

Enrolling Decisionally Impaired Adults in Research

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Overview: Research with Decisionally Impaired Adults

- Specific case of research posing more than minimal risk that does not offer the prospect of direct medical benefit
- IRB-oriented perspective; focus on process
- Specific additional safeguards

Research With Impaired or Potentially Impaired Subjects

- **Medication trial for Alzheimer's Disease**
- **Comparison of ventilation settings in ARDS**
- **ECT trial for delusional depression**
- **Clinical trial in advanced Parkinson's Dz**
- **Placebo-controlled study in acute mania**
- **Research on delirium**
- **Tryptophan depletion in autism (adults)**
- **Medication-free studies of schizophrenia**

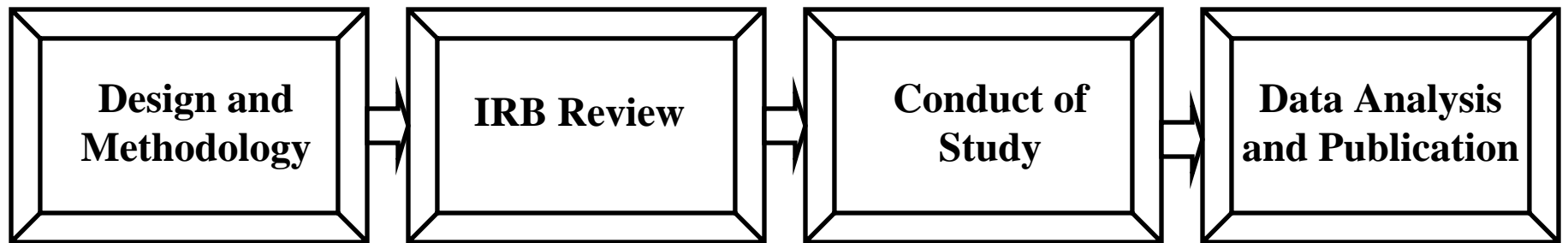
Fragile X Syndrome

- **Rare genetic disorder (~ 54,000 cases in U.S.)**
- **Boys affected more than girls**
- **Caused by silencing of a gene related to protein synthesis**
- **Clinical presentation:**
 - **Cognitive impairment/mental retardation**
 - **Seizures**
 - **Maladaptive behaviors, social anxiety**
- **Treatment is limited to non-specific symptom management**

PET Measurement of Regional Rates of Protein Synthesis in Fragile X

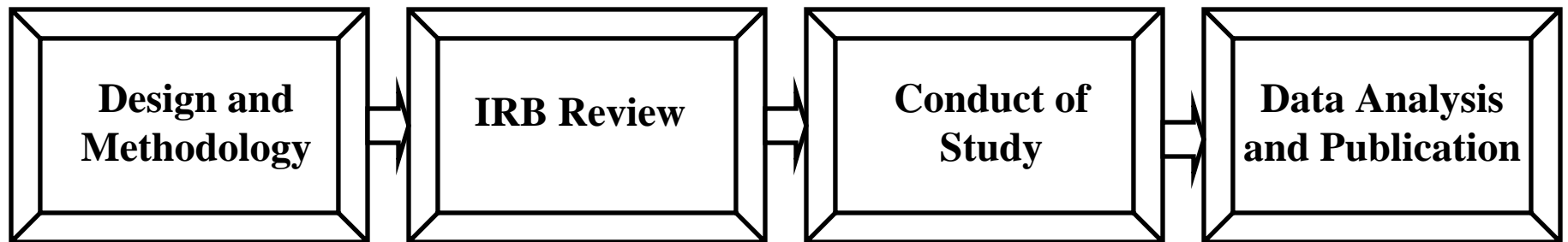
- **Substantial, specific and compelling prior science**
- **Study of subjects ages 18-24**
- **Subjects not expected to be able to give informed consent**
- **Surrogate permission for research (parents, guardians)**
- **Research will not provide direct medical benefit**
- **Protocol poses greater than minimal risks**
 - **MRI**
 - **PET scan (^{11}C -leucine) with an arterial line**
 - **Use of propofol sedation**

Research with Decisionally Impaired Subjects



Central Ethical Tension: *Medical Progress vs. Exploitation*

Research with Decisionally Impaired Subjects



Central Ethical Tension: *Medical Progress vs. Exploitation*

Regulations, Laws, Policies and Public Opinion

(OHRP, FDA, NBAC, MAS 87-4, Advocacy Groups, etc)

Regulatory and IRB Considerations

- **Non-emergency research with adults**
- **Language and overlapping domains**
 - Competence; cognitive impairment; and impaired decisionmaking capacity (DMC)
 - ability to provide informed consent for specific study
- **IRBs review protocols...clinical researchers enroll individuals**
- **Dimensional phenomena and categorical decisions**
- **Regulatory language is not particularly helpful**

45 CFR 46.111

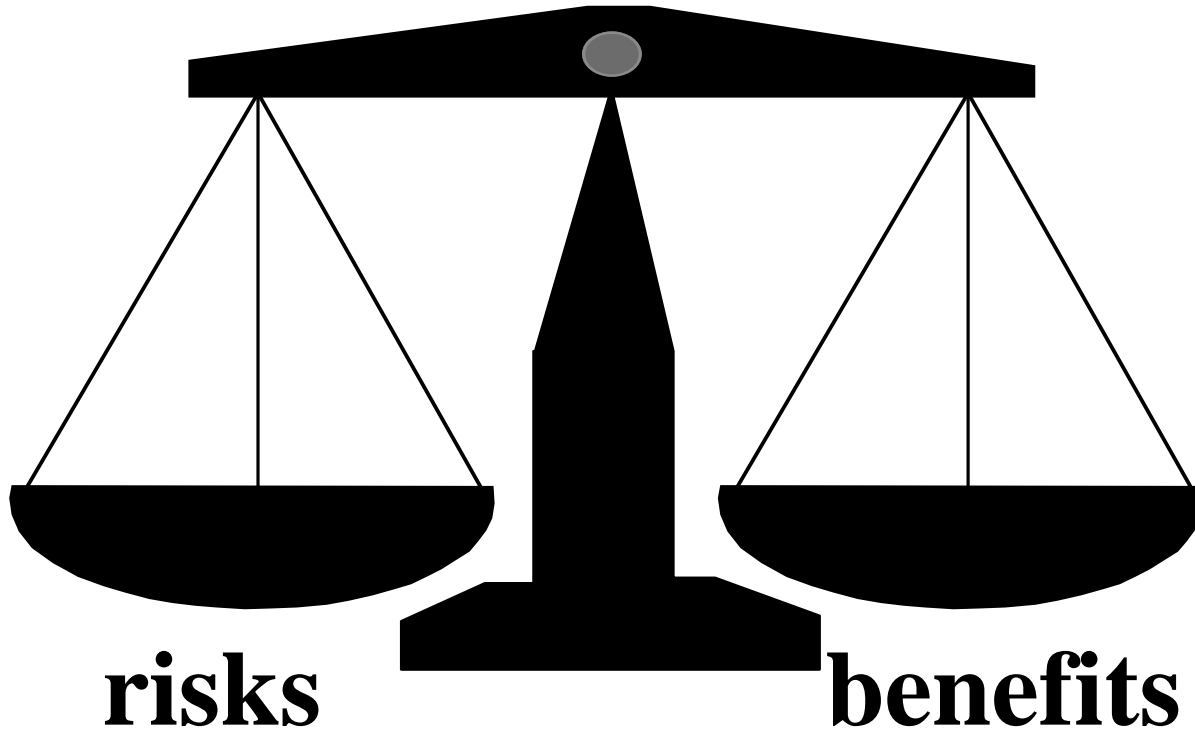
Criteria for IRB Approval of Research

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

IRB Review

- **Can the scientific question be answered with capacitated subjects?**
 - **Exceptions**
 - **Prospect of benefit**
 - **Prior commitment from subject**
 - **Minimal risk?**

Institutional Review Board



- minimal risk
- minor increment over minimal risk (children)
- greater than minimal risk

- direct benefit to the subject
- benefit to society
- (indirect benefits to subject)

Variable Risk in Research that Provides No Direct Medical Benefit

Low Risk

High Risk

simple blood draw

neuropsychological tests

MRI

lumbar puncture

arterial line

sedation

symptom provocation

brain biopsy

Variable Risk in Research that Provides No Direct Medical Benefit

Minimal Risk

More than Minimal Risk

simple blood draw	
neuropsychological tests	
MRI	
lumbar puncture	
arterial line	
sedation	
symptom provocation	
brain biopsy	

Variable Risk in Research that Provides No Direct Medical Benefit

Minimal Risk

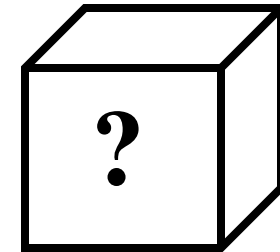
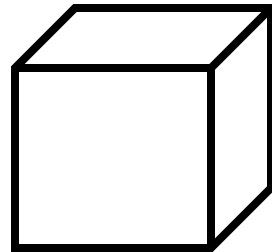
MI/MR

More than MI/MR

simple blood draw		
neuropsychological tests		
MRI		
lumbar puncture		
	arterial line	
		sedation
		symptom provocation
		brain biopsy

Categories of Risk and Benefit

Direct Benefit

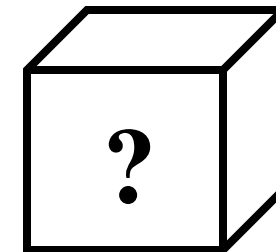
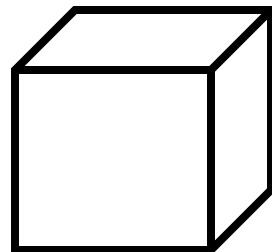


**Minimal
Risk**

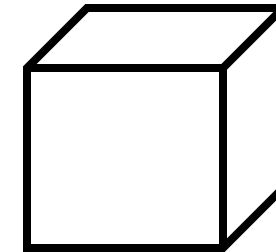
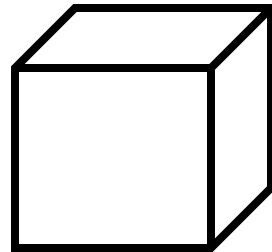
**More than
Minimal Risk**

Categories of Risk and Benefit

Direct Benefit



**No Direct
Benefit**

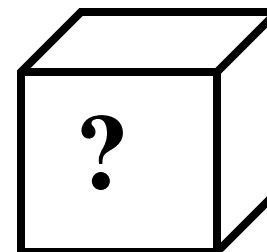
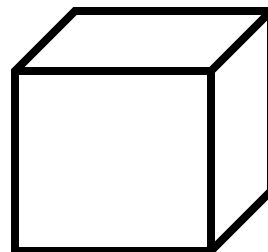
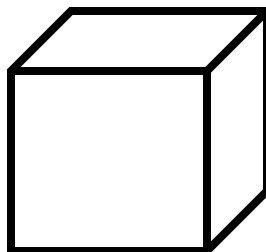


**Minimal
Risk**

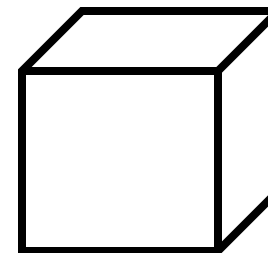
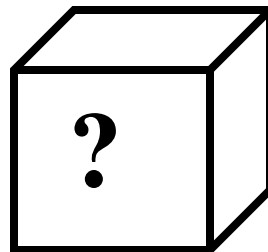
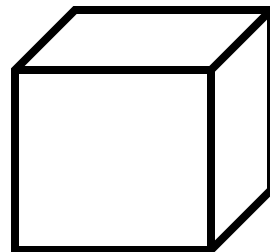
**More than
Minimal Risk**

Categories of Risk and Benefit: Research with Children

Direct Benefit



**No Direct
Benefit**



**Minimal
risk**

**Minor
increment
over
minimal risk**

**More than a
minor
increment over
minimal risk**

Will Subjects Be Able to Provide Informed Consent?

- Subjects who are currently unable to provide informed consent**
- Subjects who will become unable to provide informed consent**
- Subjects who are at increased risk of becoming unable to provide informed consent**

Assessment of Decisionmaking Capacity (DMC)

- **Presumption of capacity/competence**
- **Medical aspects of assessment of DMC**
 - **Dehydration, medication toxicity, sickness, delirium, psychosis, severe depression, grief, mania**

Triggers for Consent Assessment

- **Concern about a class of prospective subjects**
 - **Protocol designed to enroll “at-risk” subjects**
 - **Protocol that may precipitate loss of decisional capacity**

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- **Concern about a class of prospective subjects**
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 - **Protocol that may precipitate loss of decisional capacity**
- **Concern about an individual**
 - **Prior to or at the time of enrollment**
 - **During study participation**

Capacity to Give Informed Consent for Research

Does this individual have a medical, neurological or psychiatric disorder that compromises his or her capacity to understand, appreciate and reason with respect to the details of a given study?

Clinical judgment

Capacity to Give Informed Consent for Research

Does this individual have a medical, neurological or psychiatric disorder that compromises his or her capacity to understand, appreciate and reason with respect to the details of a given study?

Clinical judgment

Can this person give informed consent and should they be enrolled into the study?

Ethical judgment

Assessment of Decisionmaking Capacity (DMC)

- **Presumption of capacity/competence**
- **Medical aspects of assessment of DMC**
 - **Dehydration, medication toxicity, sickness, delirium, psychosis, severe depression, grief, mania**
- **Who does this?**
- **How is it done?**

MacArthur Competence Assessment Tool (MacCAT-CR)

UNDERSTANDING

purpose of study; what tests and procedures

major risks, discomforts and possible benefits

APPRECIATION

is the main purpose to benefit you?

differences between this study and regular care

REASONING

if you decline, what will you do instead?

whose decision, can you stop participating?

CHOICE

Decisionmaking Capacity

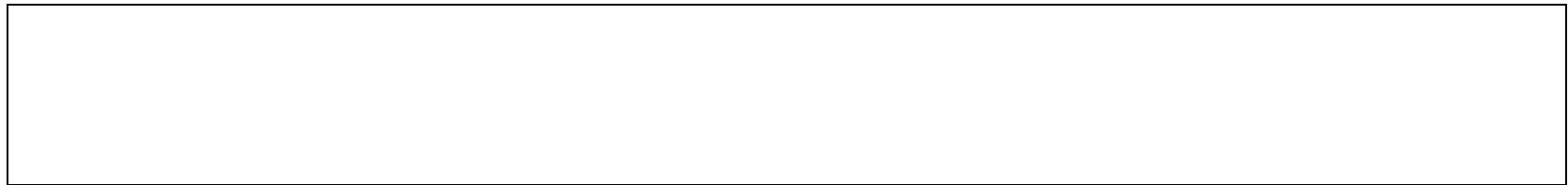
**Unable to make
decisions**



**Able to make
medical decisions**



**Fully
capacitated**



**Able to assign a
substitute
decisionmaker**



**Appreciates the
differences between
clinical care and
clinical research**

NIH Advance Directive for Health Care and Medical Research Participation

I. Durable Power of Attorney

II. Advance Directive for Health Care

III. Advance Directive for Research Participation

NIH Advance Directive for Health Care and Medical Research Participation

- If I lose the ability to make my own decisions, I do not want to participate in any medical research.
- If I lose...I am willing to participate in medical research that might help me.
- If...won't help me but might help others as long as it involves no more than minimal risk of harm to me.
- If...that won't help me but might help others even if it involves greater than minimal risk of harm to me.

Recommendations

- **Is it necessary to enroll vulnerable subjects?**
- **Decisional capacity with respect to providing informed consent for a specific study**
- **Subject vulnerability, research risks and benefits:**
 - **Determined by local IRB**
 - **Defined by study population and specific protocol rather than by diagnosis alone**

Recommendations (*Cont.*)

- **Investigators should describe in detail:**
 - methods of assessing decisional capacity
 - procedures for informed consent or proxy consent
 - provision of adequate safeguards
- **IRBs should promote increased use of:**
 - independent capacity assessment
 - consent monitors
 - legally authorized representatives
 - research advance directives
- **IRB discretion regarding intermediate risk**