Research Professionals Network
Workshop Series

WHY WE NEED IRB REVIEW

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EXCEPTIONAL CARE. WITHOUT EXCEPTION.

The University of Vermont

AIMS OF TODAY'S WORKSHOP

1. Explain the need for IRB Review
2. Summarize the criteria by which research is approved, applying 45 CFR 46.111
3. Describe the composition of the IRB Committee
4. Apply regulations to present day examples of research activities.

WHY IS RESEARCH SO HEAVILY REGULATED?

Nazi War Crimes – Nuremberg Trials (1945-1946)

20 German physicians and 3 Nazi officials were charged with crimes against humanity for conducting research procedures on concentration camp prisoners without consent.

NAZI HUMAN EXPERIMENTATION

- Experiments resulted in death, trauma, disfigurement or permanent disability, and are considered examples of medical torture.
  - Development of new weapons
  - Aid in the recovery of military personnel
  - “cure” homosexuality
  - Twin experiments
  - Freezing
  - Sterilization
  - Bomb experiments
  - High altitude
  - Malaria

Results of the trial horrified the world and led to the creation of the Nuremberg Code (1947).

A set of 10 research ethic principles for human expiration in medicine accepted by physicians worldwide.

Hohenlychen Sanatorium

THE NUREMBERG CODE

- The ***voluntary consent*** of the human subject is absolutely essential.
- The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and ***not random and unnecessary*** in nature.
- The experiment should be so conducted as to ***avoid all unnecessary physical and mental suffering and injury.***
- During the course of the experiment, the human subject should be at liberty to ***bring the experiment to an end,*** if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.
- Proper preparations should be made and adequate facilities provided to ***protect the experimental subject*** against even remote possibilities of injury, disability, or death.

TUSKEGEE STUDY - NEW YORK TIMES, 1972

- The experiment began with 600 black men, mostly poor and uneducated, from Tuskegee, Ala., an area that had the highest syphilis rate in the nation at the time
- 399 of the group had syphilis and never received deliberate treatment for the venereal infection.
- A control group of 201 had no syphilis and did not receive any specific therapy.
- As incentives to enter the “program”, the men were promised free transportation to and from hospitals, free hot lunches, free medicine for any disease ***other than*** syphilis and free burial after autopsies were performed.

WHAT WENT WRONG?

- The Tuskegee Study began 10 years before penicillin was found to be a cure for syphilis and 15 years before the drug became widely available.
- The men were never given adequate treatment for their disease.
- Even when penicillin became the drug of choice for syphilis in 1945, researchers did not offer it to the subjects.

A MORAL AND ETHICAL NIGHTMARE

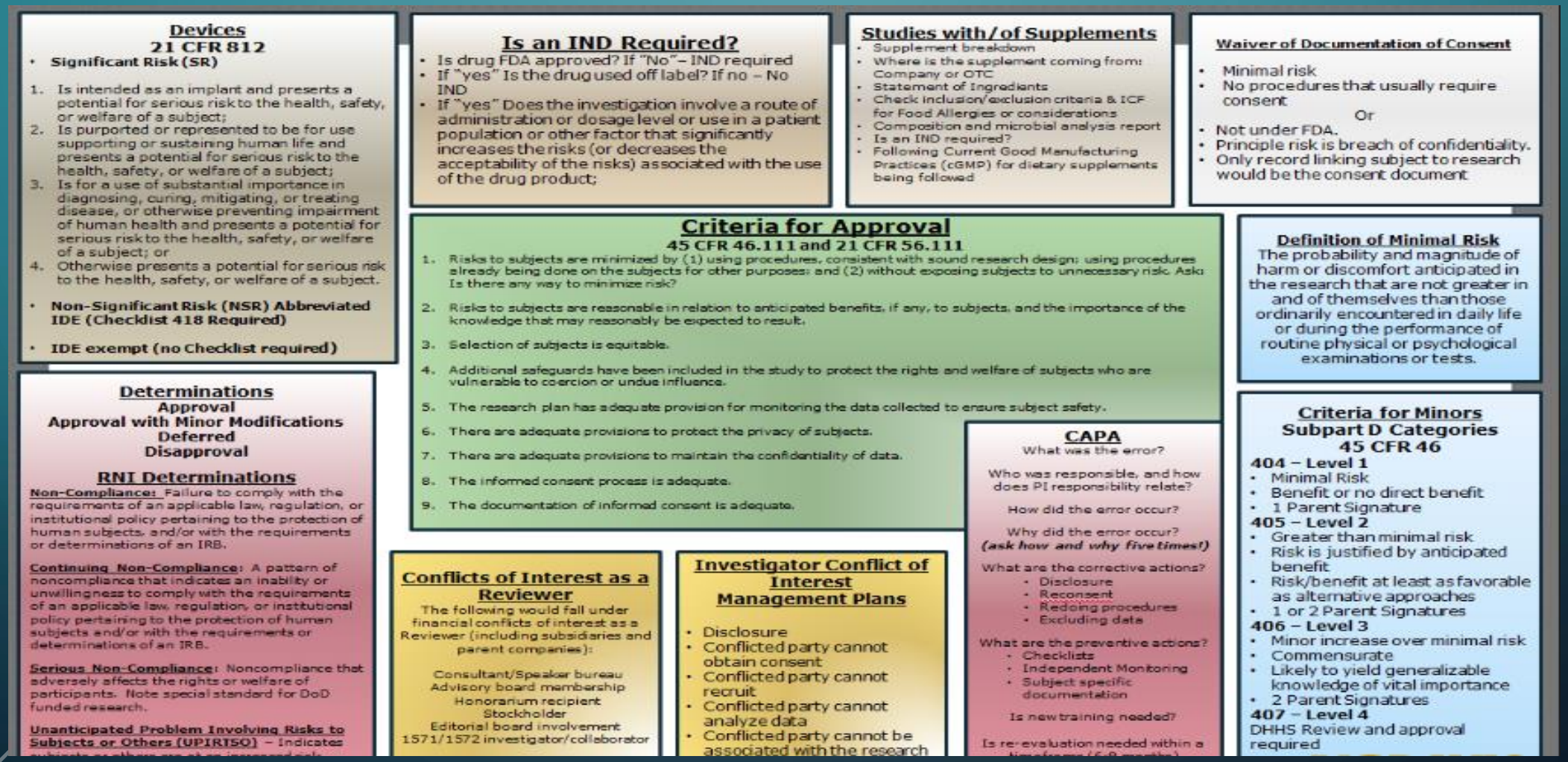
- Syphilis left untreated can cause bone and dental deformations, deafness, blindness, heart disease and deterioration of the central nervous system.
- By 1969 seven participates had died as a direct result of untreated syphilis.
- There was no evidence that researchers had informed them of the study or its real purpose.
- The men had been misled and had not been given all the facts required to provide informed consent.

PREVENTING A REPEAT OF MISTAKES

- In 1974, the ***National Research Act*** was signed into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research . The group identified basic principles of research conduct and suggested ways to ensure those principles were followed.
- Researchers must get voluntary consent
- Studies must be reviewed by Institutional Review Boards **(That's us!)** which read study protocols and decide whether they meet ethical standards.

Official apology by President Clinton in 1997

WE KNOW THERE IS A NEED FOR IRB REVIEW BUT HOW DO MEMBERS BEGIN?



HOW DO IRB'S PROTECT PARTICIPANT'S TODAY?

- 45 CFR 46.111 Criteria for IRB approval of research

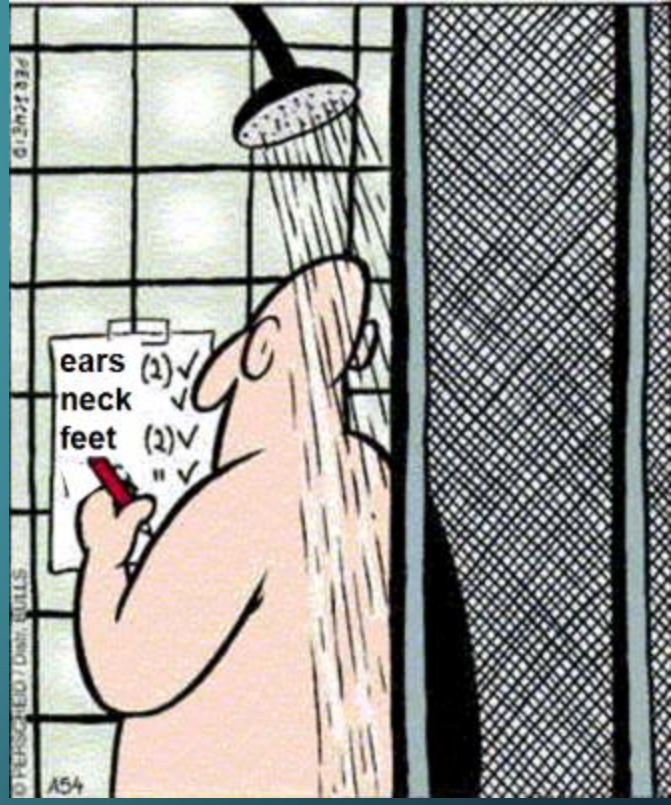
IRB Members must ensure all of the following requirements are satisfied:

1. Risks to subjects are minimized
2. Risks to subjects are reasonable in relation to anticipated benefits
3. Selection of subjects is equitable
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative
5. Informed consent will be appropriately documented
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Additional safeguards have been included in the study to protect the rights and welfare of vulnerable subjects.

ADDITIONAL SAFEGUARDS FOR VULNERABLE POPULATIONS

- Pregnant Women – Subpart B
- Fetuses – Subpart B
- Prisoners – Subpart C
- Children – Subpart D

IRB MEMBER REVIEW PROCESS



- CHECKLISTS
- ANALYSTS PRE-REVIEW
- COMMITTEE MEMBER PRE-REVIEW FORM
- ACCESS TO OUR LOCAL RESEARCH POLICY AND PROCEDURES MANUAL
- ACCESS TO FEDERAL REGULATIONS

IRB Member Reviewer Worksheet
RESEARCH PROTECTIONS OFFICE, COMMITTEES ON HUMAN RESEARCH
UNIVERSITY OF VERMONT AND UNIVERSITY OF VERMONT MEDICAL CENTER

Questions in italics are federally regulated mandated questions an IRB member must address as part of their initial review.

The remaining questions are a guide to help you complete your review and incorporate UVM and Committee policy.

IRB Number:

PI:

Protocol Title:

Reviewer: **Review Type:**

Protocol	Yes	No	N/A	Questions/Changes/Comments
Will the research contribute to generalizable knowledge and/or produce benefit and is it worth exposing subjects to some level of risk?				
Is the hypothesis clearly stated?				
Is the study design appropriate to test the hypothesis?				
Is there statistical justification for the sample size?				
Has the investigational drug/device brochure been reviewed (primary reviewer only)?				

If there is a grant proposal how does the protocol compare to the grant?

_____The title and narrative (i.e., specific aims, research plan and methods) of this IRB protocol accurately represents the accompanying grant proposal which will support the proposed research activity involving human subjects.

_____The title and narrative of this IRB protocol does not match that of the accompanying grant proposal. If the IRB protocol and grant proposal are not comparable, describe the major discrepancies below (e.g., different subject populations, hypothesis, or scope of work). Note: This category requires that the sponsor be notified of the differences.

Subject Population	Yes	No	N/A	Questions/Changes/Comments
Is the study population appropriate for the goals of the study? (consider both the nature and size of the sample)				
Are the criteria for inclusion and exclusion of subjects appropriate?				
Are screening procedures well described?				
If vulnerable populations are included, are the appropriate safeguards for the protection of the rights and welfare of these subjects appropriate to include undue influence and coercion?				
Have specific additional protections been included for research involving fetuses, pregnant women, prisoners, and children (vulnerable populations) as specified in regulations.				
For protocols including use of an investigational drug, are children and women of childbearing potential included? If no, appropriate justification must be given.				
If yes, are there appropriate precautions included? Refer to the pregnancy checklist/prisoner checklist.				

Recruitment of Subjects	Yes	No	N/A	Questions/Changes/Comments
Is the process of recruiting subjects equitable and acceptable for the project? Have appropriate efforts been made to include women, children and minorities?				
Does the recruitment tool provide enough information about the project?				
Are methods of subject recruitment legal, ethical and free from coercion or undue influence?				

Methods and Procedures	Yes	No	N/A	Questions/Changes/Comments
Are the procedures appropriate for the study? Blood draws? Scans? Survey instruments?				
Is the description of all procedures complete?				
If deception is used, are procedures relating to debriefing of subjects clearly described? (Is there a debriefing statement/consent included?				

Risk and Minimization of risks	Yes	No	N/A	Questions/Changes/Comments
Are risks minimized by use of procedures consistent with sound research design and which do not unnecessarily expose subjects to risk?				
Should this protocol be categorized as a "high risk" protocol which would require additional reporting? If so, describe additional reporting and duration. (e.g., is this a phase I protocol?)				
Are the risks (including known incidence) clearly described? (physical, psychological and social risks)				
Have adequate safeguards been adopted to reduce risk exposure as much as possible? (i.e. frequent monitoring, qualified personnel, handling of incidental findings, debriefing procedures, procedures for response to emergency situations including suicidality, mandated reporting, referral resources provided)				
Are the risks reasonable in relation to the anticipated benefits?				
Have adequate measures been taken to ensure that the occurrence of illness or injury will be detected and treated?				
Where appropriate, have alternative procedures that might be advantageous to the potential research subjects been described?				
If applicable, are reproductive risks adequately described and is appropriate birth control language included?				
Are the risks described in the protocol included in the consent form?				

Level of risk for the study:

	Minimal Risk		Greater than minimal risk

Level of risk for device study:

	Non-significant		Significant

Level of risk if study involves children:

Does this research involve children? If yes, complete the following by checking one category and make sure the requirements for the category are met within the protocol:

*_____**Not Greater than Minimal Risk** adequate provisions made for obtaining assent and permission of parent(s) or guardians*

*_____**Greater than Minimal Risk, but Presenting Prospect of Direct Benefit to Subjects**, requires: risk is justified by anticipated benefits relation of benefit to the risk is at least as favorable to subjects as presently available alternatives adequate provisions obtaining assent and permission of parent(s) or guardians*

*_____**Greater than Minimal Risk, No Prospect of Direct Benefit, but Likely to Yield Generalizable Knowledge about Subjects' Disorder or Condition** requires: risk is minor increase over minimal risk intervention/procedure presents experiences commensurate with those inherent in their actual or expected situations adequate provisions for obtaining assent & permission of parent(s)/guardians(both parents must sign)*

*_____**Research not otherwise approvable which presents an opportunity to understand, alleviate or prevent a serious problem affecting the health or welfare of children**, requires: finding that there is reasonable opportunity to further understanding, prevention or alleviation of problem review by the US Dept. of Health & Human Services Secretary*

IRB MEMBER COMPOSITION

- Scientists and non-scientists; affiliates and non-affiliates
- Different backgrounds and experience
- Knowledge of their community
- Knowledge of research protections

COMPOSITION OF THE UNIVERSITY OF VERMONT AND UVM MEDICAL CENTER'S IRB

Over 60 members dedicated to the rights and welfare of human subjects participating in research

- Medical physicians representing 10 different sub-specialties
- Ph.D.'s
- Pharmacists
- Nurses
- Lawyers
- Statisticians
- Community members

COMMITTEE MEMBERS EXPERTISE

Bioinformatics member - Hindu translated consent form was not factually correct. He was able to assist the PI with a more accurate translation

Surgeon (additionally board certified in toxicology) – helped identify misrepresented risks and inaccurate pain level descriptions in a consent. Insisted a rescue plan be in place for subjects experiencing a severe reaction to the study drug.

Research Pharmacist – noted newly missing black box warning label risks were not included on the consent form.

IT Director – consistently identifies potential data breaches and gaps within a protocol and works with the PI to rectify.

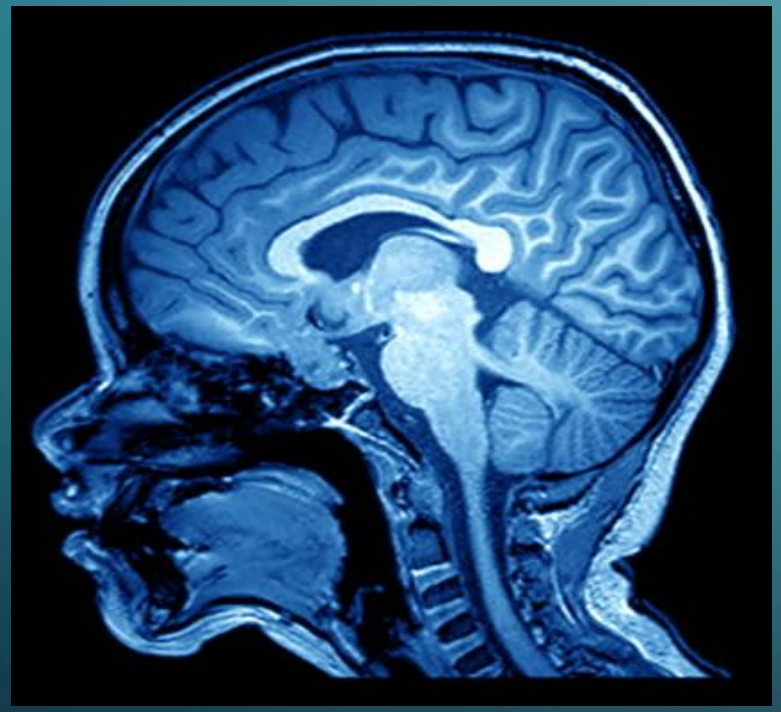
Dedicated Community Members – Found a newly released FDA drug risks omitted from the consent &protocol. Brings the perspective of the subject to the committee members with regard to lay language.

Why do we still need IRB review in 2018 with so much federal and local regulations?

A CONSTANT NEED FOR PRESENT DAY OVERSIGHT

- 2018 - Moderate Alcohol and Cardiovascular Health Trial (M.A.C.H.)
- 10 year, $100 million study, *to show that moderate alcohol consumption is safe and lowers the risk of some cardiac disease and diabetes*
- Funded through NIH, Anheuser Busch InBev, Heineken and other alcohol companies
- Trial was ended June 2018 after the PI's failed to disclose their previous conversations with the alcohol industry
- Research members gave talks strongly suggesting that the study's results would endorse moderate drinking as healthy to get companies to fund their research.
- The study design cast doubt on its ultimate credibility. This includes whether the study would effectively address other significant consequences of moderate alcohol intake, such as cancer.

"AFFECTIVE NEUROSCIENCE OF PEDIATRIC BIPOLAR DISORDER 2009-2013"



- Child psychiatrist Mani Pavuluri, M.D., University of Illinois at Chicago
- Designed to use MRI imaging to look at how the brains of adolescents (age 10-17) with bipolar disorder function during a manic state, and then again after eight weeks of treatment with lithium.
- The hope was that the results would provide new information to help identify the disease earlier, lead to treatment and potentially even reverse how the disorder affects the brain.

WHAT WENT WRONG?

- 89 of the 103 subjects enrolled in the study — 86 percent — did not meet the eligibility criteria to participate
- Failed to properly alert parents of the study's risks
- The psychiatrist's two young sons were among 132 children and teens who participated as healthy control subjects, a violation of university protocol and generally accepted research practices
- Research procedures were performed prior to consenting
- Adverse events were not reported to the IRB or NIH
- December 2017 - National Institute of Mental Health ordered the university to repay $3.1 million in grant money it had received to fund Pavuluri's study
- Dr. Pavuluri has retired from the University of Chicago June 2018

A LOCAL EXAMPLE OF WHY WE NEED IRB REVIEW

"Propofol Requirements for LMA Supreme vs Oral Airway"

- PI initiated study from Anesthesiology
- Intent was to compare a new gastric access device used for airway management during surgeries to the standard of care mask currently being used
- Subjects would receive each device while receiving propofol and then rate their discomfort during and after insertion of the device and the physicians will rate the ease of use and their satisfaction with the placement of the devices.

PROPOSED PROTOCOL

1. Normal healthy volunteers
2. Medical students were the targeted population
3. Endpoints were to determine pain and discomfort levels
4. No statistical section provided, PI indicated there was no need for a "stopping rule"

CRITERIA FOR IRB APPROVAL FOR RESEARCH

1. a. Risks to subjects are minimized.
2. b. Risks to subjects are reasonable in relation to anticipated benefits
3. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
4. Additional safeguards have been included in the study to protect the rights and welfare of vulnerable subjects.

IRB DETERMINATION - DISAPPROVED

1. Benefits are not substantial enough to outweigh the risks in this population because they are not already scheduled for surgery
2. PI did not have a plan to assess pain and relieve discomfort when participants awoke and many would be unable to speak.
3. Potential for coercion.
4. Safety stop measures must be in place while propofol is being administered

IRB REVIEW CAN DISAPPROVE A PROTOCOL TO PROTECT SUBJECTS

- The UVM Committee reviewed and disapproved the protocol in August of 2009
- 2 months (June 2009) after Michael Jackson died of acute propofol and benzodiazepine intoxication
- The use of propofol outside the setting of surgery has risks that far outweigh the benefits of sedation and research

IRB REVIEW CAN IMPROVE PROTOCOLS

- IRB members have the ability to work directly with researchers to clarify protocol issues early in the review process
- The IRB can communicate with the sponsor on behalf of the subject to improve the consent.
  - Inaccuracies, explain acronyms, improve understanding of the procedures
- Committee members identify:
  - Sensitive or anxiety provoking questions can be embedded into surveys unnecessarily.
  - Collection of vast amounts of PHI that is not needed to achieve the aim
  - The need for a consent addendum

HOW ELSE CAN IRB REVIEW PROTECT HUMAN SUBJECTS?

Identify researchers that would benefit from additional guidance from the RPO office.

Assistance of development of research tools and best research practices

Provide additional insight on recruitment strategies

Provide check in's and early monitoring visits to ensure compliance to the protocol

CASE REPORT 1– PEDIATRIC PROTOCOL

BREAK OUT INTO IRB COMMITTEES OF 3-4 MEMBERS

READ THE EXAMPLE OF A *DISAPPROVED* UVM STUDY

USE 45 CFR 46.111 CRITERIA FOR IRB APPROVAL OF RESEARCH TO GUIDE YOUR DECISIONS

CAN THE COMMITTEES COME TO THE SAME CONCLUSION AS THE UVM IRB?

45 CFR 46.111 Criteria for IRB approval of research

IRB Members must ensure all of the following requirements are satisfied:

1. Risks to subjects are minimized
2. Risks to subjects are reasonable in relation to anticipated benefits
3. Selection of subjects is equitable
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative
5. Informed consent will be appropriately documented
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Additional safeguards have been included in the study to protect the rights and welfare of vulnerable subjects.

ACTIVITY OUTCOMES

- Were you able to come to the same decision?
- Which criteria was your decision based on?

PROPOSED PROTOCOL

1. Children with and without overactive bladders
2. Children scheduled for bladder surgery and children scheduled for other types of surgery
3. Collection of bladder tissue from tissue. PI will compare collected tissue to mouse models

4. Adverse event reporting and collection is made solely by the PI.

5. Minor to no risks listed in the consent

CRITERIA FOR IRB APPROVAL FOR RESEARCH

1. a. Risks to subjects are minimized by using procedures already being performed on the participants for diagnostic or treatment purposes

   b. Risks to subjects are reasonable in relation to anticipated benefits

2. When some or all of the participants are likely to be vulnerable to coercion or undue influence, such as children…Subpart D of the DHHS and FDA regulations must be applied.

3. the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects

IRB DETERMINATION - DISAPPROVED

1. a. Benefits are not substantial enough to outweigh the risks. Half are not scheduled for bladder surgery.

   b. The Risks section is incomplete: infection, leaking of urine, bleeding, possible need for a Foley catheter should be described. The risks of the clinical procedure from those specific to the research need to be differentiated.

2. Normal child subjects can not be used because they do not fit into any allowable regulatory category. Because this research is greater than minimal risk, with no prospect of direct benefit, subjects can only be included if the research is likely to yield generalizable knowledge about subject's disorder or condition; normal subjects do not have the disorder or condition being studied

3. Adverse event oversight must be done by someone other than just the PI

CASE REPORT 2 – ANOTHER PEDIATRIC PROTOCOL

BREAK OUT INTO IRB COMMITTEES OF 3-4 MEMBERS

READ THE EXAMPLE OF A UVM STUDY FROM 1998

USE 45 CFR 46.111 CRITERIA FOR IRB APPROVAL OF RESEARCH TO GUIDE YOUR DECISIONS

CAN THE COMMITTEES COME TO THE SAME CONCLUSION AS THE UVM IRB?

45 CFR 46.111 Criteria for IRB approval of research

IRB Members must ensure all of the following requirements are satisfied:

1. Risks to subjects are minimized
2. Risks to subjects are reasonable in relation to anticipated benefits
3. Selection of subjects is equitable
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative
5. Informed consent will be appropriately documented
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Additional safeguards have been included in the study to protect the rights and welfare of vulnerable subjects.

ACTIVITY OUTCOMES

- What was your committee's decision?
- Which criteria was your decision based on?

PROPOSED PHASE I PROTOCOL	CRITERIA FOR IRB APPROVAL FOR RESEARCH	IRB DETERMINATION - APPROVED
1. Children with recurrent abdominal pain 2. Two sets of questionnaires completed six months apart 3. Risk of unpleasant feelings when recalling child's abdominal pain 4. 30 minutes to complete study 5. Informed consent submitted for review	45 CFR 46.111 all of the Criteria for IRB approval of research has been met	Approved pending minor clarifications and edits to the phase I portion.

PROPOSED PHASE II PROTOCOL

1. 25% of the children with recurrent abdominal pain participating in phase I will be asked to join phase II
2. child will drink lactulose, a mild laxative, to induce brief mild to moderate abdominal discomfort
3. Parent and child interactions will be videotaped for 20 minutes and subsequently scored for parental encouragement and reinforcement of child pain behaviors
4. Informed consent/assent submitted for review

CRITERIA FOR IRB APPROVAL FOR RESEARCH

1. When some or all of the participants are likely to be vulnerable to coercion or undue influence, such as children…Subpart D of the DHHS and FDA regulations must be applied.
2. Risks to subjects are minimized by using procedures already being performed on the participants for diagnostic or treatment purposes

IRB DETERMINATION - DISAPPROVED

1. 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." In order to approve research in this category, the IRB must find that: "(a) **the risk represents a minor increase over minimal risk;** (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; **(c) the intervention or procedures likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition;** and (d) adequate provisions are made for soliciting assent of the ·children and permission of their parents or guardians ..." The Committee was not convinced that (a) and (c) had been met.
2. It was not clear the PI could state with certainty that lactulose will not cause more than mild pain

QUESTIONS?