Research Involving Persons at Risk for Impaired Decisionmaking

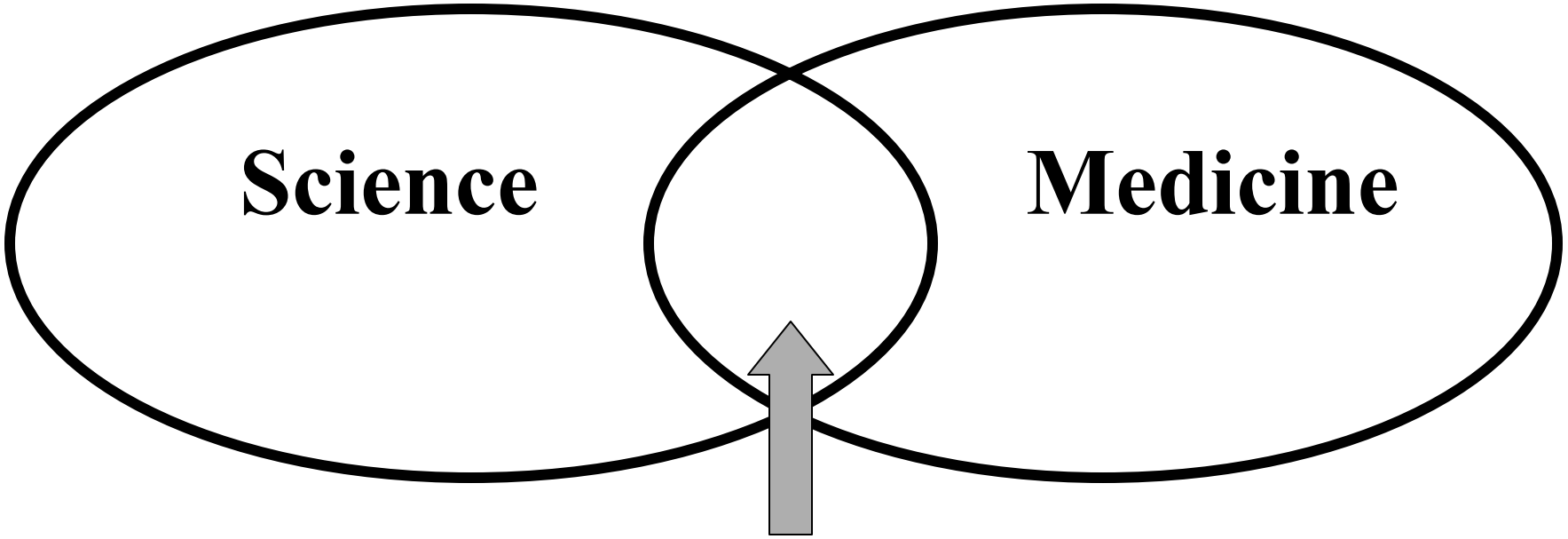
Donald L. Rosenstein, M.D.
National Institutes of Health

NIMH
National Institute of Mental Health

Overview

- **Dimensional issues and categorical decisions**
- **A recent case: the ARDS Network Trial**
- **An IRB approach to protocols involving subjects at risk for impaired decisionmaking capacity (DMC)**
- **Informed consent monitoring and Independent capacity assessment (ICA)**
- **Advance directives for research**

Competing or Integrated Agendas?



Clinical Research

Research differs fundamentally from medical care in its purpose, methods, and justification of risks

Spectrum of Clinical Research

Healthy Control

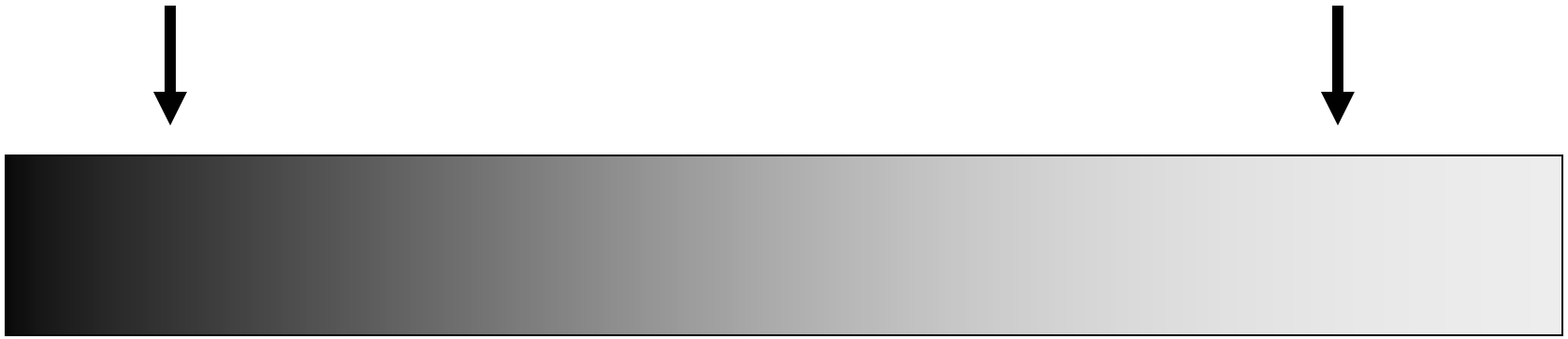
"Non-therapeutic" study

Payment

Severely Ill Patient

Clinical trial

No payment



The Acute Respiratory Distress Syndrome Network Trial

- **Multi-center (10 university centers), randomized trial of mechanical ventilation in patients with acute lung injury and ARDS**

NEJM 2000; 342:1301-8

NHLBI ARDS Network

- Cleveland Clinic Foundation
- Denver Health Medical Center
- Duke University
- Johns Hopkins University
- UCSF
- University of Colorado
- University of Maryland
- University of Utah
- University of Pennsylvania
- University of Washington
- Vanderbilt University
- Massachusetts General Hospital
- University of Michigan
- Jefferson University

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- **Comparison of lower tidal volumes with "traditional" tidal volumes**

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The Acute Respiratory Distress Syndrome Network Trial

- **Multi-center (10 university centers), randomized trial of mechanical ventilation in patients with acute lung injury and ARDS**
- **Comparison of lower tidal volumes with "traditional" tidal volumes**
- **Eligibility : intubated and mechanically ventilated**
  - **Manuscript stated "informed consent was obtained from the patients or surrogates at all but one hospital where this requirement was waived."**

NEJM 2000; 342:1301-8

The Acute Respiratory Distress Syndrome Network Trial

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- **Comparison of lower tidal volumes with "traditional" (higher) tidal volumes**
- **Eligibility : intubated and mechanically ventilated**
- **Death was primary outcome measure**

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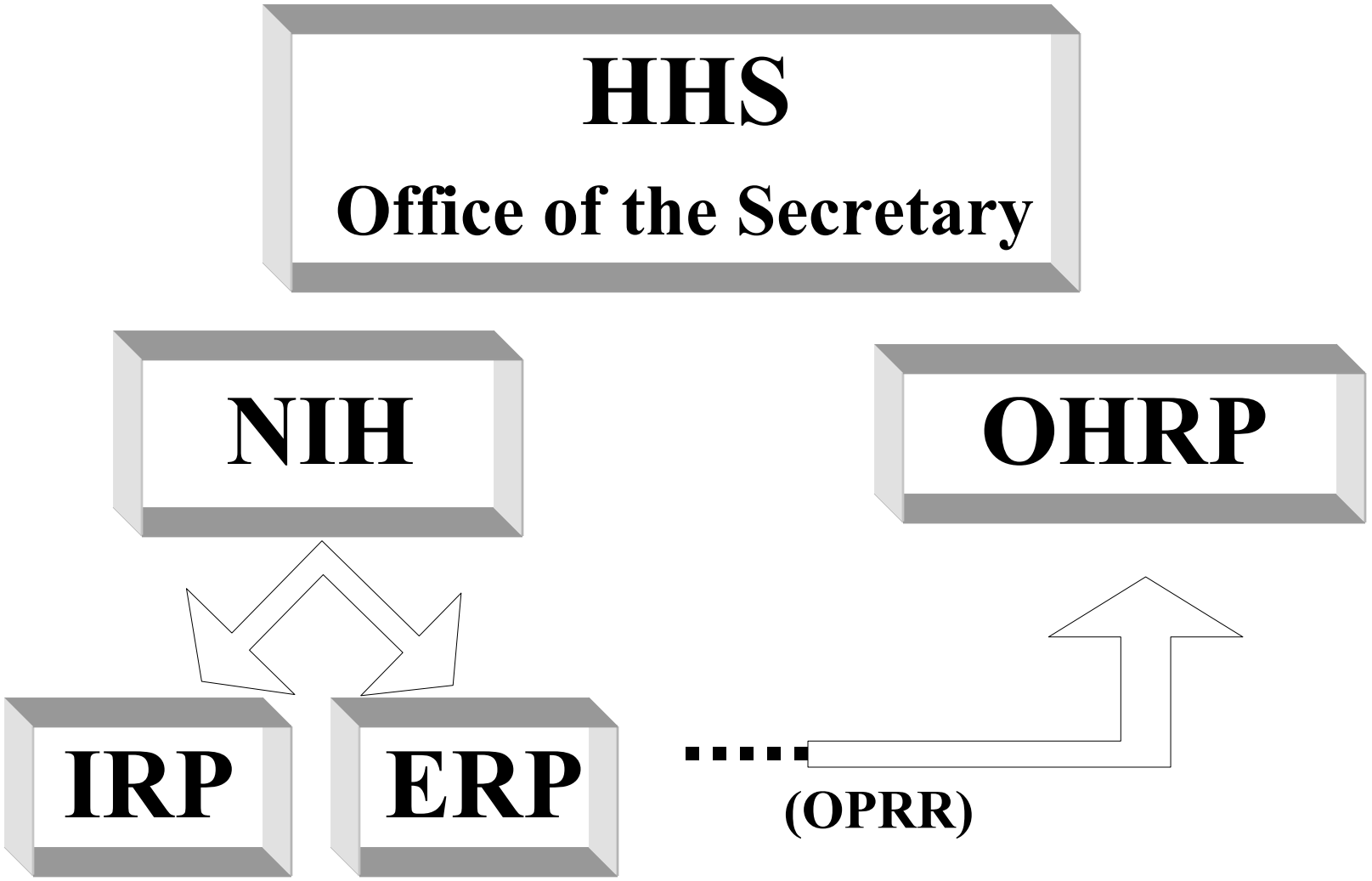
The Acute Respiratory Distress Syndrome Network Trial

- **Multicenter (10 university centers), randomized trial of mechanical ventilation in patients with acute lung injury and ARDS**
- **Comparison of lower tidal volumes with "traditional" (higher) tidal volumes**
- **Eligibility : intubated and mechanically ventilated**
- **Death was primary outcome measure**
- **Lower mortality observed in lower tidal volume group**

NEJM 2000; 342:1301-8

Department of Health and Human Services (HHS)



OHRP Findings and Concerns

- **Failure of IRB Review process**
  - **Waiver of consent**
  - **Inadequate informed consent documents**
- **Failure to obtain "legally effective informed consent of the subject or the subject's legally authorized representative"**
  - **Inconsistencies with regard to state law allowing surrogate permission**

OHRP Findings and Concerns

" OHRP is concerned that (a) both the subjects, because of their impaired mental state, and the subjects' family members, because of the psychological stress of having a critically ill family member being treated in an intensive care unit, appear likely to have been vulnerable to coercion or undue influence; and (b) the IRB failed to insure that there were additional safeguards included in the study to protect the rights and welfare of these vulnerable subjects."

OHRP Determination letter, 2/7/02

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 ?**

Defining the Scope of Impaired Decisionmaking Capacity

- **Imprecise language**
  - **competency, capacity, and consent**
  - **cognitive impairment does not necessarily mean decisional incapacity**
  - **mental disability, psychiatric illness/disorder, and vulnerability**

“capacity to give informed consent for <u>this</u> study”

Research With Impaired or Potentially Impaired Subjects

- Medication trial for Alzheimer's Disease
- ECT trial for delusional depression
- Placebo-controlled study in acute mania
- MRS study of a delirium model
- Establishing cell lines for genetics studies of mental retardation
- Tryptophan depletion in autism (adults)
- Medication-free studies of schizophrenia

The Most Contentious Case

Research

with subjects who

can not provide informed consent

that offers

no prospect of direct medical benefit

and involves

more than minimal risk

The Nuremberg Code

The voluntary consent of the human subject is absolutely essential.

1946

Central Tension

The need for improved diagnosis and treatment through research.

versus

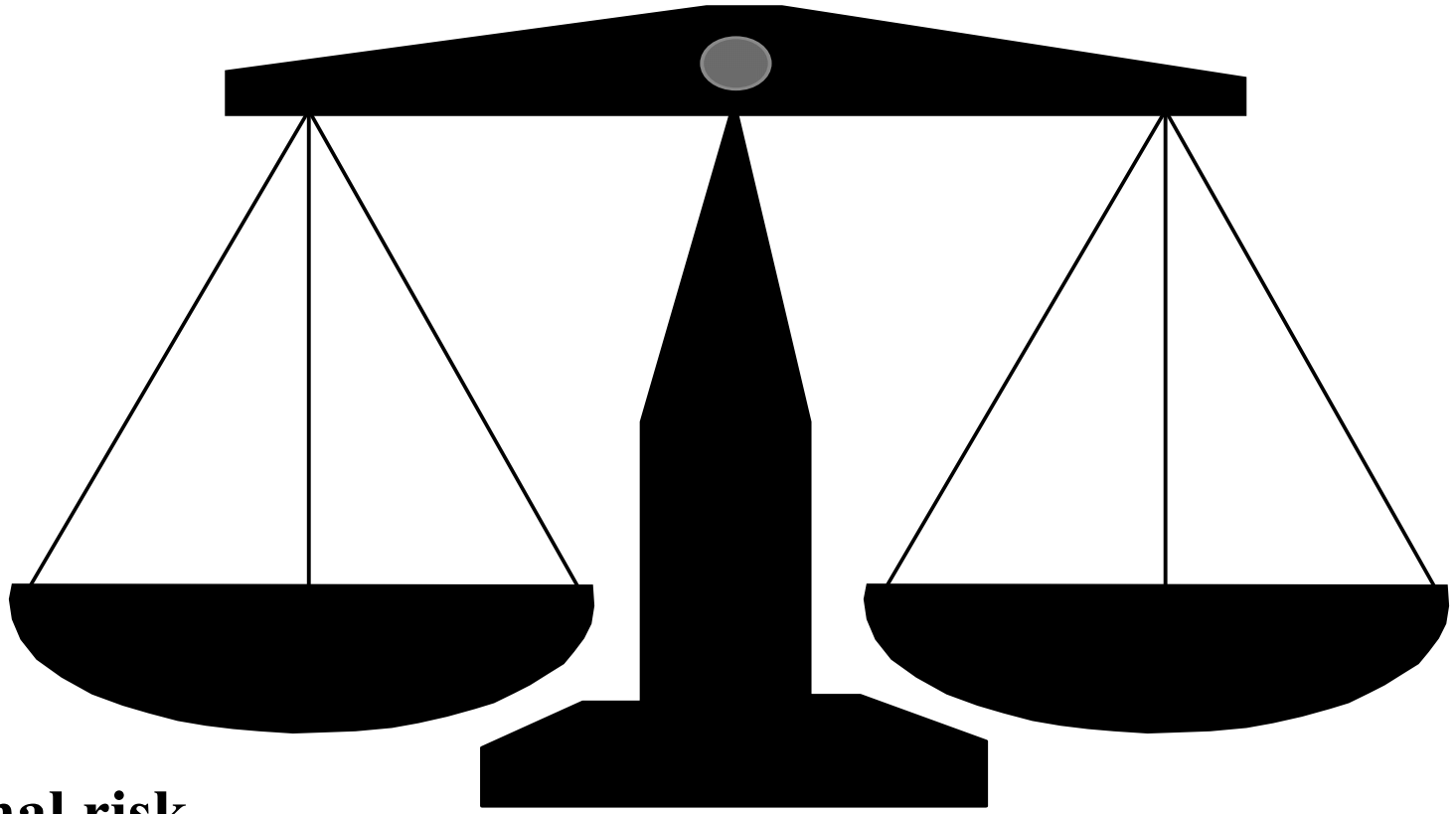
The danger of exploiting vulnerable individuals.

Ethically problematic $\neq$ **unethical**

Questions for the IRB

- **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)

Questions for the IRB

- **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?**

Factors Influencing Decisionmaking Capacity

- Memory, attention, concentration
- Conceptual organization
- Psychosis and hallucinations
- "Executive" function
- Risk assessment
- Mood
- Intuition
- Insight
- Behavior
- Duty and altruism
- "Relatedness"

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**

Questions for the IRB

- **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?**

Additional Protections

- **Clinical monitoring of ongoing research**
- **Data and safety monitoring boards**
- **Ethics consultation**

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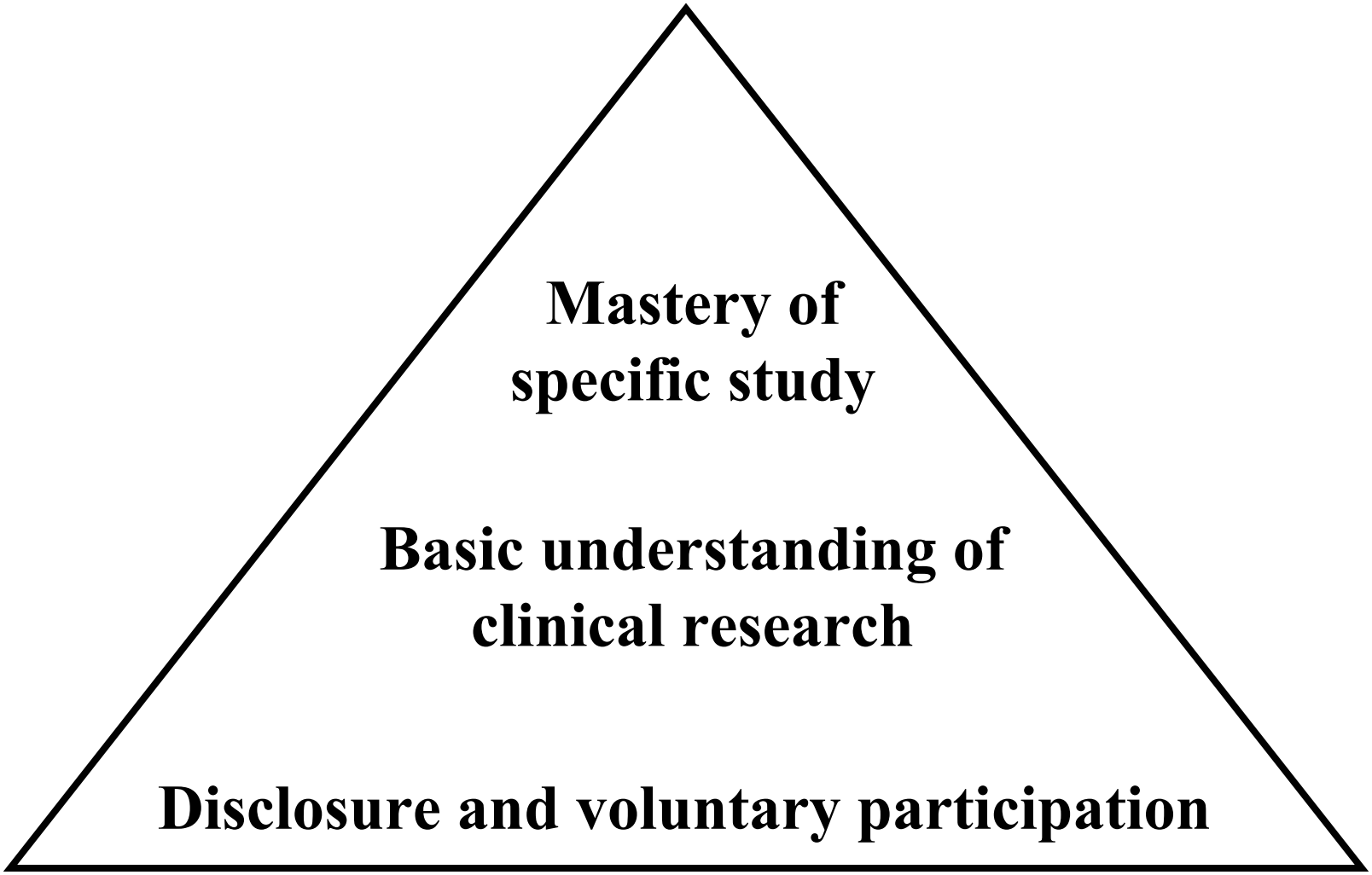
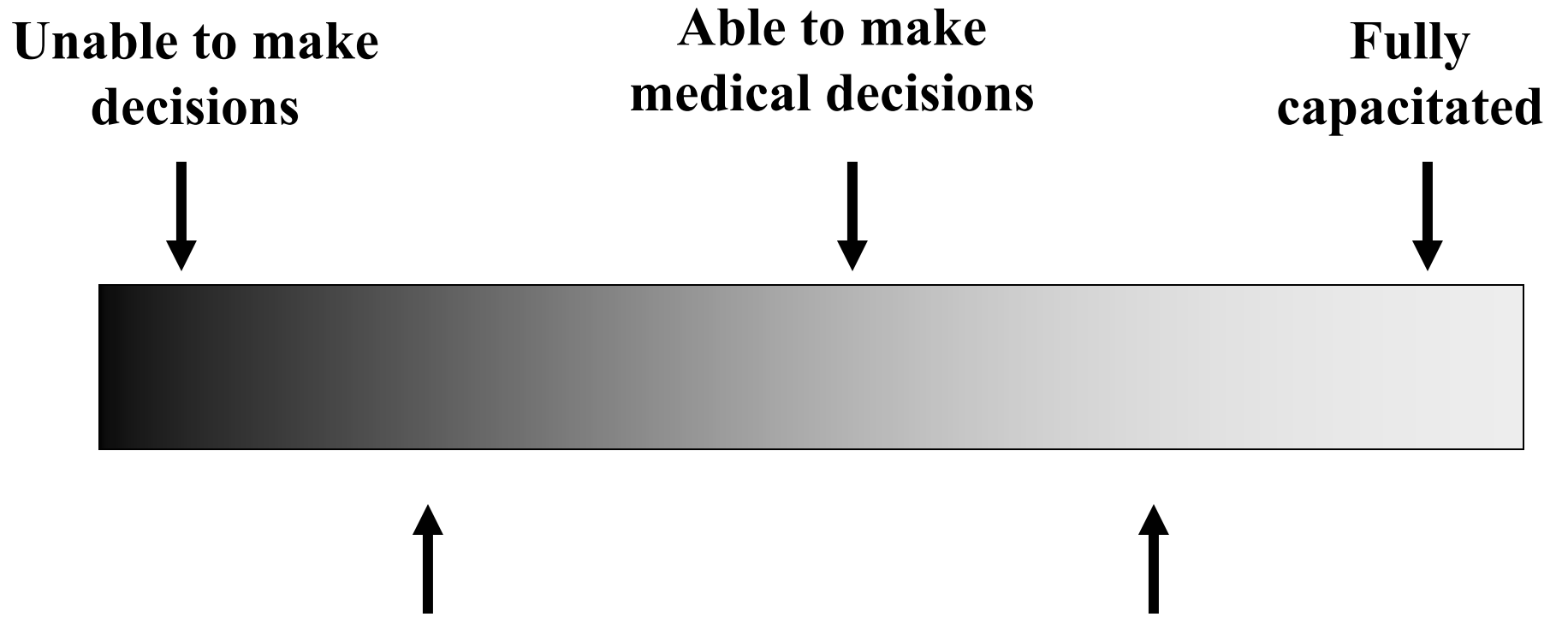
Consent Monitoring and Independent Capacity Assessment



Decisionmaking Capacity



National Bioethics Advisory Commission (NBAC) Report

"Research Involving Subjects at Risk for Impaired Decisionmaking Capacity" 1998

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"Research Involving Subjects at Risk for Impaired Decisionmaking Capacity" 1998

- **Recommendation #8:**
  "For research protocols that present greater than minimal risk, an IRB should require that an independent, qualified professional assess the potential subject's capacity to consent…"

Triggers for Capacity 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 Capacity 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**

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

Assessment of Decisionmaking Capacity

Business as usual

NIMH IRP CORE

NBAC: mandated, formal ICA

Clinical judgment of investigator

Independent, semi-structured interview based on McCAT-CR

McCAT-CR for each protocol

Additional Protections

- **Clinical monitoring of ongoing research**
- **Data and safety monitoring boards**
- **Ethics consultation**
- **Informed consent monitoring**
- **Independent capacity assessment**
- **Advance directives and legally authorized representatives (e.g., guardianship, DPA)**

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.

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