

# New IRB Member Training

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# Introduction/Orientation

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All meetings are held in Bldg 60 (The Cloisters)

- 2<sup>nd</sup> floor conference room

Parking can be validated if needed

Using NIH iRIS electronic system



# Your commitment is important

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We need your expertise to review the studies

Share the workload

Quorum

Quorum

Quorum

# What is the purpose of the IRB

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Assure the ethical conduct of human subjects research

Certify that federal and institutional requirements for HSR are met.

Research using human subjects cannot take place without approval of the IRB.

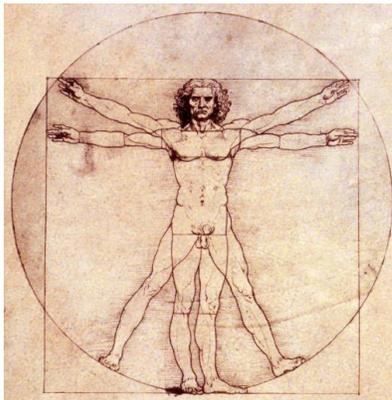
# Definition of Human Subjects Research

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## PRE-2018 COMMON RULE

Human Subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

- 1) Data through intervention or interaction with the individual, OR
- 2) Identifiable private information.



## 2018 COMMON RULE

Human Subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

- 1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- (2) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

# Definition of Minimal Risk

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During all IRB reviews, we must determine the risk level

- Minimal risk
- Greater than minimal risk

Regulatory definition of Minimal Risk:

- 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 examinations or tests.”

# From Belmont to 45 CFR 46.111

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THE CRITERIA FOR APPROVAL AND IRB REVIEW OF  
HUMAN SUBJECTS RESEARCH

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“Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions.”

- The Belmont Report

# Your mission.....

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The central task of the IRB is to determine that the proposed research meets the criteria for approval as delineated in the Federal Regulations (45 CFR 46.111).

- In doing so, the IRB assures that the proposed research is ethical.
- Fulfillment of the criteria is both necessary and sufficient to judge a study ethical and approvable.
- It is exceedingly rare that unethical research would meet the criteria for approval.

IMPOSSIBLE

# From principles to review

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## Principles

- Broad
- Not hierarchical



## Norms

- Descriptions of acceptable behaviors.



## Rules

- Guidelines that operationalize the above principles and norms.



## Decisions

- Application of the rules to specific circumstances.

# The Principles

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Respect for Persons

Beneficence

Justice

No one trumps the other!

# Respect for Persons

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## Principle

- “So act as to treat humanity, whether in thine own person or in that of any other, in every case as an end withal, never as a means only.”- Kant

## Norms

- People should be treated as autonomous agents.
  - “individual capable of deliberation about personal goals and of acting under the direction of such deliberation”-Belmont Report
- Individuals with diminished autonomy are entitled to protection.

# Respect for Persons: Regs

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## Informed consent,

- (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by [§46.116](#).
- (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by [§46.117](#).

## Privacy/confidentiality

- (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

## Voluntariness and special protections

- (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

# The transformative power of consent

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Consent makes the impermissible permissible

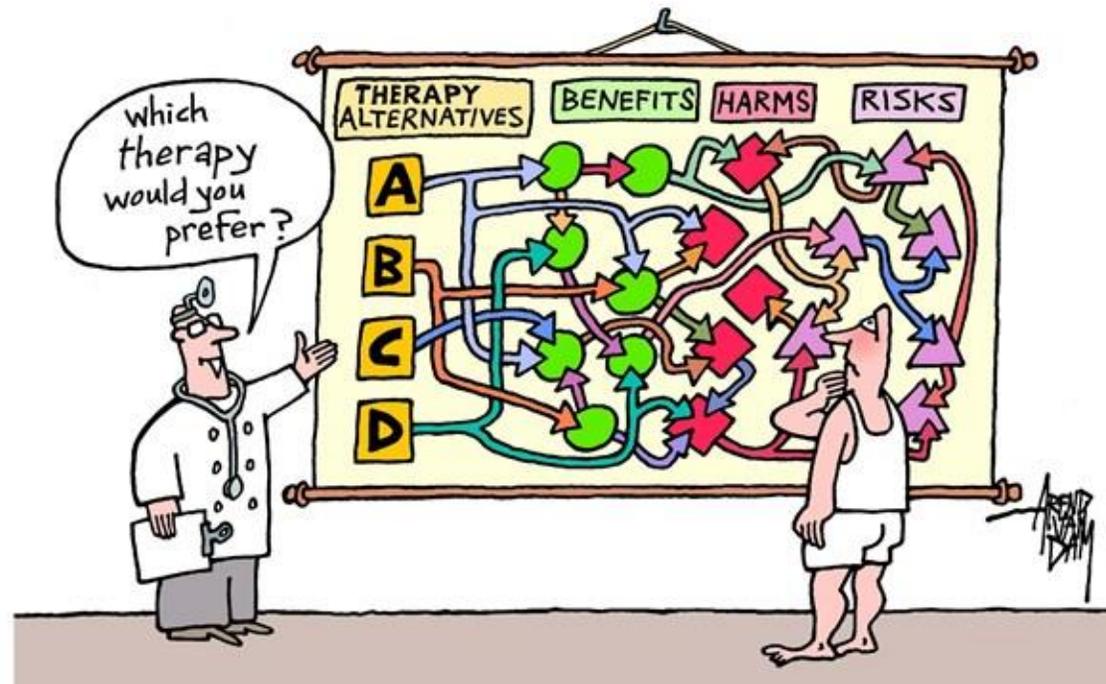
# Informed consent is not just the document

## Process of consent

- Begins with the first contact with the potential participant and ends.....?

## Informed consent requires:

- Information
- Comprehension
- Voluntariness



# How much information?

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## The standard of the “reasonable volunteer”

- “the extent and nature of information should be that such persons, knowing the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge”.
  - Belmont Report
- 45.CFR 46.116 (a)(4) The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

# Key information – revised CR

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Information essential for the person to make an informed decision whether or not to participate

Viewed from participants perspective

Not formulaic

May differ between studies

May differ between populations

# Informed Consent-Key information

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## Preamble

- The fact that consent is being sought for research and that participation is voluntary
- The purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research
- The reasonably foreseeable risks or discomforts to the prospective subject
- The benefits to the prospective subject or to others that may reasonably be expected from the research
- Appropriate alternative procedures or courses of treatments, if any, that might be advantageous to the prospective subject.

# Other “key” information

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Whether there is randomization

Whether there is a placebo arm

Whether subjects will have to discontinue current treatments.

How the treatment in the protocol is similar to, or different from, the clinical care the subject would receive if not in the protocol

Any significant costs that could be incurred as a result of participation

Compensation for injury

How much time and/or how many research visits are required for participation

Payments to subjects

Impact on the subject’s future clinical care. For example, whether use of an experimental intervention is likely to make a standard clinical intervention ineffective or unavailable after the study

Potential impact on non-participants e.g., caregivers, family members, children, partners and the public at large

Post-participation access to the experimental intervention.

# Informed Consent-new elements

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(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

- (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
- (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

# Informed Consent-new elements

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## When appropriate

- A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

# Comprehension

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Consider:

- The manner and context in which the information is presented.
- The subjects ability to understand the information.
  - Special provisions for those with limited ability to understand
  - Need for assent by participant and consent by legally authorized representative

# Voluntariness

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Consent is only valid if voluntarily given, which requires conditions free of coercion and undue influence.

- *Coercion*
  - An overt threat of harm intentionally presented by one person to another in order to obtain compliance
- *Undue Influence*
  - An offer of excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable
- Both result in persons making choices that are not congruent with their goals, values and interests

# Special protections

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Diminished autonomy

- Cognitively impaired
- Children

Pregnant women?

- Fetus is the vulnerable entity

Prisoners

Economically/socially/educationally disadvantaged

Desperately ill/dying?

# Reviewing informed consent

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## Review the process and the document

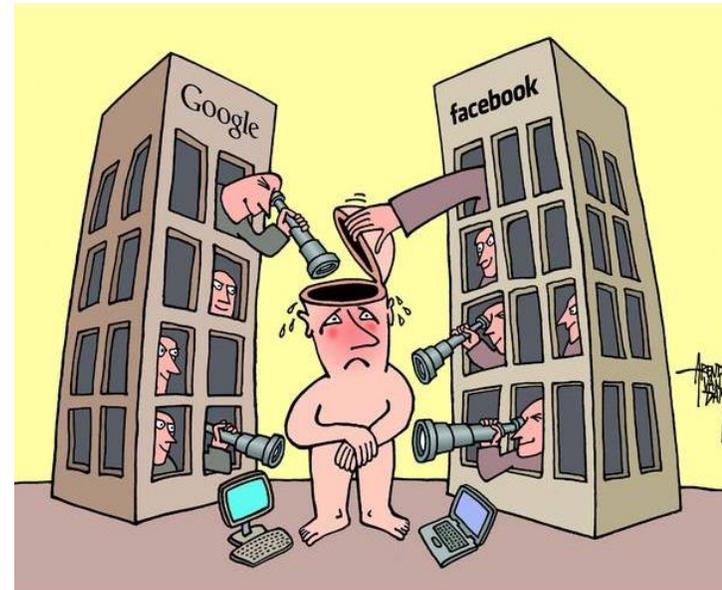
- Does the process allow for
  - 1) transfer of information
  - 2) comprehension of the information
  - 3) a voluntary decision to participate or decline
- Does the document
  - 1) contain the necessary information
  - 2) present the information in a comprehensible manner

# Protecting privacy and confidentiality

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(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- Privacy is about the person
- Confidentiality is about the data



# Informed Consent

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Use of template assures that all regulatory elements of consent are present

IRB review process includes screening of each study by staff prior to scheduling for a meeting.

Staff review will include review of the consent form for consistency, accuracy, and readability.

Changes proposed by staff will be visible in “tracked changes” version of edited consent form.

# Consent untouchables

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## NIH Required language

- Injury language
- Privacy
- Payment

# Beneficence and IRB Review of Research

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“Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of substantial benefits that might be gained from research”.

- Belmont Report

# Harm/benefit assessment

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Ideally, a systematic, non-arbitrary analysis.

“The IRBs task is not to determine whether the potential participant would judge the risk worth it, instead the IRB is to determine whether the invitation is justified”.

- Oxford Textbook of Clinical Research Ethics

# Harms and benefits

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## Benefits/harms to participants

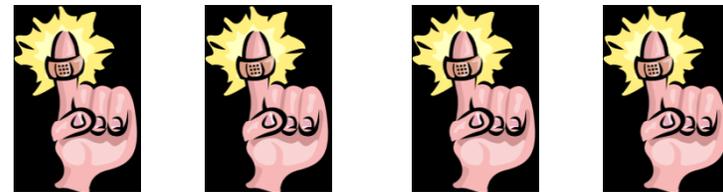
- May be to individuals and/or groups
- Direct
  - From receipt of the experimental intervention
    - uncertain
- Inclusional
  - Result from inclusion in the study, but not dependent on receiving the experimental intervention.
    - May be certain

# Evaluation of harms and benefits

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Low magnitude/low likelihood



Low magnitude/high likelihood



High magnitude/low likelihood



High magnitude/high likelihood

# Physical Risks

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Usually easiest to identify

- Drug toxicities
- Exposure to ionizing radiation
- Injuries sustained during a research related procedure
- May receive a treatment that is less effective than alternative

Considerations

- May be unpredictable and as of yet unknown
- May be delayed
- May be irreversible

# Risks

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## Psychological

- Any psychological distress occurring as a result of participation in research.

## Social

- Exist when there is the possibility that information obtained during the course of research participation could negatively impact others' perception of the participant.

## Legal

- Places participant at risk of civil/criminal liability

## Economic

- Participation could have negative financial consequence

# Benefits

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## Individual

- Access to an efficacious therapy
- Improved medical care
- Detection of a treatable condition
- Contribution to helping others

## Societal

- Knowledge that will improve care of others

No requirement to maximize benefit

# Criteria for approval

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## (1) Risks to subjects are minimized:

- (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
- (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

# Criteria for approval

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- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
  - In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).
  - The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

# Applying the criteria for approval

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Criteria 1: Minimize risk without interfering with scientific aims

Criteria 2: Once minimized, are risks reasonable in relation to anticipated benefit to subjects (if any), or the importance of the knowledge to be gained.

# Data safety monitoring

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- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
  - Data and safety monitoring plans need to be calibrated to the study.
  - Range from a formal DSMB/DMC with external membership to monitoring by the PI

# Justice

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## Principle

- “Equals ought to be treated equally and unequals unequally.”-Aristotle
- Distributive justice
  - Distribution of a scarce benefit
  - Distribution of burdens

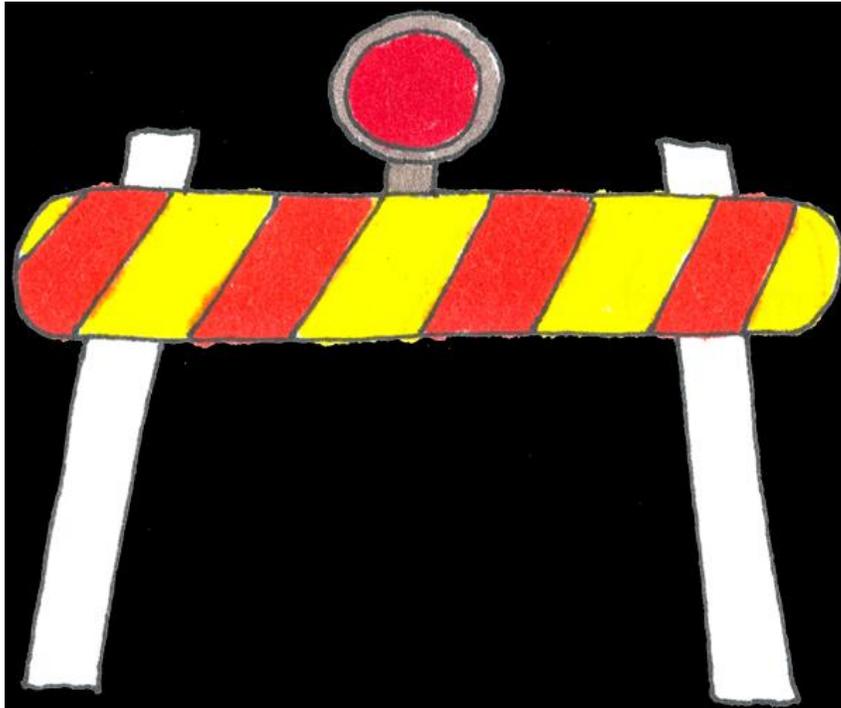
## Norms

- People must be treated fairly
  - Not the same as treating everyone equally
- People should be neither unfairly targeted nor unfairly excluded

# 2 views of Justice

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PROTECTIONIST



ACCESS



# The Bottom Line

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Justice is about fairness

- Individuals and groups should neither be unfairly targeted nor unfairly excluded.

# Criteria for approval

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- (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

# What determines appropriate subject selection?

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The most important determinant of subject selection is the scientific question.

- The population enrolled should be the one that is best able to answer the scientific question.
- Determined by the Inclusion/Exclusion criteria.

# What about race/gender/ethnicity?

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Is there a problem with under-representation in research?

Does access to health care influence access to research?

Is it the job of the IRB to fix this?

# How to evaluate equitable subject selection

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Are the I/E criteria appropriate for the study?

How are participants being recruited?

- Does it suggest targeting a population of convenience?
- Does it miss an important population that might benefit.
- Does it target a population that has no chance of benefit?

Is the inclusion of vulnerable subjects justified?

At continuing review, there is no requirement that there is proportional representation of race/gender etc in a study.

# Key Points

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The regulatory criteria for approval flow directly from the core ethical principles.

The criteria are both necessary and sufficient to assure the protection of human subjects and that the studies we approve are ethical.

Every reviewer, whether physician, scientist, non-scientist, affiliated or non-affiliated, can (and must) apply all the criteria.

# Resources

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## The Belmont Report

- <http://ohsr.od.nih.gov/guidelines/belmont.html>

Levine, Robert J. Ethics and Regulation of Clinical Research, 2nd ed. Urban & Schwarzenberg 1986

The Oxford Textbook of Clinical Research Ethics. Emanuel, E.J. et al Editors. Oxford University Press. 2008

Acknowledgements: Jeff Cooper, The Huron Group.

How to review  
a protocol

The nuts and bolts

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# COI

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You should self identify if you have a conflict of interest on a study

- Financial
- Engaged team member
- Other

May answer questions about study, but not be present for discussion or vote

# Role of Scientific reviewer

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IRB review is not NIH peer review or merit review.

- Scientific reviewers should be able to explain protocol to non-scientific members
- Scientific review should address these questions
  - 1) Is there a safer way to perform the research that would still accomplish the research aims?
  - 2) Are there procedures that would reduce subject risks without negatively affecting the research?
  - 3) Does the protocol accurately describe the risks?
  - 4) Does the protocol accurately describe the benefits?
  - 5) Is the protocol likely to yield the knowledge proposed to result
- Scientific review is not about redesigning the protocol

# The non-scientist IRB member

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What is the role of the NS?

- Present a view point that comes from outside the scientific world
- Be able to review without the intrinsic conflicts that scientific/affiliated reviewers have.
- Look at things from the participant perspective.

Don't try to review as a scientific reviewer.

Don't let jargon intimidate.

Don't focus only on consent.

You are still voting on all criteria.

# Full Board Review

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## Primary reviewer process

- Studies assigned to a primary and secondary reviewer
- All committee members should have some familiarity with each study prior to meeting

## Resolve issues prior to meeting

- Contact PI either directly, or can use HRPO staff as intermediary if you wish to maintain anonymity

## Vote at end of discussion

- Approve
- Approve with contingencies (conditional approval)
- Table (back to committee)

# Types of reviews

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New Protocols

Continuing reviews

Modifications (mods)

All study material available in NIH iRIS.

# New protocol reviews

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Most comprehensive

All criteria for approval

If a device study, NSR determination by committee

Any other regulatory determinations

- Kids/pregnant women etc

# What documents should I look at?

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The study protocol

The IB (if there is one)

The IRB application

The consent document

Data collection instruments

Recruitment materials

# Continuing reviews

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Start from the presumption that the previous review was adequate and appropriate.

Focus is on progress of the study

Any changes/new information that affect the approvability of the study?

Anything that might alter willingness of subjects to continue/enroll?

- New risk information?
- New data in the literature?

# Continuing reviews (continued)

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Assess enrollment progress

- Will they ever meet their goal?

Have there been problems?

Lots of withdrawals?

**DO NOT NEEDLESSLY TINKER WITH THE CONSENT!**

What if I find problems?

- Are they important for the approvability of the study?

# Modifications

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Changes to a previously approved protocol that are more than minor

- Have the potential to adversely affect the risk/benefit analysis
- Significant change in aims or study design.

Your review should focus on whether the proposed change alters the “approvability” of the study.

# Outcome options

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Approve as is

Approve with stipulations

Table (defer)

Disapprove

# Stipulations

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Must relate to a regulatory criteria for approval

Must be prescriptive

Any required changes to study documents (except typos, grammar etc.) must be discussed and voted on during meeting

“Suggested” changes/recommendations are not appropriate – focus on changes required for approval.

Specific regulatory determinations are necessary

- Ex: child category, signature, assent

# Reviewer presentations

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## ▶ Present key elements of study

- Be concise!
  - “This is an industry sponsored, multi-center phase 2 trial comparing std care vs std care plus investigational drug x in the treatment of disease y.
  - Don’t go into a long, detailed description.
- Think about criteria for approval in organizing your presentation.
  - Does the study meet the regulatory criteria for approval?
  - If not, which criteria?
- If device study, is it SR/NSR?
- Kids? Other special populations?

# Reviewer presentations

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Don't expect or attempt to resolve major issues about the study at the meeting.

- Do that beforehand!

If not much needs to be said, don't say much.

Don't be offended if chair moves the discussion along.

Don't excessively wordsmith the consent, or read it like a legal contract.