



IRBMED

New Member Workshop

SESSION THREE

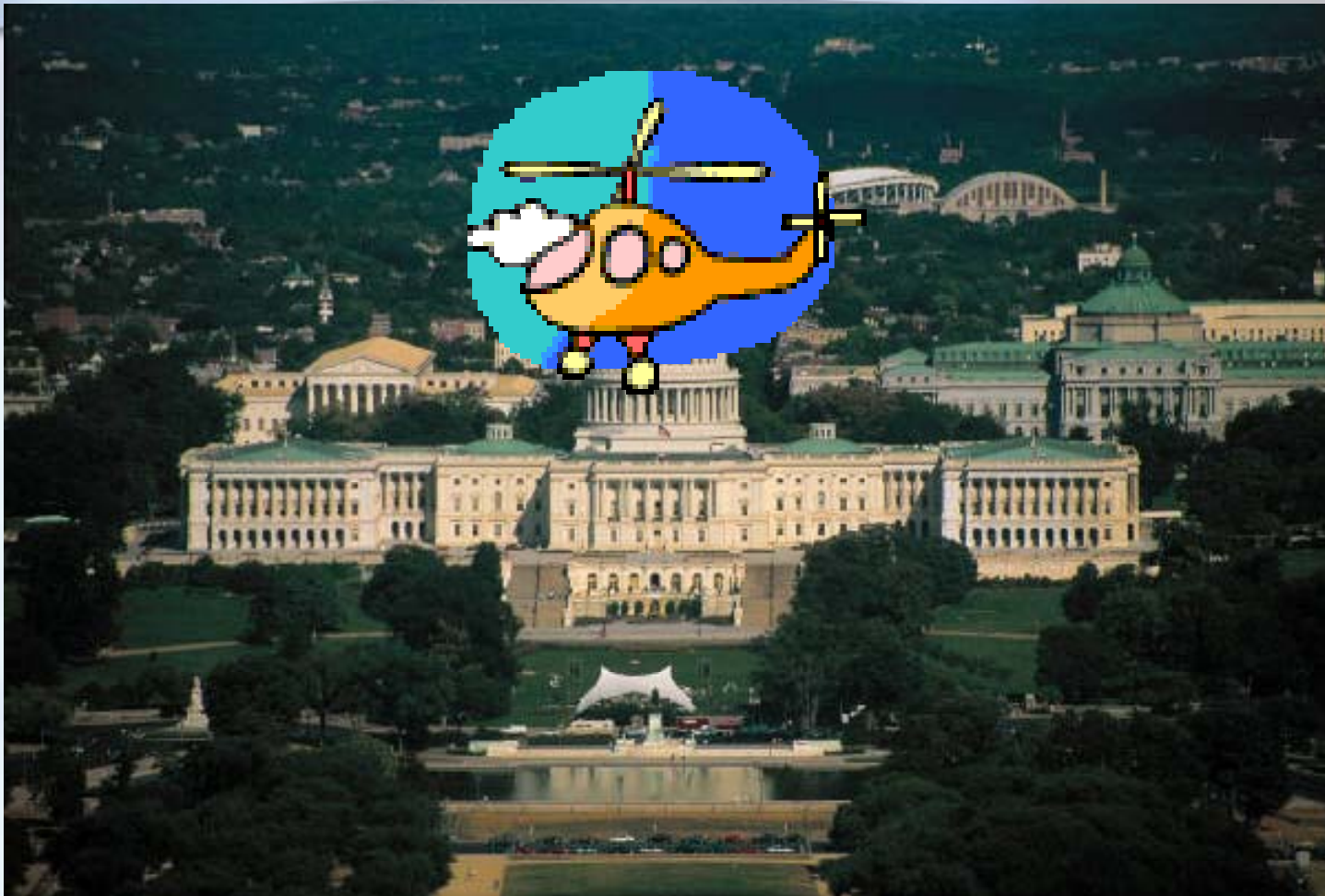


Workshop Agenda

- Regulations:
 - Prisoners
 - Pregnant women and fetuses
 - Neonates
 - Children
- Accessing Legacy
 - General Preparations for an IRB Meeting



Workshop Agenda





*Subpart C:
Additional Protections for
Prisoners Involved in Research*





Prisoners-Vocabulary

Subpart C

- 45 CFR 46 Subpart C

Prisoner Waiver

- FR 36929
 - FR=Federal Register

The 'Prisoner Regs'

HHS Secretary "Certification"

- Required for federally funded studies involving prisoners



Prisoners-Vocabulary continued

HHS “Secretary Approval”

- Required in addition to certification for some types of federally funded research involving prisoners (noted in slides #12 & 13)
- An ‘irb-like’ review of the study conducted by HHS
- Research cannot commence until and unless approved by HHS
 - Exceptions allow prisoner participation during the approval process when in the best interests of the subject



Prisoners

Possible Research Scenarios

SCENARIO #1

- Study seeks incarcerated persons as subjects

SCENARIO #2

- Previously enrolled subject becomes incarcerated

SCENARIO #3

- Prisoner presents for healthcare
 - Prisoner meets eligibility criteria for study
 - Study presents a reasonable probability of improving the health or well-being of the subject
 - Prisoner wants to participate in the study



Prisoners

Additional duties of the IRB where prisoners are involved regardless of research funding source.

- (1) The research under review represents one of the permissible categories of research.
- (2) Any possible advantages to the prisoner from participating in the research, when compared to typical prison life, are not such that the prisoner's ability to weigh the risks of the research is impaired.
- (3) Non-prisoners would be willing to accept the same risks.



Prisoners—

Additional duties continued

- (4) Subject selection within the prison is fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.
- (5) Information is presented in language which is understandable to the subject population.
- (6) Parole boards will not consider a prisoner's participation in research in making decisions regarding parole, and each prisoner is informed of this in advance.
- (7) If follow-up examination or care of participants is needed after the end of their participation, adequate provision has been made.



Prisoners

Types of Permissible Research

- Minimal risk epidemiological research to study prevalence/incidence of a disease or risk factor associations of a disease
 - Certification required if federally funded. Letter to OVPR if not federally funded.
 - Approvable under the “Prisoner Waiver”—FR 36929 (not in your reg books)



Prisoners

Types of Permissible Research continued

- Minimal risk research of possible causes, effects, and processes of incarceration, and of criminal behavior
 - Certification and secretary approval required if federally funded.
 - OVPR approval required if not federally funded.
- Minimal risk research of prisons as institutional structures or of prisoners as incarcerated persons
 - Certification and secretary approval required if federally funded.
 - OVPR approval required if not federally funded.



Prisoners

Types of Permissible Research continued

45 CFR 46 Subpart C continued

- Research of conditions particularly affecting prisoners as a class
 - Certification and approval required if federally funded.
 - OVPR approval required if not federally funded.



Prisoners

Types of Permissible Research continued

45 CFR 46 Subpart C continued

- Research offering reasonable probability of improving the health or well-being of the subject
 - Research either does not involve a “control group” or the control group offers an added benefit over standard care
 - Certification required if federally funded. OVPR approval required if not federally funded.
 - Research involves a “control group” with no added benefit over standard care
 - Certification **and secretary approval** required if federally funded. OVPR approval required if not federally funded.



*Subpart B:
Additional Protections for Pregnant Women,
Fetuses, and Neonates Involved in Research*





Vocabulary

- “Subarpt B” covers all three groups (pregnant women, fetuses, neonates)
 - 45 CFR 46 Subpart B
 - CFR=Code of Federal Regulations
 - 45 CFR 46.201-207
 - Enforced by the HHS **Office of Human Research Protections** (OHRP).
- FDA regulations require
 - IRBs provide any additional protections needed but do not specify what those should be.
 - Toxicology information on how new agents will impact pregnancy and fetuses (in the IND/IDE applications to the FDA).

Fetus Defined



- Standard medical definition—fetus comes into being at the eighth week of pregnancy
- 46.202 (c) definition—fetus means the product of conception from implantation until delivery
- Since implantation usually occurs in the first week after fertilization, the federal definition of “fetus” encompasses “embryo”



Fetus Defined--Implications

- Research involving women of child-bearing potential may require pregnancy testing and/or prevention measures



Human Embryonic Stem Cell Research

During a presentation to the board:

- Distinguish between embryonic stem cells and other stem cells types
- Clarify definitions and cell derivation in non-scientific terminology

IRB approval is not required if:

- Research involves in-vitro uses of one or more of the lines listed in the NIH Registry.

AND

- The research does not involve any of the conditions on the next slide



Human Embryonic Stem Cell Research

- IRB approval is required if:
 - Research involves nuclear transfer into human ES cells
 - Research involves in-vivo use of human ES cells
 - Research involves human ES cell lines not listed in the NIH Registry
 - Ensure that the derivation stem cell derivation complies with NIH guidelines of August 24, 2000
 - IRBMED may rely on reviews made by other IRBs
 - IRBMED legal advisors must also review the proposed use and protections



Women of child-bearing potential

- Justice principle argued to support their inclusion in research
 - Women should not be deprived of the potential benefits of research by virtue of their reproductive status
- Beneficence principle argued to support both their inclusion and exclusion
 - Inclusion for potential benefits to the woman
 - Exclusion due to possible harm to potential fetus
- Informed consent critical
- Additional safety measures may be required



Women of child-bearing potential

IRB Review and Application Issues

- Informed consent document must disclose:
 - Risks to the woman if she becomes pregnant
 - Risks to the fetus if the woman became pregnant
 - Pregnancy testing, if any, needed for the study
 - If the study includes children, a warning to the prospective subject that her parents could find out about a pregnancy
 - Birth control, if any, needed for the study
- The IRB application should explicitly indicate this population if a study includes fertile females (In eResearch, Section 9)
 - eR Section 37
 - If researcher states the study would not pose significant risks to a fetus or pregnant woman a justification or explanation of how this is so should be obvious or in the protocol or DSMP



Pregnant Women and Fetuses

- For research involving pregnant women the following criteria must be met:
 - Preclinical studies provide data to assess potential risks to woman and fetus
 - Risk to the fetus is either:
 - Not greater than minimal
 - Any risk greater than minimal holds out the prospect of direct benefit for the woman or the fetus
 - No inducements, monetary or otherwise, will be offered to terminate the pregnancy
 - Researchers can have no part in determining the viability of the fetus or timing/methods for terminating the pregnancy

45 CFR 46.204




Pregnant Women and Fetuses

- Informed Consent must include impacts on both the woman and the fetus
- Research offering prospect of direct benefit to the woman, only her signature required on ICD
- Research offering prospect of direct benefit to fetus, signature of mother and father required

Neonates

- *45 CFR 46.205*





Neonates Vocabulary

- **Live Neonate** means neonate shows evidence of life as determined by the same medical standards as are used in determining evidence of life in a spontaneously aborted embryo or fetus at approximately the same stage of gestational development. *MCL 333.2687 Sec. 2687*
- **Neonate** means a newborn §46.202 (d). FDA guidance (not regulation) defines a neonate as an infant less one month^[i] or less than 28 days old.^[ii]
- **Non-therapeutic research** means scientific or laboratory research, or other kind of experimentation or investigation not designed to improve the health of the research subject. *MCL 333.2692 Sec. 2692. As used in sections 2685 to 2691*
- **Nonviable neonate** means a neonate after delivery that, although living, is not viable §46.202 (e).
- **Viable**, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration §46.202 (h).



Neonates—Vocabulary

- Neonate—an infant less than one month old
 - Gestational age is not considered
- Viable neonate—an infant that, given the benefit of available medical therapy, will survive to the point of independently maintaining heartbeat and respiration.
- Non-viable neonate--means a neonate after delivery that, although living, is not viable
- See algorithm.



Subpart D: Additional Protections for Children Involved in Research





Children—Subpart D

- Three categories can be approved by an IRB
- Fourth category must be approved by HHS secretary if federally funded (OVPR approval required if not federally funded).
- Flow chart



Permission Waiver—OHRP

- 404—allowed if other 116(d) criteria are met
- 405, 406 and 407 allowed if one of the following applies:
 - 408(c)—Research conditions/ population for which parental permission is not reasonable (e.g. abused children) & substitute mechanism provides protection



Permission Waiver—FDA

- FDA does not allow a waiver of parental permission unless:
 - 50.23 applies
 - Emergency Room Type Research
- OR**
- 50.24 applies
 - 'Terrorism Waiver' for in-vitro devices



Permission Waiver—FDA

- FDA does not have a regulation equivalent to 408(c)
 - Research conditions/ population for which parental permission is not reasonable
- So FDA 'trumps' if a study involves an agent subject to FDA oversight



Assent—OHRP & FDA

- IRBs must determine if assent should be sought
- Assent directives may apply to some or all children in the study
 - Age, maturity and psychological state of the children should be considered



Assent—OHRP & FDA

There are 3 Waiver Options:

1. Capabilities of some or all children is so limited they cannot be consulted
2. Study offers important benefit unavailable outside of the research
 - When the study offers a treatment that is thought to be a better option than those currently available, or it offers the only alternative. (NCI)
 - Criterion of 'potential direct benefit' is not sufficient to grant this waiver.
3. Assent can also be waived under the same criteria as a consent waiver:
 - the study is minimal risk
 - subjects' rights and welfare aren't adversely affected
 - assent is not practicable (for reasons *other than* children's capabilities)
 - when appropriate, the subjects will be provided pertinent information



IRB Assent Tasks

- Judge if some or all children are capable of providing assent.
- Decide if a waiver is appropriate for some or all subjects.
- When assent is required:
 - Determine adequate provisions are made for soliciting assent
 - Consider who is in attendance, especially when sexual activity or drug use will be discussed
 - Assess the form and content of the information conveyed to the prospective subjects
 - Decide if assent **should** be documented
 - If so, how?
 - **Communicate IRB requirements to the study team**

Assent Guidelines

These are "guidelines" not "directives."

Review the fine print!

Guidelines for Use by the IRBMED in Determining When Assent of Children Should be Waived or Required ¹

In the chart below—blue fields indicate when waiver of assent is generally recommended; yellow fields indicate when assent should generally be required.

The IRB must make an assent determination for each protocol that includes children. The IRB must require child assent unless it can be appropriately waived; which waiver and the reasons for it should be clearly articulated and recorded. There are no strict age criteria in the regulations.

Age Ranges ²	Risk and Benefit Assessment of the Study or Study Arm					
	Potential of Direct Benefit <u>Unavailable</u> Outside of the Research ³		Potential of Direct Benefit that <i>is Available</i> Outside of the Research		<u>No</u> Potential of Direct Benefit	
	No more than minimal risk	Greater than minimal risk	No more than minimal risk	Greater than minimal risk	No more than minimal risk	Greater than minimal risk
0-6		W	A	I	V	E
7-13			Require or waiver #3	< 9 Require or waiver #1 ≥ 9 Require		
14-17		Waive or Require depending on the nature of the research ⁴		R E Q U I R E		
Incapacitated children who cannot be consulted, regardless of age ⁵			If capabilities of minors change such that they could later assent during the course of the research (including long-term follow-up) the IRB must determine if assent should be required at that point in time.			

Waiver Options

The IRB may waive assent when **one** or more of the following applies (convened meeting minutes/reviewer worksheet/IRB application must reflect IRB determination of which waiver(s) applies to each study **and why**):

- (1) Capabilities of children is so limited they cannot be consulted
- (2) Study offers important benefit **unavailable** outside of the research.
- (3) Under the same criteria as waiver of consent (minimal risk, assent is not practicable, waiver will not adversely affect rights and welfare of the child, pertinent information will be provided after the research).

When assent is waived the IRB may still require that researchers to explain to children that they are involved in research, what that means, and provide some explanation of the research procedures.

Assent Options



eResearch and the Kiddie Regs

eResearch **M**

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To: 06. Benefits and Risks

Note (0 Notes Total) Add Delete

6. Benefits and Risks

6.1 * Are there potential direct benefits of this research to the subjects?

Yes No Clear

6.1 must be reconciled with the board's decision and with 33.4 where the children's regulation is specified.

If the study was approved under 405/52 then YES must be checked in 6.1.



if all, or only some, of





eResearch and the Kiddie Regs

33.4 * **Permitted Categories of Research:** The federal policy and regulations governing human subject protections specify that research involving children must fall into one of the following permitted categories. Check all categories of permitted research that apply to this study.

Select at least one:


Regulatory Category	Criteria
<input checked="" type="checkbox"/> The research does not involve greater than minimal risk [45 CFR 46.404].	
<input checked="" type="checkbox"/> The research involves greater than minimal risk, but presents the prospect of direct benefit to the individual subjects [45 CFR 46.405].	<ul style="list-style-type: none"> • The risk to subjects is not greater than that presented by the approach used in the research.
<input checked="" type="checkbox"/> The research involves greater than minimal risk and no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subjects' condition [45 CFR 46.406].	<ul style="list-style-type: none"> • The risk to subjects is not greater than that presented by the approach used in the research. • The research procedures are likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for understanding or amelioration of the subjects' disorder or condition.
<input checked="" type="checkbox"/> The research does not fall under one of the previous permitted categories, but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of the children [45 CFR 46.407].	FINAL APPROVAL OF THIS APPLICATION MAY REQUIRE ADDITIONAL APPROVAL AT THE FEDERAL LEVEL. CONTACT THE IRB OFFICE FOR MORE INFORMATION.

33.4 (or 33-1.1) must reflect all arms.

33.4 must be reconciled with the board's decision



eResearch and the Kiddie Regs

10.2 * What types of informed assent for children and parental consent/permission will you use?
NOTE 'Parent' or 'Parental' below refers to parent or guardian. See Help for help selecting the appropriate category or categories. 

Select all that apply:

- Written assent for children
- Oral assent script (e.g., for young or impaired children)
- Request for waiver of documentation of child's assent (e.g., the assent process will take place but the subjects will not sign or mark a document)
- Request for waiver of oral or written child assent requirement
- Parent comprehensive written consent/permission (if accessing records prior to consent, also check "Request for waiver of parental informed consent/permission")
- Parent short form, oral script, and witness consent/permission (intended for use when parent is unable to read the consent document)
- Request for waiver of documentation of parental informed consent/permission (e.g., the consent process will take place but the parent(s) will not sign a document)
- Request to use special consent/permission process for child subjects who are wards of State or whose parental permission is otherwise not a reasonable requirement to protect them (e.g., neglected or abused children)
- Request for waiver of parental informed consent/permission requirement (e.g., some retrospective studies, screening portion of a study)
- Pre-existing consent/permission covers this activity (Describe original consent/permission process in 10.2.1)
- Exempt Research with or without informed consent/assent (appropriate only when the entire study is exempt - see section 12 for categories of exempt research)

10.2 must be reconciled with the board's determination regarding assent

When the board determines assent isn't necessary because of the capabilities of the children or because the research holds the prospect of benefit not available outside of the research:

- One of the Parent consent/permission options should be selected
- **An assent waiver box should NOT be selected!!!!**



eResearch and the Kiddie Regs

10.2 * What types of informed assent for children and parental consent/permission will you request? *NOTE 'Parent' or 'Parental' below refers to parent or guardian. See Help for help selecting the appropriate category or categories.*

Select all that apply:

- Written assent for children**
- Oral assent script (e.g., for young or impaired children)**
- Request for waiver of documentation of child's assent** (e.g., the assent process will take place but the subjects will not sign or mark a document)
- Request for waiver of oral or written child assent requirement (requires 10.2.1)**
- Parent comprehensive written consent/permission** (if accessing records prior to consent, also check "Request for waiver of parental informed consent/permission")
- Parent short form, oral script, and witness consent/permission** (typically used when parent is unable to read the consent document)
- Request for waiver of documentation of parental informed consent/permission** (e.g., the consent process will take place but the parent (s) will not sign a document). A copy of the oral script, written summary, letter, survey, or other document with the required elements of informed consent must be provided in 10-1. Note—documentation cannot be waived on studies subject to FDA oversight unless the study is minimal risk and the research does not involve any procedures for which consent would be required outside of the research context.
- Request to use substitute mechanism for parental permission where research is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects** (e.g., neglected or abused children) (Note: Parental permission cannot be substituted on studies subject to FDA oversight)
- Request for IRB to appoint an advocate for children who are wards of the state or any other agency, institution, or entity--required for studies related to the children's status as wards that are approved under §46.406 or §46.407 (see section 33)** (Note: for other studies approved under §46.406 or §46.407 where the occasional ward may be recruited the investigator must contact the IRB to appoint an advocate and the advocate must agree to the child joining the study before the child can participate.)
- Request for waiver of parental informed consent/permission requirement** (e.g., some retrospective studies, screening portion of a study). (Note: consent cannot be waived for research aspects of studies subject to FDA oversight—i.e. it may be acceptable for recruitment)
- Pre-existing consent/permission covers this activity** (Describe original



Other “Vulnerable Populations”

- Cognitively or decisionally impaired subjects
- Educationally disadvantaged
- Economically disadvantaged
- Students and employees
- Patients of the study team





Economically Disadvantaged

- Unless scientifically appropriate, a study should not be designed to target low income groups for recruitment.
- Assess financial incentives
 - Avoid 'undue influence'
 - "it is impossible to state precisely where justifiable persuasion ends and undue influence begins"



Students, Employees, and Patients of the Researcher

- Participation should not be coerced
- Grades, continued employment, promotion, health care, etc must not be threatened

'Typical' IRB requirements

- Exclude staff and students of the PI from the research
- Have someone not involved in patient care approach the subjects with the initial request.

Questions?





Case Study— Dexamethasone vs. Hydrocortisone

Study Abstract:

- Hypotension commonly occurs in preterm infants
- It can damage organs, cause cerebral palsy, brain hemorrhage, and death
- Both medicines currently used to treat pressor-resistant hypotension
- Study will determine if either drug is more effective

Null Hypothesis: There is no difference in the percent of extremely low birth weight infants whose mean arterial pressure returns to the normal range, when comparing D. to H.

Background: No study has directly compared these two drugs. Both have been used and studied in many different doses and situations. Data is lacking use of either for less than 72 hours in preterm infants.

Methodology: Alternate subjects to 48 hours of treatment with either dexamethasone or hydrocortisone

Eligible infants: Premature infants born between 24 weeks and 34 weeks gestation with hypotension that either worsens or does not improve after treatment with pressors

Risks (noted in different circumstances):

- Short-term side effects: increased blood sugar and blood pressure.
- Long-term side effects when drugs are used 72+ hours: increased risk of cerebral palsy and infection.

Potential Benefits: Knowing which medicine is more effective will help future pre-term infants

Measures to reduce risk:

- Continuous monitoring on the NICU
- Increases in blood sugar or pressure will be immediately addressed