IRB Approved!

Tips and Tricks to Smooth Sailing though the Institutional Review Board (IRB) Process

Lindsey C. Douglas
Inpatient Medical Director, Kravis Children's at Mount Sinai

Armand H. Antommaria, MD, PhD
Director, Ethics Center, Cincinnati Children's

Derek Williams, MD, MPH
Vanderbilt University Medical Center

Disclosure

- None of the presenters or any member of their immediate families has a financial relationship or interest with any proprietary entity producing health care goods or services related to the content of this CME activity.
- The presenters' content will not include discussion or reference of any commercial products or services.
- The presenters do not intend to discuss unapproved or investigative use of commercial products or services.

Learning Objectives

- To describe the key historical events in research regulation and core principles of human subjects research
- To demonstrate writing a research protocol that includes the key components required for IRB approval
- To recognize emerging issues and potential changes in human subjects research

Outline

- Introduction (5 min)
- History and Key Issues in Pediatric Research Ethics (10 min)
- Types of Review and Checklist of IRB Protocol (15 min)
- Breakout Session (20 min)
- Report Out (10 min)
- Emerging Issues in Research Ethics (10 min)
- Q & A (5 min)

Pediatric Research Ethics

Protection of Human Subjects

- Nuremberg Military Tribunals (1947)
- Jewish Chronic Disease Hospital (1963)
- Tuskegee Study of Untreated Syphilis in the Negro Male (1932-73)

- Nuremberg Code (1947)
- Declaration of Helsinki (1964)
- ”Progress report on survey of moral and ethical aspects of clinical investigation (1964).”
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1978)
- Common Rule (1981, 1991)

Nuremberg Code

- The voluntary consent of the human subject is absolutely essential.

Declaration of Helsinki

- Basic Principles
  - In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering. If at all possible, consistent with patient psychology, the doctor should obtain the patient’s freely-given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.
- Nontherapeutic Clinical Research

- Nuremberg Code (1947)
- Declaration of Helsinki (1964)
- ”Progress report on survey of moral and ethical aspects of clinical investigation (1964).”
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1978)
- Common Rule (1981, 1991)

Criteria for IRB Approval of Research

- Risks to subjects are *minimized*
- 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.
- Selection of subjects is *equitable*.
- Informed consent will be *sought* from each prospective subject or the subject’s legally authorized representative [and appropriately *documented*]
- When appropriate, the research plan makes adequate provision for *monitoring* the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to *protect* the privacy of subjects and to *maintain* the confidentiality of data.

45 CFR 46 https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.102

Subpart D – Additional Protections for Children Involved as Subjects in Research

- §46.404 Research not involving greater than minimal risk.
- §46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
- §46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- §46.407 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 https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.102

Minimal Risk

- Definition
  - 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 (italics added).
- Interpretations
  - Relativistic: Research Subjects
  - Absolute: Normal, Healthy Children/Typical/General Population

45 CFR 46 https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#46.102
Kopelman LM. Children as research subjects: a dilemma. *J Med Philos.* 2000;25(6):745-764.

Categorization of Risk by IRB Chairpersons of Common Research Procedures Performed in Healthy 11-Year-Olds (N = 188)

	No. (%) of Chairpersons Who Categorized Risk		
Procedure	Minimal Risk	Minor Increase	More Than a Minor Increase
Blood draw (10 ml)	152 (81)	32 (17)	2 (1)
MRI (no sedation)	90 (48)	66 (35)	17 (9)
Confidential survey of sexual activity	83 (44)	55 (29)	36 (19)
Allergy skin testing	43 (23)	81 (43)	51 (27)
Electromyography	17 (9)	83 (44)	77 (41)
Pharmacokinetic study (risk of death: 1/100,000)	13 (7)	56 (30)	111 (59)
Initial pediatric testing of drug found safe in 500 adults	9 (5)	43 (23)	122 (65)
LP without conscious sedation in healthy children	4 (2)	30 (16)	147 (78)
LP without conscious sedation in ill children	11 (6)	60 (32)	104 (56)

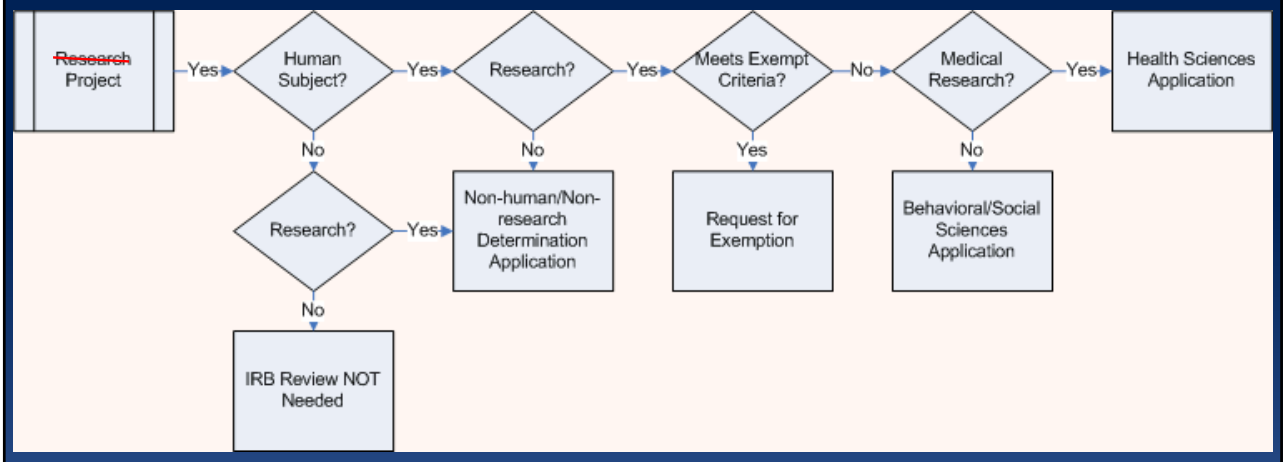
Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? JAMA. 2004;291(4):476-82.

Determining the Appropriate IRB Application for Your Research

Federal Definitions

- **Human Subject** – 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
- **Research** – a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge
- **Minimal Risk** - 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

Application Pathways



Application Pathways

- Non-Human/Non-Research
- Exempt
- Expedited
- Standard
- Other
  - Grant Review, Coordinating Center, IRBShare/SingleIRB

Non-Human/Non-Research Determination

- Study that does not include human subjects or qualify as research according to federal definitions
  - IRBs typically make this determination

Example: Vanderbilt's BioVU

De-identified DNA biorepository

Exempt Studies

- Must meet federal definition of minimal risk AND fall into one of 6 exemption categories:
  - Usual/normal educational practices ★
  - Surveys, cognitive/educational testing, public behavior (de-identified) ★
  - Surveys, cognitive/educational testing, public behavior of senior elected officials or if confidentiality protected under federal statues
  - Existing "off the shelf" data, records, specimens, etc (de-identified) ★
  - Certain federally conducted/approved studies of public benefit or service programs
  - Taste and food quality evaluation and consumer acceptance studies

Non-exempt: Expedited vs Full Review

Expedited
-Reviewed by sub-committee (analyst, reviewer, IRB chair)

-No greater than minimal risk

-Seven categories defining research eligible for expedited review

Full Review
-Convened committee review and approval process

-All studies involving greater than minimal risk and selected minimal risk studies

★ Same review criteria apply for expedited and full review proposals

Expedited Review Categories

1. Certain drug studies (no IND) and non-significant risk device studies
2. Collection of blood sample—limits on blood volumes (3ml/kg)
3. Non-invasive collection of biological specimens (hair, saliva)
4. Data collected using clinically-available, non-invasive procedures (MRI—not x-ray or CT, EEG, ECG, US, etc)
5. Non-exempt research using data (records, specimens, etc.) collected for non-research purposes
6. Data from voice, video, digital recordings
7. Non-exempt research on individual or group characteristics or behaviors (surveys, interviews, focus groups)

Protection of Human Subjects

- Risks to subjects are minimized
- Risks reasonable in relation to anticipated benefits, if any, and importance of knowledge that may be expected to result
- Selection of subjects is equitable
- Informed consent or justification supporting alteration of informed consent process
- Adequate provisions for monitoring data collected to ensure subject safety, privacy, and confidentiality
- Additional safeguards for vulnerable populations (children, prisoners, pregnant women/fetuses, mentally disabled, or otherwise disadvantaged individuals)

Protection of Human Subjects: Children

- Risks to subjects are minimized
- Risks reasonable in relation to anticipated benefits, if any, and importance of knowledge that may be expected to result
- Selection of subjects is equitable
- Informed consent or justification supporting alteration of informed consent process
- Adequate provisions for monitoring data collected to ensure subject safety, privacy, and confidentiality
- Additional safeguards for vulnerable populations (children, prisoners, pregnant women/fetuses, mentally disabled, or otherwise disadvantaged individuals)

Possible Outcomes of IRB Review

- *Approval*
  Research may begin
- *Conditional approval*
  Minor changes/clarification needed; research may begin once recommended changes are addressed
- *Defer approval*
  Major changes/clarification needed; application must be revised and resubmitted

Some overall writing pointers

- Make it easy for the reader
- First impressions count

- Keep it organized
  - Section headings, Table of Contents (consider if long protocol)
- Use the same terminology throughout the protocol
  - Abbreviations - use sparingly
- Anticipate questions and answer them proactively
  - Ex: length of stay as outcome
- Be specific in objectives/aims - no room for questions

Background

- Basics about epidemiology of disease and/or patient population
  - "This is a big problem that costs lots of money!"
- Why is this important?
- Why THIS study?

Op-ED piece - convince us!

- Lead seamlessly to the objective of the study
- Guide the reader to come to your research question on his/her own

Objective

- Be specific
- Use terminology that is accurate
  - Verbs: Evaluate, examine, study, determine (with caution)
  - Methods: Associations, risk/causes (with caution)
- Make this a separate section (easy to find again for reader)
- Link clearly to measures and outcomes
- Organize
  - Number objectives, order that makes sense, primary objective first

Outcome Measures

- Must be reproducible
- Unit of measure
- If proportion, describe denominator well

- Primary vs. Secondary Outcomes
  - Clearly separate with bullets or numbered list
  - Secondary outcomes need to be as clearly laid out as primary

Inclusion/Exclusion Criteria

- Clarity for reproducibility
- Feasibility - can you really find these patients?
- Organize
  - Bullet and/or group (demographic/clinical/lab)
  - Make it easier for reviewer to find later
- Again, answer anticipated questions proactively
  - “We excluded children under one year of age because…”

Methods

- Type of study
  - Retrospective cohort, cross-sectional survey
- Describe exactly how data will be obtained
  - Recruitment
- Data collection tools
  - MUST be included with IRB submission
  - Chart abstraction tool, survey, patient questionnaire
  - The simpler the better

Statistics

- If you're not sure - get help!

- Choose your words carefully
  - Acetaminophen causes asthma
  - Acetaminophen is associated with asthma
- Describe the exact statistical test you will use
- A word about "descriptive statistics"
  - Does "describing" match your objective?

Power Analysis

- Must include if appropriate
- Again, answer questions proactively
  - Do you have enough patients with this disease to detect the effect size you propose?
  - Will you have to recruit for 20 years to get the number of patients needed?
- 4 things needed for power analysis - solve for “n” or power
  - “n” = number of patients (in each group)
  - Effect size
  - alpha - nearly always 0.05
  - Power (1-beta) - should be over 80%

Risks and Benefits Section

- Red flag if section not included
- List all anticipated risks
  - Include the risk of confidentiality breach
  - Should be same as consent form
- Benefits
  - Careful not to overstate
  - If no direct benefit - say this clearly

Wording for Risks/Confidentiality

- Careful not to overstate the benefits or minimize risks
- Specific wording on protection of risks/confidentiality
- Acceptable wording includes:
  - "The primary human subjects risk is loss of participant confidentiality"
  - "All linkages to PHI will be destroyed as soon as possible"
  - "Confidentiality of the participants will be assured by limiting data access to the study team"
  - "Data will be stored electronically via secure, password-protected servers accessible only to key study personnel"
  - "All key study personnel are trained in the conduct of human subjects research "

Avoid common pitfalls

DON'T

- Copy/paste your grant
- Forget risk/confidentiality section
- Overstate benefits

DO

- Address triggering disclosures
- Consent at a 4th grade level
- Include all risks in consent

Making Consent Forms Understandable

- Limit most words to 1-2 syllables
- Avoid complex words
  - If alternatives are not available, explain the concept in plain language, introduce the new word, and provide a pronunciation guide
  - Example: A normal heart beat starts in the upper right chamber of the heart, or atrium (**ay**-tree-yim)
- Vary sentence length and limit most sentences to 10-15 words
- Use active voice
- Use terms consistently

https://medlineplus.gov/etr.html

Emerging Issues in Pediatric Research Ethics

Evolution of Research and Research Ethics

- Dominant Concern: Protection -> Inclusion
- Methodology: Randomized Controlled Trial -> Pragmatic Trials, Comparative Effectiveness Research, Biobanking, and "Big" Data
- *The Immortal Life of Henrietta Lacks* and the publication of the HeLa cell line genome sequence

Learning Healthcare Systems

- The obligation
  - to respect patients
  - to respect clinician judgment
  - to provide optimal care to each patient
  - to avoid imposing nonclinical risks and burdens
  - to address unjust inequalities
  - to conduct continuous learning activities that improve the quality of clinical care and health care systems
  - of patients to contribute to the common purpose of improving the quality and value of clinical care and the health care system

Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep. 2013;Spec No:S16-27.

Comparative Effectiveness Research

- Risk
- Physician Preference v. Randomization
- Informed Consent
  - No-Consent (Broad Disclosures)
  - Integrated Consent (Verbal Disclosure)

Faden R, Kass N, Whicher D, Stewart W, Tunis S. Ethics and informed consent for comparative effectiveness research with prospective electronic clinical data. Med Care. 2013;51(8 Suppl 3):S53-7 and Kim SY, Miller FG. Informed consent for pragmatic trials--the integrated consent model. N Engl J Med. 2014;370(8):769-72.

Revision to the Common Rule

- Advance Notice of Proposed Rulemaking (2011)
- Notice of Proposed Rulemaking (2015)
- Final Rule (2017)
- Effective Date (2018, 2020)

- Single-IRB review for multi-institutional studies conducted in the US
- Does not require informed consent for use of *deidentified* biospecimens
- Broad consent for the storage, maintenance, and secondary research uses of private information and *identifiable* biospecimens
- Modification of informed consent forms, e.g., initial concise and focused presentation of key information

Single IRBs for Multisite Studies

Pros

- Eliminate duplicative and potentially conflicting reviews
- Accelerate review process

Cons

- Allocation of responsibilities unclear
- Inattention to local context issues and state and local regulations
- Reduce informal interactions

Klitzman R, Pivovarova E, Lidz CW. Single IRBs in Multisite Trials: Questions Posed by the New NIH Policy. JAMA. 2017;317(20):2061-2062.

Biospecimens

- Remove Identifiers
- Retain Identifiers
  - Study Specific Consent
  - Waiver of Consent
    - Could not practicably be carried out with nonidentifiable biospecimens
  - Broad Consent and Limited IRB Review
    - If potential participant declines, waiver of consent is not permitted

Lynch HF, Meyer MN. Regulating Research with Biospecimens under the Revised Common Rule. Hastings Cent Rep. 2017;47(3):3-4.