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.

When told he requires dialysis, the patient said he wanted to “let nature take its course.”
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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
Case 2

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

Corticosteroids started for brain edema. Patient became irritable, distractible, and relatively uninterested in details of her medical care.
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Corticosteroids started for brain edema. Patient became irritable, distractible, and relatively uninterested in details of her medical care.

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?

Goals of Business

Goals of Science

Goals of Medicine

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
- Media and “watchdog” groups

- Beecher
- Katz
- Levine
- Freedman
- Appelbaum
- Kodish
- Grady
- Emanuel
- Miller
- Joffe
## Differentiating Medical Care from Clinical Research

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<td><strong>Justification of risks</strong></td>
<td>Compensatory direct medical benefit to patient</td>
<td>Value of knowledge to be gained by trial; societal benefit</td>
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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
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

<table>
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Variable Risk in Research that Provides No Direct Medical Benefit

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Categories of Risk and Benefit

Direct Benefit

Minimal Risk

More than Minimal Risk
Categories of Risk and Benefit

- Direct Benefit
  - Minimal Risk
- No Direct Benefit
  - More than Minimal Risk
Categories of Risk and Benefit: Research with Children

Direct Benefit
- Minimal risk
- Minor increment over minimal risk

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 capacititated 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.