Navigating the IRB Process

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Objectives

- Be able to describe the purpose of an IRB
- Be able to identify information that is needed by the IRB to make a determination of Human Subjects Research OR Not Human Subjects Research (NHSR)
- Be able to describe the research process
- Be able to identify information that is needed by the IRB to make a determination

What is the HRPO

- Office that provides a comprehensive and systematic mechanism designed to protect the rights, dignity and welfare of individuals who are the subjects of research conducted by the Organization's clinicians, staff, or students.
- Components:
  - **Institutional Review Board (IRB)**: Coordinates and supports the activities of the three federally mandated Human Research Review Committees (IRBs) responsible for reviewing and approving all human research protocols and reviewing reportable new information.
  - **Education and Outreach:** Provides education and training of the Carilion Clinic human research community, including IRB members. Conducts interactive Research Education Sessions (RES) through the review of study files and data collection tools at the discretion of the IRB Committees or HRPO Director, or at the request of the researcher.
  - **Quality Assurance/Quality Improvement**: Supports internal continuous quality improvement through evaluation, assessment, and action of the program.

“To use human beings as subjects in medical experiments – or any type of research – is a special privilege which carries with it special ethical responsibilities.”

-- Harold T. Shapiro

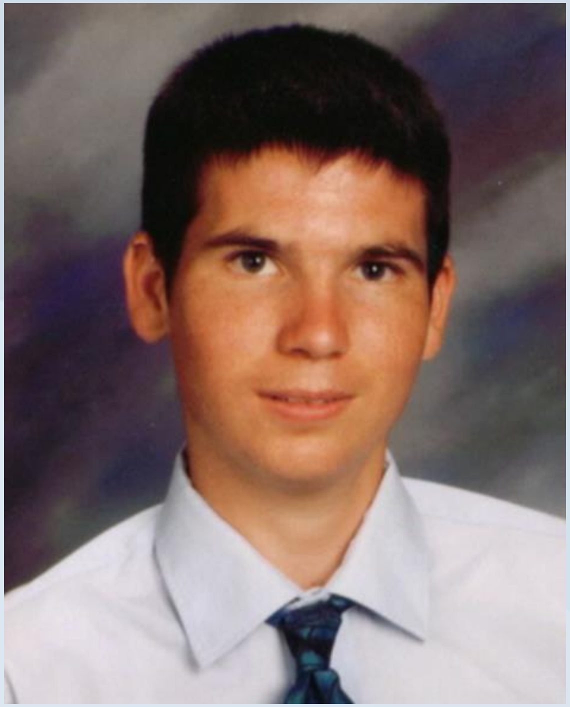
What is an IRB's Purpose?

- Protect the rights and welfare of human research subjects.

What is an IRB?

- Committee composed of at least 5 members
- Expertise appropriate to the research
- At least one scientist, one non-scientist
- At least one member not otherwise affiliated with the institution
- Regulated by OHRP, FDA, state laws, and local policy

Research Volunteers



Jesse Gelsinger, 18, first person publicly identified as having died in a clinical trial for gene therapy.

Ellen Roche, 24, healthy volunteer who died 28 days after inhaling hexamethonium

Outcomes

- 1974: IRB review mandated by Congress
- "Common Rule" (1991, 2018/2019)

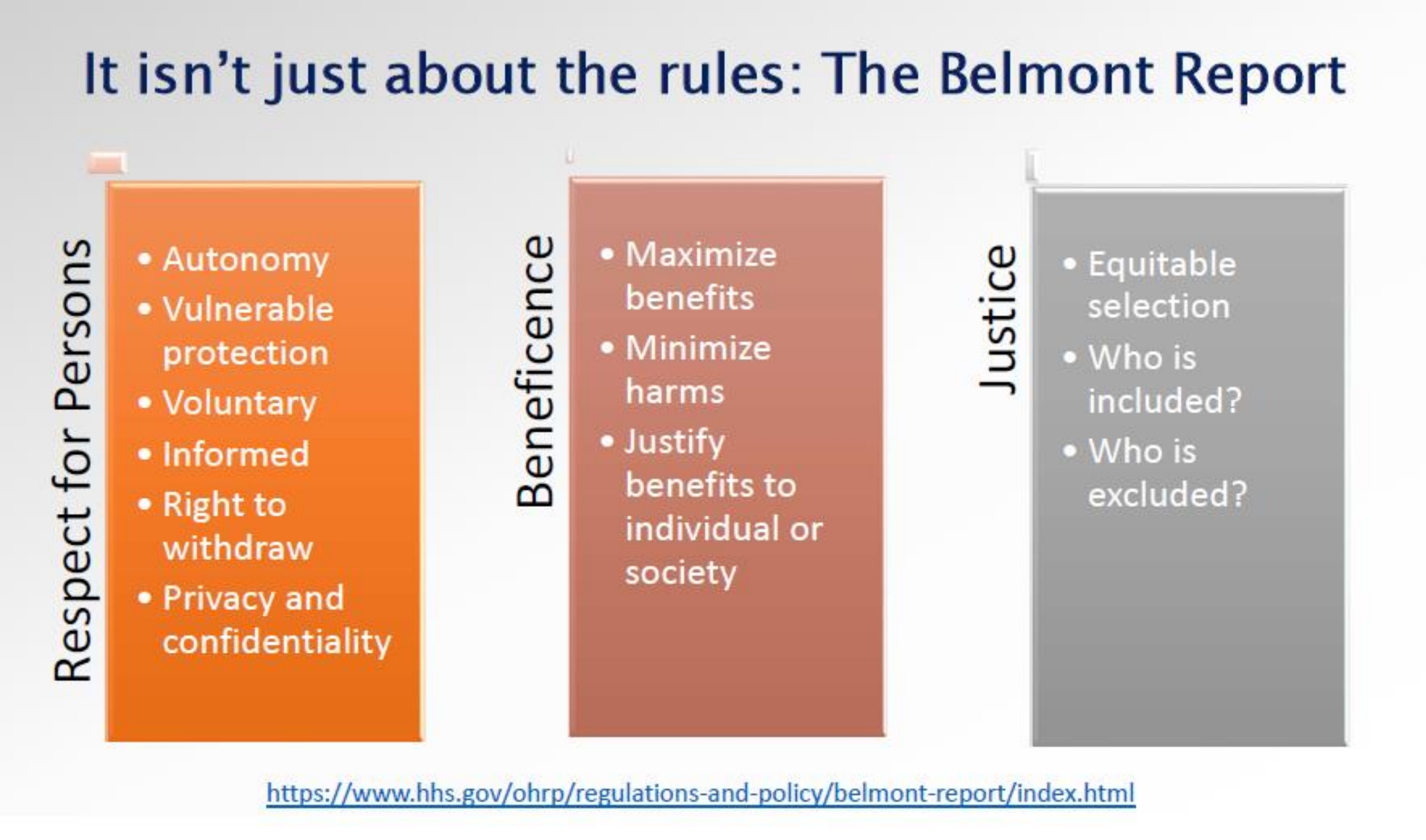
45 CFR 46: Protection of Human Subjects

Subpart A: The Common Rule - Basic Protections

Subpart B: Pregnant Women, Fetuses & Neonates

Subpart C: Prisoners

Subpart D: Children



It isn't just about the rules: The Belmont Report

Respect for Persons

- Autonomy
- Vulnerable protection
- Voluntary
- Informed
- Right to withdraw
- Privacy and confidentiality

Beneficence

- Maximize benefits
- Minimize harms
- Justify benefits to individual or society

Justice

- Equitable selection
- Who is included?
- Who is excluded?

https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Research Ethics: A Shared Responsibility

Regulatory Agency

IRB

Research participant

Sponsor

Research Team

Research Process at Carilion

- Complete online CITI training in Biomedical Research AND Good Clinical Practice (if FDA regulated or NIH-funded) AND COI (if externally funded)
- Consult with HART if will need any data extracted from medical records or using REDCap for data storage
- Have the PI submit the REDCap R&D Department Level Review Form, which will need signoff by the Department Chair or Nursing Leadership
- If externally funded, ensure Annual COI disclosure is accurate
- Submit IRB Application, which requires PI and Chair signoff

Note: Collaboration between Carilion and VT should be discussed with each IRB BEFORE the IRB application is started.

IRB Pre-review Process of Submission

- Assessment of review type and risk determination (NHSR, Exempt, Expedited, Full Board)
- Verification of completion
- You will receive feedback on your application with requested clarifications or changes
- IRB process will be on hold until you respond
- IRB will ensure all questions have been addressed
- Will then proceed to signoff or Full Board Review

IRB Review Methods

- Determination of Not Human Subjects Research (NHSR)
- Exempt (minimal risk)
- Expedited (minimal risk)
- Full Committee Review (greater than minimal risk OR the committee needs to make a risk assessment)

Human Subjects Research definitions

- Research: a systematic investigation designed to develop or contribute to generalizable knowledge
- Human Subject: a *living* individual about whom an investigator conducting research obtains
  - data through interaction or intervention with the individual, or
  - identifiable private information or identifiable biospecimens

Determination of Not Human Subjects Research (NHSR)

- Determined to not meet Human Subjects Research definition, and therefore does not require IRB review
- QI/QA is ONE type of NHSR determination
- Later changes do not need to be submitted to IRB unless change would impact NHSR determination
- REDCap (preferred) or secure shared drive for data storage
- HIPAA for healthcare use applies

Similarities Between Research and QI

- May involve human participants
- Are concerned with inquiry
- Are processes in which empirical or systematic inquiry generates a question that data collection is designed to answer
- Propose a set of outcome measures that will support proposal
- Testing solutions
- Involve critical evaluation of data

Quality Improvement

Goal: Correct workflow processes, improve efficiencies, reduce variations in care, address clinical administrative or educational problems, improve a specific institutional practice in comparison with an established standard or goal

What are we trying to accomplish?

How will we know that a change is an improvement?

What changes can result in improvement?

Human Subjects Research vs. Quality Improvement

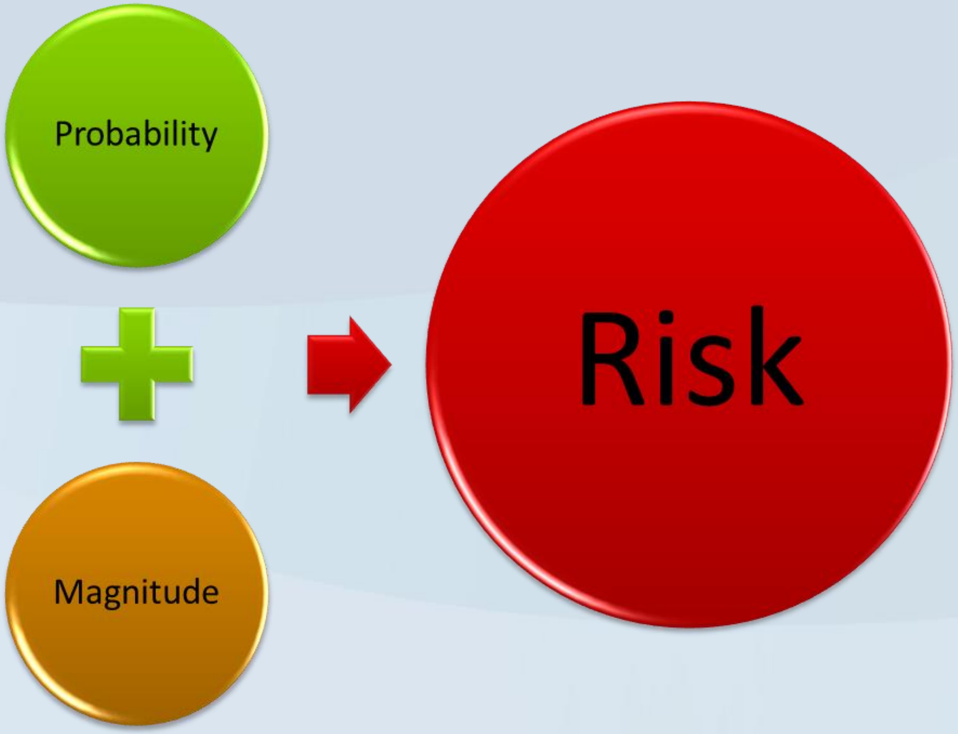
	Human Subjects Research	Quality Improvement
Purpose	systematic investigation designed to develop or contribute to generalizable knowledge	designed to implement knowledge, assess a process or program through established/accepted standards
Starting Point	knowledge-seeking is independent of routine care and intended to answer a question or test a hypothesis	knowledge-seeking is integral to ongoing management system for delivering health care
Design	follows a rigid protocol that remains unchanged throughout the research	adaptive, iterative design
Benefits	might or might not benefit current subjects; intended to benefit future patients	directly benefits a process, system or program; might or might not benefit patients
Risks	may put subjects at risk	does not increase risk to patients, with exception of possible patients' privacy or confidentiality of data
Participant Obligation	no obligation of individuals to participate	responsibility to participate as component of care
Endpoint	answer a research question	improve a program, process or system
Analysis	statistically prove or disprove hypothesis	compare program, process or system to established standards
Adoption of Results	little urgency to disseminate results quickly	results rapidly adopted into local care delivery
Effect on program or practice	Findings of the study are generally not expected to immediately affect or change practice	Findings of study are expected to directly and immediately affect institutional practice
Publication/Presentation	investigator obliged to share results	QI practitioners encouraged to share systematic reporting of insights

Based on information from https://www.thehastingscenter.org/wp-content/uploads/The-Ethics-of-Using-QI-Methods.pdf

Risk Determination

- *Minimal risk* means that probability and magnitude of harm or discomfort anticipated in research are not greater in and of themselves than those ordinarily encountered in daily life or during performance of routine physical or psychological examinations or tests.
    - » 45 CFR 46.102(i)
    - » 21 CFR 50.3(k)

Risk Assessment



Probability

Magnitude

Risk

Exempt from IRB Review

- Very Minimal Risk research that falls into specific categories defined in the regulations
- Reviewed by single member of IRB
- CITI training is required
- Abbreviated IRB application
- Written consent may not be required
- Does not require Annual Continuing Review
- Amendments submitted when a change could impact risk level
- PRE required when appropriate
- Closure requested
- REDCap (preferred) or secure shared drive for data storage
- HIPAA for research use applies (waiver needs to granted, when appropriate)
- Only the IRB can make the determination of Exempt - this cannot be determined by researchers!

Exempt Categories

1. Education research in commonly accepted educational settings
2. Surveys, interviews, educational tests, public observations (that do not involve children)
3. Benign behavioral interventions short in duration
4. **Secondary research use of identifiable data or specimens (note: can not be exempt if PHI shared outside of a HIPAA covered entity)**
5. Federal research/demonstration projects
6. Taste and food evaluation studies

Expedited Review

- Minimal Risk research that falls into specific categories defined in the regulations
- Expedited does not mean “fast”; it is a federal term used for research that must meet specific criteria (DHHS 45 CFR 46.110)
- Reviewed by single member of IRB
- **Usually** does not require Continuing Review
- All changes must be submitted as amendment and approved before implementation
- PRE required when appropriate
- May or may not require CR (if not, brief Annual Check-In required)
- Closure required
- REDCap (preferred) or secure shared drive for data storage
- HIPAA for research use applies (waiver needs to granted, when appropriate)

Expedited Review Categories

1. Clinical studies of drugs and medical devices only when certain conditions are met
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture in certain populations and within certain amounts
3. Prospective collection of biological specimens for research purposes by noninvasive means
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.
5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes
6. Collection of data from voice, video, digital, or image recordings made for research purposes
7. Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies

Full Board Review

- Greater than minimal risk research, or research that requires a risk determination by the full board
- Research determined to be greater than minimal risk always requires Continuing Review at least annually
- All changes must be submitted as amendment and approved before implementation
- PRE required when appropriate
- Closure required
- REDCap (preferred) or secure shared drive for data storage
- HIPAA for research use applies (waiver needs to granted, when appropriate)
- Committee meets twice a month

Components of the IRB Application

- Administrative
- Description
- Purposes, Objectives
- Study Design
- Statistical Analysis
- Subject Population
- Informed Consent
- Data Protection Plan/Confidentiality
- Study Procedures
- Recruitment
- Risks, Risk Minimization, and Benefits
- Costs and Compensation
- Safety and Monitoring/DSM
- Other study specific info

Good IRB Application/Protocol Writing Matters!

Costs of a badly written protocol?

- IRB will not approve
- Participants harmed or put at risk for data that does not have a benefit
- Inaccurate or biased results
  - Delayed FDA approval of a beneficial drug/device
  - FDA approval of a drug/device that does not have benefit or has unknown risks
- Monetary costs, including time
- Not reproducible

Administrative Information

- Descriptive title
- Sponsor
- Version number and version date
- Research team, responsibilities, required training
  - Only list those team members who are engaged in human subjects research!
- Location
- Collaborators
  - VTCSOM and VT are considered collaborators
- Funding/Sponsor
- Other study identifiers (IND#, Sponsor protocol #), as applicable
- Department Chair sign-off (scientific integrity, sufficient resources, investigator time commitment)
- Investigator signoff (at the end of IRB application)

Background and Rationale

- Brief, non-technical summary
- Detailed Introduction including background, rationale, and literature review
  - Provide scientific basis for the research question
  - Summary/Introduction
    - Brief description of what is currently known about the drug and/or disease condition to be studied
    - Background information
    - Justification for dose
    - Route of administration

*Not doing thorough literature search could put participants at risk or result in the IRB determining the study is not justifiable (ex: question already answered, risks not worth the potential benefit)

Study Design

- Description of the research study
  - Retrospective or prospective
    - Important in determining the type of IRB review
    - If retrospective, need dates
  - Study design
  - Randomization schedule, if applicable
- Description of study phases

Study Population

- Demographic information such as age, gender, ethnicity, health status
- Total number of subjects (describe if this number is including screen failures/subject withdrawals)
  - Ensure there is an adequate patient population early on!
- Inclusion/Exclusion criteria and method of verification
  - Age restrictions
  - Diagnostic methods (Hgb $\geq$ 12) to determine eligibility
  - Pre-existing conditions
  - Disallowed concomitant medications and/or treatment
- Inclusion of vulnerable populations (if applicable)

Informed Consent

- Provision of information so that the individual can make a voluntary, uncoerced decision whether to enroll and continue to participate.
- An ongoing process, not a document.

Informed Consent

- Written informed consent typically required if you are interacting with subjects OR collecting private health information from them
- Consent should include information about the purpose of the study, procedures, alternatives, and contact information
- Written consent can be obtained through a paper form or eConsent (REDCap)
- Verbal consent or waiver of consent may be granted in certain limited circumstances

Beyond the Form – Process Note

- Who obtained consent?
- Was amount of time sufficient?
- What questions did the participant ask?
- Were all questions addressed?
- Did participant receive all materials necessary to make informed decision?
- Was any COI disclosed?
- Was participant provided with copy of consent?

Remember:

- Even though you may have access to patient data for clinical care, you may not use it for RESEARCH without IRB approval.
- You have to have the consent of the patient/subject, **or** a waiver in writing from the IRB. Those are the only two permissible routes to research use.

When is Re-consenting Needed?

- When new information becomes available that may impact the risks and voluntariness of research;
- When participant enrolled as minor and has reached age of majority;
- If LAR provided initial consent but participant is now able to provide own consent;
- Should be described in IRB application if expected that participants may later be able to/need to provide consent

At any of these stages the participant may refuse to re-consent and withdraw from the study.

Data Protection Plan/Confidentiality

- Confidentiality refers to the researcher's agreement to handle, store, and share research data to ensure that information about research participants is not improperly divulged.
- Requirements for confidentiality protections apply to Protected Health Information/Personally Identifiable Information (PHI/PII) obtained:
  - preliminary to research (e.g., PHI/PII is obtained from private records to assess eligibility or contact prospective participants);
  - during data collection, analysis, and dispensation; and
  - after study closure (if PHI/PII is retained).

Routine Precautions to Protect Confidentiality

- Using minimum PHI/PII necessary to conduct the research
- PHI/PII are replaced with research identification codes (ID Codes)
- Access to master code lists or key codes is limited.
- Master lists are stored separately from the data and destroyed as soon as reasonably possible.
- Contact lists, recruitment records, or other documents that contain PHI/PII are destroyed when no longer required for the research.
- Research files stored securely, preferably in REDCap or in a secured Carilion shared drive
- Files are stored in a password protected computer, in a password-protected file and/or encrypted
- Research data/specimens are stored securely in locked cabinets or rooms.
- Files containing electronic data are closed when computers will be left unattended.
- Consent and HIPAA authorization forms are stored securely in locked cabinets or rooms, separately from the research data.
- Research staff are trained in the IRB-approved methods for managing and storing research data/specimens

Study Procedures

- Stepwise description of all study procedures described in detail
  - Initial evaluations, screening tests, required lab tests
  - Screening and allocation of subjects to study groups
  - Procedures for carrying out research-specific physical exams, vital signs, etc.
  - Estimate length of time for each procedure and overall visit
  - Required documentation and data collection tools to be utilized at each time point
  - Safety assessments at specific time points
  - Study visit schedule is helpful if multiple visits with numerous procedures

Helpful hints

- Build in study visit windows to allow flexibility and prevent protocol violations
  - Ex: a follow-up PET scan must be conducted on Day 30 **(+/- 5 days)** after the research drug infusion
- Differentiate between procedures for clinical care and research
- Clarify when common variation among clinicians for standard medical practice is permitted

Minimization of Risk

How Do We Assess?

- Identify the probabilities of harm
- Identify the magnitude of harm:
  - Severity
  - Duration
  - Reversibility
  - Number of people affected
- Identify safeguards, alternative procedures
- Make a plan to manage problems
- Data Safety Monitoring Plan (scheduled interim analysis)

What are the risks?

Types of Risks:

- Physical
- Psychological
- Financial
- Social
- Loss of Privacy/Confidentiality

Magnitude of Risks:

- Duration
- Frequency
- Aggregated effects
- Transience and reversibility

The proposing investigator must think of the <u>worst-case scenario</u> for every aspect of the study and have a plan in place to ensure subject safety if that scenario emerges.

Research Team Responsibilities

- The Principal Investigator is responsible for everything related to the study, including training of all sub-investigators
- Must have any changes to the study approved by the IRB
- Must report any serious adverse events, unanticipated problems, or other reportable events
- Must have the study re-approved by the IRB at least every 12 months.
- Must notify the IRB of final results and the conclusion of the study

Common Stumbling Blocks

- Study team: Incomplete CITI training
- Insufficient literature search: Has someone else already answered your question? What does your study add to what is known?
- Hypothesis: What question do you hope to answer? How will you know?
- Procedures/Method: Be clear what is research vs. what is standard care
- Statistical plan: Is it appropriate for your hypothesis and are there enough potential subjects?
- Risks: Once they're acknowledged, describe ways to reduce the chances of them happening.
- Inattention to detail: Signatures and departmental signoff required, CV of the principal investigator, lack of detail or inconsistent information
- Failure to respond to feedback: If no response to stipulations or other communications within 45 days, application may be withdrawn

CITI Training

- On-line course found at: www.citiprogram.org
- Biomedical training must be completed for all study team members before the IRB will accept the application.
  - Takes about 5-6 hours to complete.
- Covers areas such as history of research, ethics, consent process & HIPAA
- This is the bare minimum…GCP may also be required.
- Additional clinical research training and research study specific training encouraged!
  - SOCRA, ACRP

Post-approval

- PI to meet with research team regularly to review documentation of newly screened participants and consent forms
- Follow the protocol and maintain detailed and organized records
- Use the most recent IRB **stamped** informed consent document
- Draft a consent checklist
- Only personnel listed on IRB-approved application mat conduct study procedures
- If you realize you need to make changes, amend and get IRB approval BEFORE implement
- Prepare a complete Regulatory Binder
- Report violations promptly---what went wrong, why it happened, how you’ll prevent future problems (CAPA).

Approval Lapses

- All protocol-related activity involving participants must cease until approval is renewed (even if CR already submitted to the IRB)

  Exception: Protocol-related activity necessary for patient safety (example- a blood test to monitor for adverse effects of study drug). However, must contact IRB and receive permission

- If the sponsor or the FDA puts the study ‘on hold’:
  - Notify the IRB immediately and include reason.
  - See above.

PRIS3M

- https://carilionclinic.imedris.net

- Log in using Carilion username and password
- Your account in PRIS3M is created at your first log in
- If cannot find study team member that has a Carilion email, they must log in to the system one time
- External team members should be listed under “Collaboration” section
- System uses “Smartform”; application builds as you go
- User Manuals available under Help button

We welcome your questions!

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