Institutional Review Board

Fundamentals and Applications

Dr. Priya Manohar
Chair, RMU – IRB

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Motivation: Why IRB is needed?

- Past abuses in clinical research have led the Federal Government to mandate that researchers safeguard the rights and welfare of the people who are the subjects of their activities.
- Institutions that undertake clinical and/or government-funded research, including government facilities, are required to have an "Institutional Review Board (IRB)" and appropriate procedures and documentation to ensure that human subjects are protected.
- Federal laws govern the conditions under which research related to human subjects is to be conducted.
- Robert Morris University is committed to these laws based on moral, ethical, and legal grounds.

Applicable Documents: Legal and Ethical Basis for IRB

- The IRB is guided by Title 45 Code of Federal Regulations (CFR) Part 46
- The Ethical Principles and Guidelines For the Protection of Human Subjects of Research is provided by The Belmont Report
- Except for those categories specifically exempted or waived under 45 CFR 46.101 (b) (1-6) all other research will be reviewed by the IRB
- PA State Law Article §49.76 Research and Publication – Protection of Human Subjects
- RMU IRB Polices and Procedures Manual, June 2016

What is IRB's authority? What are IRB's tasks?

Federal regulations stipulate that an IRB can:

- Approve research.
- Disapprove research.
- Modify research.
- Conduct continuing reviews.
- Observe / verify changes.
- Suspend or terminate approval.
- Observe the consent process and the research procedures.

What are the possible consequences of not following IRB regulations?

- Suspension of research project
- Suspension of all of a PI's research projects
- Inability to use data or publish results
- Notification of sponsors, regulatory agencies, and funding agencies of noncompliance
- Debarment by FDA from using investigational products
- Inability to receive funding from federal grants
- Additional monitoring and oversight by the IRB and/or third party monitoring of research activities
- Termination of employment
- Loss of licenses
- Immediate shut-down of ALL research at an organization

RMU IRB – Where do I Start?

- Go to http://irb.rmu.edu/
- Create an account for yourself – if you are a RMU student, faculty or staff your RMU account (sentry secured login and password) will work
- Get appropriate CITI training on IRB – go to: https://www.citiprogram.org/
- Click on the big, red "Online IRB Application" button at the bottom of the page to apply online for IRB approval
- Your academic supervisor / project advisor must approve your application
- You should expect IRB's response within 2/3 weeks of submission
- Fill-in online IRB Application Form and submit
- More information on RMU IRB contact:

Lisa P. Nauman
Grants & IRB Speciaiist
Academic Affairs
irb@rmu.edu
412-397-6227 Phone
412-397-2528 Fax
Patrick Henry 210
Moon Campus

Essential Elements of IRB Application

- Informed Consent
- Recruiting Human Subjects for Research
- Background Research – must not be an ad hoc research – conduct literature search, form a hypothesis, exhibit due diligence in designing the experiment before attempting research on human subjects
- Research Protocol – what are the research procedures?
- Risks and Rewards – what would these procedures do to human subjects?
- Information and data security, protection of privacy

Informed Consent – 1: Basics

- Usually a paper and pencil based form is filled out and signed by the subject, however increasingly modern online tools are being used (they are covered in a separate slide).
- Prospective participants in a research study must understand the purpose, the procedures, the potential risks and benefits of their involvement, and their alternatives to participation.
- While a consent document gives this information, the opportunity to discuss any questions or concerns with a knowledgeable research team member is also important.
- Informed consent is about one's understanding and willingness to participate in a study and not about signing a form.
- Informed consent for minor children (under the age of 18) must be obtained from their parents or legal guardians.
- Making an informed decision about participating in research includes subjects having an understanding of the possible risks and benefits to their involvement, and knowing that they do not have to volunteer and can withdraw at any time.

Informed Consent – 2: Children's Consent

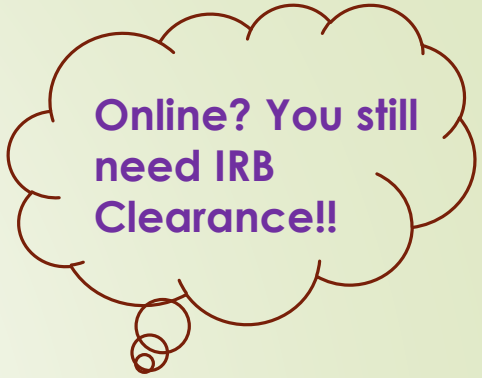
- If the minor is between the ages of 13 and 17, the parent or guardian **and** the child must give informed consent.
- If the minor is below the age of 13, the informed consent of the parent or guardian must be obtained and the child must be given an explanation of the research. This may entitle the use of a consent form especially prepared to facilitate the understanding by a minor of such age.
- Language level of the consent letter must be appropriate for the age of the child/minor so they can understand properly.

Informed Consent – 3: Ethical Principles

- **Autonomy:** Autonomy means that each person should be given the respect, time, and opportunity necessary to make his or her decisions. Prospective participants must be given the information they will need to decide to enter a study or not to participate. They should not be pressured to participate. The principle of autonomy requires that protection be given to potentially vulnerable populations such as children, the elderly, the mentally ill, or prisoners. Individuals in these groups may be incapable of understanding information that would enable them to make an informed decision about study participation. They are considered potentially "vulnerable." Consequently, careful consideration of their situation and needs is required and extra care must be taken to protect them.
- **Beneficence:** Beneficence obligates the researcher to secure the well-being of all study participants. It is the researcher's responsibility to protect participants from harm, as well as ensure that they experience the possible benefits of involvement.
- **Justice:** The concept of justice may be questioned when decisions are being made regarding who will be given the opportunity to participate and who (and for what reason) will be excluded. Participants should not be selected due to class, gender socioeconomic status, or race unless justified by study objectives.

Informed Consent – 4: New Tools

- Social networking websites (Facebook, Twitter, LinkedIn)
- Organizational websites
- Intercampus communication (calendars, newsletters)
- Podcasts
- Online video advertising (YouTube)
- Blogs
- Electronic bulletin boards (disease/disorder specific social and support groups)
- Email list-serves
- Text messaging
- Online marketplaces to recruit research subjects (Amazon Mechanical Turk, ClearVoice, GfK KnowledgePanel)
- Online research databases
  - National Institutes of Health's (NIH) ClinicalTrials.gov
  - CenterWatch
  - ResearchMatch.org
  - National Cancer Institute's (NCI) comprehensive cancer database-PDQ
  - AIDS Clinical Trials Information Service (ACTIS)



Informed Consent – 5: Assessment of Online Recruiting Tools

- If information posted on a website goes beyond just a directory listing with basic descriptive information such as title, purpose, summary is given then informed consent is not required. However, if information such as risks and benefits or compensation information is given, then IRB review of that multi-media tool and its IRB approval is required.
- When assessing **eIC** forms (electronic Informed Consent forms) pay attention to risk and benefit information to ensure it is presented in a fair and balanced manner.
- Make sure the information provided is not misleading.
- Address potential undue influence when the research offers either monetary or non-monetary incentives. (DHHS 2005)
- Other federal agencies that give more information on this topic:
  - US Department of Health and Human Services (DHHS)
  - DHHS's Office of Human Research Protection (OHRP)
  - National Institute of Health (NIH)
  - U.S. Food and Drug Administration (FDA)
  - Health Insurance Portability and Accountability Act (HIPAA) of 1996
  - Government agencies: DoE (Education), DOE (energy), NSF, DoD (defense), VA (veterans affairs)

Informed Consent - 6: Informed Consent Forms

- **Requirements of the Research Subjects:** Research subject must have a capacity to consent, the ability to exercise individual power of choice free from constraint or coercion, and an understanding of the information relevant to the decision. The ability to decide is based on four domains:

1. **Understanding**: The ability to understand information relevant to the decision to participate in a study, for example, the procedures, alternatives, potential risks and benefits, voluntariness, and ability to withdraw.
2. **Appreciation**: The ability to apply the information to one's own situation, for example, an understanding that:
   - The study may not provide direct benefit
   - The study protocols may be different from the current standard of care
   - The study may provide indirect benefits to others
3. **Reasoning**: The ability to incorporate information with personal values and potential consequences, for example, the ability to consider the relationship between the risks and benefits of a study.
4. **Expression of Choice**: The ability to freely choose to participate in a study, the ability to clearly communicate their choice to participate or not, including being able to express their option to withdraw.

Informed Consent – 7: How to Write Forms?

- National Cancer Institute (NCI) and Centers for Disease Control and Prevention (CDC) have come up with some general guidelines for writing IC forms. These recommendations are as follows:
- Using plain and simple language
- Avoiding abbreviations and jargon
- Limiting sentences to 8-10 words
- Avoiding long paragraphs
- Presenting one idea or concept at a time
- Writing at 8th grade reading level or below

Being Fair in Recruiting Subjects

- Researchers need to ensure **fair** procedures and outcomes in selecting subjects for research
- **Bias and Convenience Free Selection:** must not be a matter of **convenience** (e.g. a family member), should be free from bias and preferences, must be free of coercion, be aware that injustice may occur based on social, racial, cultural and sexual biases; economic conditions may also affect subject selection process (e.g. poor / disadvantaged populations may get selected or get excluded)
- **Personal Fairness:** must not offer potentially beneficial research only to those people that the researcher favors and select only undesirable persons for risky research, must not mislead subjects, must not give false information
- **Social Fairness:** must not place more burden on already burdened people, must not choose a certain class or group of people over others based on preferences – should not lead to a situation where one class bears the burden of research while the other class enjoys the benefits of research
- **Unequal power relationships:** be aware of unequal power relationships – such as teacher – student, boss – employee, adult – child, jailor – prisoner, doctor – patient and so on. Where such relationships exist, one must take extra care so that voluntarism is protected

What important things IRB Committee Members are looking for in a proposal?

- How will your research affect human test subjects? What are the risks – emotional trauma, physical, information security, breach of privacy, unfair treatment?
- What type of test subjects are you using? (minors, pregnant women, prisoners?)
- How will you gain access to test subjects?
- What is your test protocol/research design/method?
- Have you done your homework? – in other words, are you re-inventing the wheel?
- Have you passed (scored 80% or more on) your CITI training modules?
- How will you protect information and privacy?
- How appropriate is your survey or test instrument?
- How is your informed consent letter? Does it have the IRB contact information?
- What incentives (if any) are you offering the test subjects?

Basic Protection Principles

- IRB procedures are applicable to all - faculty, staff, and students
- IRB procedures are applicable regardless of where the research is actually conducted - research could be conducted outside RMU campus, outside city, state or country but RMU IRB approval still required
- Must have IRB approval upfront, i.e. prior to starting the research – must NOT seek retrospective approval for research that is underway or already completed
- Researchers must inform all subjects:
  - That they are part of a study
  - What might cause them stresses or potential harm
  - Fully inform the subjects of their right to withdraw from the study at any time for any reason with no penalties whatsoever
  - The IRB contact information (phone number / email)
- Must secure participant's written consent (or parent/guardian)
- Must make every effort to preserve participant's privacy and confidentiality
- Adequate additional protections are ensured for special groups including **pregnant women, prisoners,** and **children** as required by subparts B, C, and D of 45 CFR 46.

What research gets reviewed?

- Answer: all research involving human subjects must be reviewed by the IRB, even if the investigator believes the study qualifies for exemption.
- If the Principal Investigator (PI) plans to publish research, the proposal must go before the IRB Committee prior to starting research, regardless of type of application review.
- Title 45 CFR 46 identifies three categories of IRB reviews: See the following slides for Exempt, Expedited and Full reviews.

Exempt IRB Review

- Research conducted in established or commonly accepted educational settings (schools, colleges, universities), involving normal educational practices, such as research on regular and special educational instructional strategies, research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods
- Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless subjects can be identified directly or indirectly, or any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation

Exempt IRB Review (contd.)

- Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects
- Research and demonstration projects which are conducted by or subject to the approval of Department or Agency Heads, and which are designed to study, evaluate, or otherwise examine public benefits or service programs
- Taste and food quality evaluation and consumer acceptance studies if the food is safe to consume without additives and does not contain any non-FDA/EPA approved substances

Exempt IRB Review (contd.)

- RMU Polling Institute -- opinion polls are traditionally considered exempt research
- The Oral History Center conducts interview projects - these are exempt
- Exempt research for children:
  - A chart/medical record review may be conducted if permission was granted at the time of admission for chart reviews for such purposes,
  - No identifying information is to be collected from the chart/medical record (i.e., name, address, phone number…)
  - Observational studies may be considered exempt as long as videotaping or audiotaping is not involved, and no identifying information is recorded
  - Educational Research conducted in educational settings, involving normal educational practices, such as regular and special education instructional strategies

Expedited IRB Review

- study involves no more than minimal risk and falls within one of the expedited categories such as:
- Clinical studies of drugs and medical devices only when the drugs or devices have been approved for marketing and are used as prescribed
- Collection of data from audio or visual recordings
- Research involving data, documents, records or specimens collected for non-research purposes, such as medical records
- Collection of data through non-invasive procedures routinely employed in clinical settings, excluding x-rays or microwaves
- Collection of blood samples by finger stick or venipuncture from non-pregnant healthy adults in amounts less than 550 ml in an eight-week period and no more than twice per week
- …

Full IRB Review

- A full review is conducted when research procedures pose risks to subjects or when subjects are, as a group, belonging to a vulnerable population. The IRB is particularly concerned with research involving the following:
- subjects under the age of 18
- pregnant subjects
- frail elderly subjects
- incarcerated subjects or persons under a correctional sentence (parolees)
- mentally impaired subjects
- giving false or misleading information to subjects
- withholding information such that subjects' consent is in question
- procedures for debriefing subjects
- biomedical procedures
- procedures that are novel or not accepted practice
- risky procedures or harmful effects, including discomfort, risk of injury, invasive procedures, vulnerability to harassment, invasion of privacy, controversial information, or information creating legal vulnerability

Reporting of Continuation/Changes

- PI must inform IRB if:
  - The project needs extra time
  - There are significant changes to research protocol
  - There are changes in personnel or
  - There are changes in materials used
  - There are changes in survey instruments
  - The study is prematurely terminated

Violations of Ethics in Research Involving Human Subjects

- Many instances in history have indicated that research was conducted on humans without their consent and with disastrous results for the subjects
- A couple of case studies are presented here that would underline the importance of modern IRB process:
- World War II Nazi doctors – 1939 - 1946
- US Public Health Service Tuskegee Study – 1932 - 1972

Case 1 : Nuremberg Code

- At the end of World War II, 23 Nazi doctors and scientists were put on trial for the murder of concentration camp inmates who were used as research subjects. Of the 23 professionals tried at Nuremberg, 15 were convicted, 7 were condemned to death by hanging, 8 received prison sentences from 10 years to life, and 8 were acquitted.
- Included in the legal judgment and sentences handed down at the culmination of the trial were ten points describing required elements for conducting research with humans. These points became known as the Nuremberg Code.
- In summary, the Nuremberg Code includes the following guidance for researchers:
  - Informed consent is essential.
  - Research should be based on prior animal work.
  - The risks should be justified by the anticipated benefits.
  - Only qualified scientists must conduct research.
  - Physical and mental suffering must be avoided.
  - Research in which death or disabling injury is expected should not be conducted.

Case 2 – Study of Untreated Syphilis in Black Males

- Project initiated the US Public Health Service to document natural history of syphilis in African American men
- Hundreds of men with and without syphilis were recruited in this study
- Deliberately misinformed them about necessary treatment such as spinal tap
- In 1940s penicillin became available to treat syphilis but the subjects were denied this medication
- The study resulted in 28 deaths, 100 disability, and 19 cases of congenital syphilis
- Ethical violations: lack of informed consent, deception, withholding information, withholding available treatment, putting individuals and families at risk, exploitation of vulnerable population

Some other cases

- Among the first human subject research experiments to be documented were vaccination trials in the 1700s. In these early trials physicians used themselves or their family members as test subjects.
- Louis Pasteur (1822-1895) "agonized over treating humans," even though he was confident of the results obtained through animal trials. He finally did so only when he was convinced the death of the child, the first test subject, "appeared inevitable."
- The era of modern science started in the 1900s and the progress of medicine began to accelerate. Walter Reed's well-known experiments to develop an inoculation for yellow fever were at the forefront of these advances. These experiments, however, unlike earlier experiments with vaccinations, were carefully scrutinized.

Summary

- IRB clearance is required prior to starting research that involves human subjects
- Informed consent requires communication, volunteerism, freedom of choice and withdrawal from research at any time, fair treatment
- Principles of fairness and justice are at work in the recruiting process
- Due diligence is expected in research design
- Research protocols must minimize potential for harm to humans
- Data and information security and privacy protection are included in IRB
- RMU IRB application form is available online
- Remember who is **Lisa Nauman**!