Research Involving Persons at Risk for Impaired Decisionmaking

Donald L. Rosenstein, M.D.

Office of the Clinical Director

National Institutes of Health

The views expressed here are mine and do not represent the position of the Department of Clinical Bioethics, NIMH, NIH or of the Department of Health and Human Services.

NIMH
National Institute of Mental Health

Overview

- **Non-emergency research with adults**
- **Three protocols to frame the core issues**
- **Definitions and overlapping domains**
  - competence
  - cognitive impairment; decisionmaking capacity (DMC)
  - ability to provide informed consent, vulnerability
- **Dimensional phenomena and categorical decisions**
- **IRB-oriented perspective; focus on process**
- **Specific additional safeguards**

Case 1: Medication trial in Huntington's Disease

- **Familial neurological disorder**
- **Progressive and catastrophic**
  - **Neurologic impairment, psychiatric symptoms, dementia, and death**
- **Current treatment is supportive, symptomatic and of modest benefit at best**
- **Values and preferences can be known**
- **Analysis of this study is focused on risks to subjects and (direct) benefits for subjects**

Case 2: Tryptophan Depletion Study in Adults with Autism

- **Profound developmental disorder:**
  - **impaired speech, communication, learning and social interactions**
  - **Inability to provide consent; parental permission**
- **Symptomatic treatments only**
- **Values and preferences are harder to know**
- **Dietary manipulation designed to provoke symptoms to learn about neurobiology (non-specific mechanism)**
- **No direct medical benefit from study participation**

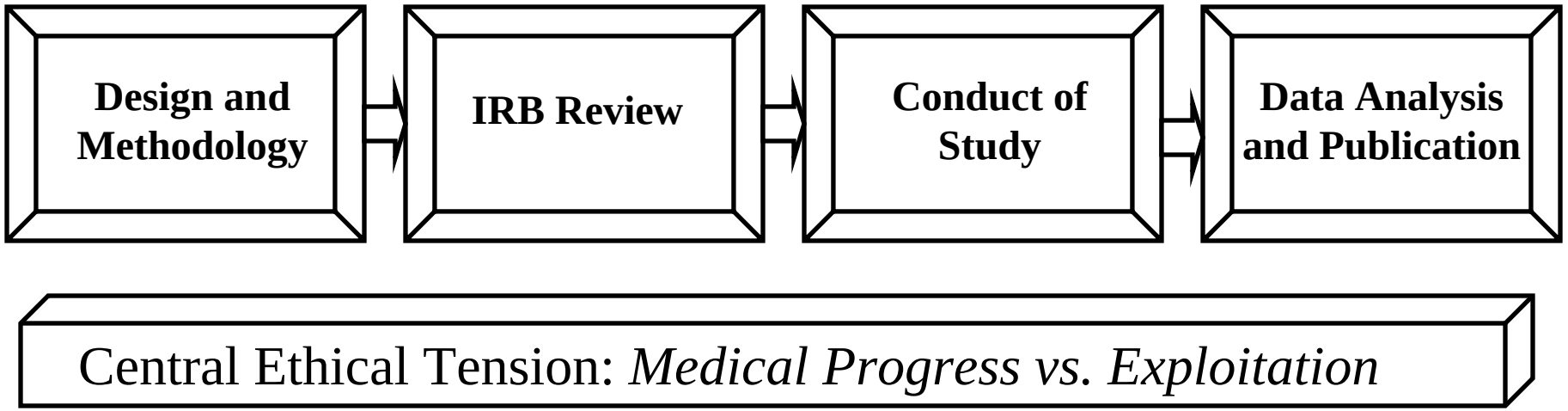
Case 3: Fragile X Syndrome

- **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



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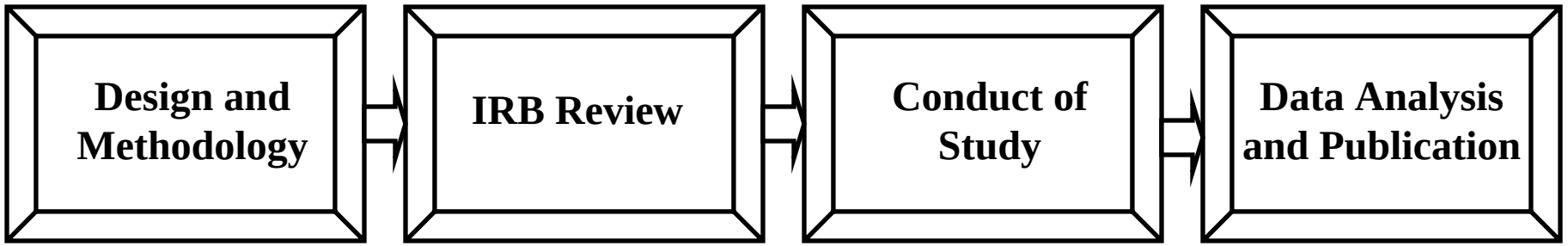

Central Ethical Tension: *Medical Progress vs. Exploitation*

Regulations, Laws, Policies and Public Opinion

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

Wendler and Prasad, Ann Intern Med, 2001

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.

Central Questions

1. **Who is vulnerable because of a mental disability?**

2. **What are the appropriate additional safeguards for vulnerable subjects?**

3. **How can these safeguards be optimally implemented ?**

Design and Methodology

- **Subject population**
  - **Subjects unable to provide informed consent**
  - **Early stage and at-risk subjects**
- **Nature of study (medication free, CNS active drug)**

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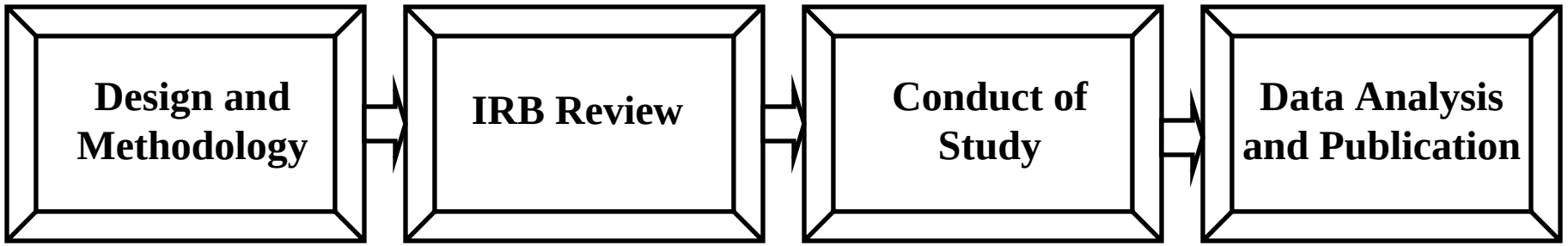
- **Nature of study (medication free, CNS active drug)**
- **Scientific review**
  - **value**
  - **“necessity” requirement for “non-beneficial” research with subjects unable to provide consent (Wendler et al, IRB 2003)**
  - **feasibility**

Research with Decisionally Impaired Subjects



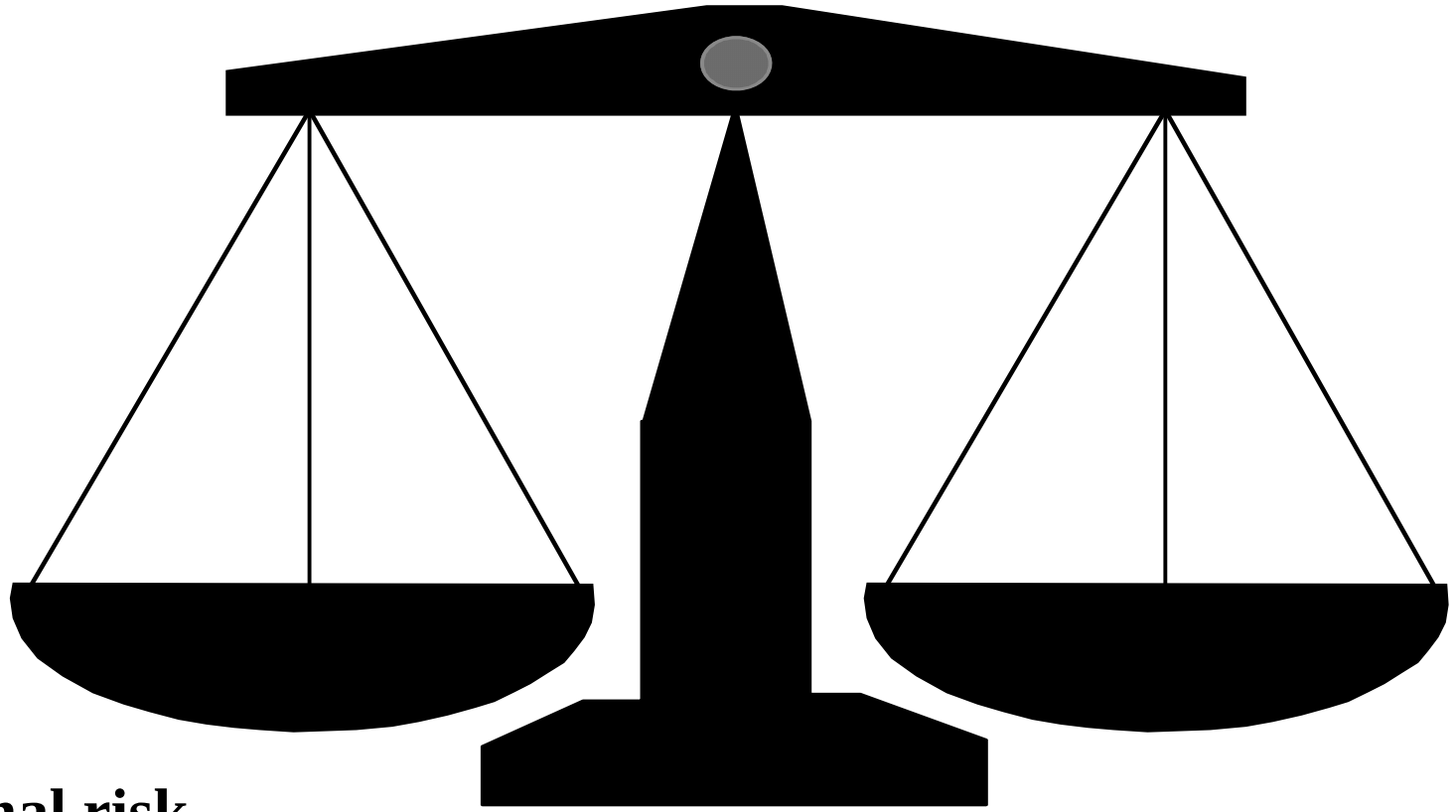
IRB Review

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

IRB Review

- **Can the scientific question be answered with capacitated subjects?**
- **What are the relevant risks and benefits?**

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

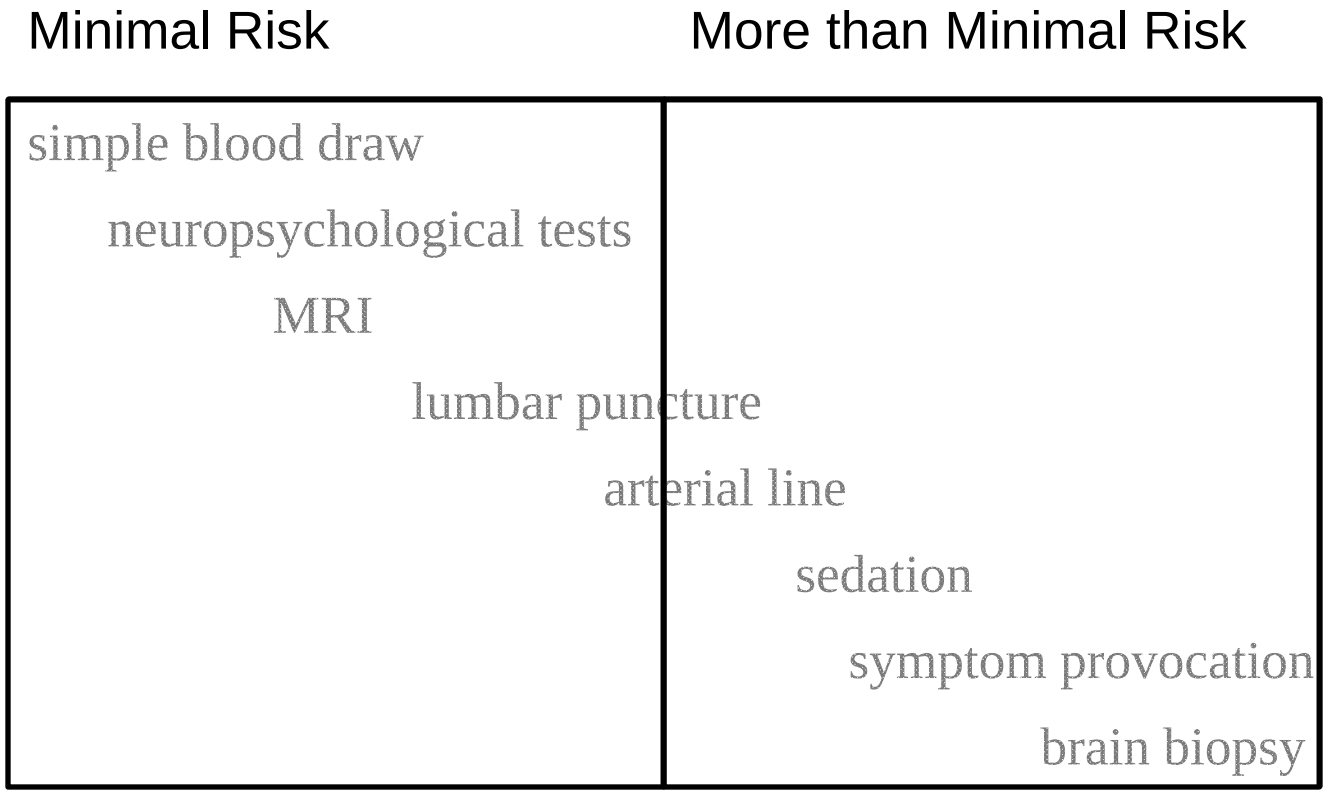
arterial line

sedation

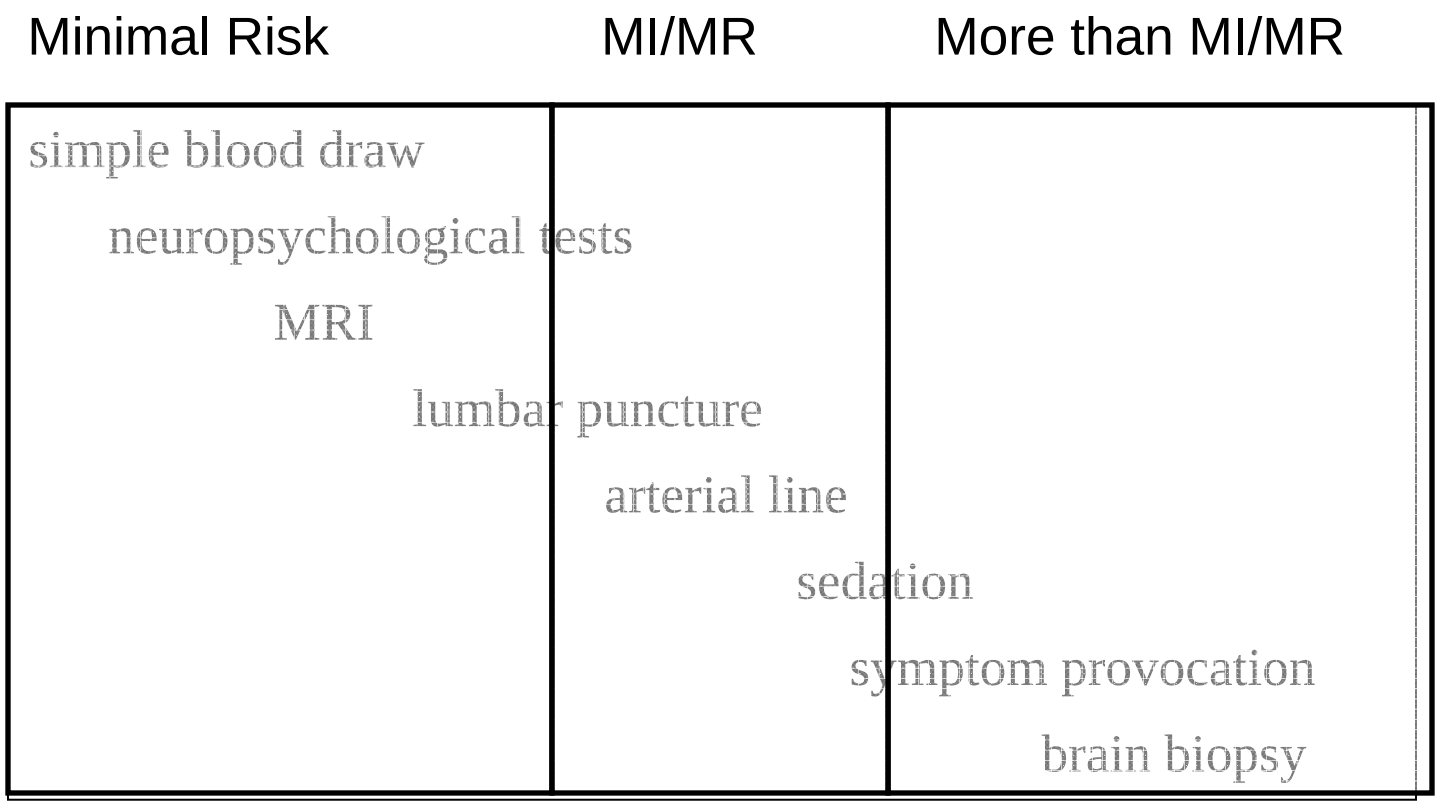
symptom provocation

brain biopsy

Variable Risk in Research that Provides No Direct Medical Benefit



Variable Risk in Research that Provides No Direct Medical Benefit



IRB Review

- **Can the scientific question be answered with capacitated subjects?**
- **What are the relevant risks and benefits?**
- **What is the nature of the anticipated decisionmaking impairment?**

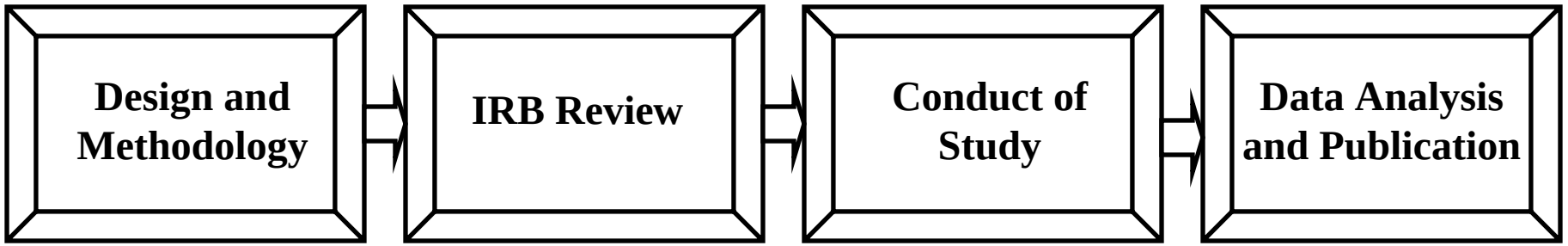
Will Subjects Be Able to Provide Informed Consent?

- **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**

IRB Review

- **Can the scientific question be answered with capacitated subjects?**
- **What are the relevant risks and benefits?**
- **What is the nature of the anticipated decisionmaking impairment?**
- **Are adequate safeguards in place?**

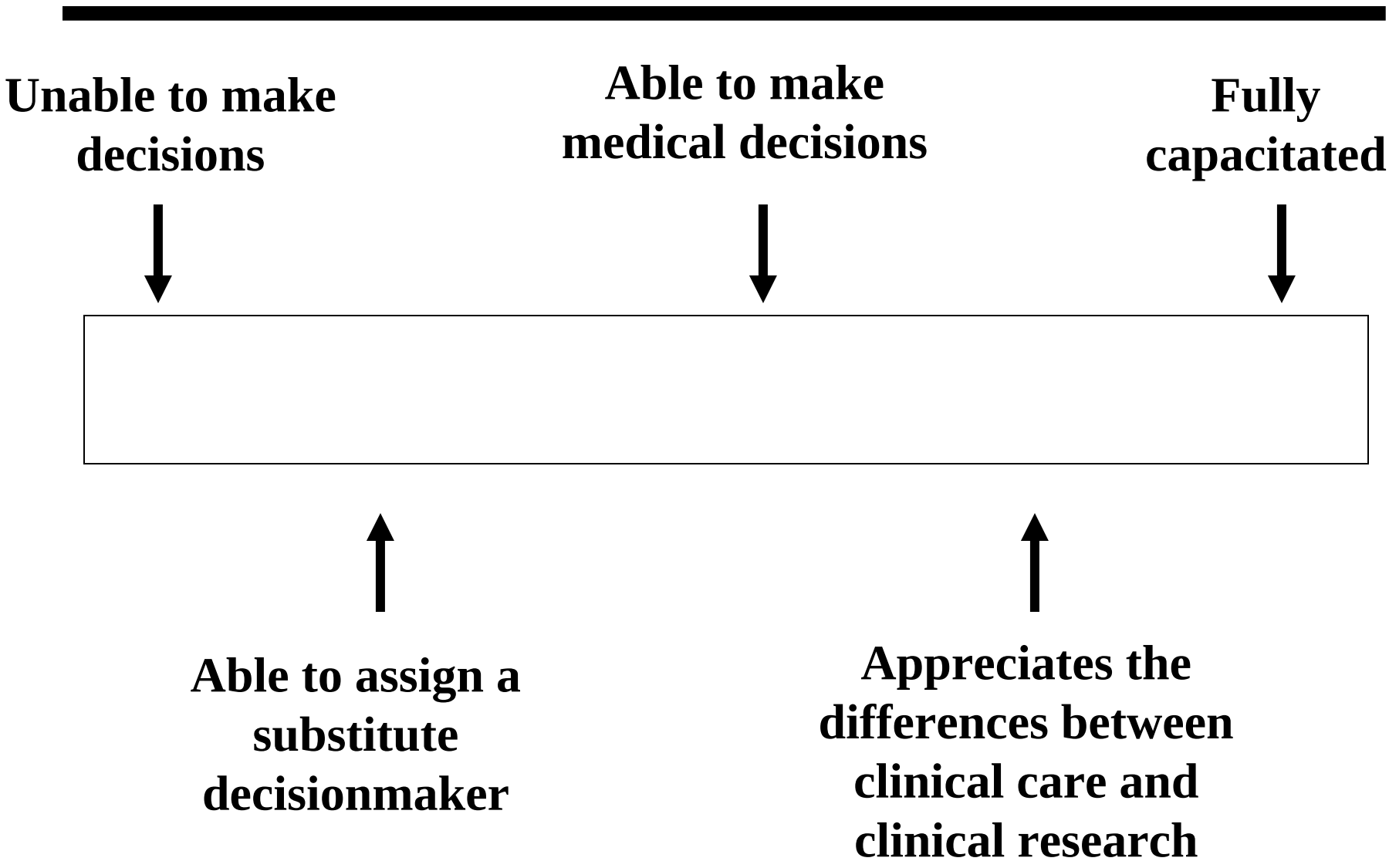
Research with Decisionally Impaired Subjects



Conduct of Study

- **Recruitment**
- **Capacity/consent assessment**

Decisionmaking Capacity



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

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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

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**

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
- Concern about an individual
  - Prior to or at the time of enrollment
  - During study participation

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**

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- **Presumption of capacity/competence**
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- **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

Individuals with Schizophrenia…

- **are at increased risk for impaired decisonmaking abilities**
  - **Carpenter 2000; Grisso and Appelbaum 1995; Moser 2002**
- **are likely to be able to provide IC for a clinical trial**
  - **Carpenter 2000; Moser 2002**
- **can clearly improve ability to provide IC with an educational intervention**
  - **Carpenter 2000, others**

Conduct of Study

- **Recruitment**
- **Capacity/consent assessment**
- **Research authorization**
  - **– informed consent**
  - **– surrogate authorization**

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.

Conduct of Study

- **Recruitment**
- **Capacity/consent assessment**
- **Research authorization**
  - **– informed consent**
  - **– surrogate authorization**
- **Post-decision questionnaire (PDQ) (Wendler, 2004)**
- **Monitoring of subject status and ongoing consent**
- **Study termination**

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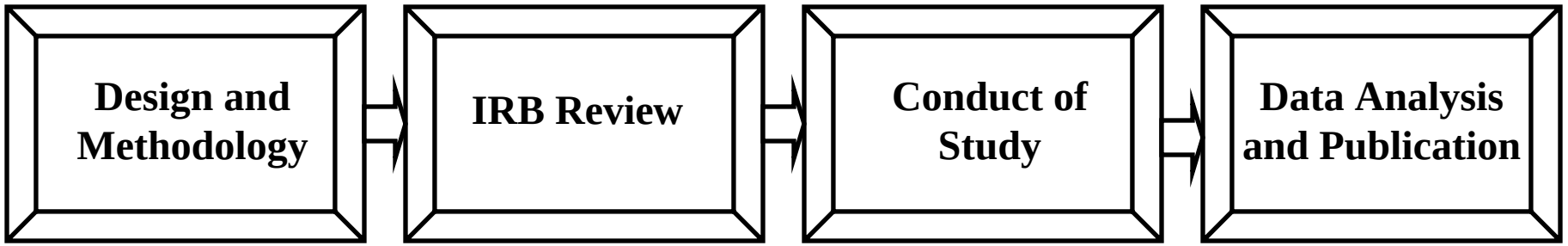

Data Analysis, Publication and Research Feedback to Participants

- Details of methods
- Disclosure of conflicts of interest
- Information-sharing with subjects
  - individual findings
  - aggregate data

Summary and 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**

Summary and 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**