on the Office for Human Research Protections (OHRP) website is the origin of the term, “IRB Authorization Agreement”.

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 sIRB Review Policy

- Previously independent IRB review for multi-site research
- Revised NIH Policy applies to domestic sites of NIH funded multi-site research where each site will conduct the same protocol
- Policy aims to streamline the IRB review process for sites that are conducting the same protocol.

It does ***not*** apply to career development, research training or fellowship awards.

WIRB serves as the Reviewing IRB for research subject to the NIH sIRB Review Policy

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

DHHS Cooperative Research

- Supported by any Federal Department or Agency
- Non-exempt, cooperative research
  - *"those projects …that involve more than one institution"*
- Conducted at domestic sites
- Reviewing IRB determined by Federal Agency
- **Effective date: January 20, 2020**

Consortiums or other Groups

- Perinatal Research Consortium (PRC)
- StrokeNet
- NeuroNext

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

CU **relies on** University of Cincinnati for StrokeNet & **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 Investigator 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?

Columbia University Irving Medical Center:

- 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)