New IRB Member Training

NICOLE GRANT

1

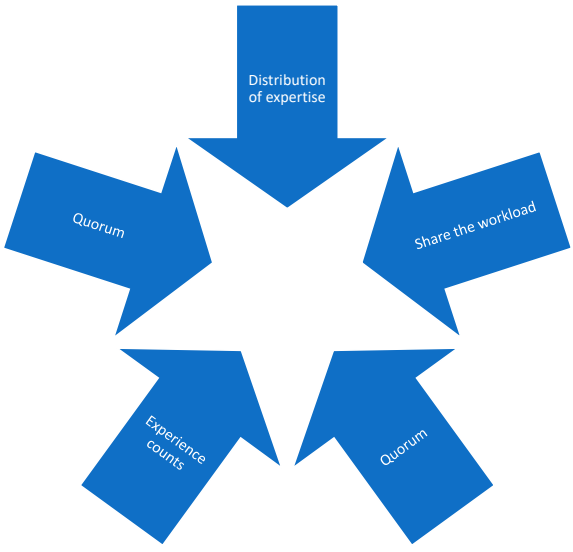
Introduction/Orientation

All meetings are held via Zoom

Using NIH PROTECT electronic system

2

3



Your commitment is important

4

What is the purpose of the IRB

Assure	Assure the ethical conduct of human subjects research
Certify	Certify that federal and institutional requirements for HSR are met.
Research	Research using human subjects cannot take place without approval of the IRB.

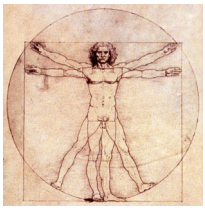
5

Definition of Human Subjects Research

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.

6

Definition of Minimal Risk

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."

7

From Belmont to 45 CFR 46.111

THE CRITERIA FOR APPROVAL AND IRB REVIEW OF HUMAN SUBJECTS RESEARCH

8

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

- The Belmont Report

9

Your mission……

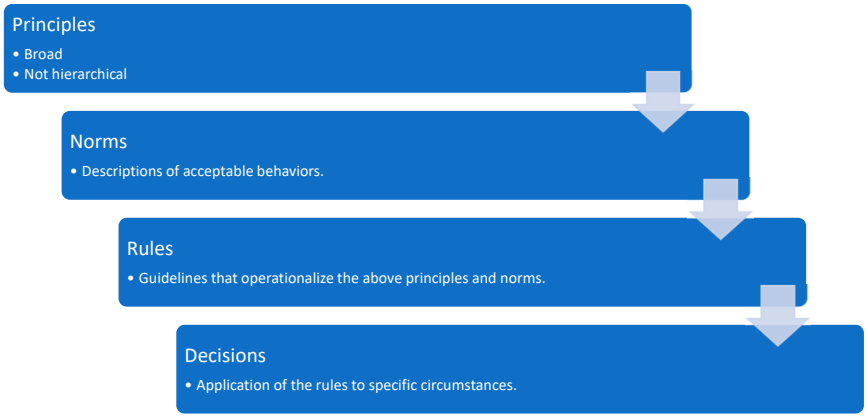
The central task of the IRB is to determine that the proposed research meets the criteria for approval as delineated in the Federal Regulations (45 CFR 46.111).

- 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

10

From principles to review



11

The Principles

Respect for Persons

Beneficence

Justice

No one trumps the other!

12

Respect for Persons

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.

13

Respect for Persons: Regs

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

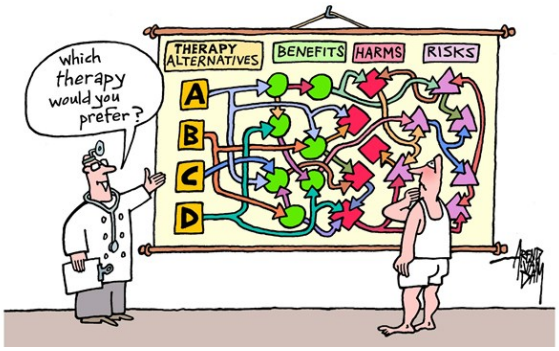
- (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights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

14

The transformative power of consent

CONSENT MAKES THE IMPERMISSIBLE PERMISSIBLE

15



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

16

Purpose of Informed Consent

- Purpose is to provide the information that people need to make an informed decision about whether or not to participate in the research
  - This information helps the individual determine if the research is consistent with their own goals and values
- Ethical imperative based on Belmont principle of respect for persons
  - *Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied* (National Commission 1979)
- The document is a basis for a meaningful exchange between the investigator and the subject
- Strengthens trust with the researcher
- Thorough understanding may also enhance subject safety during the research

17

Application of the Belmont Principle of Respect for Persons: Three Key Elements in the Informed Consent Process

Facilitate	Promote	Disclose
Facilitate understanding • facilitate the understanding of what has been disclosed	Promote voluntariness • promote voluntariness of the decision about whether to participate in the research under conditions free of coercion and undue influence	Disclose information • disclose information to potential research subjects needed to make an informed decision

18

Is Information in the Consent Document Communicated Effectively?

- Some of the changes in the Revised Common Rule (2018) related to informed consent were intended to improve the presentation of material in the consent form
- Stemmed from concerns within the research community that consents had become too lengthy and complex
- Among other items, the 2018 Rule added 2 requirements for consent forms included in studies that receive initial approval on and after January 21, 2019
  - **A key information section** must be included at the beginning of the consent form
  - Information must be presented based on the **reasonable person standard**

19

Is the Information Being Communicated Effectively? Key Information Section

"Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. (45 CFR 46.116a.5.i)"

- Intended to help people determine whether or not they want to participate in the study by providing information that is likely to be most important to the specific persons or group(s) who may consider enrollment in the protocol.

20

Informed Consent-Key information

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.

21

Reasonable Person Standard

Revised Common Rule (2018) "*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 ….*" (45 CFR 46.116 (a)(4))

- Historically, decisions about whether doctors' disclosures to patients are adequate have typically been made by referencing what a medical professional would disclose (professional standard)
- Some have challenged standard as not sufficiently respectful of the individual's autonomy and believe that doctors should disclose what patients reasonably need and want to know (the reasonable patient standard)
- The Belmont Report (1979), similarly, endorsed a "reasonable volunteer" standard

22

Informed Consent—required elements

- A statement that the study involves **research**
- An explanation of the **purposes of the research**
- The expected **duration** of the subject's participation
- A description of the **procedures** to be followed
- Identification of any procedures which are **experimental**
- A description of any **reasonably foreseeable risks or discomforts** to the subject
- A description of any **benefits** to the subject or to others which may reasonably be expected from the research
- A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject

23

Informed Consent—required elements

- A statement describing the extent, if any, to which **confidentiality** of records identifying the subject will be maintained
- **For research involving more than minimal risk**, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained
- An explanation of **whom to contact** for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
- A statement that **participation is voluntary**, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled

24

Informed consent—when appropriate

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently **unforeseeable**
- Anticipated circumstances under which the subject's **participation may be terminated** by the investigator without regard to the subject's consent
- Any **additional costs** to the subject that may result from participation in the research
- The consequences of a subject's decision to **withdraw from the research** and procedures for orderly termination of participation by the subject
- A statement that significant **new findings** developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject
- The approximate **number of subjects** involved in the study

25

Informed Consent-new elements with rCR

(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.

26

Informed Consent-new elements

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).

27

Comprehension

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

28

Factors Affecting How People Make Decisions

- Literacy rates and level of understanding
- Culture
  - Consider cultural group or social groups, being studied
  - Cultural competency: ability of investigator to understand and respond effectively to the cultural and linguistic needs brought by the subject to the research encounter
- Situation in which research will take place
- Personal values
  - Personal health decisions
  - Decisions about participating in health research

(continued)

29

Factors Affecting How People Make Decisions-continued

- Education including ability to find health information
- Medical vulnerability
- Perceptions of choices
- Understanding of health care and familiarity with health-related research
- Knowledge of medical words
- How information is presented and communicated
- Motivation-potential therapeutic misconception and therapeutic misestimation

30

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*
  - Occurs when there is 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

Voluntariness

31

Consent Process should be described in the Protocol

Plans for the consent process (how, where, when etc.) need to be anticipated and included in the protocol:

- Where and when will consent be obtained?
- How will coercion or undue influence will be minimized?
- Will consent be done in person, or by telephone/videoconference?
- Will the consent be provided in advance of the discussion?
- Will the consent be provided electronically or in hard copy?
- How much time will the potential subject be provided to consider their participation?
- Who will answer questions from the subject?
- Will the potential subject be provided the opportunity to consult with others (family, friends, private physician) prior to providing consent?

32

Special protections

- Diminished autonomy
  - Cognitively impaired
  - Children
- Pregnant women?
  - Fetus is the vulnerable entity
- Prisoners
- Economically/socially/educationally disadvantaged
- Desperately ill/dying?

33

Informed Consent

- 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 (PICO).

34

Reviewing informed consent

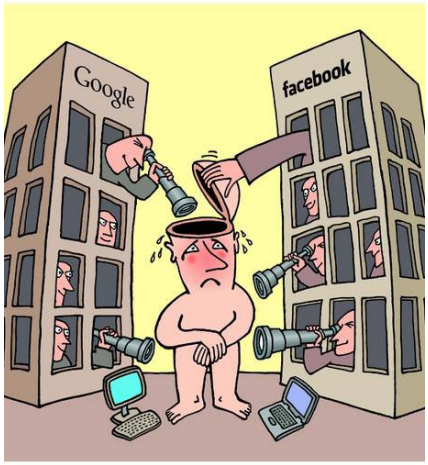
Review the process and the document
- Does the *process* allow for
  - 1) transfer of information
  - 2) comprehension of the information
  - 3) a voluntary decision to participate or decline
- Does the *document*
  - 1) contain the necessary information
  - 2) present the information in a comprehensible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

35

Consent untouchables

NIH Required language
- Injury language
- Privacy
- Certificate of Confidentiality

36



Protecting privacy and confidentiality

(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

37

Beneficence and IRB Review of Research

38

"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

39

Harm/benefit assessment

Ideally, a systematic, non-arbitrary analysis.

"The IRB's 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

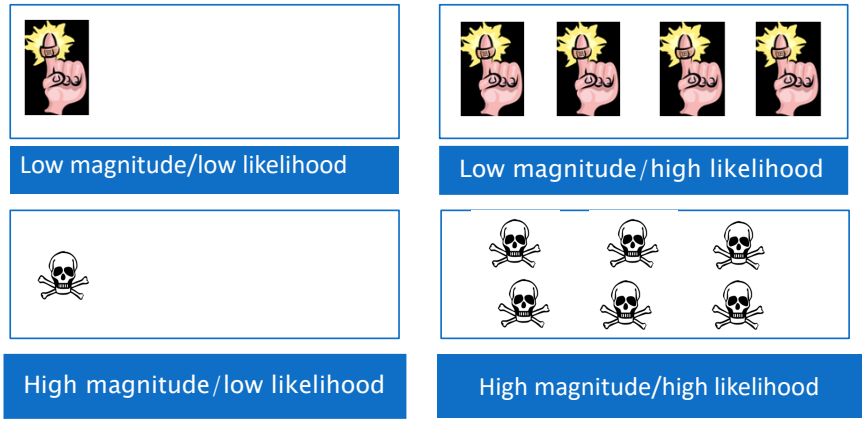
40

Harms and benefits

Benefits/harms to participants
- May be to individuals and/or groups
- Direct (from the research intervention)
  - From receipt of the experimental intervention
    - Uncertain
- Inclusional (clinical benefit)
  - Result from inclusion in the study, but not dependent on receiving the experimental intervention.
    - May be certain

41

Evaluation of harms and benefits



42

Physical Risks

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

43

Risks

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

44

Benefits

Individual

- Access to a potentially efficacious or novel therapy
- Detection of a treatable condition

Societal

- Knowledge that will improve care of others in the future

No requirement to maximize benefit

45

Justification

Difficult to justify exposing humans to risk or inconvenience or expending resources if the knowledge expected to result has no value or is not important

(Emanuel et al. 2000; Casarett et al.2002; CIOMS 2016; Shah & Rid 2017; Wendler & Rid 2017, others)

Which benefits count when determining the reasonableness of risks?

46

Criteria for approval

(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.

47

Criteria for approval

- 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.

48

Clinical benefits vs. Research benefits

Important in decisions about minimizing and justifying risks and assessing risk/benefit	Important in participant understanding of research
• Consideration of existing alternatives • Comparison to a baseline (potential benefits and risks beyond those in clinical care)	• e.g. reducing possible therapeutic misconception, other misunderstandings.

49

Applying the criteria for approval

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.

50

Data safety monitoring

- 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

51

Justice

Principle

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

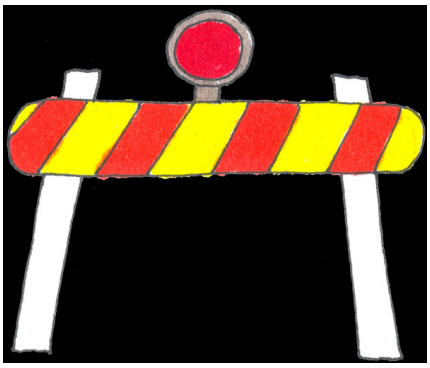
Norms

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

52

2 views of Justice

PROTECTIONIST



ACCESS

53

Justice is about fairness

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

The Bottom Line

54

Criteria for approval

- (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.

55

What determines appropriate subject selection?

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.

56

What about race/gender/ethnicity?

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?

57

How to evaluate equitable subject selection

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.

58

Key Points

- 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.

59

Resources

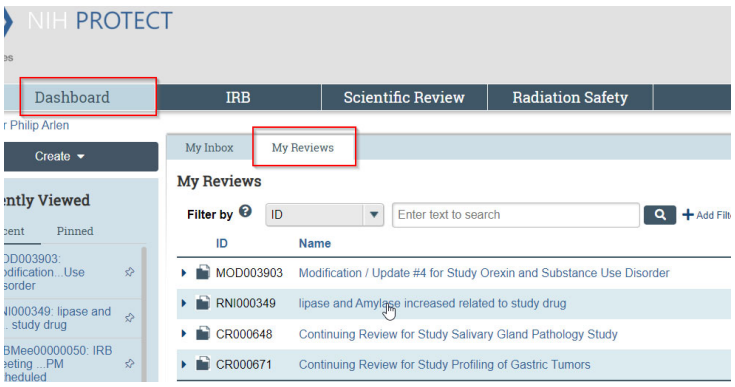
The Belmont Report
- http://ohsr.od.nih.gov/guidelines/belmont.html

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.

60



How to review a protocol: The nuts and bolts

61

COI

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

62

Role of Scientific reviewer

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

63

The non-scientist IRB member

What is the role of the NS?

- Present a viewpoint 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.

64

Full Board Review

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

Resolve issues prior to meeting
- Contact PI either directly using the clarification activity in PROTECT, or can use IRBO staff as intermediary if you wish to maintain anonymity

Vote at end of discussion
- Approve
- Approve with modifications (modifications required to secure approval)
- Deferred (must come back to committee)

65

Types of reviews

- New Protocols
- Continuing reviews
- Modifications (mods)
- Potential unanticipated problems (reportable new information)

66

New protocol reviews

Most comprehensive

All criteria for approval considered

If a device study, NSR determination must be made by the committee

Any other regulatory determinations

- Children
- Pregnant women
- Cognitively impaired
- Waiver of consent

67

What documents should I look at?

The IRB application

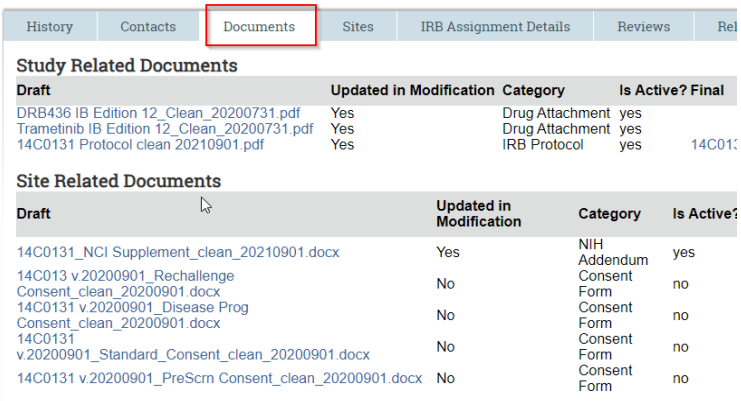
The study protocol

The IB or package insert

The consent document

Data collection instruments

Recruitment materials



68

Continuing reviews

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?

69

Continuing reviews (continued)

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?

70

Modifications

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.

71

Outcome options

- Approve
- Approve with modifications (modifications required to secure approval)
- Deferred (must come back to committee)
- Disapprove

Specific regulatory determinations are necessary, e.g.:

- Pediatric category
- signature
- assent

72

Stipulations

- 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.

73

Reviewer presentations

- 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?

74

Reviewer presentations

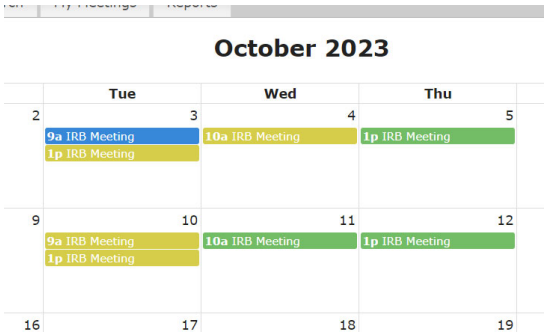
Don’t expect or attempt to resolve major issues about the study at the meeting.
- Do that beforehand!

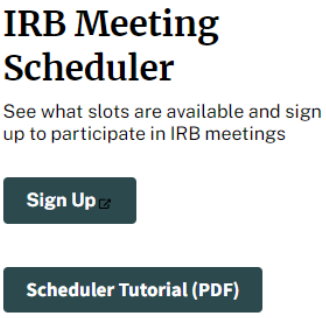
If not much needs to be said, don’t say much.

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

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

75





How to sign up for a meeting

76