Human Research Determination

Allison Blodgett, PhD, CIP
Director of IRB Operations
University of Massachusetts Medical School

Institutional Review Boards (IRB)

- Committee established to comply with federal regulations
- Protect the rights and welfare of all human subjects who volunteer to participate in research studies
- Review and approve protocol submissions, progress reports, modifications, and reports of new information/events

Guiding Principles

- **Respect for Persons (autonomy)**
  - Individuals should be treated as autonomous agents
  - Persons with diminished autonomy may need additional protections
- **Beneficence**
  - The principle of *beneficence* obligates the researcher to maximize possible benefits and minimize possible harm
- **Justice**
  - This principle requires that participants be treated fairly and involves questions such as: Who should bear the risks of research, and who should receive its benefits?

Federal Regulation / "Common Rule"

- The Code of Federal Regulations Title 45 Public Welfare Department of Health and Human Services National Institutes of Health Office introduced the proposal for Protection from Research Risks Part 46 Protection of Human Subjects

The Code Defines:

- IRB membership
- Criteria for approval of study
- Requirements for informed consent
- Documents for informed consent
- Keeping of IRB records

Definitions:

- Research – a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge
- Human subject – a living individual about whom an investigator (professional or student) conducting research obtains
  - Data through intervention or interaction, or
  - Identifiable private information

Definitions:

- Research – a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge
- Human subject – a living individual about whom an investigator (professional or student) conducting research obtains
  - Data through intervention or interaction, or
  - Identifiable private information

The Revised Common Rule (Jan 2019) includes the prospect of generating IPI

What needs IRB review?

- Activities that meet both of these definitions (research + human subject) require approval by the IRB
- Understanding the human subject activities in the project insures accuracy in the proposal

Case #1:

- Dr. Cimoneg is proposing to perform genomic studies on DNA samples that have been collected and banked by Dr. Michaels.
- Dr. Michaels maintains a database with the private identifiable information on the samples, but does not provide any identifying information with the samples.
- Is Dr. Cimoneg involved human subjects research?

OHRP Guidance OHRP – Guidance on Research Involving Coded Private Information or Biological Specimens

- OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.
- For example, OHRP does not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met:

- the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
  - **the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances,**
  - there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
  - there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

Is Dr. Cimoneg involved human subjects research?

- No
- Since Dr. Cimoneg is NOT receiving:
  - Data through intervention or interaction, or
  - Identifiable private information

Case #1A

- Dr. Cimoneg decides to apply for NIH funding for the project discussed in the previous slide.
- Dr. Michaels is listed as Key Personnel on the NIH proposal.
- Does the research involve human subjects?

Maybe

- Dr. Michaels DID obtain:
  - Data through intervention or interaction, or
  - Identifiable private information
- Cannot comply with the guidance since Dr. Michaels is the keeper of the code and key personnel.

Case #2

- Dr. Smith obtains samples of fat tissue that are discards from surgery. The samples are transferred to Dr. James for banking. Dr. Smith includes the following information about the patient to Dr. James for their biorepository:
  - Diagnosis, age, gender, race, ethnicity
- Is this human subject research?

YES

- The researchers would need IRB approval to collect the data since Dr. Smith is collecting:
  - Data through intervention or interaction, or
  - Identifiable private information

Case # 3

- Dr. Johnson received a grant to study the effects of alcohol on the elderly. Her grant ended July 31, 2011. Once her study was over she created a copy of the database and removed all private identifiable information. She currently uses the de-identified information for analysis.
- Is this human subject research?

NO

- The research is permanently closed to enrollment at this Institution.
- All subjects enrolled at this Institution have completed all-research related interventions and interactions, including interventions and interactions related to collection of long-term follow-up data.
- No additional identifiable private information about the subjects is being obtained by this Institution's investigator.
- Analysis of private identifiable information at this Institution is completed. (This can be checked even if a statistical center at another Institution will analyze private identifiable from subjects enrolled at this Institution.)

Quality Improvement ?

- Yes….if…..?
- No….if…..?
- Maybe if….?

Investigator Obligations:

- Do not commence research until you have the IRB approval letter **and** obtained all other required approvals,
  - Radiation Safety, Biosafety, COI Committees
  - Protocol Review Committees (Cancer, or CCTS PRC for Investigator-Initiated greater than minimal risk research that would not otherwise be peer reviewed)
  - Approvals of departments or divisions that require approval
- Comply with all requirements and determinations of the IRB.
- Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.

- Ensure that research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
- Investigators and research staff are required to complete initial training and continuing training at least every three years.
- Personally conduct or supervise the research.
- Conduct the research in accordance with the relevant current protocol approved by the IRB.

- Unless the IRB affirmatively approved a protocol to include the following populations, such subjects may **not** be enrolled:
  - Adults unable to consent
  - Children
  - Neonates of uncertain viability
  - Nonviable neonates
  - Pregnant women
  - Prisoners
  - Individuals unable to speak English

- When consent, permission, or assent are required by the IRB ensure that they are obtained and documented in accordance with the relevant current protocol as approved by the IRB.
- Follow the [Organization's] requirements to disclose financial interests.
- Retain research records (including signed consent documents)
- Employ sound study design in accordance with the standards of your discipline and design studies in a manner that minimizes risks to subjects.
- Update the IRB with any changes to study personnel.

- If you are the lead investigator of a multi-site study, ensure there is a plan to manage of information that is relevant to the protection of subjects, such as Unanticipated Problems Involving Risks to Subjects or Others, interim results, and protocol modifications, and submit that plan to the IRB with your protocol.
- If you plan to conduct community-based participatory research, you may contact the Community Engagement Group for information.

Consequences of not Obtaining IRB Approval

- Data collected may not be used.
- Publication may be rejected.

Institutional Consequences

- Jesse Gelsinger dies at 18 at UPenn
- Volunteered for gene transfer study
- What went wrong…(20 page FDA letter) Failed to …
  - Immediately report SAEs
  - Follow approved protocol
  - Incorporate FDA requests to consent form
  - Notify FDA of animal tests which suggest risk to humans
  - Ensure only eligible subjects were enrolled
  - Disclose conflict of interest

New York Times

- **WASHINGTON, Jan. 21**— The Food and Drug Administration temporarily shut down human gene therapy experiments at the University of Pennsylvania today after an inspection uncovered "numerous serious deficiencies" in ensuring patient safety during a clinical trial that cost an 18-year-old Arizona man his life. The decision to place the entire program -- eight experiments, including five active clinical trials in diseases ranging from cystic fibrosis to breast cancer -- on "clinical hold" is highly unusual. The hold is indefinite, agency officials said, and will not be lifted until the agency is convinced that the university's Institute for Human Gene Therapy can follow federal rules designed to protect study volunteers from harm.

- What do you do if you have questions whether IRB review is needed or if you think the research involving human subjects is not in compliance?
- Contact the IRB.

HUMAN RESEARCH DETERMINATION, FEASIBILITY & RESOURCES REVIEW

July 11, 2018

Covered Elements

- Element III.1.C. Researchers employ sound study design in accordance with the standards of the discipline. Researchers design studies in a manner that minimizes risks to participants.
- Element III.1.D. Researchers determine that the resources necessary to protect participants are present before conducting each research study.
- Element III.1.E. Researchers and Research Staff recruit participants in a fair and equitable manner.

Resources

- Feasibility Checklist
- Policies:
  - Investigator Guidance (HRP-800)
  - Worksheets - Criteria for Approval (HRP-400), Advertisements (HRP-402), and Payments (HRP-403)
- Protocol Review Committees
  - Cancer
  - CCTS for Investigator-Initiated greater than minimal risk research that would not otherwise be peer reviewed

ELEMENT III.1.C. SOUND STUDY DESIGN

Sound Study Design

- Assess if the research will address the needs of UMMS, UMMHC patients, or community
- Determine if study is realistic within existing constraints
- Maximize the chance of successful completion of the study while protecting human subjects.

Sound Study Design: Feasibility

- Is the protocol well designed?
- What experience does the research team have with similar studies?
- Are there plans for subject recruitment and retention?
- Are there plans for data collection and storage?
- Is the budget adequate to complete the research? Answer the research question?

Sound Study Design: Policies

HRP-400, IRB Criteria for Approval Worksheet:

Evaluate whether identified resources are sufficient, including:

- Time to conduct and complete the research
- Qualifications of investigators and research staff
- Access to eligible population appropriate to meet recruitment goals
- Medical or psychosocial services that subjects may need as a consequence of participation in research

ELEMENT III.1.C. MINIMIZE RISK

Minimize Risk: Feasibility

- Are frequent and/or Adverse Events (AEs) expected?
- Are there factors likely to impede enrollment?
  - Age, medical restrictions, frequency of visits, procedural discomfort, washout period, exclusions from other trials, duration of participation, other medical conditions
- Are there other considerations which would increase the complexity of conducting the study?

Minimize Risk: Policies

HRP-400 IRB Criteria for Approval Worksheet:

- Risks to subjects are reasonable in relation to anticipated benefits/importance of the knowledge expected to result
- Minimize risks to subjects by using procedures which:
  - Are already being performed on the subjects for other purposes
  - Don't unnecessarily expose subjects to:
    - Physical risks
    - Psychological risks
    - Social risks
    - Legal risks
    - Economic risks

ELEMENT III.1.D RESOURCE AVAILABILITY

Resource Availability

- Arrange for adequate resources to conduct research
  - Personnel
  - Time
  - Access to study population
- Monitor study progress to identify and address when additional resources are needed

Resource Availability: Feasibility

- What is the source of patients, will the PI have access to this population?
- Are there competing trials ongoing or in the pipeline?
- Are there specific facility requirements or qualifications, equipment, material handling?
- Is staffing sufficient to conduct the trial?

Resource Availability: Policies

HRP-800 Investigator Guidance:

- Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to:
  - sufficient investigator time,
  - appropriately qualified research team members,
  - equipment, and
  - space.

ELEMENT III.1.E FAIR & EQUITABLE RECRUITMENT

Fair and Equitable Recruitment

- Avoid practices that place participants at risk for coercion or undue influence
- Plan for recruitment and retention of an unbiased/representative patient population

Fair & Equitable Recruitment: Feasibility

- Are the inclusion/exclusion criteria reasonable to meet enrollment?
- Are the study timelines reasonable to meet enrollment?
- Have interpretation and, if necessary, translation services been planned?

Fair and Equitable Recruitment: Policies

HRP-402, Advertisements Worksheet

- Advertisement doesn't
  - imply benefits beyond what is in the consent and protocol
  - Include exculpatory language
  - Emphasize the payment with larger or bold type
  - Promise free treatment when intent is no additional charge for research participation
  - describe "new treatment, "new medication" or "new drug" without explaining it is investigational
  - include coupon/discount for product once it is approved
- Advertisement limited to the information needed by the public to determine eligibility and interest
- Advertisement claims are consistent with FDA labeling

Fair and Equitable Recruitment: Policies

HRP-403, Payments Worksheet

- The amount/method/timing of payment is neither coercive nor presents undue influence
- Credit for payment is progressive and not contingent upon completing the entire study
- Any bonus for completion wouldn't unduly influence subjects to stay in the study if they would have otherwise withdrawn
- All information concerning payment is described in the consent document

Important Contact Information

- Human Research Protection Program
- Oversee research protection for human subjects, provide training for investigators and research staff, ensure compliance with University policies, federal regulations, state laws and national standards
  - irb@umassmed.edu 508-856-4261
  - Director: Allison Blodgett
- CCTS Office of Clinical Research (OCR)
  - Assistance with contracts, budgeting, OnCore study set up
  - clinicalresearch@umassmed.edu 508-856-5200
  - Director: Danielle Howard

Important Contact Information

- CCTS Accelerator
  - Feasibility assessments, recruitment and retention consultations, IND consultations, protocol review
  - Clinical Research Navigator Ann.han@umassmed.edu
  - 508-856-1960
- CCTS Clinical Research Center (CRC)
  - Specimen processing facilities, clinical exam rooms, nursing and regulatory coordinator staff to conduct clinical research procedures
  - clinicaltrialsunit@umassmed.edu 508-856-2800
  - Manager: Celia Hartigan

Important Contact Information

- Science Participation Research Center (SPRC)
  - Special population consultations, cultural competency training, community and patient participation
  - German.chiriboga@umassmed.edu 508-856-8977
  - Project Director: German Chiraboga
- Research Computing Services
  - De-identified data, identified data, building and managing online surveys and databases using REDCap
  - ClinicalDataPortal@umassmed.edu

https://umassmed.service-now.com/sp

Important Contact Information

- Investigational Drug Service (IDS) Pharmacy
  - ids@umassmemorial.org 774-443-8667
- Radiation Safety
  - radsafety@umassmed.edu 508-856-3208
- Institutional Biosafety Committee (IBC)
  - Colleen Driskill, 508-856-5527
- UMMS Department of Emergency Medicine
  - EmergencyMedicineResearch@umassmed.edu
- Students as Study Subjects Ad Hov Advisory Group