Enrolling Decisionally Impaired Adults in Research

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Case 1

36 y/o single man with end stage renal disease (ESRD) and moderate depression.

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Case 1

Adults are presumed competent

Substitute Decision-maker?

36 y/o single man with end stage renal disease (ESRD) and moderate depression.

Medical and neuropsychiatric effects

Impact on DMC, informed consent

Meaning to pt?

When told he requires dialysis, the patient said he wanted to "let nature take its course."

Suicidality; legal issues

Psychiatry and ethics consultations called simultaneously to evaluate his decision-making capacity.

The consult question:

Is he able to refuse life-sustaining treatment?

Factors Influencing Decisionmaking Capacity

- **Memory, attention, concentration**
- **Conceptual organization**
- **Psychosis and hallucinations**
- **“Executive” function**
- **Risk assessment**
- **Mood**
- **Intuition**
- **Insight**
- **Behavior**
- **Sense of duty**
- **“Relatedness”**

MacArthur Competence Assessment Tool (MacCAT)

UNDERSTANDING

purpose of tests and procedures

main risks, discomforts and benefits

APPRECIATION

how is this information relevant to your particular case?

REASONING

analysis of data in service of thinking through the decision

if you decline, what will you do instead? Why?

CHOICE


UNC

Case 2

68 y/o woman with advanced breast cancer hospitalized following a seizure. MRI revealed brain metastases.

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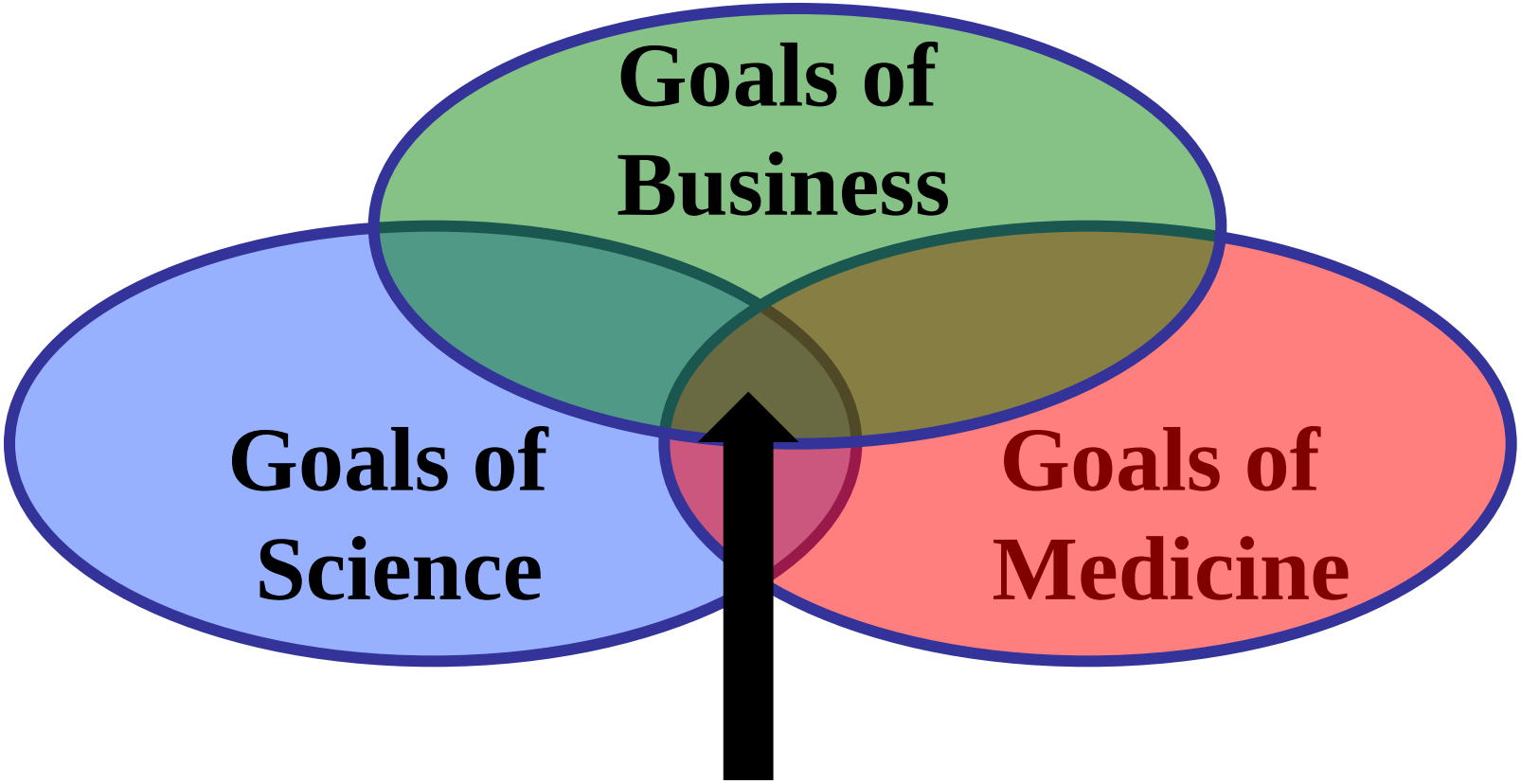
She was eligible for a phase 1 clinical trial of a new chemotherapeutic agent but her oncologist (and study PI) had questions about the potential subject's ability to provide informed consent.

Competing or Integrated Agendas?



Clinical Research

Variations on a Theme: *Research Differs from Care and Researchers Differ from Clinicians*

- Nuremberg Code (1948)
- Declaration of Helsinki (1964)
- The Belmont Report (1979)
- Reports of National Commissions and Advisory Groups
- The Code of Federal Regulations (45 CFR 46) “The Common Rule” (1981)
- Media and “watchdog” groups

- Beecher
- Katz
- Levine
- Freedman
- Appelbaum
- Kodish
- Grady
- Emanuel
- Miller
- Joffe

Differentiating Medical Care from Clinical Research

	Medical Care	**Clinical Research**
Primary purpose	To provide personalized care: here and now	To answer scientific questions: benefit to future patients

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Justification of risks	Compensatory direct medical benefit to patient	Value of knowledge to be gained by trial; societal benefit

MacArthur Competence Assessment Tool (MacCAT-CR)

UNDERSTANDING

purpose of study; research-specific tests and procedures

major research-related risks and possible benefits

APPRECIATION

is the main purpose to benefit you?

differences between this study and regular medical care

REASONING

if you decline, what will you do instead?

whose decision, can you stop participating?

CHOICE

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

Concerns about Decisionmaking Capacity

- **Individual subjects**
  - **Prior to or at the time of enrollment**
  - **During study participation**
- **A class of prospective subjects**
  - **Protocol designed to enroll “at-risk” subjects**
  - **Protocol that may precipitate loss of decisional capacity**

Case 3: Fragile X Syndrome Protocol

- 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 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**

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 and Protections

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

Variable Risk in Research that Provides No Direct Medical Benefit

Low Risk **High Risk**

simple blood draw

neuropsychological tests

MRI

lumbar puncture

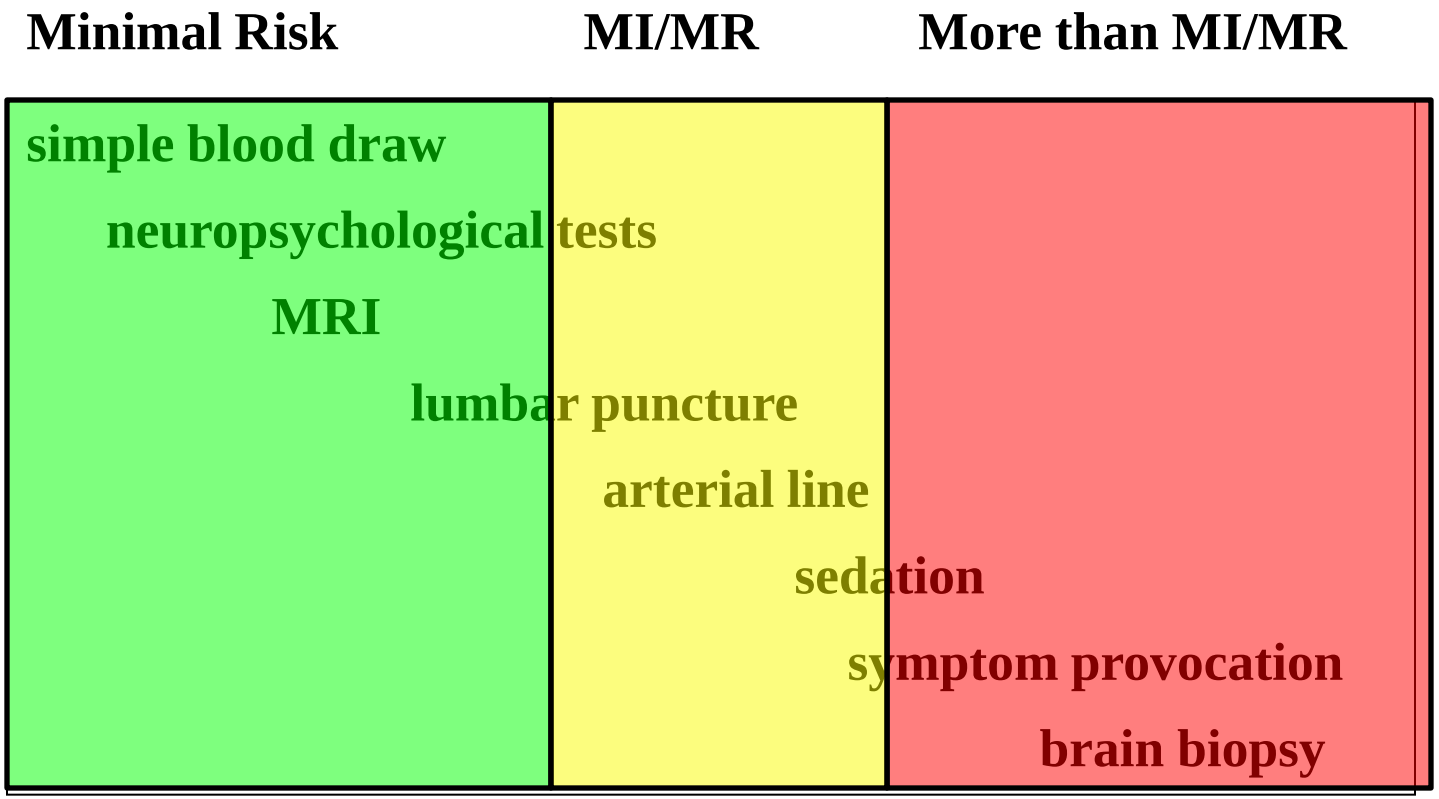
arterial line

sedation

symptom provocation

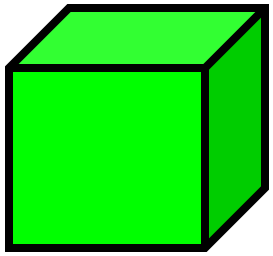
brain biopsy

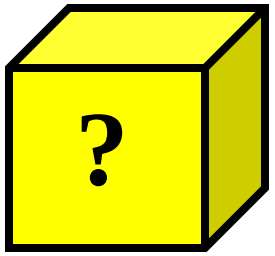
Variable Risk in Research that Provides No Direct Medical Benefit



Categories of Risk and Benefit

Direct Benefit



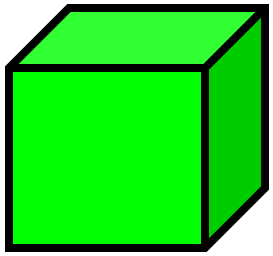


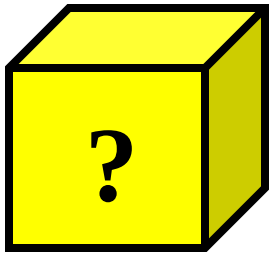
Minimal Risk

More than Minimal Risk

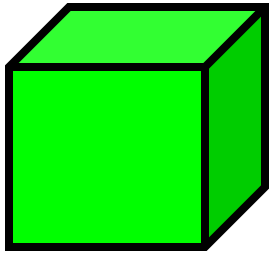
Categories of Risk and Benefit

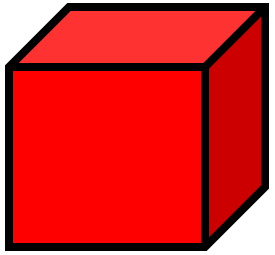
Direct Benefit





No Direct Benefit





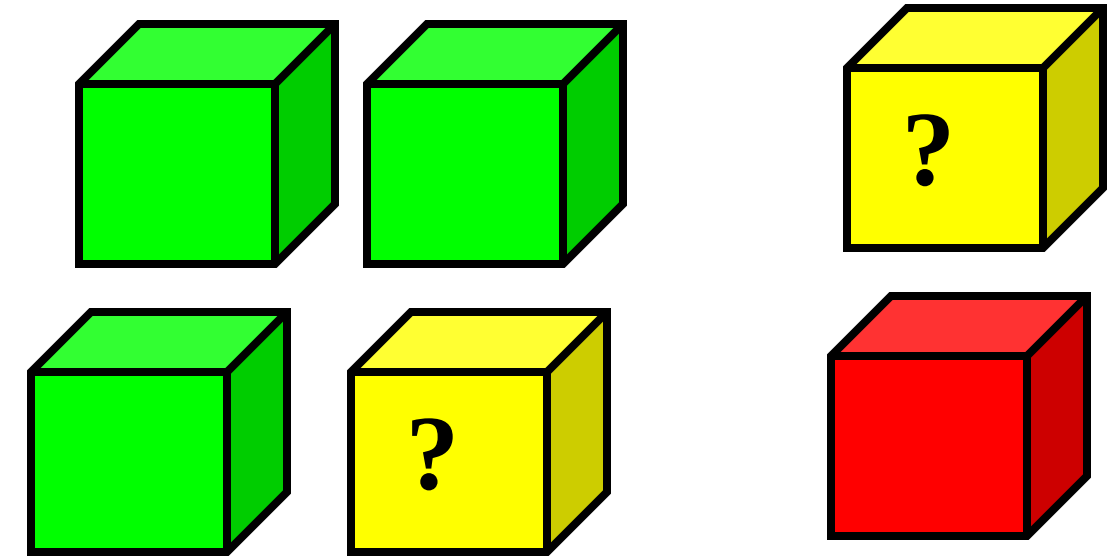
Minimal Risk

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

IRB Review and Protections

- Can the scientific question be answered with capacitated subjects?
  - Exceptions
    - Prospect of benefit
    - Prior commitment from subject
    - Minimal risk?
- **Enhanced informed consent processes**
- **Independent capacity assessment and protocol monitors**
- **DPA and research advanced directive**

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.