

IRBMED Regulations 103

Vulnerable Populations

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Workshop Agenda

- Prisoners
- Pregnant women, fetuses, women with child-bearing potential
- Neonates
- Cognitively Impaired Subjects
- Other Vulnerable Populations



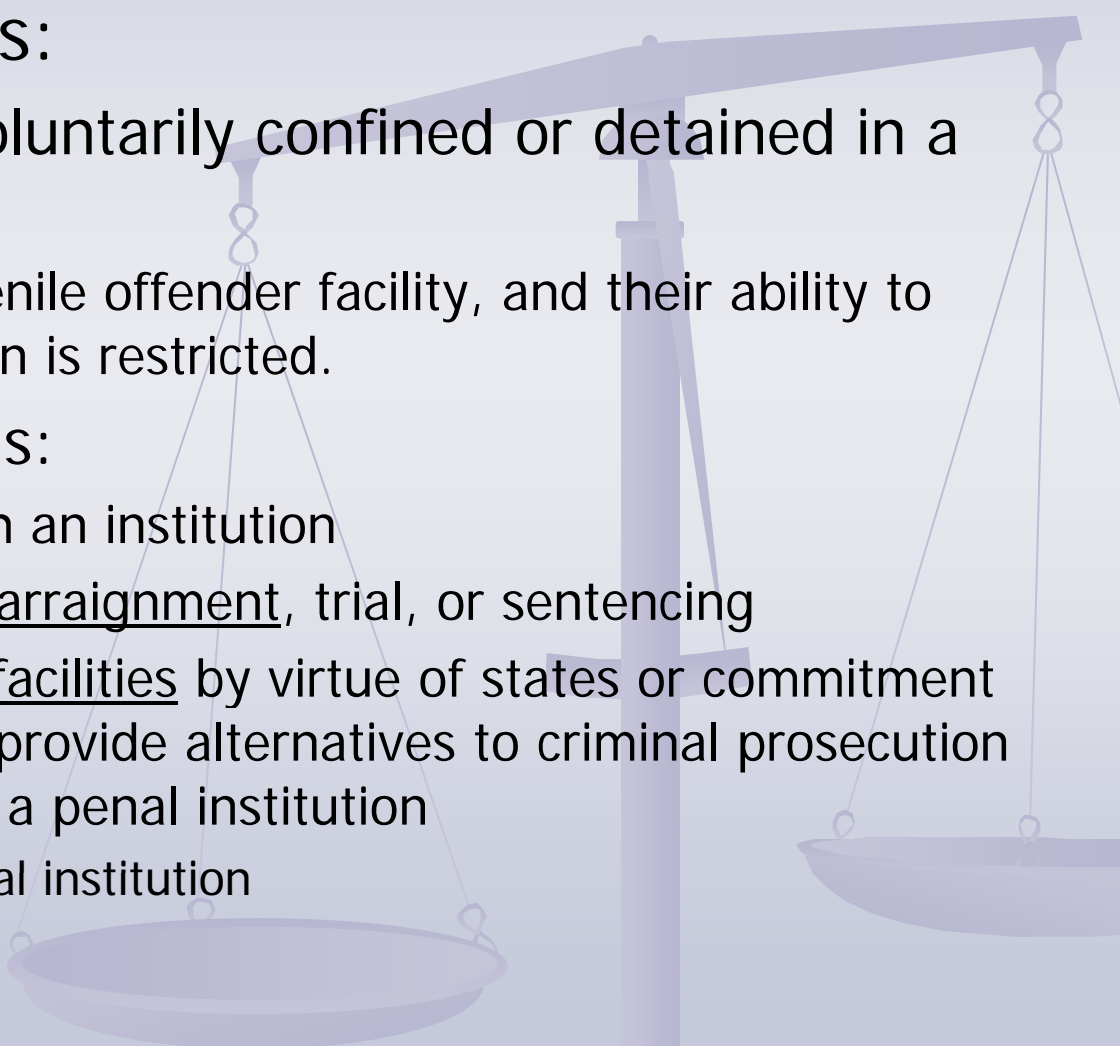
Objectives

- Provide a foundational understanding of the federal regulations written for the protection of special populations
 - Review the additional processes and constraints when research includes other vulnerable populations
 - Review way to improve IRBMED/ Researcher communications and research applications
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Additional Protections for Prisoners Involved in Research



Prisoners-Vocabulary



- A “prisoner” means:
 - Any individual involuntarily confined or detained in a penal institution
 - Prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted.
 - Includes individuals:
 - Sentenced to such an institution
 - Detained pending arraignment, trial, or sentencing
 - Detained in other facilities by virtue of states or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution
 - Example—mental institution

Prisoners-Vocabulary

The
Prisoner
Regs

"Subpart C"

- 45 CFR 46 Subpart C
 - CFR=Code of Federal Regulations

Prisoner Waiver

- FR 36929
 - FR=Federal Register

- Enforced by HHS Office of Human Subject Protections (OHRP)
- There are no additional protections for prisoners in the FDA regulations except that FDA requires IRBs to provide any additional protections needed but does not specify what those should be.



Prisoners-Vocabulary *continued*

FEDERALLY FUNDED RESEARCH REQUIRES:

"Certification"

- Certification to the DHHS Secretary required for federally funded studies
- UM sends letter to OHRP 'certifying' how the regulations have been addressed

SOME RESEARCH MAY ALSO REQUIRE:

DHHS *"Secretary Approval"* or Approval from *UM Office of the Vice President for Research*

- Another review of the study is conducted by HHS or OVPR
- Required only for particular categories of research

Prisoners

Five Types of Permissible Research

1. Minimal Risk Epidemiological Research

- Research about the prevalence/incidence of a disease or risk factor associations of a disease

2. Minimal Risk Research of Criminal Behavior and Incarceration

- Research about the causes, effects, and processes

3. Minimal Risk Research of Prisons or of Prisoners



Prisoners

Five Types of Permissible Research *continued*

4. Research of Conditions Particularly Affecting Prisoners as a Class

- Includes studies of all risk levels
 - Not limited to minimal risk
- Requires DHHS Secretary approval if the study is federally funded
 - Research cannot commence until and unless approved by HHS
- Requires UM Office of the Vice President for Research (OVPR) if not federally funded.
 - Research cannot commence until and unless approved by OVPR

Prisoners

Five Types of Permissible Research *continued*

5. Research Offering Reasonable Probability of Improving the Health or Well-being of the Subject

- If research involves a control group AND the control group offers no added benefit over standard care, study requires:
 - DHHS Secretary approval if federally funded.
 - Research can commence prior to approval by HHS.
 - UM Office of the Vice President for Research if not federally funded.
 - Research can commence prior to OVPR approval.

Prisoners

How might a prisoner end up in your study?

SCENARIO #1

- Epidemiological studies of non-rare diseases or diseases/conditions likely to include incarcerated persons

SCENARIO #2

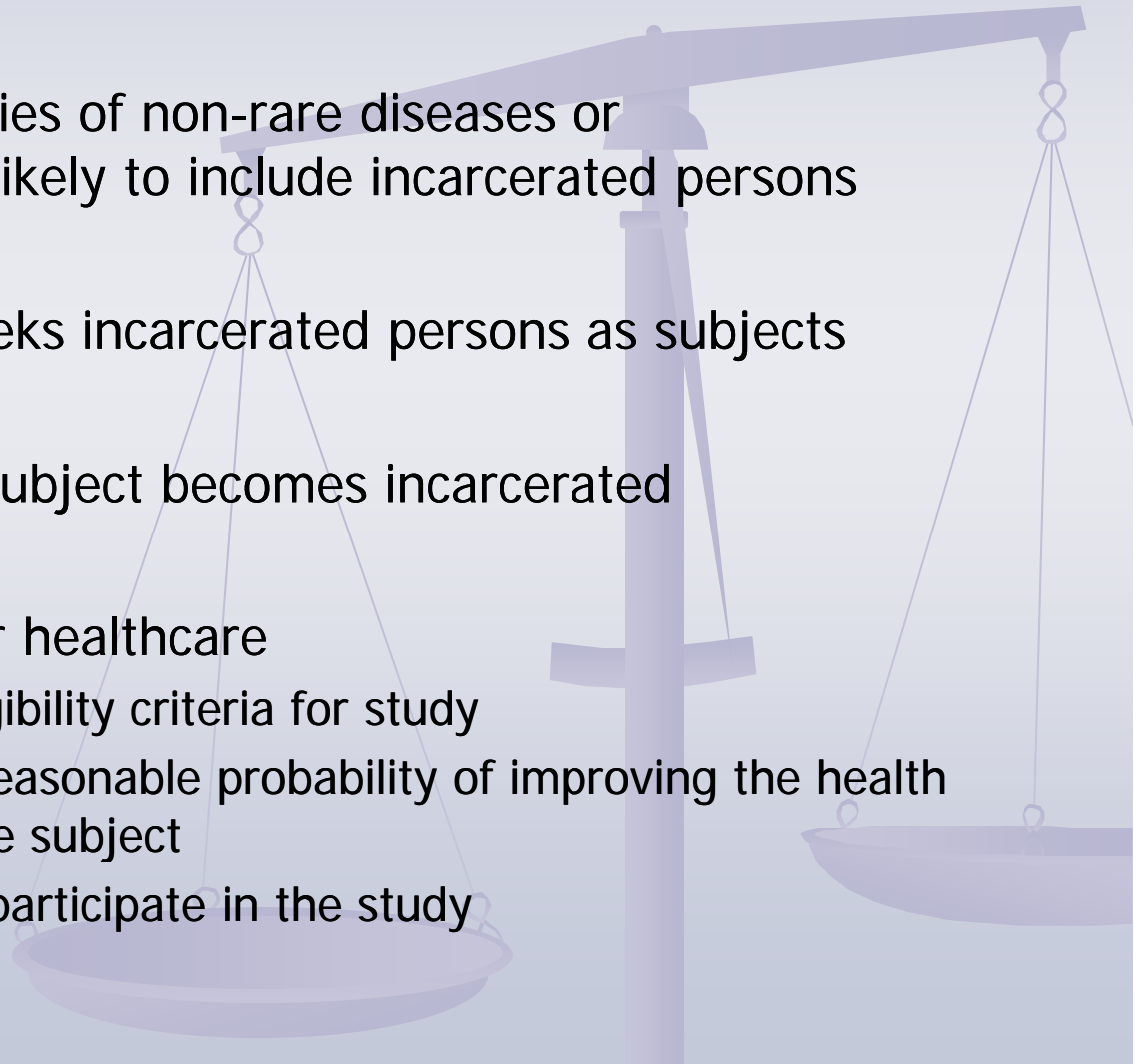
- Study specifically seeks incarcerated persons as subjects

SCENARIO #3

- Previously enrolled subject becomes incarcerated

SCENARIO #4

- 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



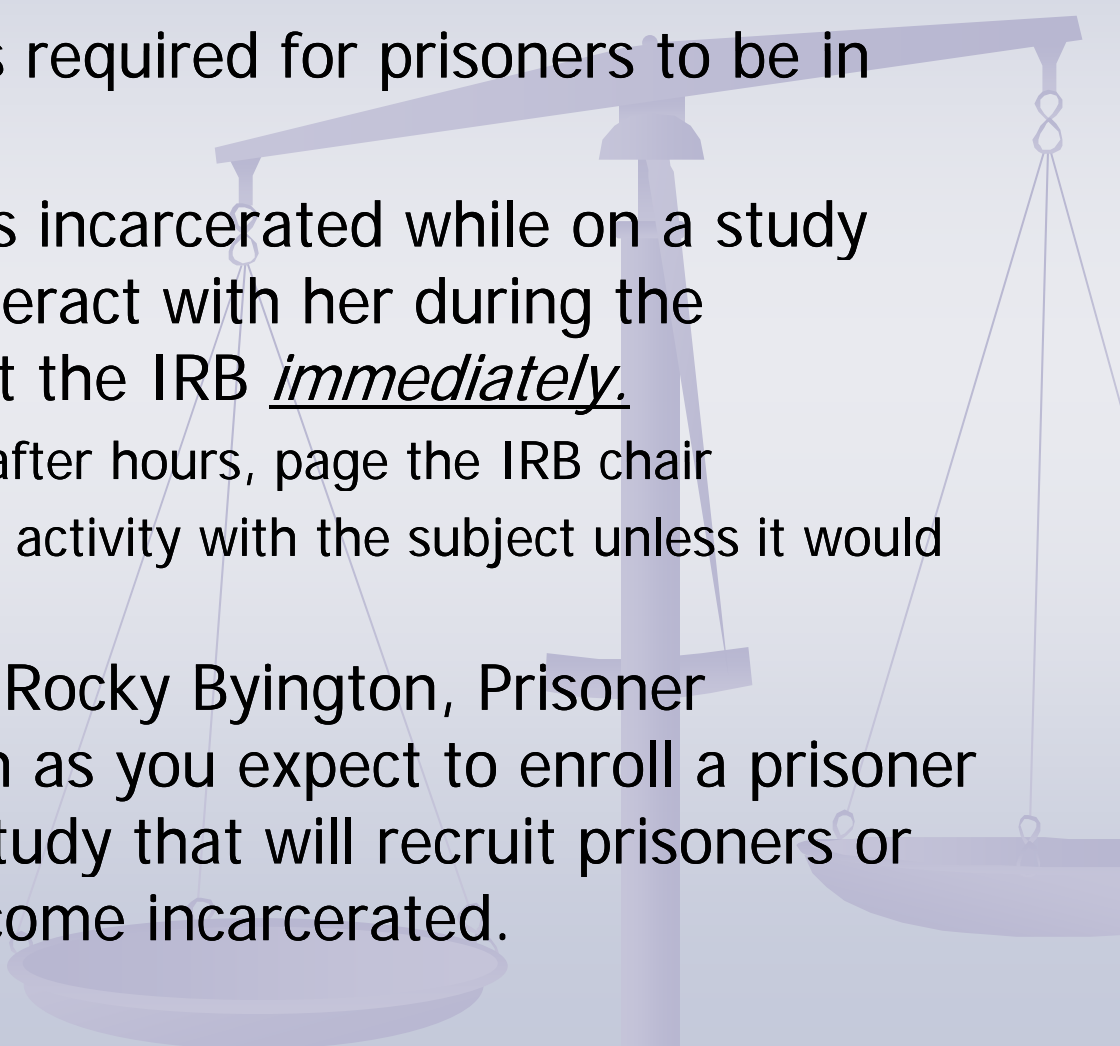
Prisoners

ADDITIONAL OBLIGATIONS WHEN PRISONERS ARE INVOLVED IN A STUDY	
IRB	Study Team
Determine if the study is one of the permissible categories of research	Contact Prison Warden <ul style="list-style-type: none"> • Obtain written assurances
Determine that non-prisoners would be willing to accept the same risks	Contact IRB immediately (previously approved studies that did not specifically target prisoners) <ul style="list-style-type: none"> • Call office, after hours page IRB chair • Submit an ORIO • Amend study
Certify federally funded studies with HHS	
Assure subject selection within the prison is fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners	
Assure that any possible advantages to the prisoner from participating in the research, when compared to typical prison life, are not of such that the prisoner's ability to weigh the risks of the research is impaired	
Assure information is presented in language which is understandable to the subject population	
Assure 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	
If follow-up examination or care of participants is needed after the end of their participation, assure adequate provision has been made to provide it	



Prisoners

IRB Review and Application Issues

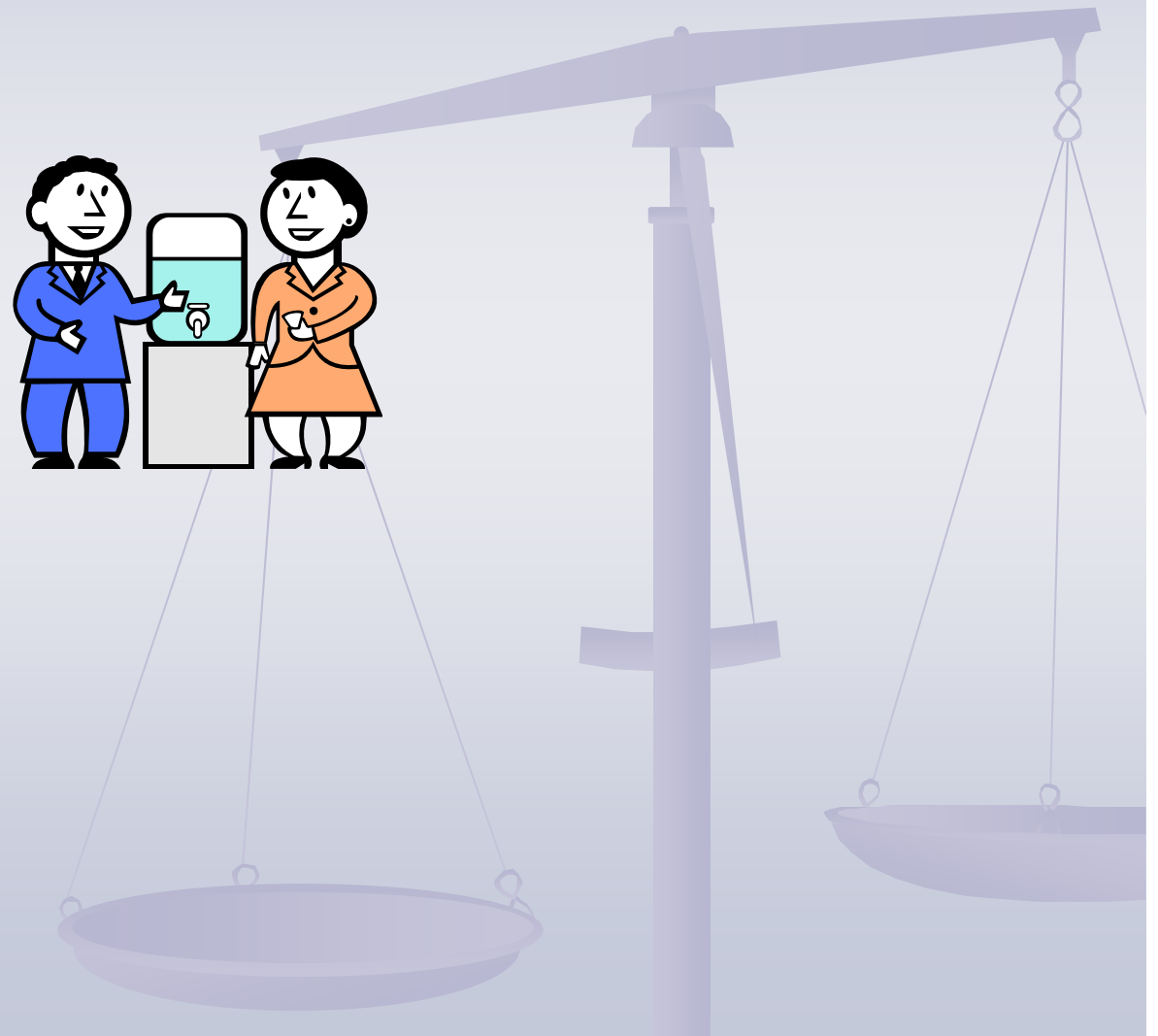
- Prior IRB approval is required for prisoners to be in research.
 - If a subject becomes incarcerated while on a study AND you need to interact with her during the incarceration contact the IRB immediately.
 - Call the IRB office—after hours, page the IRB chair
 - Discontinue all study activity with the subject unless it would harm the subject
 - At IRBMED, contact Rocky Byington, Prisoner Coordinator, as soon as you expect to enroll a prisoner or are preparing a study that will recruit prisoners or persons likely to become incarcerated.
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Vocabulary for everyone else (other than prisoners)

Definition of Minimal Risk 45 CFR 46.102(i)

The probability and magnitude of harm or discomfort anticipated as a result of participation 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 examination or tests.

Break Time

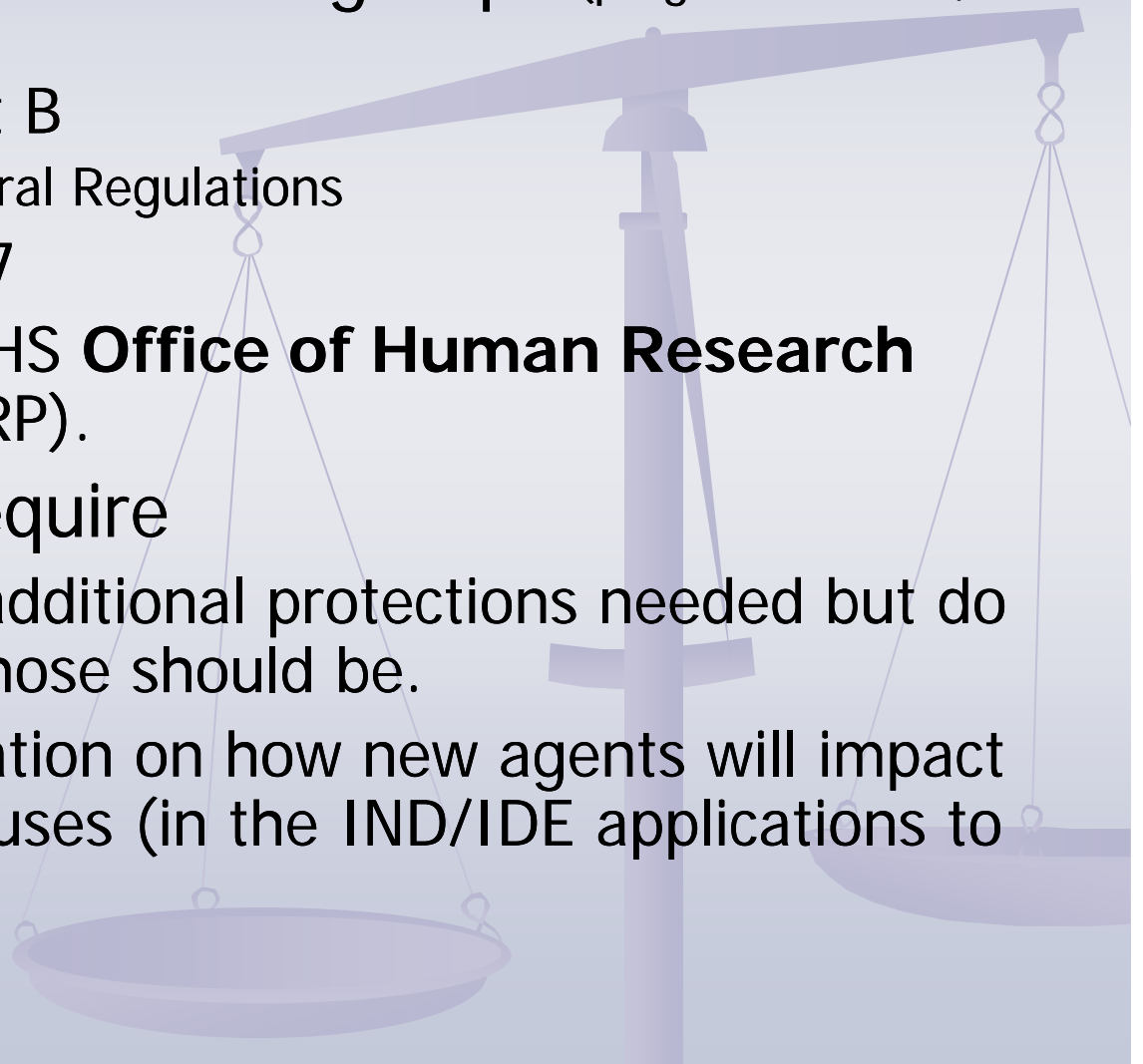


Additional Protections for Pregnant Women, Fetuses and Neonates Involved in Research



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).



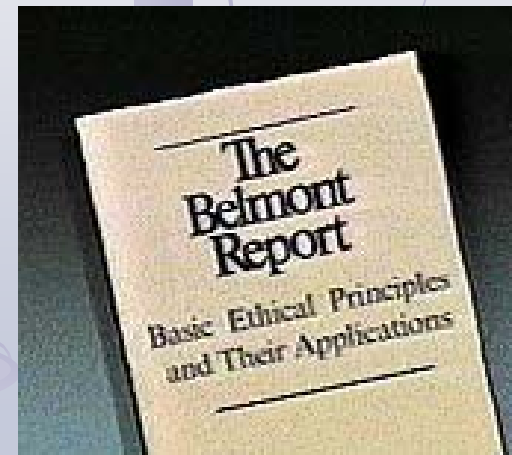
Fetus-Vocabulary



- 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 the embryo
 - *Thus, research involving subjects who may not know they are pregnant or may become pregnant require special protections under this regulation.*

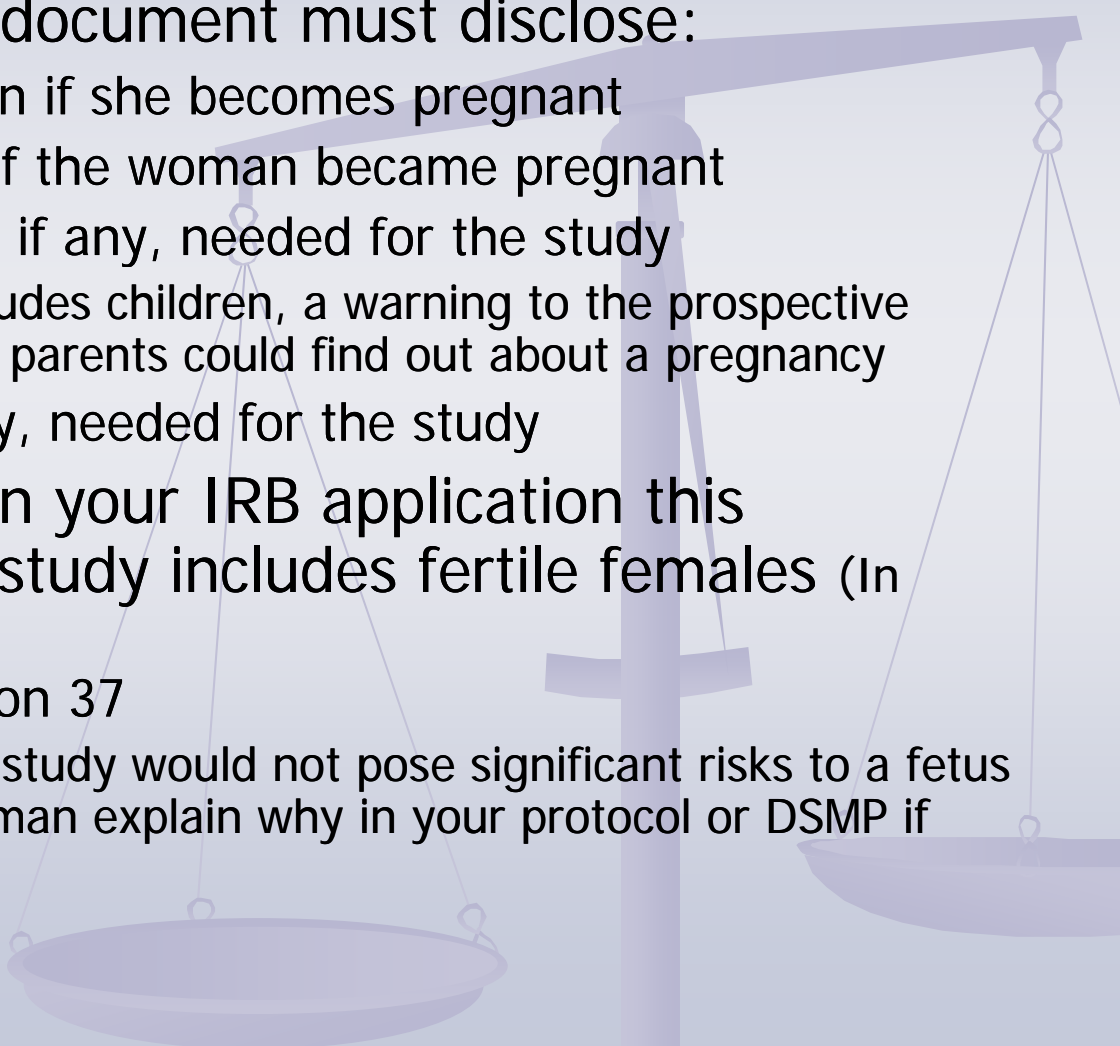
Women of child-bearing potential

- Justice principle supports their inclusion in research
- Beneficence principle argued to support both their inclusion and exclusion
 - Exclusion due to possible harm to potential fetus
- Informed Consent critical



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
 - Explicitly indicate in your IRB application this population if your study includes fertile females (In eResearch, Section 9)
 - Complete eR Section 37
 - If you state the study would not pose significant risks to a fetus or pregnant woman explain why in your protocol or DSMP if needed.
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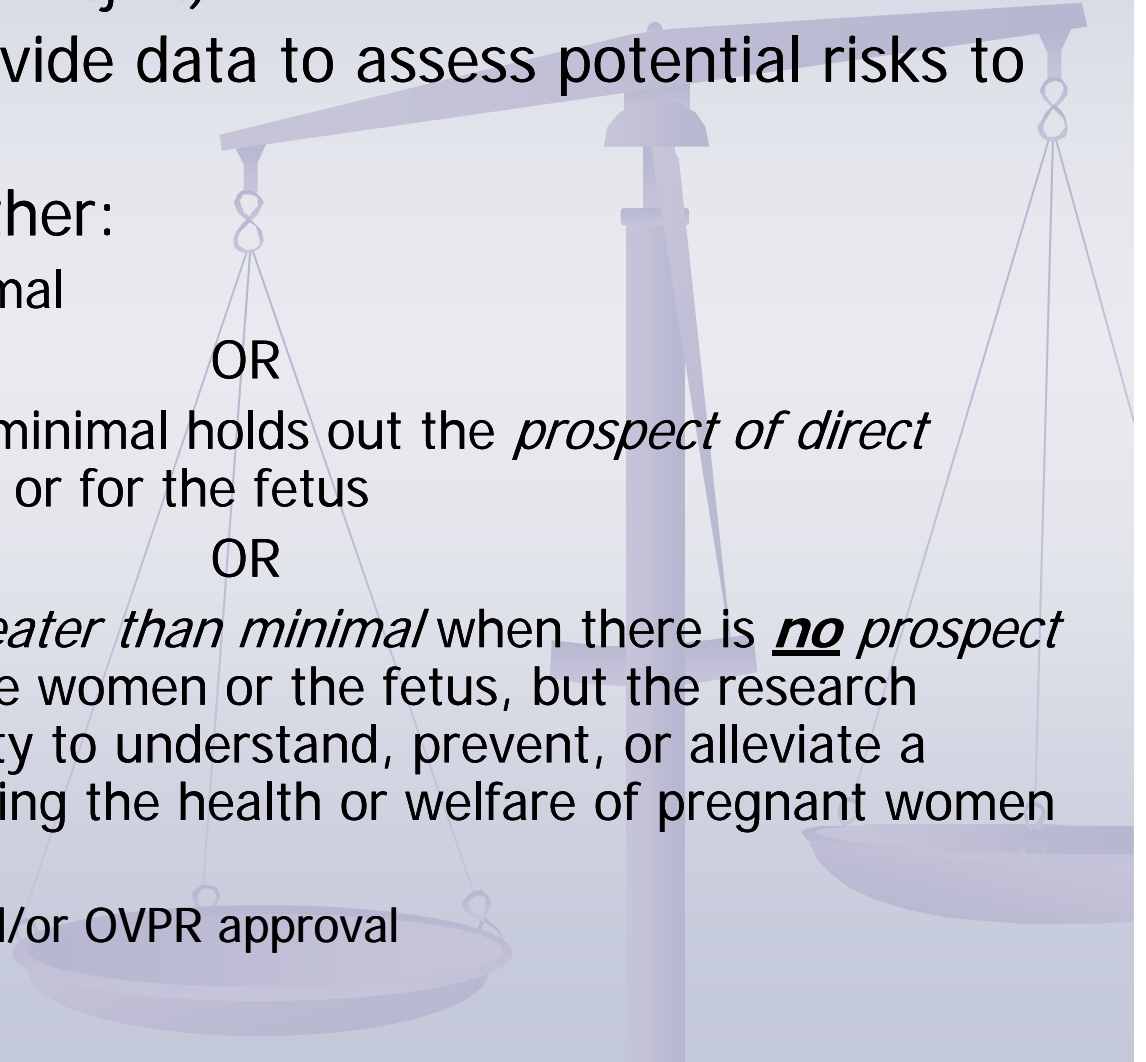
Stem Cell Issues



- In your IRB application, clearly distinguish between human embryonic stem cells (hESC) and other stem cells
 - hESC are those derived from human embryos.
 - Use of these cells requires additional oversight at UM. Contact the IRB for more information if you plan to use them.
 - If you are using stem cells from umbilical cords or other NON-hESC make sure the protocol and application make it clear.

Pregnant Women and Fetuses

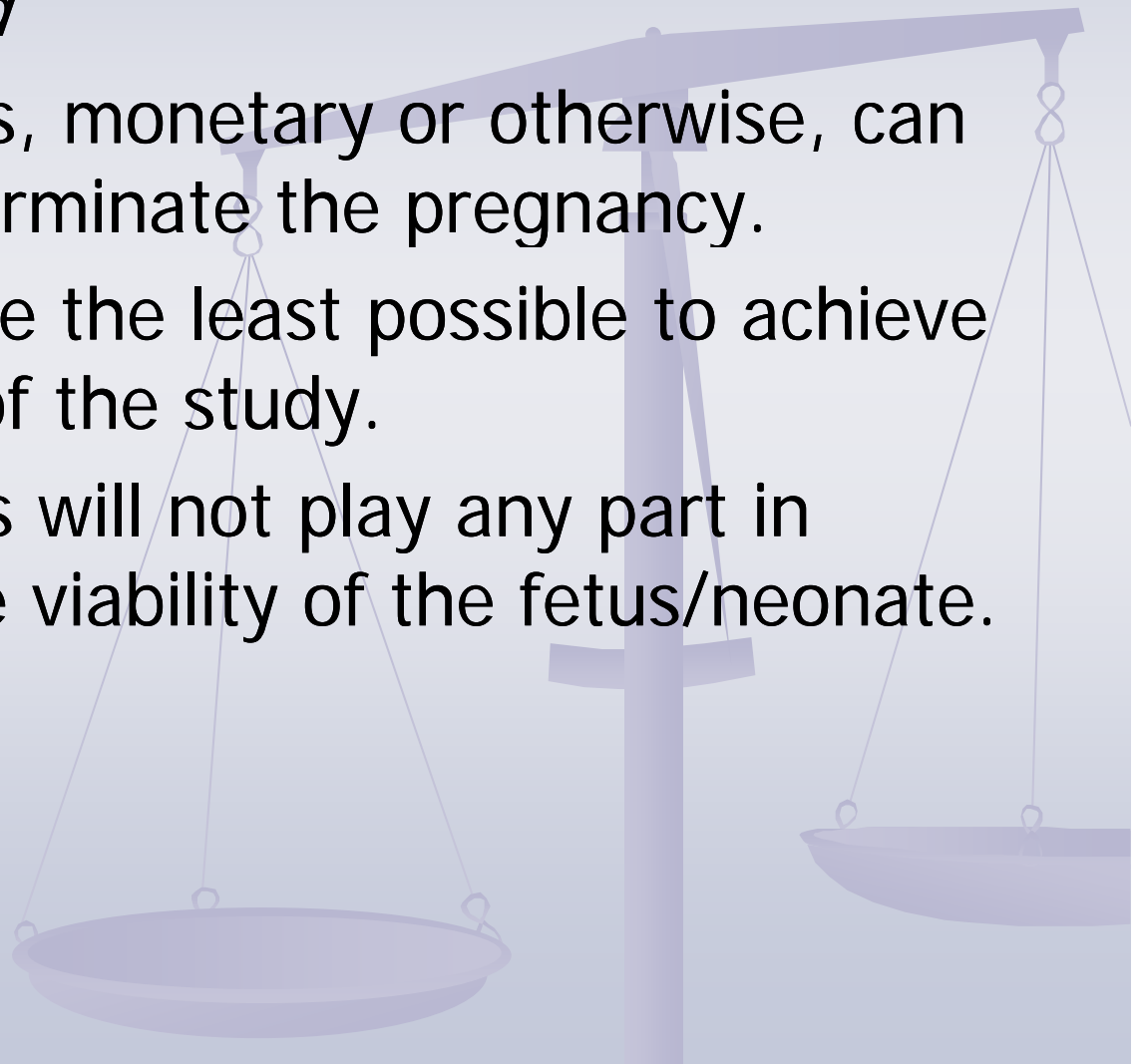
- The following criteria must be met (regardless of which, woman or fetus, is the subject):
 - Preclinical studies provide data to assess potential risks to woman and fetus
 - Risk to the fetus is either:
 - Not greater than minimal
 - OR
 - Any risk greater than minimal holds out the *prospect of direct benefit* for the woman or for the fetus
 - OR
 - *Risk to the fetus is greater than minimal* when there is **no** *prospect of direct benefit* for the women or the fetus, but the research presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses
 - Requires federal and/or OVPR approval



Pregnant Women and Fetuses

Criteria *continued*

- No inducements, monetary or otherwise, can be offered to terminate the pregnancy.
- Any risk must be the least possible to achieve the objectives of the study.
- The researchers will not play any part in determining the viability of the fetus/neonate.



Pregnant Women and Fetuses

IRB Review and Application Issues

- Informed Consent Document:
 - Must include risks to and impacts on both the woman and the fetus
 - If research offers prospect of direct benefit to the woman, only her signature required
 - If research offers prospect of direct benefit to the fetus, signatures of both the mother and the father required
 - Add an additional signature line to the form



Pregnant Women and Fetuses

IRB Review and Application Issues *continued*

- Provide pre-clinical data if the study involves risk.
 - Provide explanations of this data and justifications for the risk in proportion to the risk level
- eR Section 9—indicate this population
- Complete eR Section 35 and 41*
 - Make sure the regulation indicated in 35.1 matches up with the benefit and risk information provided in section 6.
 - If the study includes different arms with different risk/benefit assessments indicate the regulation appropriate for each arm.

*Data analysis only studies complete 35-1 instead of 35 and 41.

Pregnant Women and Fetuses

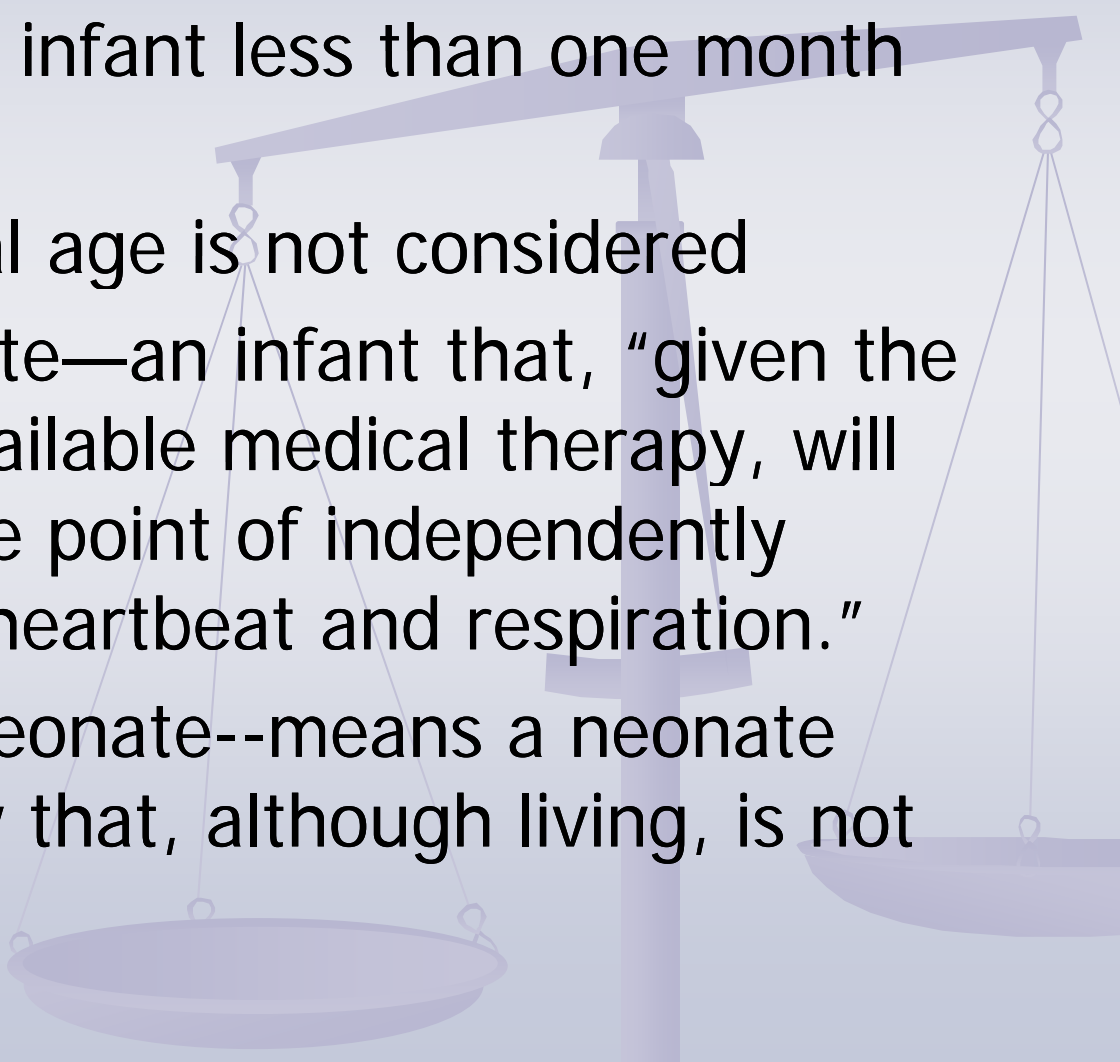
IRB Review and Application Issues *continued*

- When researchers are also care-providers clearly indicate in the protocol and application (35.2.4) the plan to avoid researcher involvement in viability decisions.
- For higher risk studies, consult with the IRB during pre-submission.
 - Consider consultation with the Pediatric Ethics Committee if study involves challenging ethical issues

Neonates



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
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Neonates—Regulations

45 CFR 46 Subpart B

- [See algorithm.](#)

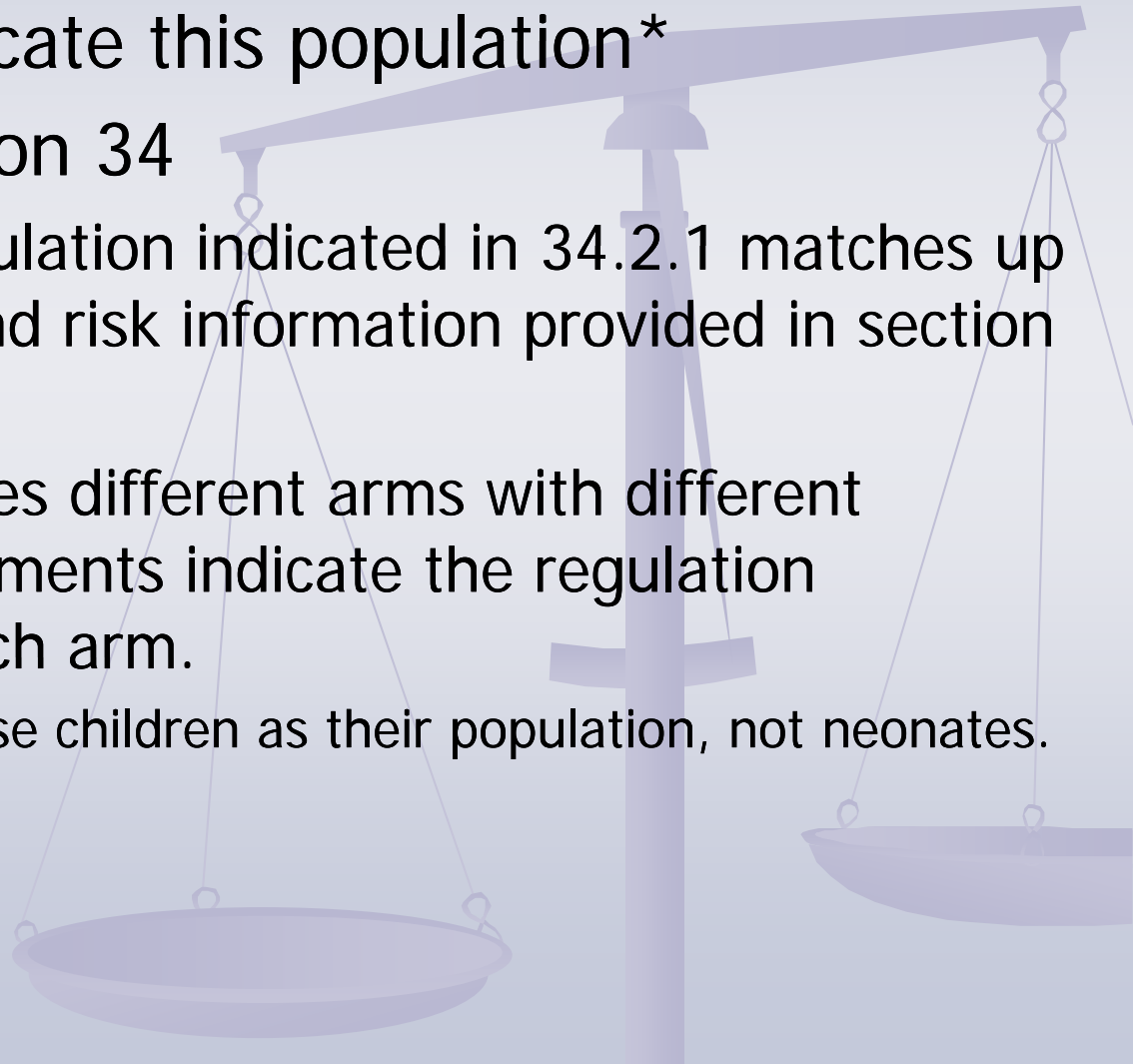


Neonates

IRB Review and Application Issues *continued*

- eR Section 9—indicate this population*
- Complete eR Section 34
 - Make sure the regulation indicated in 34.2.1 matches up with the benefit and risk information provided in section 6.
 - If the study includes different arms with different risk/benefit assessments indicate the regulation appropriate for each arm.

*Data analysis only should choose children as their population, not neonates.

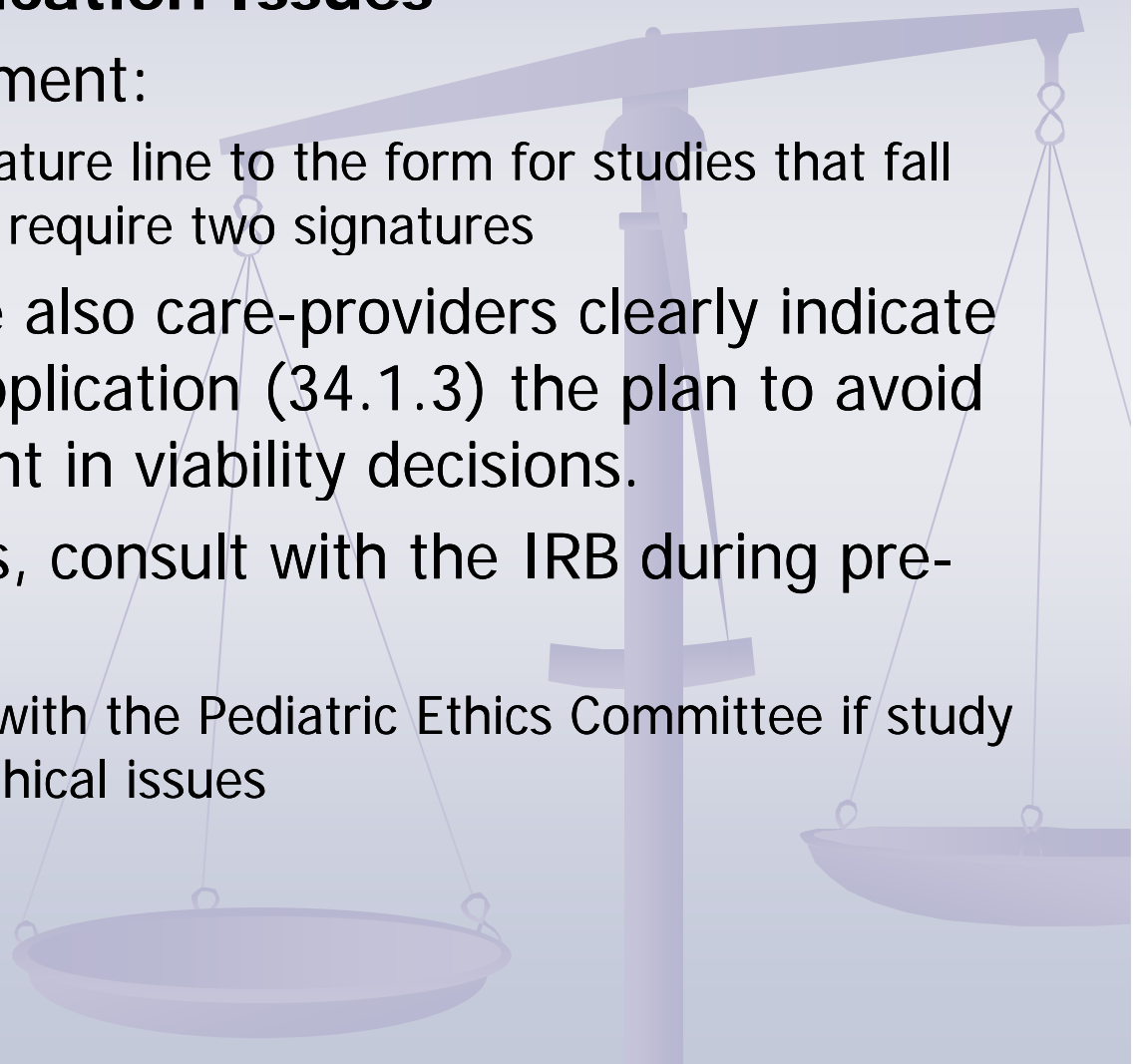


Neonates

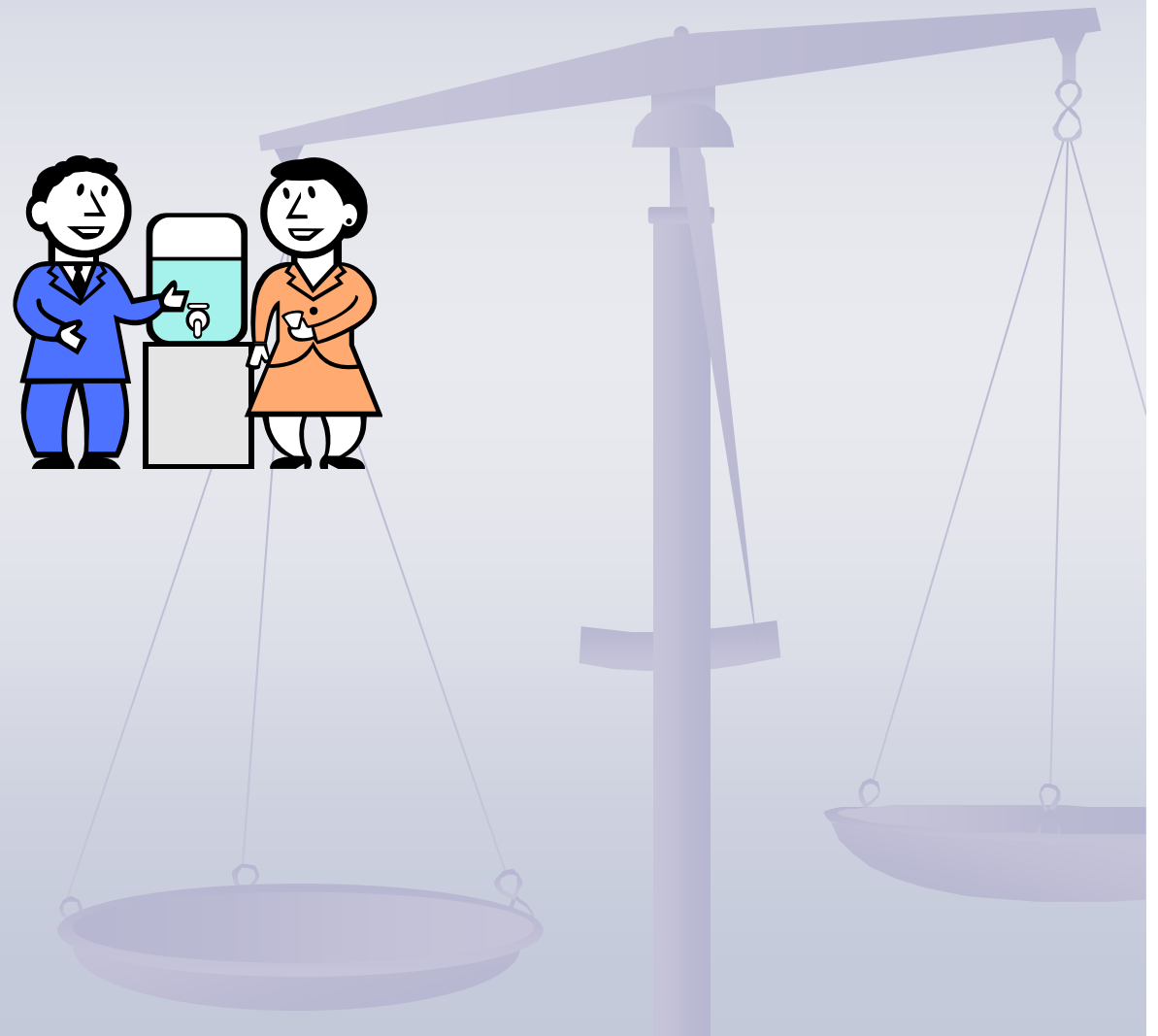
IRB Review and Application Issues

Informed Consent Document:

- Add an additional signature line to the form for studies that fall under regulations that require two signatures
- When researchers are also care-providers clearly indicate in the protocol and application (34.1.3) the plan to avoid researcher involvement in viability decisions.
- For higher risk studies, consult with the IRB during pre-submission.
 - Consider consultation with the Pediatric Ethics Committee if study involves challenging ethical issues



Break Time

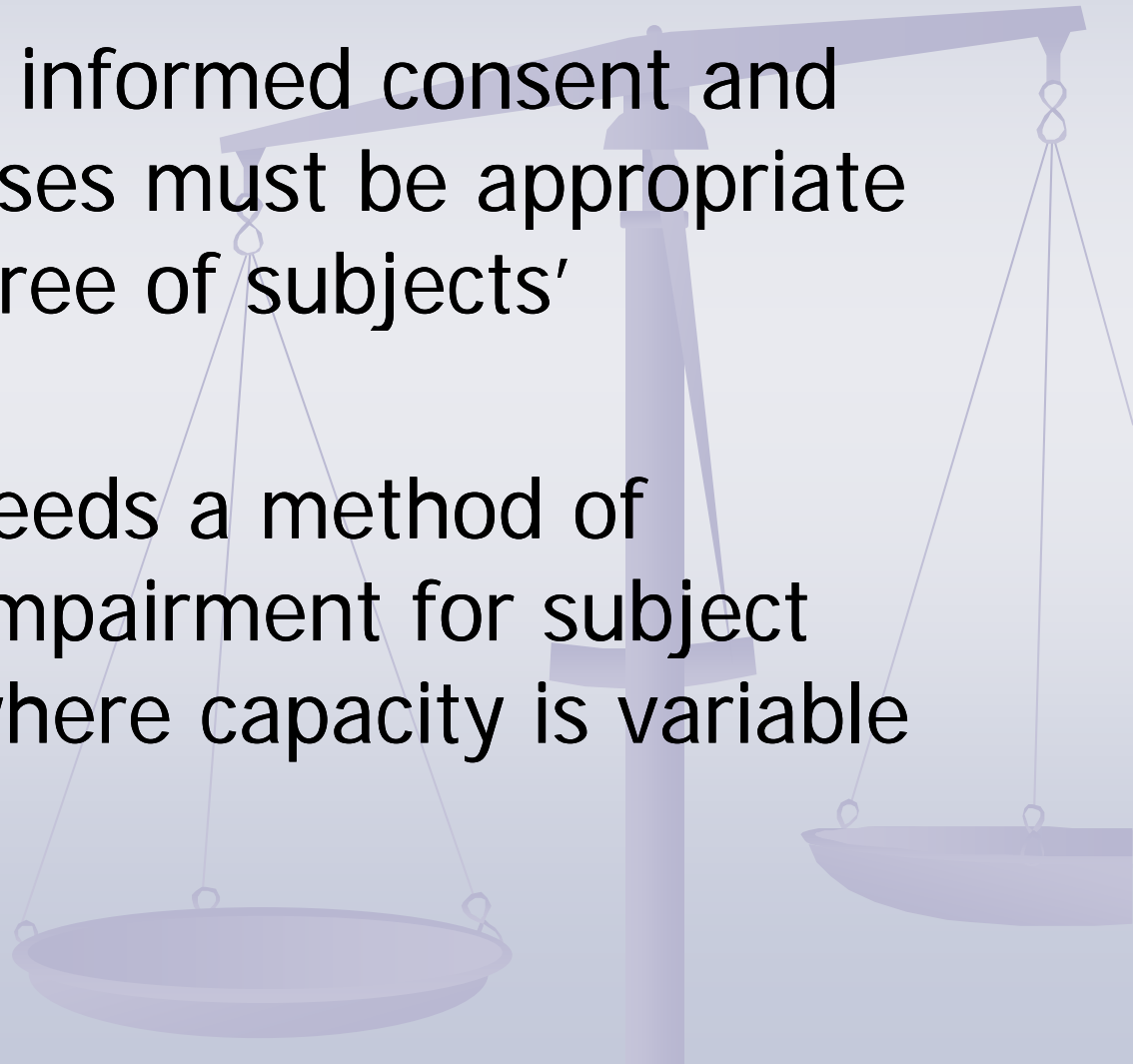


Cognitively Impaired / Decisionally Impaired Subjects

- UM “Cognitively Impaired Subjects” policies apply to any adult research subject unable to exercise her or his autonomy sufficiently to provide informed consent.
- In other words—if you need to get consent from someone other than one or more of your subjects, the policies apply to your study.

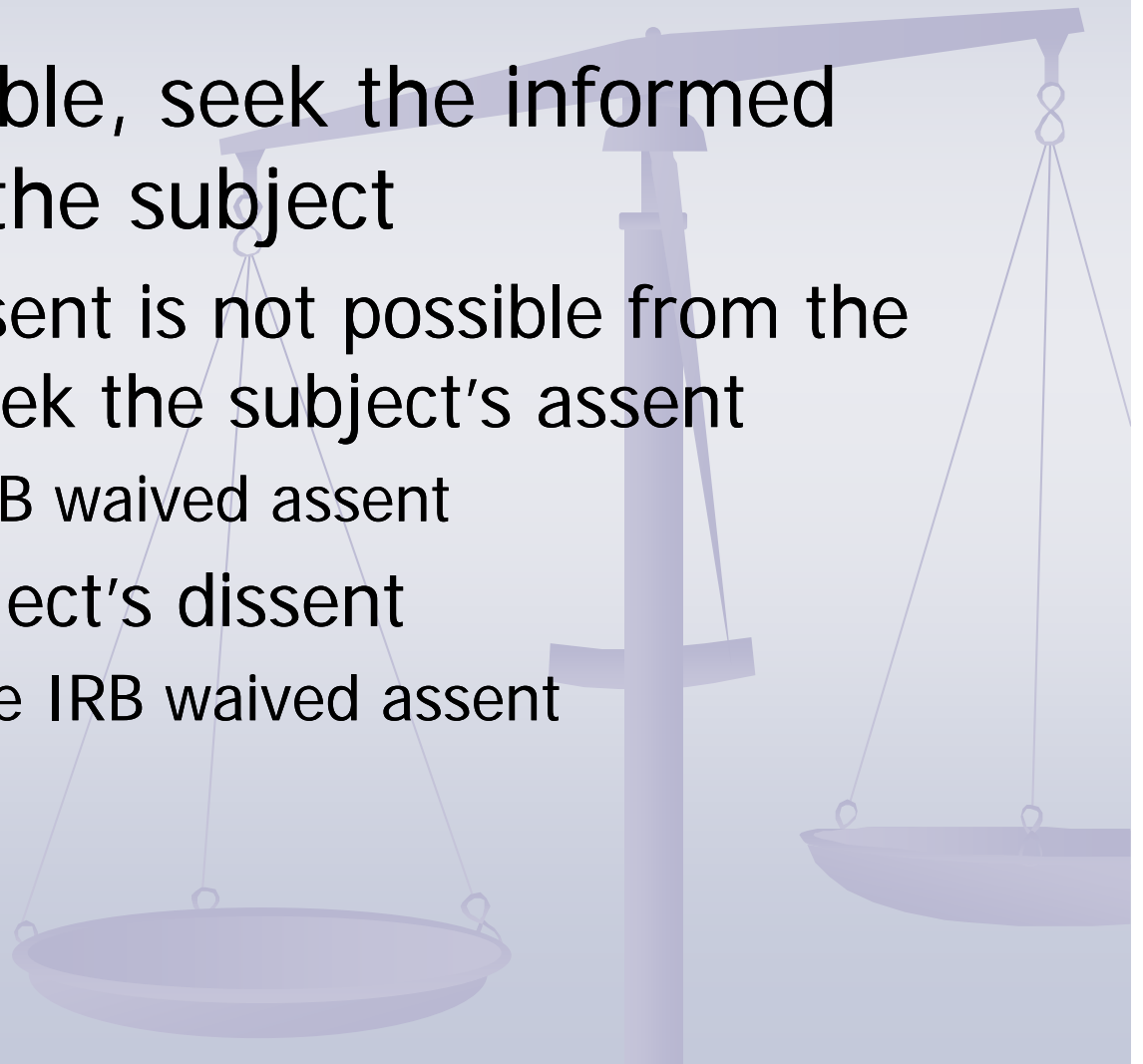
Cognitively Impaired Subjects

- Study design, informed consent and assent processes must be appropriate given the degree of subjects' impairment
- Study team needs a method of determining impairment for subject populations where capacity is variable



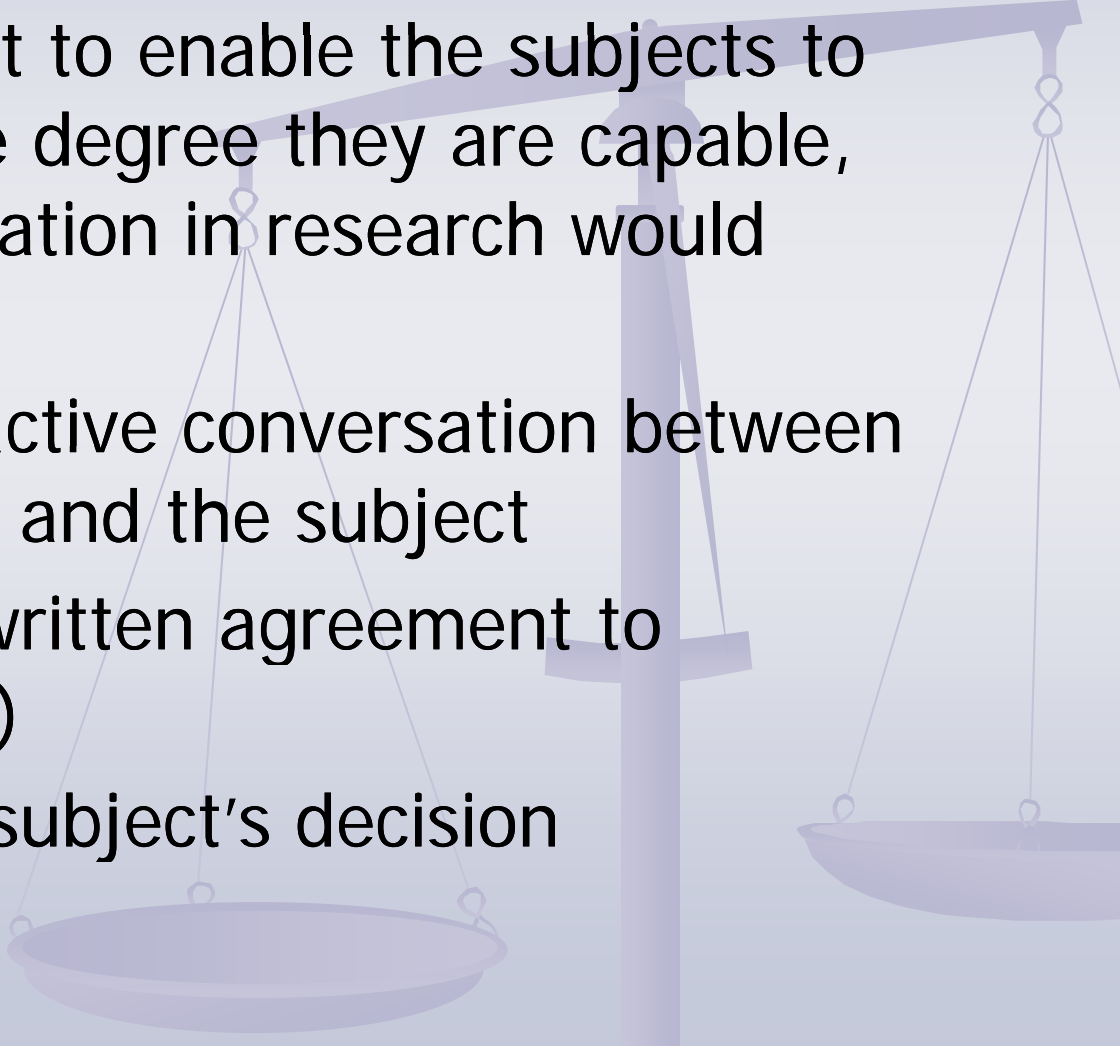
Cognitively Impaired Subjects

- When possible, seek the informed consent of the subject
 - When consent is not possible from the subject, seek the subject's assent
 - Unless IRB waived assent
 - Honor subject's dissent
 - Unless the IRB waived assent



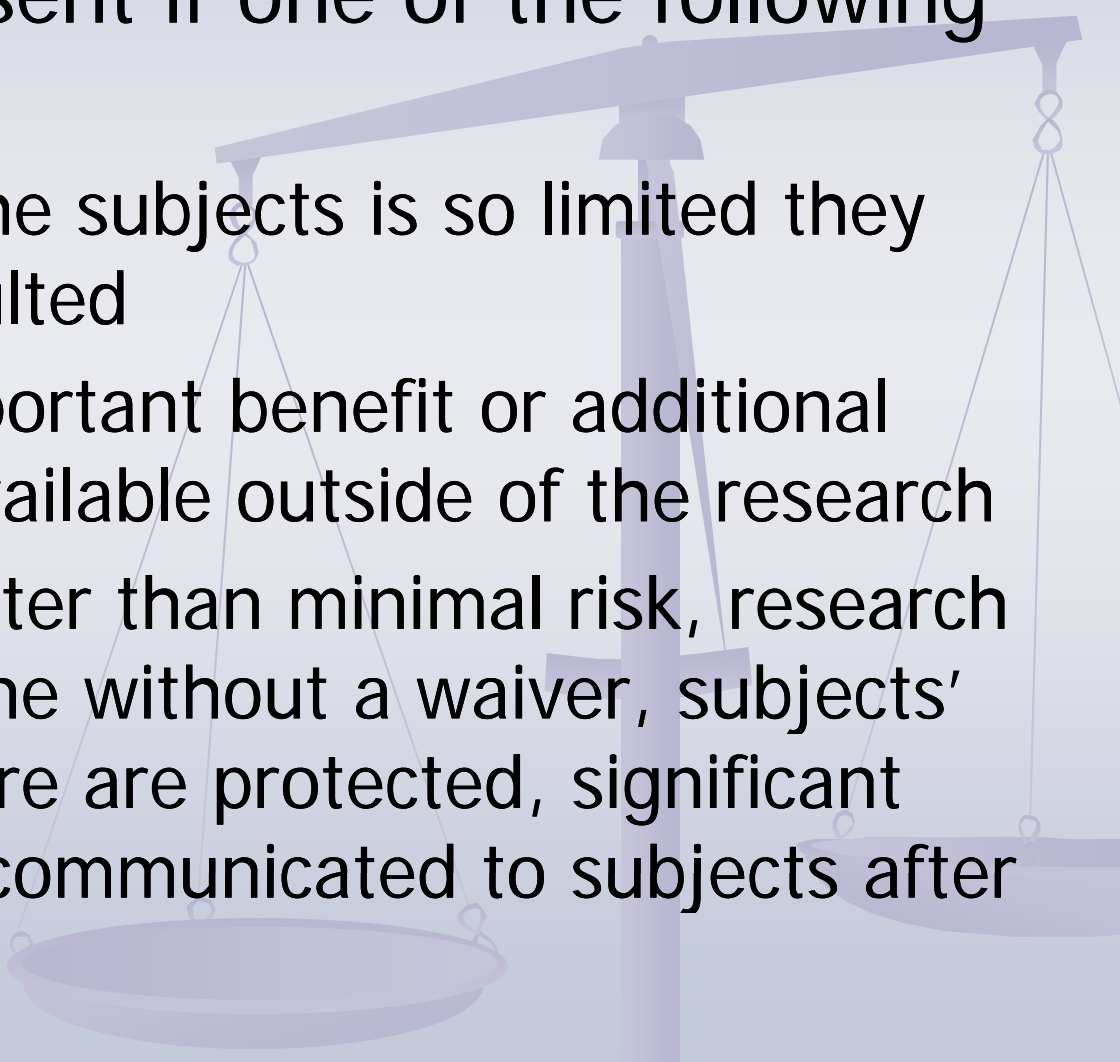
Cognitively Impaired Subjects

What is Assent?

- A reasonable effort to enable the subjects to understand, to the degree they are capable, what their participation in research would involve.
 - An ongoing, interactive conversation between the research team and the subject
 - Active spoken or written agreement to participate (or not)
 - Adherence to the subject's decision
- 

Cognitively Impaired Subjects

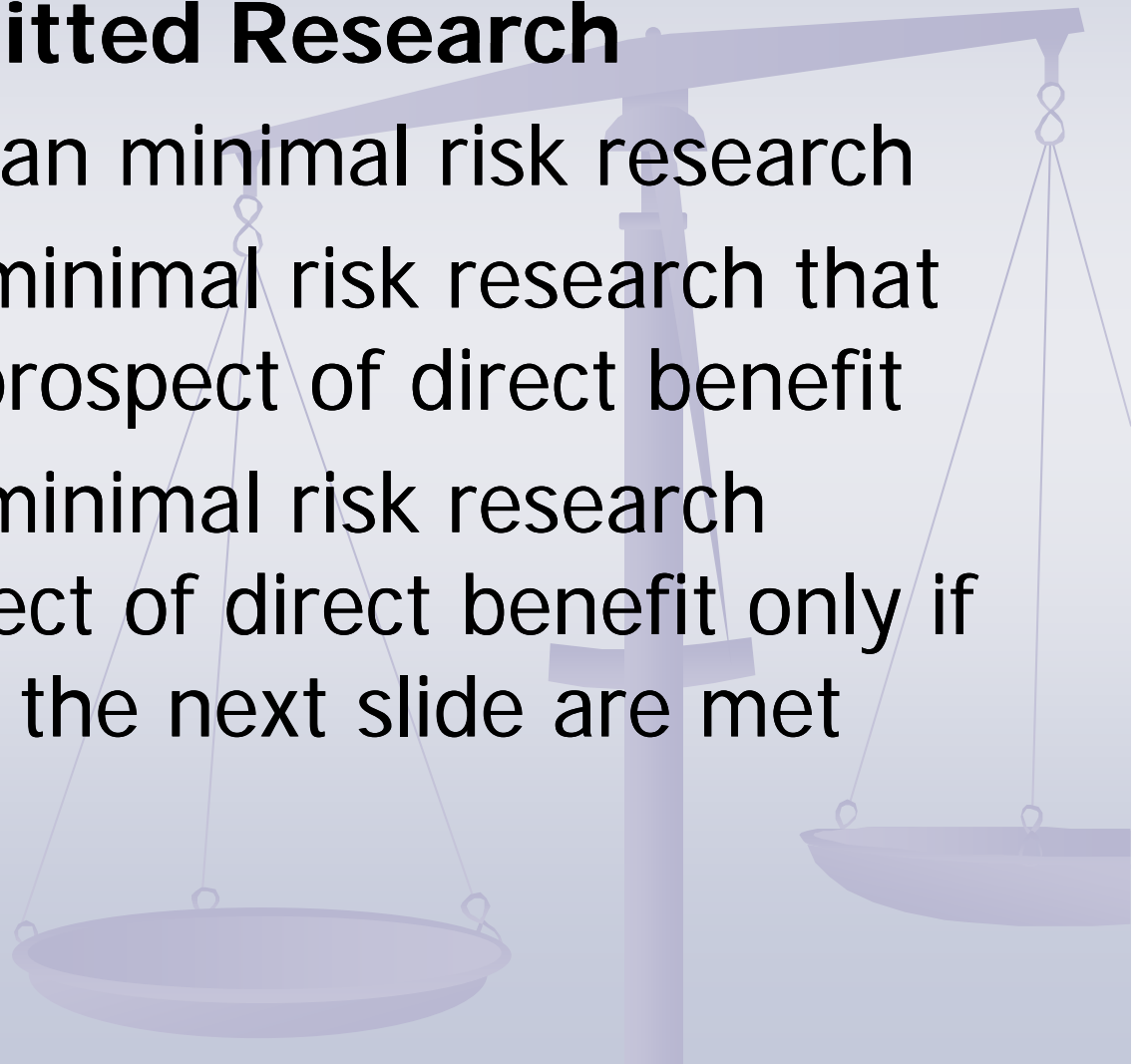
Assent Waivers

- IRB can waive assent if one of the following applies:
 1. Capabilities of the subjects is so limited they cannot be consulted
 2. Study offers important benefit or additional monitoring unavailable outside of the research
 3. Study is no greater than minimal risk, research could not be done without a waiver, subjects' rights and welfare are protected, significant findings will be communicated to subjects after the study.
- 

Cognitively Impaired Subjects

Types of Permitted Research

- Not greater than minimal risk research
- Greater than minimal risk research that presents the prospect of direct benefit
- Greater than minimal risk research without prospect of direct benefit only if the criteria on the next slide are met



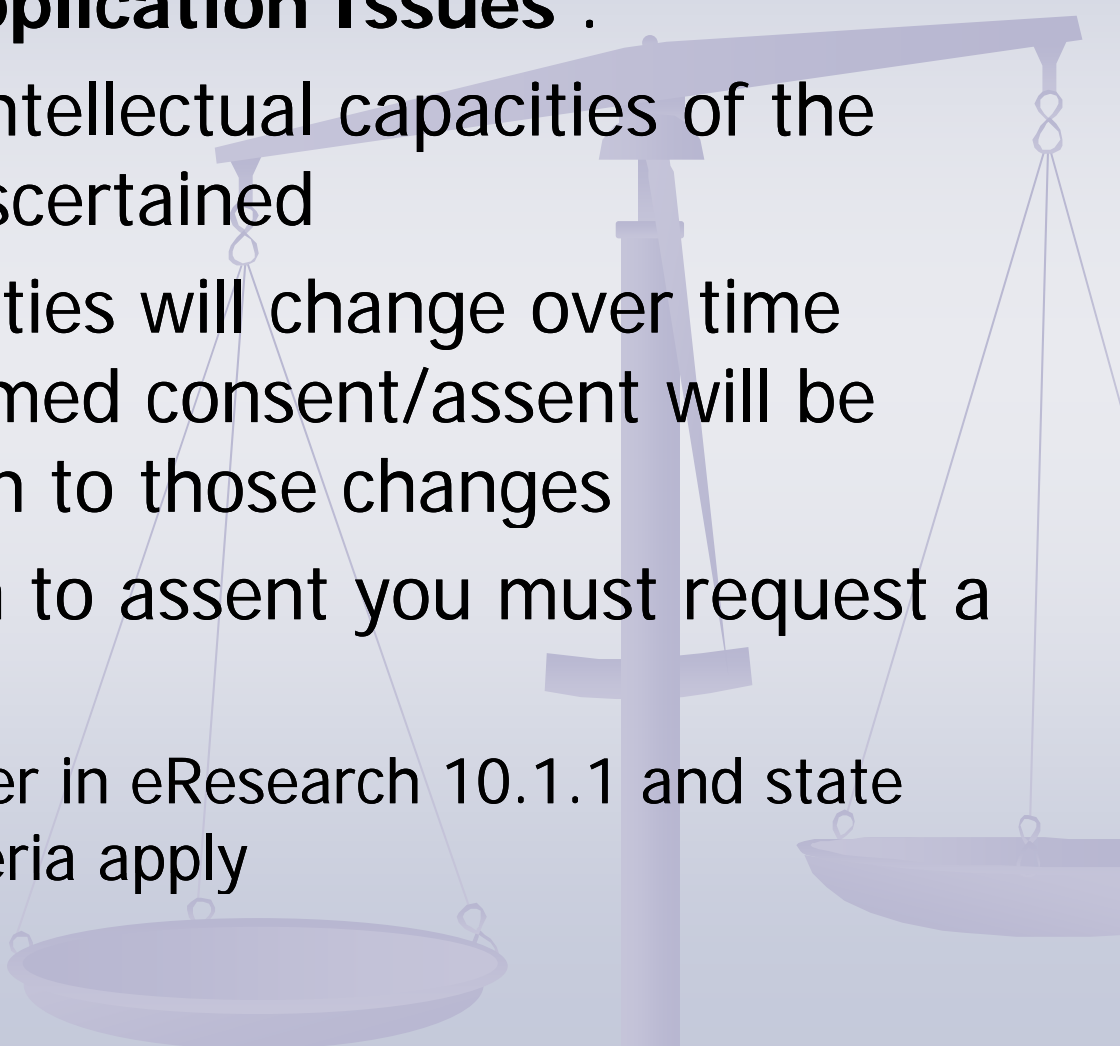
Cognitively Impaired Subjects

Research lacking direct benefit is allowed if:

- The research helps further understand, prevent, or alleviate a serious problem affecting the cognitively impaired.
- Approval is secured from the Institutional Official or Deputy Institutional Official (OVPR).
Steps include:
 - Notice of the proposal is posted to the HRPP website for review and comment
 - Consultation with a panel of experts in pertinent disciplines

Cognitively Impaired Subjects

IRB Review and Application Issues :

- Explain how the intellectual capacities of the subjects will be ascertained
 - If subjects' capacities will change over time explain how informed consent/assent will be handled in relation to those changes
 - If you do not plan to assent you must request a waiver
 - Request the waiver in eResearch 10.1.1 and state which waiver criteria apply
- 

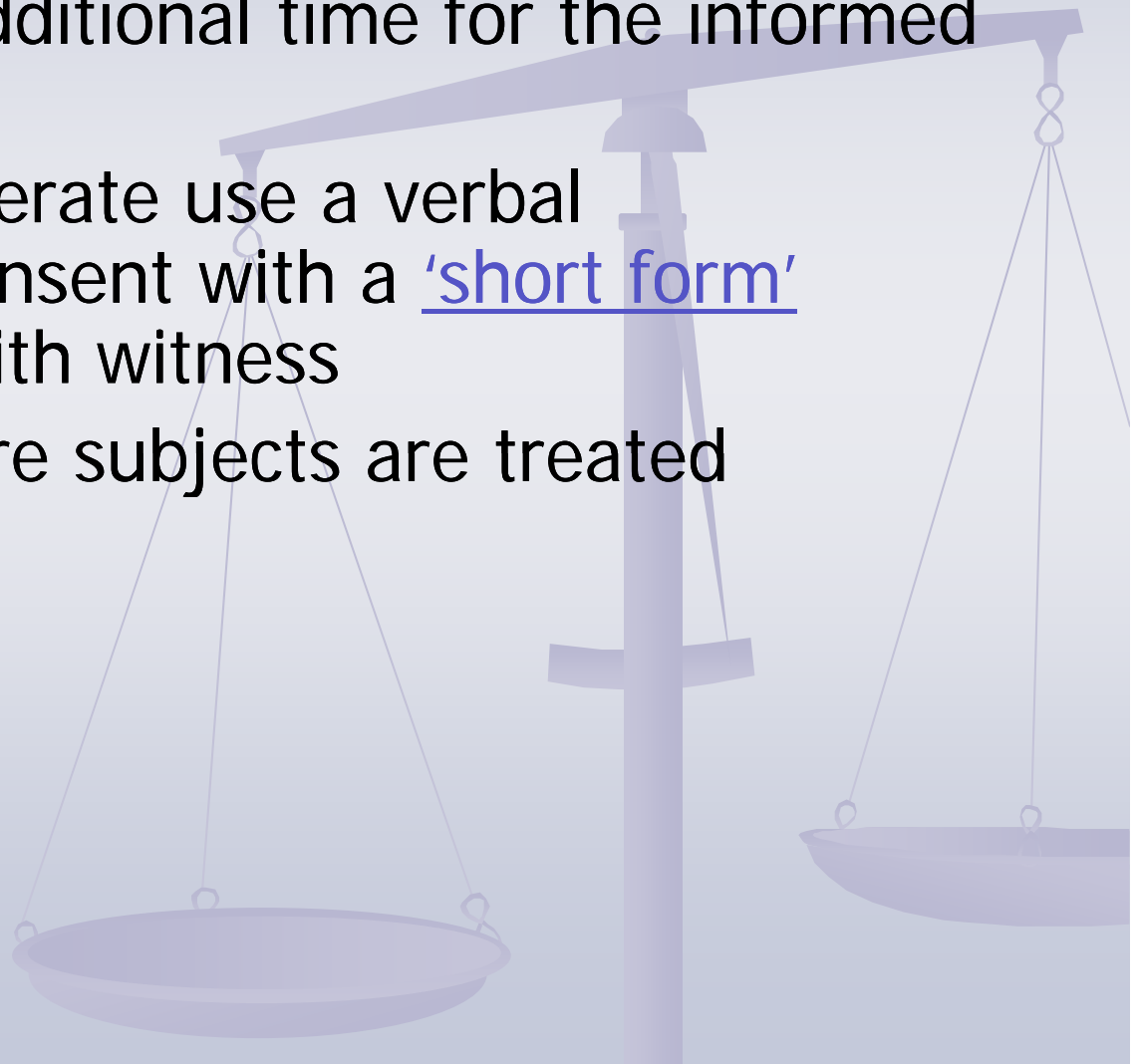
Other “Vulnerable Populations”

- Educationally disadvantaged
- Economically disadvantaged
- Students and employees
- Patients of the study team



Educationally Disadvantaged

- Allow adequate/additional time for the informed consent process
- If subjects are illiterate use a verbal comprehensive consent with a 'short form' written consent with witness
- Take care to assure subjects are treated respectfully



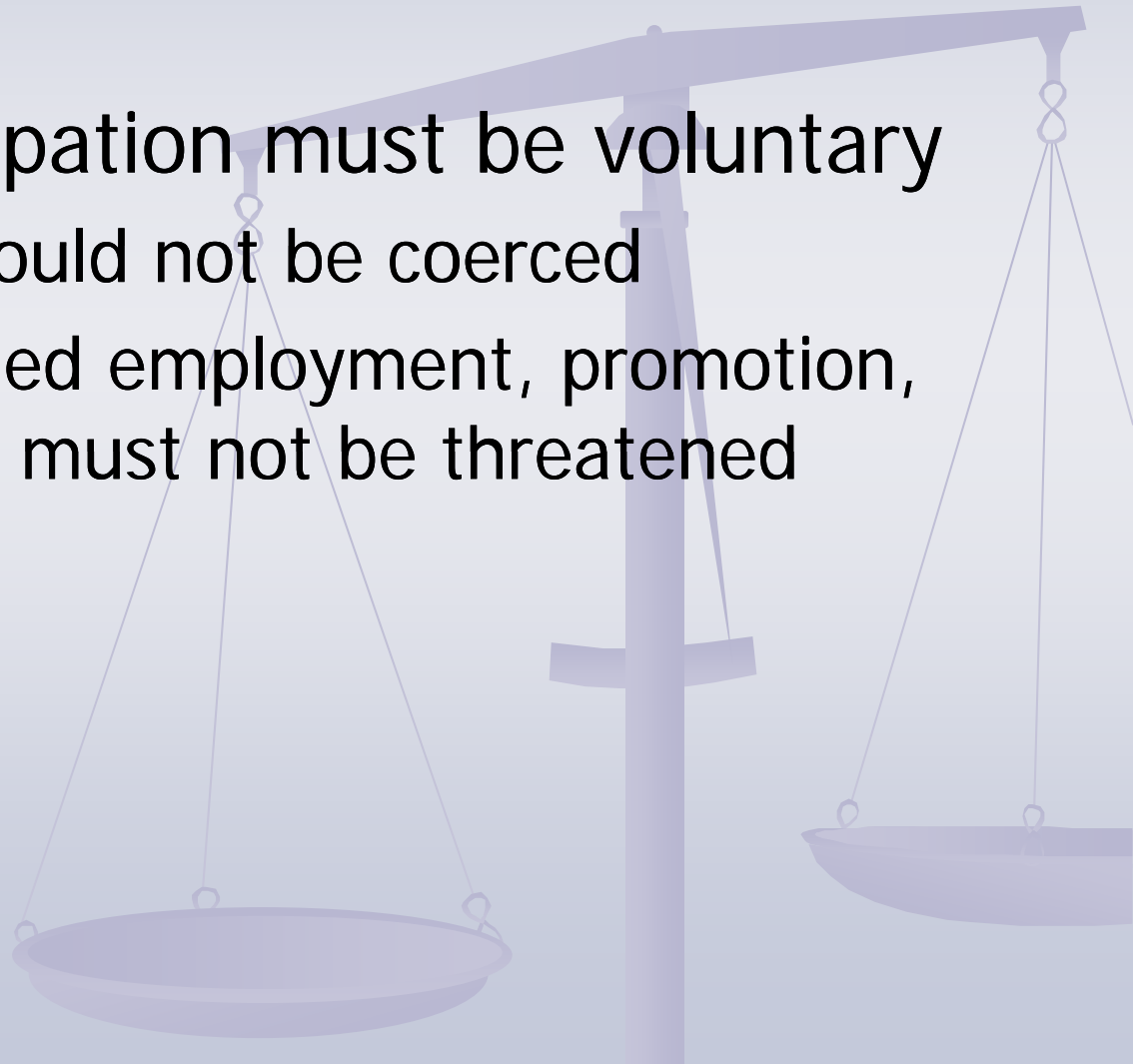
Economically Disadvantaged



- Unless scientifically appropriate, do not target low income groups for recruitment.
- Determine financial incentives fairly
 - Avoid 'undue influence'
 - "it is impossible to state precisely where justifiable persuasion ends and undue influence begins"
 - In the IRB application explain your rationale

Students, Employees, and Patients of the Researcher

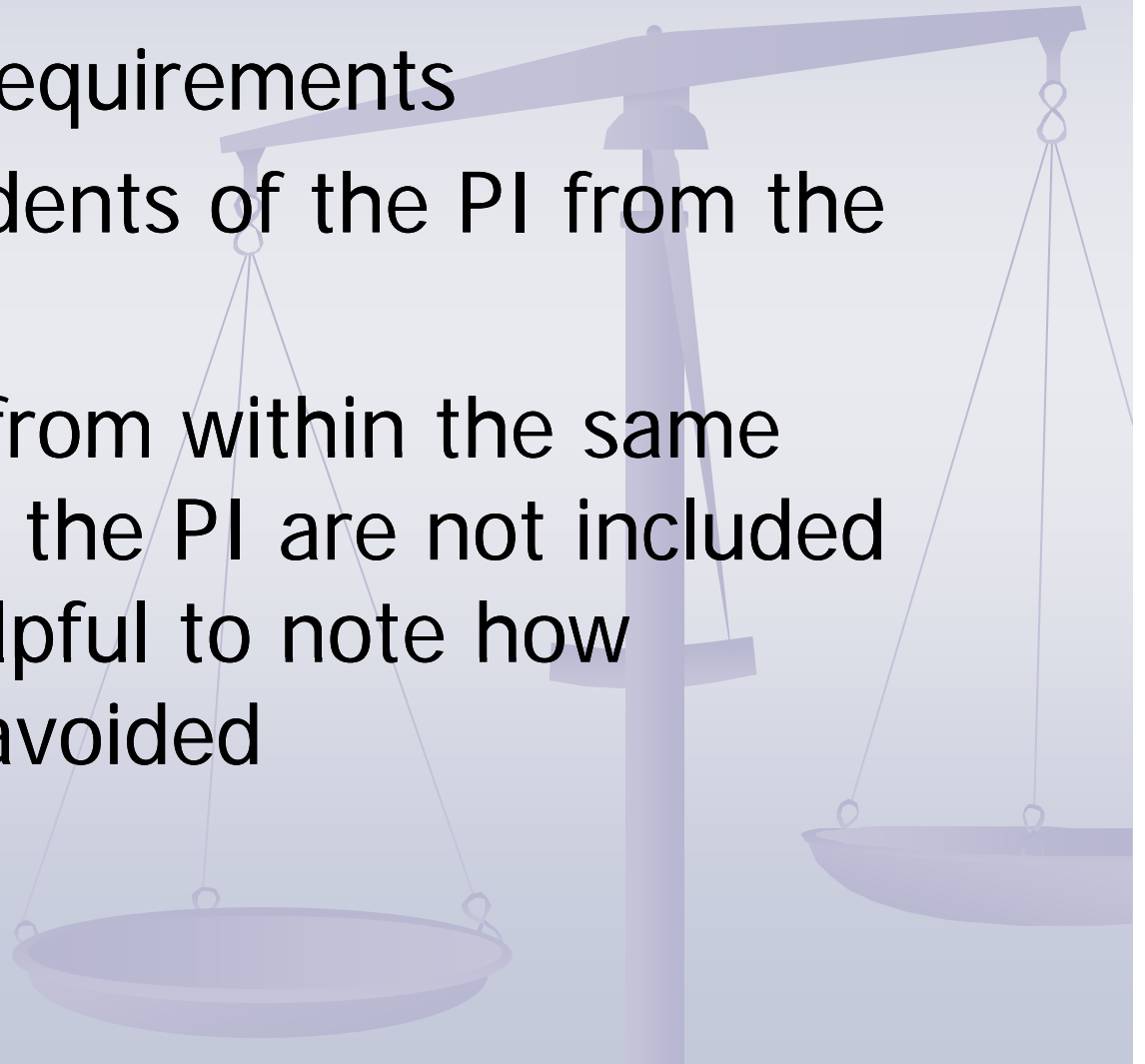
- Research participation must be voluntary
 - Participation should not be coerced
 - Grades, continued employment, promotion, health care, etc must not be threatened



Students

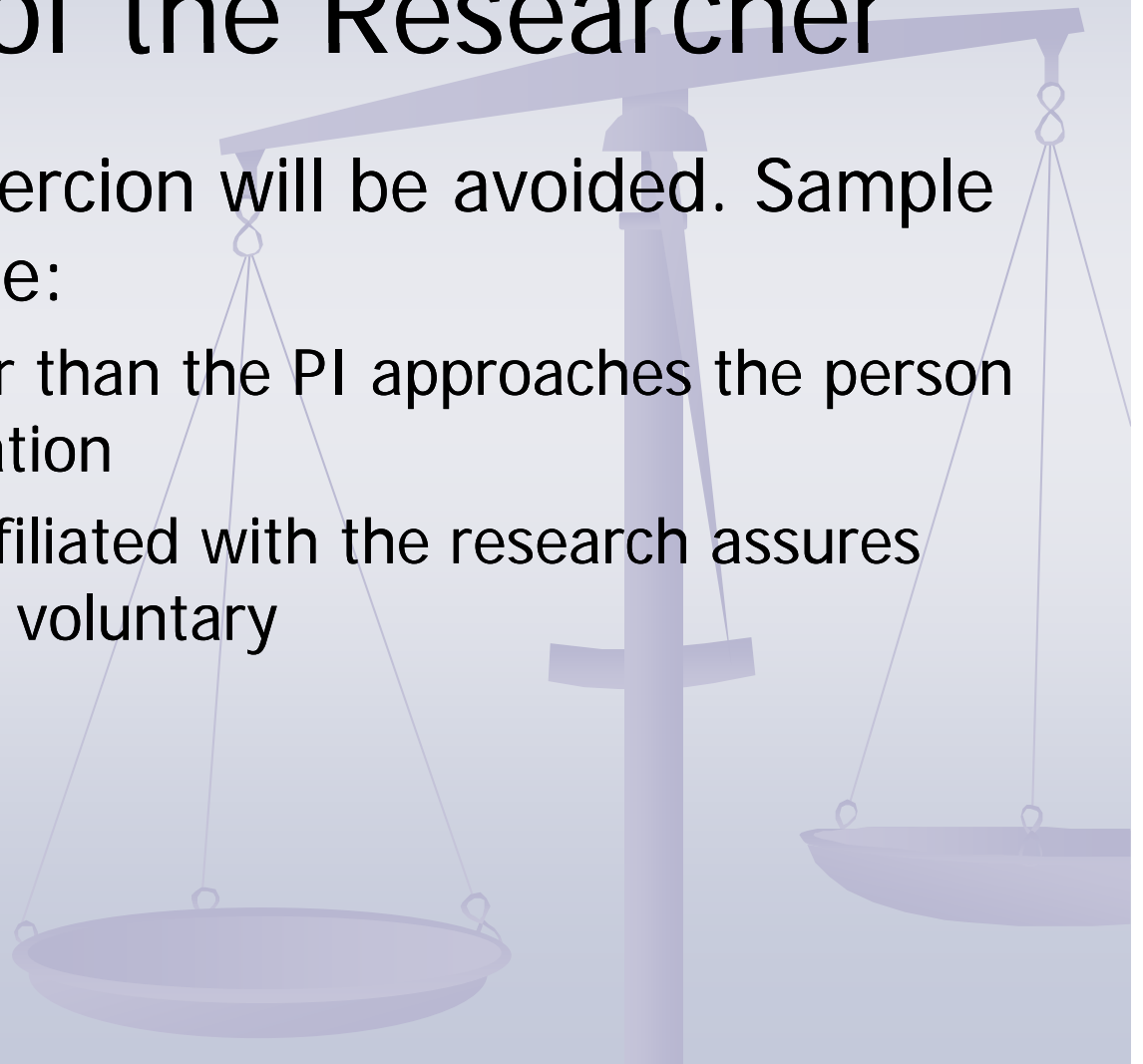
'Typical' IRB requirements

- Exclude students of the PI from the research
- If students from within the same discipline as the PI are not included it can be helpful to note how coercion is avoided

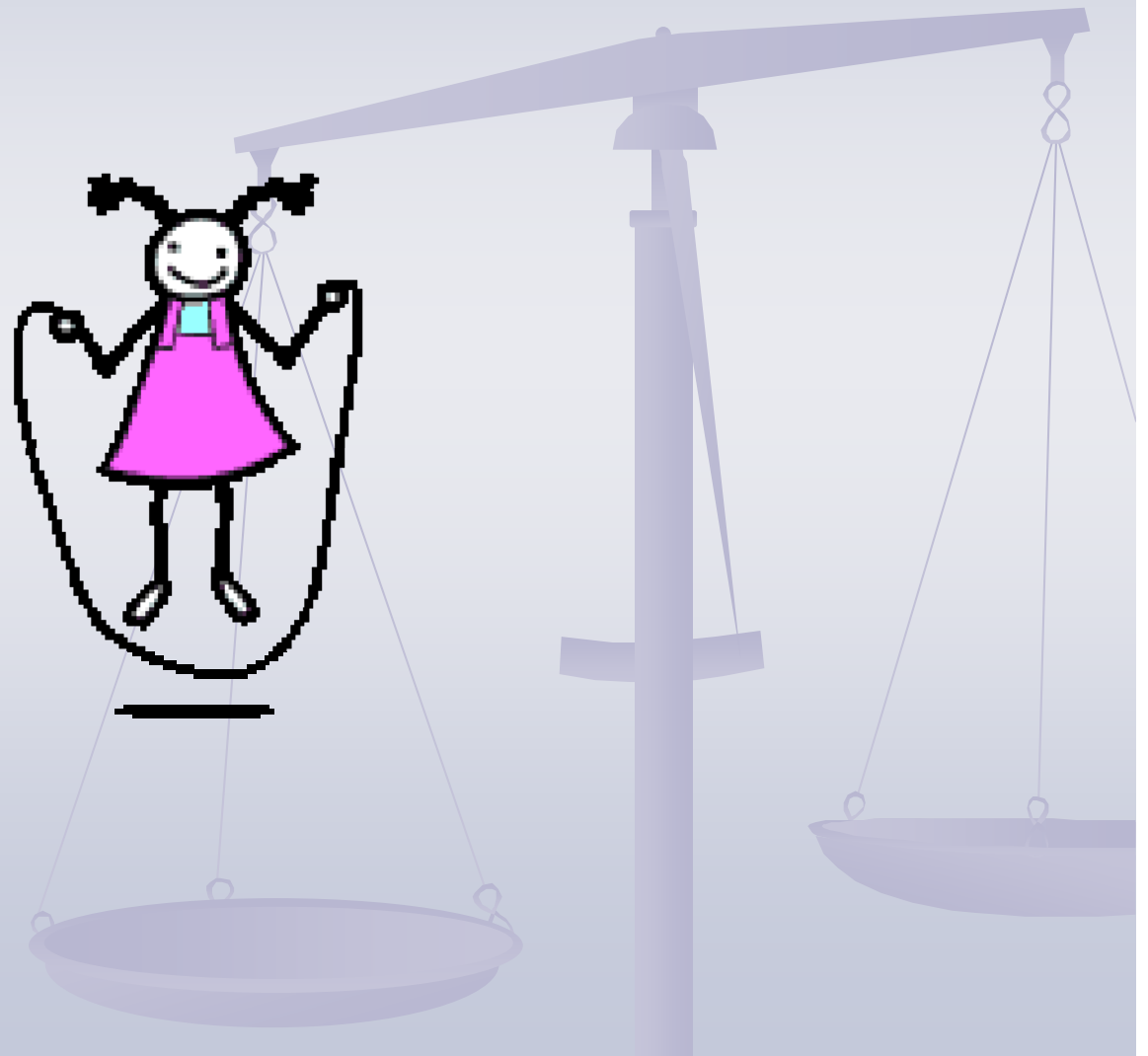


Students, Employees, and Patients of the Researcher

- Explain how coercion will be avoided. Sample methods include:
 - Someone other than the PI approaches the person about participation
 - Someone unaffiliated with the research assures participation is voluntary



Questions?



Parting Words



- Start planning early when a special population is to be recruited
- Act immediately when a subject becomes incarcerated
- Remember mandates in the regulations are outside of an IRB's discretion
- Email irbmed@umich.edu with questions