Research Involving Adults With Impaired Decision-Making Capacity

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The views expressed in this talk are my own. They do not represent the position or policy of the NIH, DHHS, or US government.

I have no conflicts of interest to disclose.
Henry Beecher’s 1966 NEJM article describing 22 (notorious) examples of ethical violations...

- 9 of 22 examples involved at least some people who probably had difficulty providing informed consent:
  
  - Ex 4: “mental defectives and delinquent juveniles” given hepatotoxic drug, biopsies taken, re-challenged with same drug (in one case re-re-challenged!)
  
  - Ex 8: 44 pts “second to tenth decade” in age, extreme hypotension induced by drug or maneuvers, with femoral or internal jugular cannulation; confusion induced on purpose.
  
  - Ex 7 and 9: experiments on unconscious patients
  
  - Ex 14, 15: study of “impending coma” by giving nitrogenous substances in patients with “chronic alcoholism and advanced cirrhosis”; cannulation of hepatic and renal veins, worsening of confusion, etc.
  
  - Several examples involving children (and infants)
Commissions, work groups, advisory committees, revision efforts over the years...

- **President’s Commission, 1982**: Making Health Care Decisions: The Ethical And Legal Implications Of Informed Consent In The Patient-practitioner Relationship.
- **Maryland Attorney General's Research Working Group, 1998**.
- **New York Department of Health Advisory Work Group** on Human Subject Research Involving the Protected Classes, 1999.
- **Secretary's Advisory Committee on Human Research Protections (#2!), 2009**: Recommendations from the Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research
- **NPRM** and final revision of **Common Rule 2017**
Outline

• Decision-making capacity and impairment

• Are studies with people lacking (or at risk of lacking) decision-making capacity (DMC) permissible?

• If yes, then who should give consent? How should they decide?

• Should there be limits to risks in such research studies? Other protections?

• Brief overview of NIH policy and procedures, as a current example.
DECISION-MAKING CAPACITY (DMC) AND IMPAIRMENT
Decision-Making Capacity (DMC)

- Part of the informed consent doctrine
  - Decision-Making Competence/Capacity
  - Adequate disclosure
  - Voluntary decision
Functional Model of DMC

• Presumption of capacity

• Cannot be justified by “senile” “unsound mind” etc.

• Actual abilities relevant to the decision

• Threshold is affected by context, especially risk-benefit.

• Task specific
Definitions

- *Adjudicated capacity/competence*—what a judge determines

- *Capacity/Competence*—a clinician’s approximation of what the courts might say; usually this carries the day.

- Abilities relevant to capacity (e.g., Grisso and Appelbaum 1988):
  - Understanding
  - Appreciating
  - Reasoning
  - Communicating a stable choice

- The *degree of abilities* can usually be measured reliably and validly (e.g., by instruments such as MacCAT-CR). But determination of capacity/competence using that data is a judgment call.
Some disorders elevate risk for incapacity

- Cognitive disorders
  - Neurodegenerative—Alzheimer’s Disease, Fronto-Temporal Dementia, etc
  - Neurodevelopmental disorders
  - Injury—strokes, TBI, post-infection, etc
  - Acute confusional states (delirium)
- Psychotic disorders (including mania)
- Mood disorders when severe
- Eating disorders when severe
- Other? Extreme personality disorders? Severe addictions?

- NB: risk factor ≠ incapacity!
Prevalence of decisional incapacity: Very rough estimates (Kim, 2010)

- General hospital inpatients: 30-40%
- Nursing homes: 44-69%
- Psychiatric hospital/units: 30-86%
- Chronic psychoses: ~25-50%
- Mild-moderate depression: Relatively little impact
- Depression, inpatients: 5-24%
- Severely depressed (inc. those with psychosis and cognitive impairment): prob >25%
Impaired decisional capacity is common in Alzheimer’s disease research

- 40% of pts with even Mild Cognitive Impairment (MMSE 27.8±1.8) lack capacity to consent to RCT (Jefferson, JAGS 2008)

- 62-76% of AD patients (MMSE 22-23) in a typical RCT probably lack capacity (Kim, AJP 2001; Warner, JME 2008)

- On the other hand...
CATIE Schizophrenia Study: Understanding Score Distribution at N=900 (S. Stroup)
CATIE Schizophrenia Study:
Appreciation Score Distribution
Are studies with people lacking (or at risk of lacking) DMC permissible?
Federal regulations clearly allow it in theory...

– Legally authorized representatives (46.102c)
  • But defers to local and state laws to define LAR
  • Therefore, OHRP guidance turns on state and local laws
  • Revised Common Rule: when no applicable law, institutional policy on surrogate decision-making

– Few jurisdictions have clear policies.
  (e.g., California, New Jersey, Virginia have ‘modern’ laws; some states have other regulations or guidance, e.g., Maryland AG; but most states not clear)
One area of wide agreement: probably the most important ‘advance’ ethically

• Involving those lacking DMC (or at risk) must be specifically justified:

  – Research cannot be done without them.
  
  – Research focused on disorder causing incapacity.
  
  – Rarely, OK for other reasons (to avoid discrimination)
HHS Secretary’s Advisory Committee Human Research Protections (SACHRP), 2009

• “At best, the field is characterized by a patchwork of IRB policies and research practices.”

• SACHRP 2009 report
  – http://www.hhs.gov/ohrp/sachrp 20090715letterattach.html
WHO SHOULD GIVE PERMISSION/CONSENT, I.E., SERVE AS SURROGATE DECISION-MAKER?

45 CFR 46.102(c): Legally authorized representative [LAR] means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research.
LAR types: pros and cons

• Legal guardians—appointed by a judge
  – Legal clarity but no necessary link to subject’s values

• Health care proxies (DPOA)
  – Subject’s own choice but must extrapolate to research decision

• De facto family (often legally defined health care surrogate)
  – Reflects reality of most situations; but not as clear as DPOA in terms of subject’s preference of surrogate

• Research proxy
  – Research advance directives—nice idea… but unrealistic
  – Concurrent proxy directives—feasible and important
HOW THE ELDERLY LOSE THEIR RIGHTS

Guardians can sell the assets and control the lives of senior citizens without their consent—and reap a profit from it.

By Rachel Aviv

From the New Yorker, Oct 9, 2017
SACHRP, 2009: proposed hierarchy

1. As per state or local law, if there is one.
2. DPOA for healthcare
3. Legal guardian
4. Spouse or equivalent
5. Adult child
6. Parent
7. Brother or sister
8. Adult in a special care and concern relationship
Survey of U.S. public (n=1463): Family member as LAR for dementia research? (Kim et al 2009, *Neurology*)

<table>
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<tr>
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<td>72%</td>
<td>83%</td>
<td>71%</td>
<td>68%</td>
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Public attitudes toward family surrogate consent for dementia research: after one day deliberation exercise (n=173) (Kim et al 2011, *Neurology*)

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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>% probably allow</td>
<td>51</td>
<td>19</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>% definitely allow</td>
<td>33</td>
<td>76</td>
<td>38</td>
<td>76</td>
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Comments during deliberation....


- Participant A: “But if the answer is ‘no,’ that surrogates can’t give consent, then there is no hope for ever getting anywhere. So the answer has to be in my mind, ‘yes.’ “

- Participant B: “By voting ‘nay’ against surrogate empowerment, what you’re essentially doing is voting ‘no’ on every other family. You’re putting yourself in a position of impacting every family who has an Alzheimer’s patient.”
“So it seems as though we almost have no choice but to have some form of surrogate consent, and our challenge is . . . How do we make it work? How do we build protections for, you know, the Alzheimer’s victim . . . the patients . . . “
How much freedom or leeway would you give [your family member] to go against your preference and instead [do opposite of your current preference]?

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<th>DD participants after deliberation (N=168)</th>
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<tr>
<td>LP</td>
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<tr>
<td>%</td>
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<tr>
<td>No leeway</td>
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<tr>
<td>Some leeway</td>
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**DD participants after deliberation (N=168)**

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<tr>
<td>No leeway</td>
<td>24</td>
<td>24</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Some leeway</td>
<td>59</td>
<td>57</td>
<td>61</td>
<td>52</td>
</tr>
<tr>
<td>Complete leeway</td>
<td>17</td>
<td>20</td>
<td>15</td>
<td>20</td>
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RISK-BENEFIT LIMITS?
Most common approach among IRBs (probably)

• Prospect of direct benefit

• No prospect of direct benefit
  – Minimal risk
  – Minor increase over minimal risk
  – Greater than minor increase—IRB cannot approve (in pediatric research, requires special HHS review)
SACHRP, 2009

In re research w/o prospect of direct benefit

• ‘...vitally important but ethically acceptable research would be prohibited by adopting “minor increase over minimal risk” as an upper limit of risk.’

• “In exceptional circumstances,” research with moderate risk of harm or discomfort OK if:

  – Safeguards appropriate to this degree of risk in place

  – Research must be of vital importance in the understanding, prevention or alleviation of a serious problem affecting the health or welfare of the study population.
OTHER PROTECTIONS?
IMPORTANCE OF CONTEXT
Mr. A with Alzheimer’s disease

- Not able to give independent consent

- Retired professor—financially stable, psychosocial resources to seek out clinical trial, spouse and adult children supportive and involved.

- Enrolls in an RCT of a novel intervention
  - Only minor adverse effects seen (1000 people with more advanced AD have received the intervention so far)
  - Goal of slowing down disease

- Strongly desires to be in the study
  - Altruistic motive
  - A desire for benefit—felt to be worthwhile gamble
In contrast.... Mr. S with schizophrenia

- Meets threshold for capacity; so can (in theory) consent for self.

- Single, estranged from family, unemployed, socially isolated, racial/ethnic minority.

- RCT of a compound that is already marketed
  - Not a new paradigm
  - In theory, different formulation to optimize effect
  - Marketing considerations are probably part of reason for RCT

- No strong incentive to enroll
Other protections and considerations commonly mentioned in various documents

- Well-defined capacity assessment procedures
  - Including: capacity to appoint a proxy
- Respect preserved abilities
  - Assent, Dissent, and collaborative decisions
- Subject advocates
- Study partners
- Consent and study monitors
- Assessment of appropriateness of surrogates
- Other?

NB: should be tailored to context—as contexts do vary a great deal...
NIH HRPP Policy 403: Research Involving Adults Who Lack DMC to Consent to Research Participation

• Must have prior IRB approval to enroll decisionally impaired persons.
  – Their involvement must be justified
  – Plan for assessing capacity (does not specify who)
  – Plan for identifying LAR eligibility and obtaining IC
  – Risk level and prospect for benefit specified
  – [Assent and dissent—not addressed but should assume to apply]
  – Any additional safeguards (e.g., monitoring)
  – If subjects have capacity but expected to lose it, describe how this will be handled.
Policy varies by risk-benefit category

A. Minimal risk (MR)

B. Prospect of direct benefit to subjects

C. No prospect of DB; no greater than minor increase over MR ("and does not adversely affect rights, safety, welfare...")

D. Other
Policy 403

• Study categories
  – A, B, C: Minimal or minor increase over minor risk; or, prospect of benefit
  – D: Other (requires special NIH IO approval)

• LAR Hierarchy for A, B, C
  – Guardian who is authorized for research consent
  – DPA for health care
  – Next of kin list in order: Spouse/DP, adult child, parent, adult sibling, other relative.

• LAR for D:
  – guardian or DPA only
Greater than minor increase over minimal risk, no prospect of benefit

• Special review by panel convened by NIH Institutional Official.
• The panel must find that the knowledge to be obtained is of:
  – vital importance; cannot reasonably be obtained with those who can consent; cannot be obtained with less risk
  – Risks not excessive
  – Address whether additional conditions/protections needed
What the new policy would look like, using old policy categories: i.e., old policy was very complicated!

<table>
<thead>
<tr>
<th>Risk-Benefit</th>
<th>LAR type</th>
<th>DPA or Guardian</th>
<th>Concurrent DPA (only if person currently capable of appointing DPA)</th>
<th>De facto (family) surrogate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR or Prospect of direct benefit</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (per hierarchy)</td>
<td></td>
</tr>
<tr>
<td>No prospect DB and minor increase in risk (for higher risk → special panel)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
Sometimes regulations do get simpler!

<table>
<thead>
<tr>
<th>Type of LAR</th>
<th>Type of study</th>
</tr>
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<tbody>
<tr>
<td>Any LAR on list (Guardian, DPA, Family list)</td>
<td>Any type that does not require special NIH panel</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
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