Focus on Criteria for Approval in IRB Review

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Before Powerpoint.

Criteria for approval of research

45 CFR 46.111; 21 CFR 56.111

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent is sought from each subject
- Informed consent is documented
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Criteria for approval of research

45 CFR 46.111; 21 CFR 56.111

- IRB must be satisfied that all the review criteria have been met in order to approve a protocol
- IRB must have sufficient information upon which to base its decision
  - if information related to criteria for approval is not available, or if the PI cannot be directed to make specific changes, then the protocol must be tabled

Criteria for approval of research

IRB

ETHICS & HUMAN RESEARCH

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INFORMED CONSENT SUPPLEMENT

A Review of OHRP Compliance Oversight Letters

BY KRISTINA BORROR, MICHAEL CAROME, PATRICK MCNEILLY, AND CAROL WEIL

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A PUBLICATION OF THE HASTINGS CENTER

The Office for Human Research Protections (OHRP), a component of the Department of Health and Human Services (HHS), is responsible for oversight of compliance with HHS regulations governing research with humans (HHS regulations).[1] Institutions that undertake human subjects research conducted or supported by HHS must sign a written Assurance committing them to compliance with these regulations. Many institutions extend the Assurance of Compliance to all human subjects research, regardless of the source of funding.

In carrying out its oversight responsibilities, OHRP evaluates all written substantive allegations or indications of noncompliance with HHS regulations. Sources of allegations or indications of noncompliance include research subjects or their loved ones, the institution itself, internal institutional whistle-blowers, patient/subject advocates, and OHRP staff who raise concerns based on published accounts of clinical trials in the scientific literature or the lay media.

If OHRP has jurisdiction over the human subjects research that is allegedly in noncompliance with HHS regulations, it notifies the relevant institution of the allegations and asks the institution to conduct an investigation. The institution is asked to provide OHRP with a written report on the outcome of the investigation accompanied by IRB documents and any other materials relevant to the inquiry. After reviewing these materials and, in certain cases conducting telephone interviews with key individuals at the institution, OHRP issues written determinations regarding whether research was reviewed and conducted in accordance with the HHS regulations, and may require corrective actions. In a limited number of cases, OHRP conducts on-site evaluations of an institution's program for protecting human subjects before making determinations.

Partly in response to a request by the Institute of Medicine for information about OHRP oversight activities involving human subjects research,[2] OHRP's Division of Compliance Oversight reviewed 269 compliance oversight determination letters issued to 155 institutions between October 1, 1998 and June 20, 2002 (fiscal year 1999 through fiscal year 2002).[3] The letters include those in which OHRP made a definitive finding of noncompliance with HHS regulations and/or expressed concern about apparent regulatory or other deficiencies that resulted in the institution taking corrective action. The institutions in the sample include state and private universities, private research institutions, medical schools, academic

Kristina Borror, Michael Carome, Patrick McNeilly, and Carol Weil, "A Review of OHRP Compliance Oversight Letters," *IRB: Ethics & Human Research* 25 No. 5 (2003): 1-4.

IRB Eth Hum Res 25:1, 2003

- "We have determined that the IRB, when reviewing protocol applications, lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111"

OHRP Common Findings of Non-compliance

Exercise 1

- for each question in application, assign (1) one or more regulatory criteria (§46.111), or (2) Belmont or other ethical principle(s), or (3) other Federal law or regulation (including subparts to 45 CFR 46), State law or Institutional requirement(s)
- if there is a question that cannot be classified as above, why is the information important to the IRB (or HRPP)?
- is there any information missing from the IRB application which would be relevant to the criteria for approval?

"Gee, I don't know... I guess if I had to choose between you I'd say that Jerry's formula has the most hideous side effects."

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Risks to subjects are minimized …

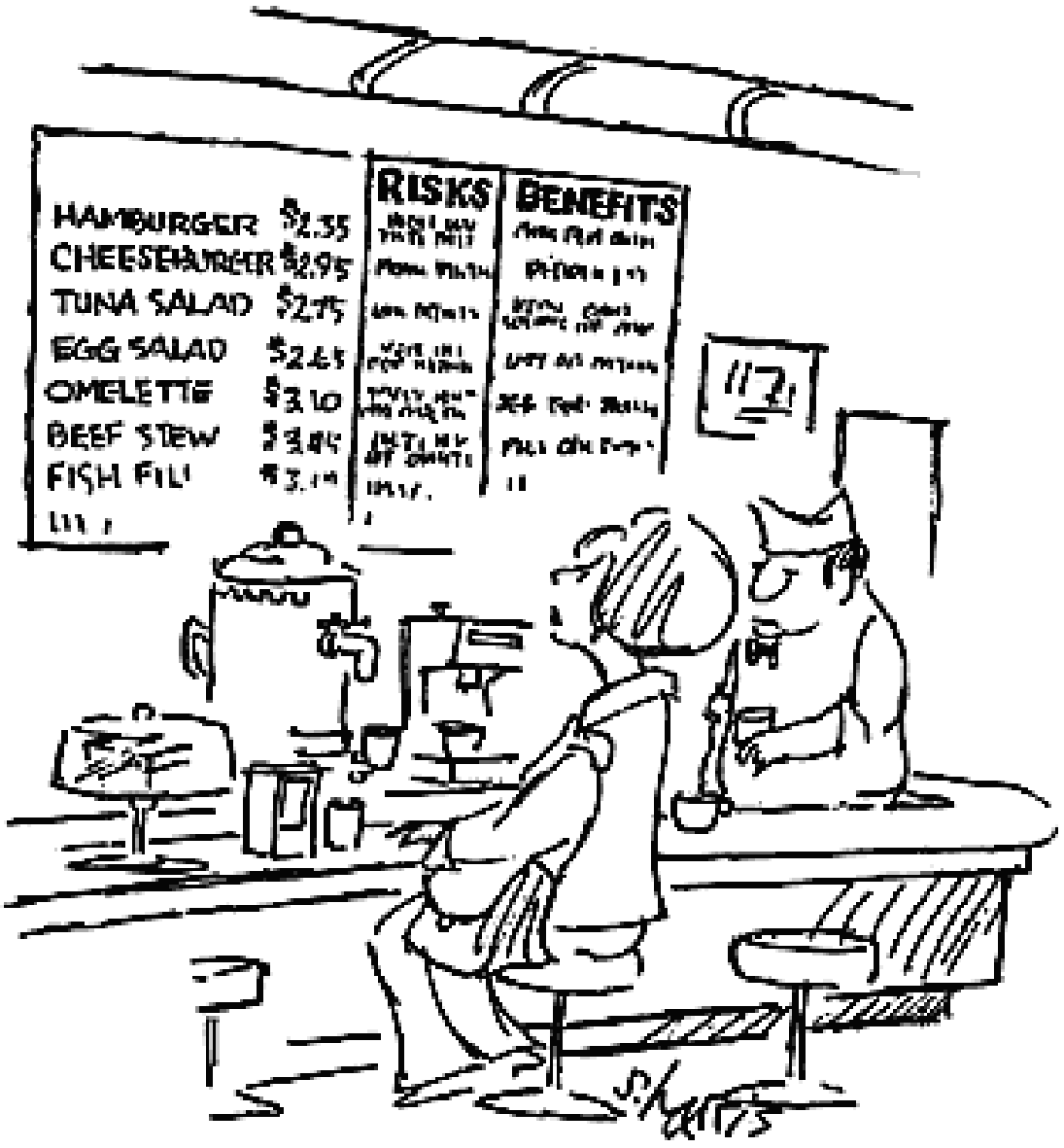
- What are the potential harms of the research?
  - types of risk (physical, psychological, social, legal, economic, …)
  - potential harm to whom? Subject or others (secondary subjects, communities, society)
- Are risk of those harms occurring minimized?
  - alternatives, precautions, contingencies

Risks to subjects are minimized …

- Study design, methods and procedures
- Vulnerable Subjects
- Inclusion/Exclusion criteria
- Confidentiality
- Privacy
- Risks
- Minimization of Risks
- Data and safety monitoring
- Alternatives
- Cost/Compensation/Incentives
- Subject Identification
- Recruitment

Risks to subjects are minimized …

- Study design, methods and procedures (A.4, B.3.1, B.3.2)
- Vulnerable Subjects (A.2.4, A.2.5. A.2.A thru F)
- Inclusion/Exclusion criteria (A.3)
- Confidentiality (A.10, A.11, A.12)
- Privacy (B.1.8, B.3.5)
- Risks (A.6)
- Minimization of Risks (A.6)
- Data and safety monitoring (A.7)
- Alternatives
- Cost/Compensation/Incentives (B.4, B.5)
- Subject Identification (B.1.3, B.3.1)
- Recruitment (B.1, D.1.6 [undue influence])


HAMBURGER $2.35
CHEESEBURGER $2.95
TUNA SALAD $2.75
EGG SALAD
OMELETTE
BEEF STEW
FISH FILI
RISKS
BENEFITS

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Risks to subjects are reasonable in relation to anticipated benefits …

- what are the potential benefits to the subject?
  - types of risk (physical, psychological, social, legal, economic, …)
- what are the potential benefits to others? Will valuable data be generated by the research?
  - scientific design
  - resources (can the research be conducted?)
- What is the balance between risk to the subject and benefits to the subject and/or benefits to society?

Risks to subjects are reasonable in relation to anticipated benefits …

- Background and Rationale
- Study design, methods and procedures
- Risks
- Potential Benefits
- Risk / Benefit Analysis
- Alternatives
- Resources available

Risks to subjects are reasonable in relation to anticipated benefits …

- Background and Rationale (A.1, A.2)
- Study design, methods and procedures (A.4, B.3.1, B.3.2)
- Risks (A.6; also see previous)
- Potential Benefits (A.5)
- Risk / Benefit Analysis
- Alternatives
- Resources available (partially B.1.7 ["address the likelihood that you will have access to the projected number of subjects identified in A.2."] and 3.1, 3.2 [funding])

"Do a double-blind test. Give the new drug to rich patients and a placebo to the poor. No sense getting their hopes up. They couldn't afford it even if it works."

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Selection of subjects is equitable …

- Does the research inappropriately target a group for inclusion (especially if that group is vulnerable)?
- Does the research inappropriately exclude a group who might benefit?
- Is the selection of subjects (inclusion and exclusion criteria) justified by the science rather than convenience?

Selection of subjects is equitable …

- Study Population
- Inclusion/Exclusion
- Vulnerable Subjects
- Subject Identification
- Recruitment

Selection of subjects is equitable …

- Study Population (A.2)
- Inclusion/Exclusion (A.3, A.3.2 ["Justify any exclusion based on race, gender or ethnicity"])
- Vulnerable Subjects (A.2.4, A.2.5)
- Subject Identification (B.1.3, B.1.11 [equal access to participation among women and minorities])
- Recruitment (B.1, B.1.4 [enrolling non-English speaking subjects])

At last Igor finds a body with the appropriate consent form.

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Informed consent is sought and documented …

- What is the consent process?
  - who is involved? where will consent be negotiated? how long will be allotted?
  - how is the risk of coercion or undue influence minimized?
  - how will comprehension be assessed?
- How is capacity to consent assessed?
- What is the process for assent (for children and cognitively impaired persons)? Permission from parents and LARs?

Informed consent is sought and documented …

- Informed Consent process
  - assessment of comprehension
  - assessment of capacity
- Waiver of Consent
- Waiver of documentation of consent
- Vulnerable subjects
- Deception (information withheld)

Informed consent is sought and documented …

- Informed Consent process (D.1)
  - assessment of comprehension?
  - assessment of capacity (A.2.E.2, A.2.E.4)
- Waiver of Consent (D.3.1)
- Waiver of documentation of consent (D.2)
- Vulnerable subjects (D.1.1, D.1.3, D.1.4)
- Deception (information withheld) (D.3.3)

"Mr. Harrison already sees you."

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Adequate provisions for monitoring data …

- What is the data and safety monitoring plan?
  - who will be monitoring the data, what will they be monitoring, how frequently?
  - if appropriate, what are the subject withdrawal criteria?
  - if appropriate, what are the stopping rules based on safety, efficacy and futility?

Adequate provisions for monitoring data …

- Data and safety monitoring plan
  - subject withdrawal
  - stopping rules

Adequate provisions for monitoring data …

- Data and safety monitoring plan (A.7.1, A.7.2, A.7.5)
  - subject withdrawal (A.7.3)
  - stopping rules (A.7.4)

"Your medical records are safe with us. We take patient privacy very seriously."

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Adequate provisions to protect privacy of subjects …

- How will potential subjects be identified and approached?
  - how did the investigator know the potential subject might be eligible for the research?
  - did access to that information violate the person's privacy?
- Where will consent be negotiated?
- Who will be involved in the process of consent?

… and maintain confidentiality of data

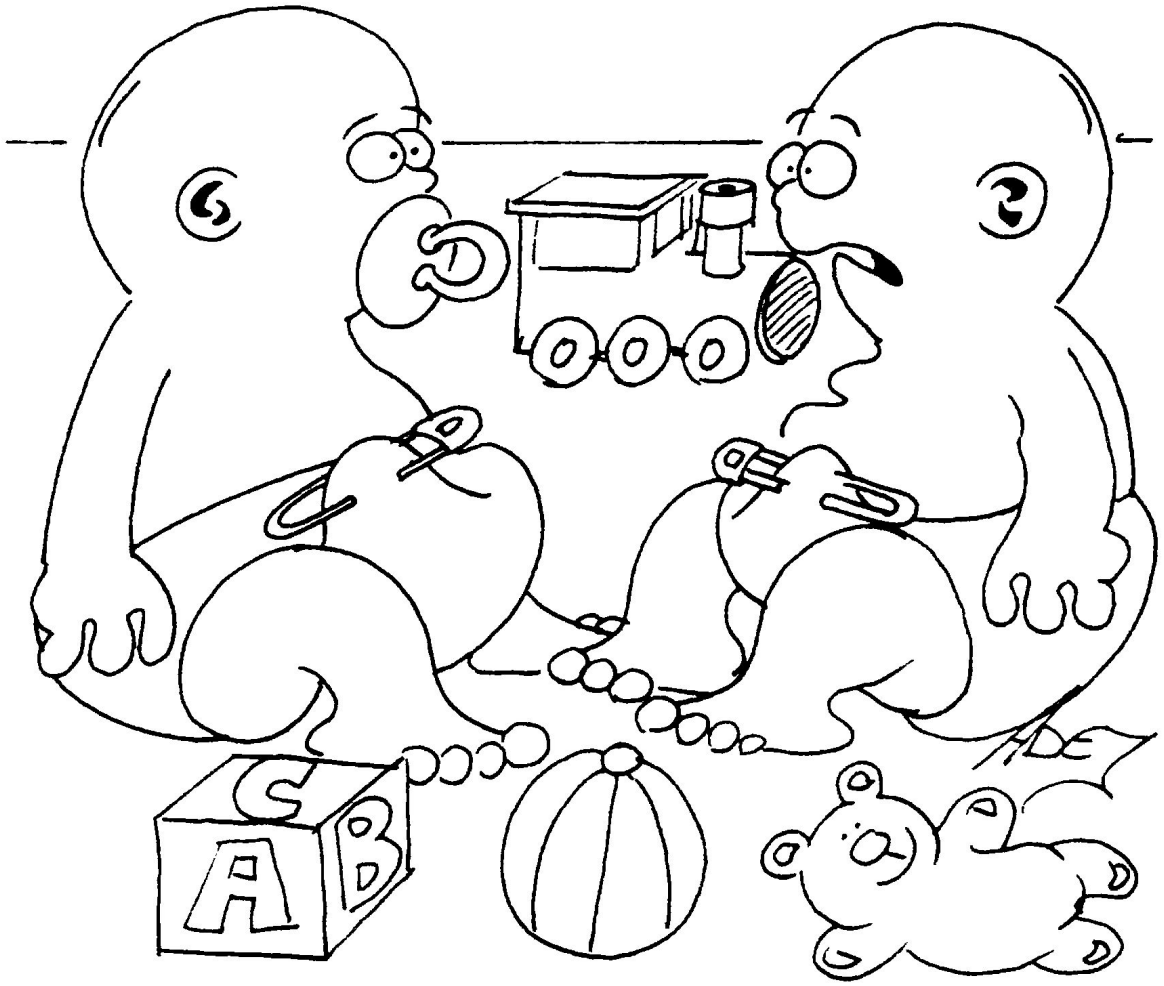
- How will data be secured?
  - will PHI be leaving the covered entity?
- Who will have access to data?
- When will the data be discarded, and how?

Adequate provisions to protect the privacy and maintain confidentiality

- Privacy
- Subject identification
  - ethical access
- Subject contact
- Confidentiality

Adequate provisions to protect the privacy and maintain confidentiality

- Privacy (B.1.8, B.3.5)
- Subject identification (B.1.3)
  - ethical access
- Subject contact (B.1.9, B.1.10)
- Confidentiality (A.9, A.10, A.11, A.12, B.2.1)



Fat, bald and incontinent. Life seems to have dealt us a glancing blow."

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Additional safeguards for vulnerable subjects

- Is inclusion necessary? Is exclusion unfair?
- If inclusion is necessary, are there adequate protections?
  - do prospective subjects have difficulty providing voluntary, informed consent?
  - are prospective subjects at risk for exploitation?
  - if so, how can these risks be minimized?
- Are conditions for informed consent satisfied?
  - information, comprehension, voluntariness

Additional safeguards for vulnerable subjects

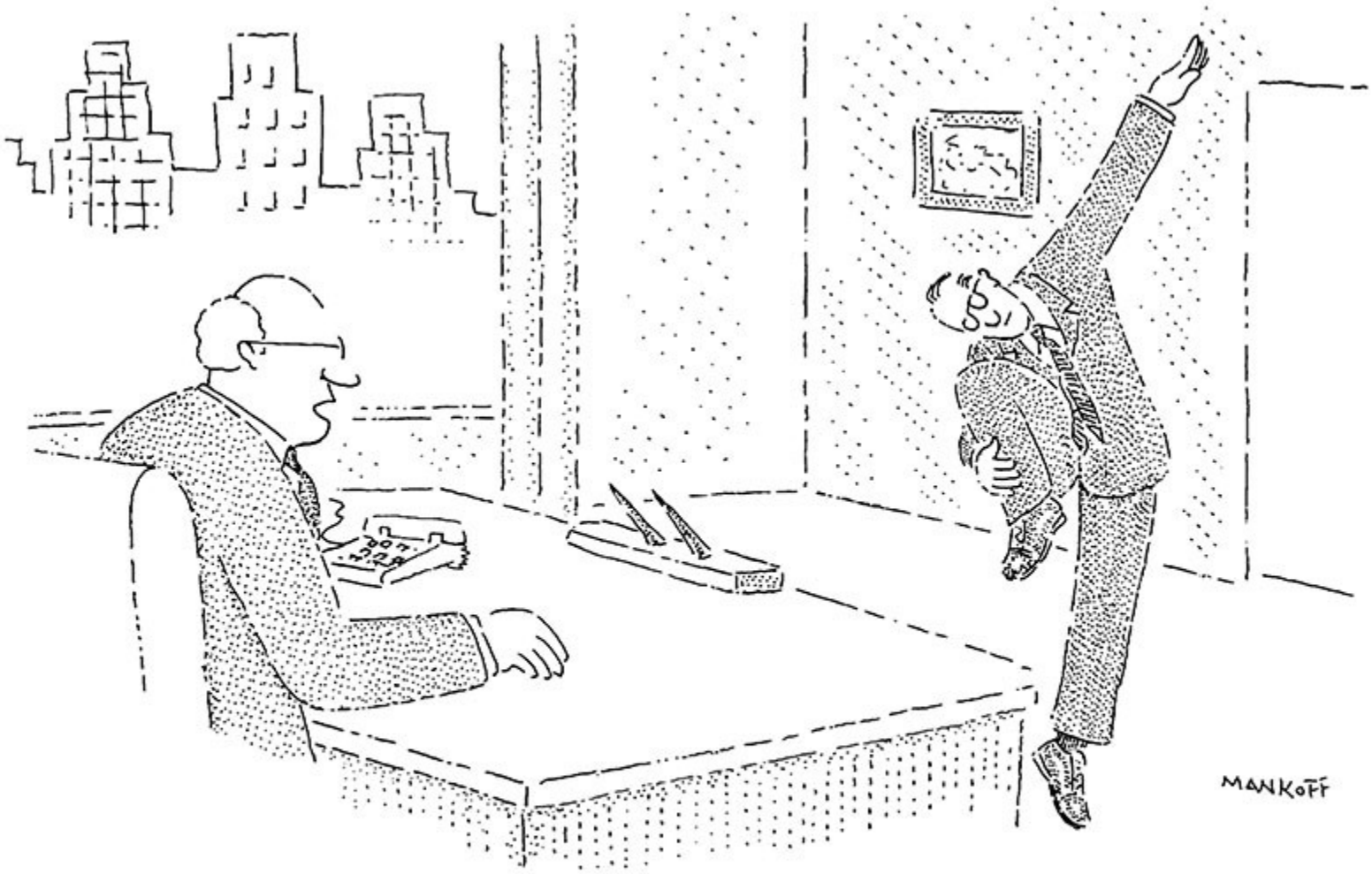
- Study Population (Inclusion / Exclusion)
- Vulnerable Populations
- Risks
- Minimization of Risks
- Informed Consent/Assent/Permission

Additional safeguards for vulnerable subjects

- Study Population (Inclusion / Exclusion) (A.3)
- Vulnerable Populations (A.2.4, A.2.5, A.2.A-F)
- Risks (A.6)
- Minimization of Risks (A.2.A-F, A.6)
- Informed Consent/Assent/Permission ((D.1.1, D.1.3, D.1.4)

Criteria for IRB approval

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent sought and documented
- Adequate provision for monitoring data
- Adequate provisions to protect privacy of subjects and confidentiality of data
- Additional safeguards for vulnerable populations



"Say what's on your mind, Harris—the language of dance has always eluded me."

Exercise 2

- Identify the application questions:
  - which would require that the study be tabled if not answered adequately
  - that produce the most discussion (controverted issues) at IRB meetings
  - that investigators are most likely to answer incorrectly

Exercise 2

- Identify the application questions:
  - which would require that the study be tabled if not answered adequately

- these are questions related to
  - regulatory criteria for approval
  - key ethical issues
  - institutional policies
- should be the focus of the review
- how do you (as chairs) stress them (and make sure they are appropriately discussed)?

Exercise 2

- Identify the application questions:
  - that produce the most discussion (controverted issues) at IRB meetings

- these are (probably) questions
  - related to key ethical issues
  - most interesting to board members
  - least understood by board members

- how do you (as chairs) handle them?

Exercise 2

- Identify the application questions:
  - that investigators are most likely to answer incorrectly

- Why?
  - Is the application question unclear?
  - Is the board unclear on the “right answer”?
  - Is there a “right” answer?

- How do you (as chairs) handle these during the meeting?

"I'm sorry, sir, but Dostoyevsky is not considered summer reading. I'll have to ask you to come with me."

Exercise 3

- Transfer model protocol to template for presentation at the IRB meeting ("presentation format")

Review presentation template

- Title:
- PI:
  - *if student, is there adequate oversight?*
- Funding source:
- COI:
- Study sites (local sites, relying sites, international sites):
  - *reliance agreement in place?*
  - *for international research, is there a local IRB/REC review? does the PI and IRB have sufficient understanding of local conditions?*

Review presentation template

- Purpose:
- Background and Rationale:
  - *Is the background adequately described? Does it justify conducting the study?*
    - Background and Rationale (II.3)
    - Protocol
- Accrual (including expected duration of study):
  - *Is target accrual justified statistically? Is it feasible?*
    - Accrual (II.4)
    - Statistics (II.4A2)

Review presentation template

- Study population (including vulnerable subjects):
  - *Is the subject selection equitable? Are there vulnerable subjects?*
    - Inclusion (II.9) and Exclusion (II.10)
    - Age Range (II.6)
    - Race & Ethnicity (II.7)
    - Gender (II.5)
    - WOCBP, pregnant women, breast-feeding (II.11A, B, C)
    - Vulnerable subjects (II.8A, B)
    - Children (II.6C)
    - Wards (II.6C)
    - Pregnant Women (II.11B)
    - Non-English speaking (II.29F)
    - Capacity (II.8A)

Review presentation template

- Study Design / Methods
  - *Is the design clear? Is the design adequate to answer the scientific question?*
  - *Are there design features of note (for example, placebo, phase 1, deception, tissue banking, genetic testing)?*
    - Methods (II.12)
    - Standard of care
    - Genetic Testing (II.12E)
    - Tissue Banking (II.12F) and Data Banking (II.15E)
    - Deception (II.32)
    - Contraception (II.11A) - see Policies 3.9, 3.10
    - Statistical Analysis (II.12G)
    - Prior IRB Review (II.24)

Review presentation template

- Drugs and Biologics:
  - *Is there an investigational drug?*
  - *Does the use of an approved drug require an IND?*
    - Drugs and Biologics (II.13)
- Devices:
  - *Is there an investigational device? Is it significant risk (SR) or nonsignificant risk (NSR)?*
  - *Does the research involve an in vitro device (IVD)?*
    - Devices (II.14)

Review presentation template

- Confidentiality
  - *Are confidentiality protections adequately described?*
  - *Is there adequate justification for keeping identifiers?*
    - Storage of Data (II.15A)
    - Identifiers (II.15B)
    - Disclosure to Others (II.15C)
    - Data Banking (II.15E)
- Privacy:
  - *Are privacy protections adequately described?*
    - Privacy (II.15D)
    - Identification of subjects (II.25)
    - Ethical Access (II.25) - see also Subject Identification

Review presentation template

- Risks:
  - *Are risks adequately described? Do they match CF and IB?*
    - Risk Classification (II.17)
    - Risks (II.16)
    - Financial Obligations (II.22)
- Minimization of Risks:
  - *Are risks identified and minimized?*
  - *Is the Data & Safety monitoring plan adequate? Withdrawal criteria?*
  - *Is there a DSMB? Are there stopping rules?*
    - Minimization of Risks (II.18)
    - Methods (II.12) including Protocol (Dose modifications)
    - DSMB (II.18B)
    - Withdrawal criteria (II.18D) and Stopping Rules (II.18E)
    - Resources (II.18F)

Review presentation template

- Potential Benefits:
  - *Are potential benefits to subjects (and others) adequately described?*
    - Potential Benefits to the Subject (II.19) and to Society (II.20)
    - Scientific Justification (II.3)
- Alternatives:
  - *For therapeutic research, is standard care adequately described? Do subjects receive at least standard of care?*
    - Alternatives (II.21)
- Risk/Benefit Analysis:
  - *Is Risk/Benefit acceptable? For therapeutic research is R/B at least as favorable as alternatives?*
    - Risks (II.16)
    - Benefits (II.19, II.20)

Review presentation template

- Cost/Compensation:
  - *Are additional costs to subjects clear (and minimized)? Is reimbursement for costs offered?*
  - *Is compensation reasonable?*
    - Financial Obligations (II.22)
    - Compensation (II.23) - see Policies 3.7, 3.8
- Subject Identification/Recruitment
  - *Is process of identification and recruitment adequately described?*
  - *Does the investigator have ethical access to potential subjects?*
    - Method of Identification/Recruitment (II.25) - see Policies 3.5, 3.6
    - Ethical Access (II.25) - see Policy 3.12

Review presentation template

- Informed consent process (including assent)
  - *Is the process of informed consent (and assent) adequately described?*
    - Process of IC (II.29)
    - Documentation (II.30)
    - Non-English speaking (II.29F)
    - Short Form - see Policy 5.6
    - Waiver (II.26)
    - Waiver of signed form (II.27)
    - Assent (II.8)
    - Information Purposefully Withheld (II.32)

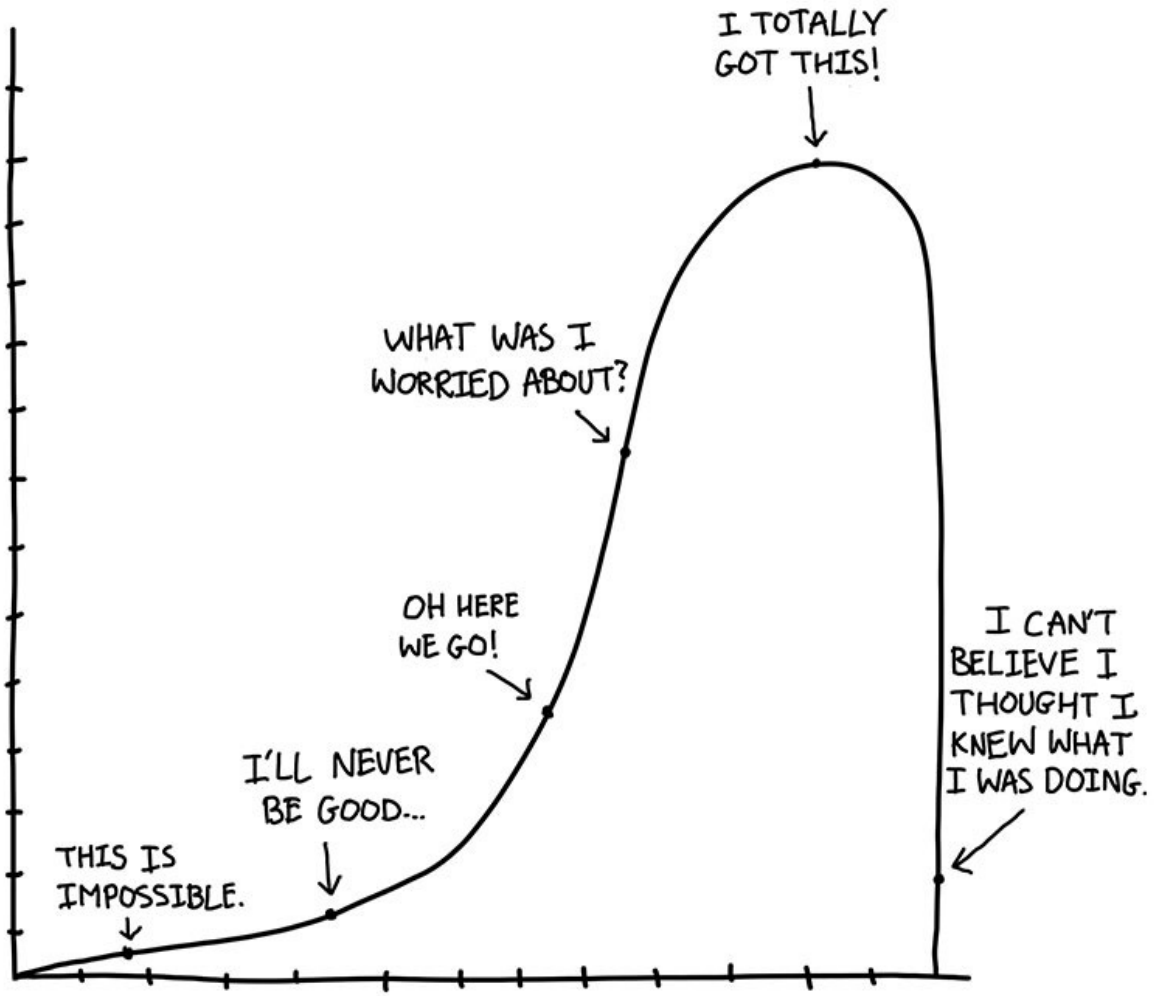
Review presentation template

- Informed Consent Form:
  - *Does the Executive Summary meet readability standards?*
  - *Is the ICF well organized and understandable?*
  - *Does information in the ICF match relevant sections of the IRB application?*
- Assent Form/Information Sheet:
- Recruitment materials, surveys, other documents:
  - *are recruitment materials appropriate?*
  - *do all subject facing materials meet readability standards*

Review presentation template

- Special populations / subjects:
  - *Children*
    - *Does research satisfy satisfies requirements of subpart D?*
    - *What is the specific §46 category? How many parent signatures? Is assent required?*
  - *Prisoners*
    - *Does the research satisfy the requirements of subpart C?*
    - *What is the specific §46.306 category? Is certification needed?*
  - *Pregnant Women*
    - *Does the research satisfy the requirements of subpart B? Who must provide consent?*
  - *Cognitively impaired*
    - *Does the research satisfy the requirements of HRPP policy? How is capacity assessed? Is assent required?*

LEARNING CURVE



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