Initial Review of Human Subjects Research at Convened Meetings of the PHRC/IRB

(Full Board Review of New Protocols)

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Outline:

- Intake and scheduling for IRB review
- Regulatory criteria for new approvals
- Studies involving vulnerable populations
- Studies involving drugs
- Studies involving devices
- Committee's overall determination
- Submitting a 'Response to Review'

This roundtable will *NOT* discuss Insight submission process

For most hyperlinks, you need to be logged into Research Navigator

Intake

- Prepare study documents and submit application through Insight https://insight.partners.org/public/
- Intake person determines appropriate review:
  Expedited or Full Board

Expedited review:

- Research is no more than minimal risk (IRB decides) AND
- Entire proposal falls into expedited review categories of the Federal Register. http://www.hhs.gov/ohrp/policy/expedited98.html
- Application forwarded to expedited review team

Examples: blood draws (with restrictions), noninvasive sample collection (urine), noninvasive data collection (MRI scans without contrast), previously collected data/samples, survey/focus groups.

Intake

Full Board review:

- Research does not meet criteria for expedited review
- Intake confirms that required documents are submitted
  - **Tip:** Use the intervention/interaction submission checklist

https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/_layouts/15/WopiFrame.aspx?sourcedoc=%7B6004F66C-2CF7-46D6-AA99-3B0F50BA4EB0%7D&file=New_Intervention_or_Interaction_Protocol_Submission_Checklist%20(2).doc&action=default

Common Issues:

- **Detailed Protocol** is the ruling document
  Corporate sponsor's protocol is the Detailed Protocol
  (NIH) grant proposal is *NOT* a Detailed Protocol
- **Protocol Summary** = summary + how study is implemented at Partners sites (Site restrictions, if any)
- **Twin studies** – same protocol at MGH and BWH. Submit as one application OR 2 separate identical applications (both cases work together!)
- Use the correct and most recent **PHRC template** for Protocol Summary (PS) and Consent Form (CF)
  - (PS) https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/Pages/IRB-Forms.aspx
  - (CF) https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/Pages/Research-Consent-Form-Templates.aspx

Common Issues:

Tip: carefully read the grey instruction boxes on the Protocol Summary template to provide the requested information

STANDARD OF CARE

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Note: This may differ from standard care at local hospitals or the rest of the US

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Scheduling for Full Committee Review:

- IRB submission is determined complete ->
  - Schedule on 1st available initial review meeting agenda
  - Scheduling is 1st come 1st serve
    - For fully complete submissions

- IRB 5 (formerly MGH A) and IRB 1 (formerly BWH A) meet on alternate weeks.
  - Review at IRB 1 or IRB 5
  - DOES NOT MATTER which institution research is conducted!

Criteria for Approval
(45 CFR 46.111 and 21 CFR 56.111)

a) All of the following requirements need to be satisfied:

1) Risks to subjects are minimized

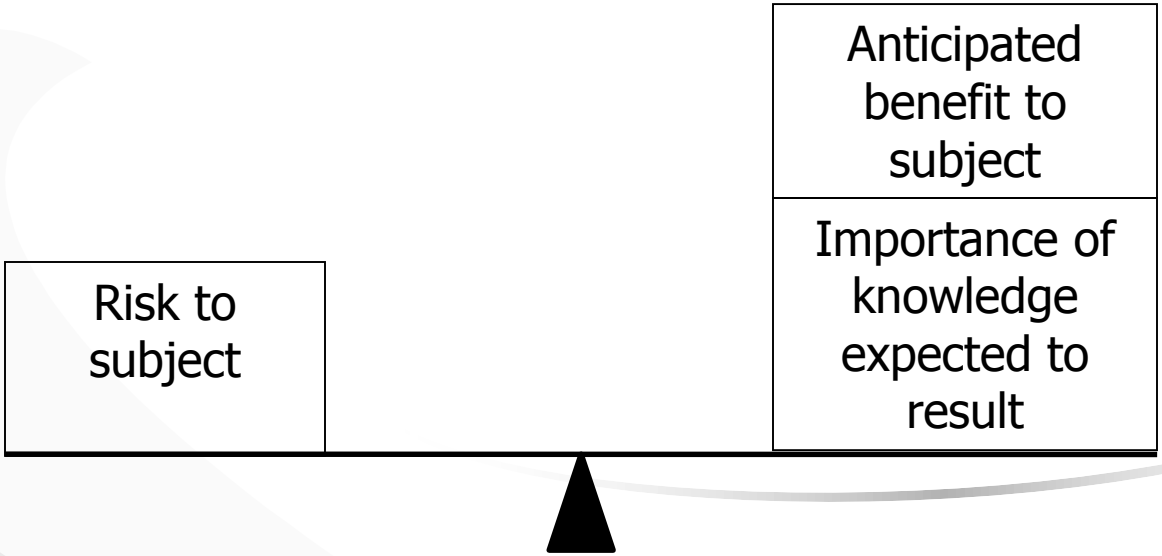
- Can less risky procedures answer the research question?
- Can fewer procedures answer the research question?
- Are the procedures truly needed?
- Can additional procedures reduce the study risk?
- Can different eligibility criteria reduce the study risk?
- Are procedures already performed for clinical care?
- Is research staff qualified?

Criteria for Approval
(45 CFR 46.111 and 21 CFR 56.111)

a) All of the following requirements need to be satisfied:

2) Risks to subjects are reasonable in relation to anticipated benefits (if any) to subjects, and to the importance of the knowledge that may reasonably be expected to result [from the research]

- What if there is no anticipated benefit to the subject?
- Knowledge -> requires good scientific design



Criteria for Approval
(45 CFR 46.111 and 21 CFR 56.111)

a) All of the following requirements need to be satisfied:

3) Selection of subjects is equitable

- Fair
- Just
- Equal
- Burdens distributed fairly?
- Benefits distributed fairly?
- No population unfairly targeted?
- No population unfairly excluded?

Criteria for Approval
(45 CFR 46.111 and 21 CFR 56.111)

a) All of the following requirements need to be satisfied:

4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative

- Provide person with enough information to understand and make a decision to participate – communication!
- Non-English speaking subjects require the presence of a medical translator and witness
- Circumstances of consent process: location, timing, who is obtaining consent (undue influence/coercion)
- Waiver - emergency research (public review)
- Alteration - research involving (authorized) deception and debriefing

Criteria for Approval
(45 CFR 46.111 and 21 CFR 56.111)

a) All of the following requirements need to be satisfied:

5) Informed consent will be appropriately documented

- Signed (and dated) consent forms
- Non-English speaking subjects use of complete translated consent document (no benefit or more than minimal risk)
  OR use of "short form" (direct benefit and/or low risk)
- Waiver of written consent –> verbal consent
  - no more than minimal risk AND
    no procedures for which written consent is normally required outside of research context.
  - consent is only document linking subject to study and the main risk is potential harm resulting from such a breach (e.g., cultural taboo)

Criteria for Approval
(45 CFR 46.111 and 21 CFR 56.111)

a) All of the following requirements need to be satisfied:

6) The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects

- Monitor individual subject safety
- Monitor conduct of research
- Monitor of data collected (interim analysis)
- Who reviews the data?
- What data are reviewed?
- When are data reviewed?

Criteria for Approval
(45 CFR 46.111 and 21 CFR 56.111)

a) All of the following requirements need to be satisfied:

7) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data

- **Privacy:** about people and their interest in controlling access to information about themselves
- **Confidentiality:** about data and agreement with subject about how data are to be handled

Criteria for Approval
(45 CFR 46.111 and 21 CFR 56.111)

b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects

- Specific regulations for [pregnant women* final rule] and fetuses, children, and prisoners. There are other vulnerable populations.
- Is there a power differential? (mentor/student, direct supervisors/employees, economic, educational)
- Communication issues? (non-English speaking)
- Decisional issues? (impaired decision making)
- Excessive motivation factors? (life threatening disease, coercive remuneration)

Studies Involving Children

1) Magnitude of **risk** to child

Minimal risk (per federal regulations) =

"The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations."

Minor increase over minimal risk

Reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations

More than minimal risk

Example: investigational drug studies

Studies Involving Children

2) Possible **benefit**

- Direct benefit to the child
- Generalizable knowledge which is of vital importance for the understanding the child's disorder/condition
  - Healthy children have no disorder or condition

Categories of Research with Children

approvable by IRB

- **No more than minimal risk** (45 CFR 46.404)
- **More than minimal risk but prospect of direct benefit to individual subjects** (45 CFR 46.405)
  - risk must be justified by the anticipated benefit.
  - risk/benefit ratio at least as favorable as available approaches.
- **Minor increase over minimal risk and no prospect of direct benefit to individual subjects but is likely to yield generalizable knowledge about the subject's disorder or condition** (45 CFR 46.406)
- **Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children** (45 CFR 46.407)
  - Additional requirements such as expert review (federal level) and public review and comment

Studies Involving Pregnant Women

(45 CFR 46 subpart B) ** see FINAL RULE changes**

- **Preclinical study data** assessing potential risks to pregnant women and fetuses
- **Direct benefit to**
  - Woman
  - Fetus
  - Both
  - Neither
- **Risk to the fetus**
  - Minimal risk and can't obtain knowledge otherwise
  - Only caused by the intervention and benefit to woman or fetus
  - Risks are minimized

Studies Involving Pregnant Women

(45 CFR 46 subpart B) * see FINAL RULE changes**

- **Informed consent**
  - Fully informs the woman about the reasonably foreseeable impact of the research on the fetus
  - Obtained from pregnant woman
  - Also obtained from father depending upon who will directly benefit from participation

If enrolled subject becomes pregnant AND the study is not approved for pregnant subjects -> all study procedures with this subject must be stopped immediately.

Contact the IRB right away!

Studies Involving Prisoners
(45 CFR 46 subpart C)

- Partners IRB does not meet the regulatory requirements to review research involving prisoners. (Required to cede review to HSPH IRB)

- If one of the enrolled subjects in your study becomes incarcerated, *contact the IRB right away!*

  - Study procedures must be **stopped** until IRB approval for the inclusion of prisoners is obtained. There are some exceptions. *contact the IRB right away!*

Impaired Decision-Making Capacity
(temporary and permanent)

- Necessary and appropriate?
- How are subjects recruited?
- Are risks justified by the potential benefit?
- How will capacity be determined?
- Possible that capacity may be regained during study?
- Is consent from a legally-authorized representative (surrogate) acceptable?
- What approach will be taken if the subject regains the capacity to consent during the study?

Studies Involving Drugs
(21 CFR 312)

Drugs are defined by intended use:

- diagnosis, cure, mitigation, treatment, or prevention of disease
- to affect the structure or any function of the body

Examples:

- dietary supplements (Vit D to improve bone strength in anorexia)
- Probiotics
- absolute alcohol (alcohol injections into cysts)
- "Cheerios *prevents* heart disease"

Studies Involving Drugs
(21 CFR 312)

IND (Investigational New Drug) Regulations

- Any drug that is NOT approved by the FDA (i.e., not marketed) is considered "investigational drug"
  - IND is required

- Marketed drugs (off label use)
  - May require an IND
  - May be exempt from IND requirement
  - Determined by the IRB. However, FDA has ultimate authority

Studies Involving Drugs
(21 CFR 312)

Off label use of marketed drug is **exempt** from IND regulations if:

- Data are not submitted to FDA for new indication, change in labeling and/or advertising

AND

- Does not significantly increases the risks (or decreases the acceptability of the risks)
  - Factors to consider:
    - Change in route of administration
    - Change in dosage level
    - Change of patient population
    - Other

Tip: Submit document with justification why each of these criteria are met

Studies Involving Devices
(21 CFR 812)

Depends on **how the device is used** in the study, not on the device itself:

- Requires IDE (Significant Risk ("SR") device study)
- No IDE required, but adhere to abbreviated IDE requirements (Non-Significant Risk ("NSR") device study)
- Exempt from IDE regulations
- Not subjects to IDE regulations

Determination made by the IRB. But, FDA has ultimate authority on this

IDE = Investigational Device Exemption

Studies Involving Devices
(21 CFR 812)

NSR device study vs SR device study

- **SR** = Device presents a potential for serious risk to the health, safety, or welfare of a subject

  -> requires IDE application be submitted to FDA

- **NSR** = Device does not meet criteria for SR

  -> IDE application not needed, but study must comply with the abbreviated IDE requirements
  - NSR study is **NOT** exempt from IDE regulations!
  - **Note**: document with justification that none of the SR criteria are met must be submitted

Insight - IDE exempt vs NSR

Investigational Device Exemption (IDE)

Is this medical device being studied under an IDE?

NSR/SR

○ Yes ◉ No

Is the investigation exempt from the IDE requirement:

○ Yes ● No

Significant Risk (SR) versus Nonsignificant Risk (NSR) Device Determination

The IDE regulations describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). SR device studies require an IDE from the FDA. NSR device s
regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The judgment about whether a study poses a significant risk is base
significance of the potential harm that may result from participation in the study, including the use of the device.

Is the device intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject?

○ Yes ○ No

Investigational Device Exemption (IDE)

Is this medical device being studied under an IDE?

EXEMPT

○ Yes ◉ No

Is the investigation exempt from the IDE requirement:

● Yes ○ No

Select ONE appropriate exemption from the IDE requirement:

☐ Clinical research studies of diagnostic devices are exempt from the IDE regulations if the testing: (i) is non-invasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.

☐ A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution if the testing is not for the pur
of determining safety or effectiveness, and does not put subjects at risk.

☐ A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Studies Involving Devices
(21 CFR 812)

Device studies Exempt from IDE Requirements

- **Marketed device (FDA approved)** being used for indications in the FDA approved labeling
- ***Non-invasive diagnostic device**
  - No invasive sampling
  - Doesn't introduce energy into the subject
  - Not used for diagnosis without confirmation of diagnosis by another established test
- **Consumer preference testing**
  - Testing a modification or combination of devices in commercial distribution
  - Not to determine safety/efficacy
  - Doesn't put subjects at risk

Studies Involving Devices
(21 CFR 812)

Not Subject to IDE Regulations

- Device is not being studied for safety or efficacy, but rather is being used to study **human physiology**

AND

- the risk from the device is minimal (determined by the IRB)

Studies Involving Devices
(21 CFR 812)

Has the FDA made a determination about the device?

yes → **Submit the FDA determination letter**

no ↓

Is the device, as used in this study, one of the following investigations?

- used for an FDA approved indication
- a non-invasive diagnostic device and is not used for diagnosis without confirmation by established product/procedure
- undergoing consumer preference testing of a modification or combination devices in commercial distribution
- a custom device made in a specific form for that patient, and not generally available to others

yes → **Exempt from IDE requirements 21 CFR 812**

no ↓

Is the device being studied for safety and/or effectiveness?

yes → **Is this a significant risk (SR) device study?**
Does the device present a potential for serious risk to the health, safety or welfare of a subject?

no ↓

Is the device being used to study human physiology or monitor responses?

yes ↓

Device is not subject to IDE regulations 21 CFR 812

no ↓ **Non-significant Risk Device Study** Sponsor does not need to submit an IDE application to FDA but must meet abbreviated IDE requirements.

yes ↓ **Significant Risk Device Study** Sponsor must submit an IDE application to FDA for approval.

Committee's Overall Determination

- **Approval**
  - You are good to go - very unlikely
- **Requires modifications**
  - Revisions are needed to secure final approval
  - Response can be reviewed by the Chair in the office
- **Deferral**
  - Not all criteria for approval were met
  - Response needs to be reviewed by the same panel
- **Disapproval**
  - The protocol as proposed cannot be approved
  - Serious revisions or study design changes are required to be reconsidered by the same panel - very rare

Response to Review

The Insight response document -> self contained document

- Provide point by point complete response to each question
  - Do NOT just refer to the study documents in which a revision was made
  - Specify to which document(s) and to what page #s revisions were made

    Changes were made in the Protocol Summary p.2 [not preferred]

    Individuals with a CrCL > 60ml/min will be excluded. Revision was made in the Protocol Summary p.2 [preferred]
- Submit a clean and marked copy for each document that was revised

Response to Review

The Insight response document -> self contained document

- Additional changes, not requested by the Committee, state point by point:
  - what change was made
  - justification for additional change
  - document + page# revision was made to

Questions?

Sheldon Ratnofsky (IRB 5) at sratnofsky@partners.org
OR
Jill Manning (IRB 1) at jmanning7@partners.org

For more information log onto Research Navigator
and visit our website @
https://partnershealthcare.sharepoint.com/sites/phrmapply/aieipa/irb

Insight: https://insight.partners.org/public/

Expedited categories:
http://www.hhs.gov/ohrp/policy/expedited98.html

Submission checklist:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/_layouts/15/WopiFrame.aspx?sourcedoc=%7B6004F66C-2CF7-46D6-AA99-3B0F50BA4EB0%7D&file=New_Intervention_or_Interaction_Protocol_Submission_Checklist%20(2).doc&action=default

PS – template:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/Pages/IRB-Forms.aspx

CF – template:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/Pages/Research-Consent-Form-Templates.aspx