PROTECTING HUMAN SUBJECTS in Biomedical RESEARCH: WORKING WITH THE IRB

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Human Subjects Protection is a Shared Responsibility

IRB

Investigator/Researcher

Institution
Powell's Mission Impossible

How medical testing has turned millions of us into...

Human Guinea Pigs
Belmont Principles (1978) are the ethical foundation of federal regulations for research

- Respect for persons → informed consent, privacy & confidentiality
- Beneficence → benefit/risk or burden assessment
- Justice → distribution of risk and benefit, inclusion/exclusion
Federal Regulations and Policy stemming from Belmont Principles

45 CFR 46 – DHHS Policy for Protection of Human Research Subjects- Subpart A

“The Common Rule” – adopted by 17 federal agencies, including FDA-regulated research in 1991

21 CFR 50, 56, etc.
* FDA research regulations
Protective Mechanisms Established by the **Common Rule**

- Institutional Assurances of compliance with regulations (FWA)

- Review of research by an Institutional Review Board (IRB) or Ethics Committee

- Prospective informed consent of subjects
Institutional Review Board (IRB)

- Established to provide ethical review of research
- Assure that federal regulations are followed
- Members include researchers, non-researchers and members of the local community
- 5 IRBs at VCU – including Western IRB
- Regulatory and ethical charge: protect ‘human subjects’ in ‘research’
Activities needing IRB approval

DHHS (Common Rule) definitions

☐ RESEARCH –
A systematic investigation designed to develop or contribute to generalizable knowledge.
45 CFR 46.102(d)

☐ HUMAN SUBJECT
A living individual about whom an investigator…conducting research obtains
1) data through intervention or interaction with the individual, or
2) identifiable private information
45 CFR 46.102(f)
Activities needing IRB approval
FDA definitions

☐ CLINICAL INVESTIGATION OR EXPERIMENT

Clinical investigation’ or experiment involves a test article and one or more human subjects and that either:
- is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or
- is not subject to requirements for prior submission to the FDA, but the results of which are intended to be submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

☐ HUMAN SUBJECT

An individual who is, or becomes, a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.
Start with ‘research’

- ‘Systematic’: use of statistical analyses, scientific methods
  AND
- What about ‘generalizable’?
Is the intent of this project to contribute to knowledge in the field or discipline?
Are there hypotheses or research questions?
Will analysis of data lead to generalizable claims, inform policy?
Is there an intent to publish or present the project as research?

If ‘yes’ >>>>>> the project is research
Generally NOT ‘generalizable’, i.e. Not usually defined as research needing IRB approval

- Quality improvement/ QA projects – *designed with goal of improving institutional/organizational practice*
- Resource utilization review
- Case report or case series – *if no systematic investigation, i.e. no statistical or data analysis; no outcome measures*
- Public health practice – *surveillance, program evaluation*
- Survey/questionnaire development – *no data retained for research purposes*
What about ‘human subjects’?

- More straightforward
  - Interventions or interactions with persons
  - Access to **identifiable** personal data

- Secondary data sets without ANY identifiers or **codes** generally do not involve human subjects

  Note difference between **anonymous** (absolutely no links) and **de-identified** (codes are retained)

- **Suggestion**: Refrain from the word ‘research’ if project not to be considered human subjects research under IRB purview
Guidance on “Activities needing IRB Approval”

- Refer to this PowerPoint presentation for more information and examples:
  "How do I determine if my project is 'human subjects research?"
- Guidance from the Office of Human Research Protections (OHRP):
  - [OHRP Human Subject Research Decision Charts](http://www.hhs.gov/ohrp/pubs/dcm/dcm1209.html)
  - [OHRP Guidance Document: Coded Private Information or Biological Specimens](http://www.hhs.gov/ohrp/pubs/dcm/dcm1211.html)
  - [OHRP Quality Improvement Frequently Asked Questions](http://www.hhs.gov/ohrp/pubs/dcm/dcm1213.html)
Examples of biomedical projects that will likely require IRB submission

- Chart/medical record reviews to address hypothesis or research question(s)
- Surveys, including Internet-based surveys
- Randomized intervention and control group
- Creating data registries/tissue banks
- Data analysis of primary or secondary data from data registries or tissue repositories that contain identifiers or codes
- Creation of, or contribution to, a data registry or specimen bank
At VCU, PI determines if project is human subjects research (but IRB determines if ‘exempt’ applies):

**HOWEVER, if ...**
- there is a question
- a QA/QI project *might* become research
- there is *potential* to publish or present as research

**THEN...**
- Contact ORSP or OECO or IRB member with questions
- Submit to the IRB if unsure: protect your ability to present or publish and ensure subjects are protected
Entry into VCU human subjects research protection process: The IRB

- Website – Institutional Review Board (IRB)

  http://www.research.vcu.edu/irb/index.htm

  Activities needing IRB approval
  Types of IRB review
  Forms
  Required education
  Guidance
  Research volunteers
  Contact Us

- For IRB purposes a researcher who is a student or in a training role may NOT be the PI
HIPAA for research is coming to the IRB!

- Specific rules for protecting research subjects within the covered entity:
  - preparatory to research
  - authorizations (waivers)
  - etc.

- IRB definitely thinks about privacy!
- Watch IRB website for info on HIPAA implementation
Assessing Protocol for ETHICAL Treatment of Research Subjects

- Respect for persons
  - Is the informed consent process appropriate?
  - Is subject autonomy respected?
  - Are special additional protections needed for vulnerable populations?
  - Is subject privacy protected? Will confidentiality be maintained?

- Beneficence
  - Have all risks been identified?
  - Are risks minimized?
  - What are the benefits of participation? Are they maximized?
  - Is the study design adequate?
  - Is the investigator’s experience adequate?

- Justice
  - Is subject selection equitable?
  - Will likely participants also be likely beneficiaries?
  - Are any groups unfairly excluded?
Types of IRB Review

- Level of potential risk to subjects determines type of review

Exempt ------- Expedited ------- Full board

Low risk -----------------> High risk

(no greater than minimal risk)

(Guidance on determining review type is embedded in Initial Submission form)

www.research.vcu.edu/forms/vcuirb.htm)
Definition of Minimal Risk
45 CFR 46.102(i)

“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 examination or tests.
"Risk/Benefit Assessment"

IRB also considers the risk of criminal/civil liability, financial risk, employment risk, stigmatization, insurability, and embarrassment in deciding if risk is truly minimal.
Other considerations may also count as contributing to ‘vulnerability’:

- Language
- Culture
- Current Events or Incidents
- Age (elderly)
- Age (adolescents)
- Educationally, economically disadvantaged
- Transient or Permanent Cognitive Impairment
- Substance Use
- Health Status
- Students
- Employees
Populations specifically protected in federal regulations

- Pregnant women - Subpart B
- Prisoners – Subpart C
- Children – Subpart D
Exemption Categories: 45 CFR 46 101 (b)

1. Typical educational practices
2. **Educational tests, surveys, interviews, or observation of public behavior (non-sensitive, generally no identifiers)
3. Research with elected public officials, appointed public officials, candidate for public office)
4. **Existing data, documents, pathological specimens, if publicly available or recorded to be unidentifiable
5. Evaluation of public benefit service programs
6. Taste and food quality evaluation and consumer acceptance studies
Categories for Expedited Review:

Initial Review

- Clinical studies: IND/IDE NOT required
- Blood sample collection (routine methods – small amounts)
- Prospective collection of biological samples—noninvasive means
- Data collected though noninvasive means (routinely practiced in clinical settings)
- Materials (data, documents, specimens etc.) have been collected or will be collected for non-research purposes
- Collection of voice, video or digital data for research purposes
- Individual or group behavior, surveys, interviews, oral histories
Informed Consent for Exempt Studies?

☐ No formal informed consent document needed for ‘exempt’ research >>> identifiers not collected & very low risk

☐ But for surveys... subjects deserve to know that they are participating in VCU research project, that their participation is voluntary, and that they do not need to answer every question

☐ Include such information at the top of a survey or questionnaire.
Exempt <<< Review >>> Expedited

- Minimal risk
- One IRB or Exempt Panel reviewer
- Does not include identifiers, with some exception
- Topic generally not sensitive
- Non-vulnerable populations

- Minimal risk research
- One IRB reviewer outside of convened meeting
- May include identifiers (direct or indirect)
- Topics not sensitive OR may include some sensitive topics, but confidentiality securely protected
- Populations may include regulated vulnerable & others with adequate protections
Exempt from formal informed consent requirement, but subjects deserve to know about the research.

Consider a formal informed consent process OR justify a waiver of consent.

Exempt from continuing IRB review.

Requires IRB continuing review at least annually.

Fits one of 6 categories of research.

Fits one of 7 expedited categories.
Required elements of informed consent

BASIC ELEMENTS 45 CFR 46.116(a)

Expedited and Full Board Reviews

☐ Statement that the study involves research
☐ Reasonably foreseeable risks/discomforts
☐ Reasonably expected benefits
☐ Disclosure of appropriate alternative procedures
☐ Confidentiality of identifiable records
☐ For high risk, what happens if injured in research
☐ Whom to contact about research, problems, or concerns
☐ Participation is voluntary, refuse to participate without penalty, and discontinue participation at any time
Informed Consent
Some considerations:

- Must contain required regulatory elements
  - follow ICF template to ensure inclusion of all required elements of disclosure

- Waiver of some or all elements of informed consent/permission may be appropriate:
  - research is no greater than minimal risk
  - no impact on rights or dignity of participants
  - not practicable to obtain informed consent
  - provide debrief after the research, as appropriate
IC: More considerations

- Waiver of documentation of informed consent may be appropriate – this needs to be justified

- If children will be research subjects, parental permission and child’s assent is required; same may apply to decisionally impaired adults

- Separate regulatory protections and IC inclusions for prisoners, and pregnant women/fetuses/neonates (even if not targeted)
Full Board Review

- If the research does not meet criteria for exempt or expedited it is classified as a Full Board study (it is likely greater than minimal risk)
- If research is FDA-regulated but not industry-sponsored, it will go to VCU IRB and be reviewed as full board
- Discussed at monthly meeting of IRB panel and motions for changes or approval done by majority vote
VCU IRB process

- Complete application (from website), get appropriate signatures and submit to IRB office (800 E. Leigh St.)
- Assigned to one of four VCU IRB panels (A,B,C,D)
- Assigned to a “primary reviewer” who is a member of one of the panels (& secondary reviewer for full board)
- If exempt or expedited study, primary reviewer responsible for approval
- If full board, reviewer presents study at monthly IRB panel meeting and full panel discusses and votes
- Expedited and full reviews have annual continuing review – submit at least 2 months before expiration
VCU IRB process (cont.)

- IRB approval = receipt of a formal approval letter – no research begins/no modifications implemented prior to receipt of letter

- Implementation of research must reflect the protocol approved by the IRB

- Proposed changes to the protocol are submitted to, and approved by, the IRB, before implementation – includes PI change

- Report unanticipated problems to the IRB – if relevant, use “Change in Research” form
What you can do to facilitate the IRB review process?

- CITI training completed for all key personnel
- **Assure a high quality submission**
  - Submission forms completed fully & accurately
  - Research synopsis clear and complete
  - All supplementary materials included (e.g., recruitment ads, letters to participants, questionnaires/surveys, consent forms (if needed), etc.)
- Clearly describe other non-VCU entities who are ‘engaged’ in the research
  
- Ensure that you respond promptly to IRB communication
What does the IRB look for?

☐ Are the research question(s) and/or aims of the research study clearly stated?
  ■ Adequacy of background section & literature review

☐ Is research method CLEARLY described?
  ■ When, where, how and who of recruitment
    ■ Recruitment materials included
  ■ Details about data collection
    All data collection instruments included
  ■ *Are the research interventions clearly distinguished from standard of care interventions?
What does the IRB look for? (cont.)

- Is analysis plan described in adequate detail — qualitative and quantitative data?
- Are the risks & burdens balanced by the potential benefits of the research?
  - Are the risks to participants adequately assessed
  - Are the burdens adequately assessed (time, inconvenience, etc.)?
  - Are potential benefits stated? Are they overstated?
  - What are the plans for data and safety monitoring while the study is being conducted?
What does the IRB look for? (cont.)

- Are the findings of the research likely to contribute to knowledge development that balances potential risks and burdens?
  - Quality of the “science”

- Are participants appropriately informed about the study? Is the consent form included (if relevant) and “understandable” by the potential participants?
What does the IRB look for? (cont.)

- Is the privacy/confidentiality of subjects protected?
- What protections are in place if a research registry will be developed?
- How are the research materials being protected (e.g., locked in a file cabinet, electronic data protections, etc.)?
- If an FDA-regulated study, ensure you have supplied IND or device information, sponsor materials
When you are preparing your IRB Application:

- Seek consultation from someone on the IRB from your area, from an experienced researcher, from ORCE
- Call the IRB office or ORCE for consultation
- Review the WPPs and IRB guidance on the website (links on application)
- Good planning makes a good submission!
Working with the IRB as the research study continues

- All changes to the research must be reviewed and approved by the IRB
  - Submit new versions of related documents with new date footer, along with a cover letter

- Report all unanticipated problems: not anticipated, increased risk to participant or others, related or possibly related

- Report protocol deviations that were carried out to mitigate risk to a participant

- Report protocol violations in a similar fashion as unanticipated problems
Working with the IRB as the research study continues

- Continuing review (CR) at least a 10-12 month basis
  - Although IRB sends courtesy letters of upcoming CR deadlines, it is the PI’s responsibility to submit materials to prevent study expiration
  - Keep a regulatory file/binder with all official IRB communication so most recent approved documents can easily be submitted for CR
  - The CR report is a way of demonstrating the quality of the research procedures to the IRB

Note not-for-cause IRB Support Visits (post-approval compliance monitoring)
21 CFR 56.111 & 45 CFR 46.111

Criteria for Approval of Research

1. Risks minimized
2. Favorable risk-potential benefit analysis
3. Equitable subject selection
4. Informed consent process
5. Informed consent documented
6. Data monitored for safety
7. Privacy protected; confidentiality maintained
8. Safeguards for vulnerable individuals
Questions?

- [www.research.vcu.edu/irb/guidance.htm](http://www.research.vcu.edu/irb/guidance.htm)
  - Written policies and procedures
  - Post-approval study evaluation tool
- Office of Research Subjects Protection
  828-0131 – IRB submission process
- Office of Research Compliance & Education
  827-2157 ([msmarkow@vcu.edu](mailto:msmarkow@vcu.edu)) – ethical issues, including design, informed consent process, recruitment, unanticipated problems, protocol deviations, issues related to compliance, COI, etc.