Research Involving Adults With Impaired Decision-Making Capacity

Scott Kim, MD, PhD

Department of Bioethics
Clinical Center | NIH

scottkimbioethics.org

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-rechallenged!)
  - 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…

- **National Commission**, 1978: *Research Involving Those Institutionalized As Mentally Infirm.*
- **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.
- **National Bioethics Advisory Commission**, 1998: *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity.* Washington, D.C.
- **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*
- **Presidential Commission** for the Study of Bioethical Issues, **2015**.
- **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%

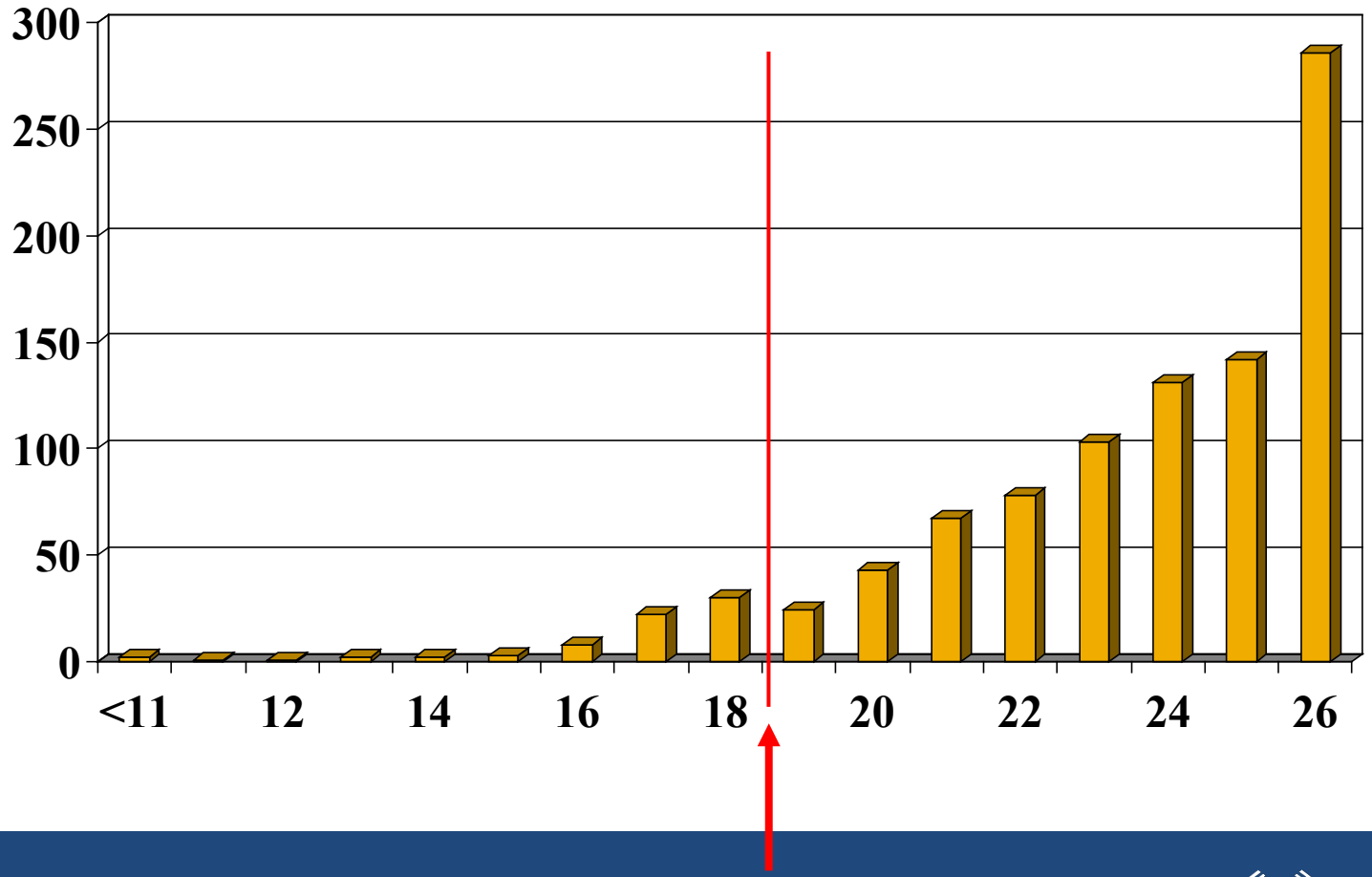
Impaired decisional capacity is common in Alzheimer's disease research

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

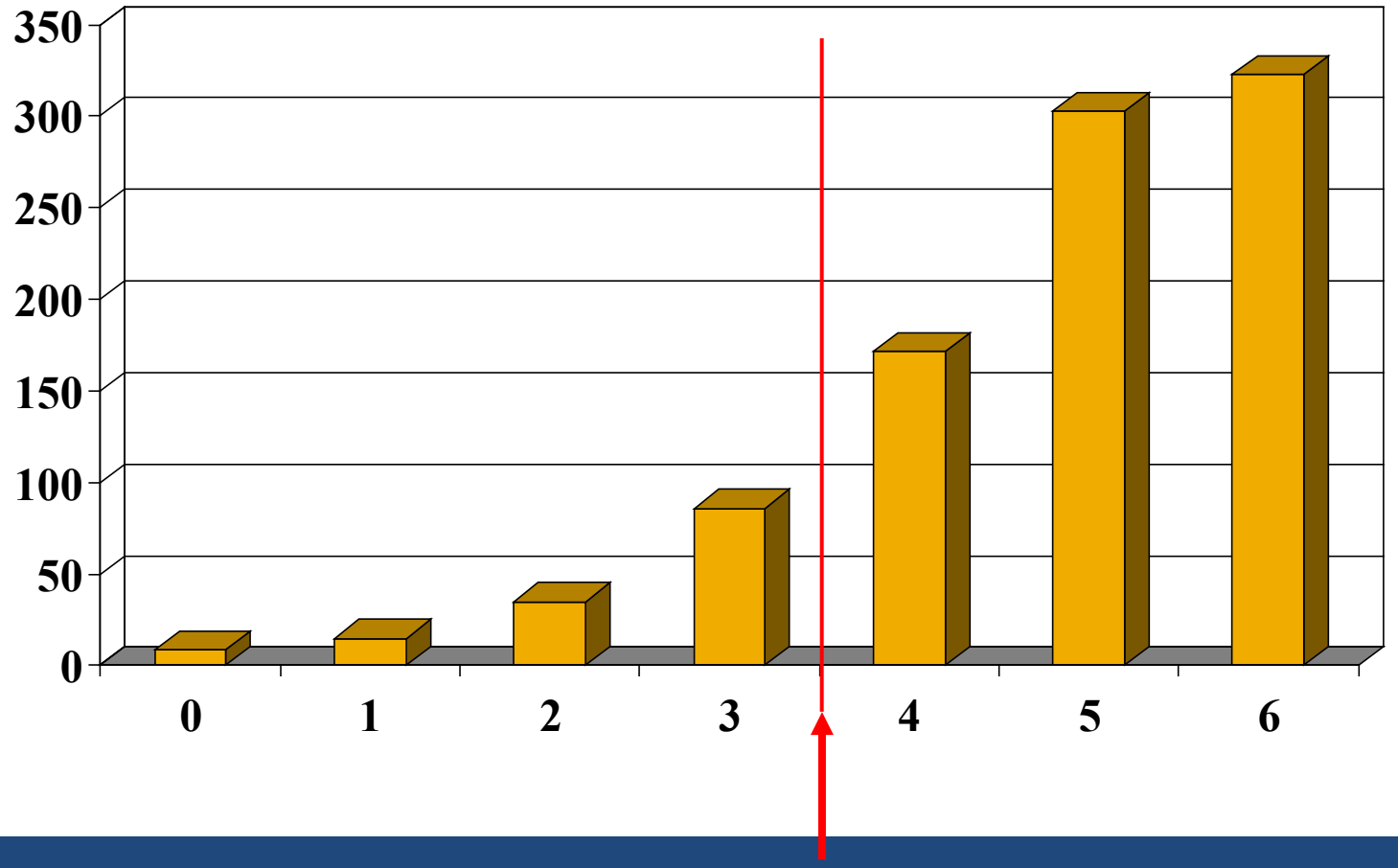
- 62-76% of AD patients (MMSE 22-23) in a typical RCT probably lack capacity (Kim, *AJP* 2001; Warner, *JME* 2008)

- 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

A REPORTER AT LARGE OCTOBER 9, 2017 ISSUE

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*)

	Lumbar Puncture	Drug RCT	Vaccine RCT	Gene transfer
If patients cannot make their own decisions about being in [study scenario], should our society allow their families to make the decision in their place? [% def/prob yes]				

Survey of U.S. public (n=1463): Family member as LAR for dementia research?

(Kim et al 2009, *Neurology*)

	Lumbar Puncture	Drug RCT	Vaccine RCT	Gene transfer
If patients cannot make their own decisions about being in [study scenario], should our society allow their families to make the decision in their place? [% def/prob yes]	72%	83%	71%	68%

Public attitudes toward family surrogate consent for dementia research: after one day deliberation exercise (n=173) (Kim et al 2011, *Neurology*)

	LP		Drug RCT		Vaccine RCT		Gene transfer	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
% probably allow	51	19	56	21	46	28	39	27
% definitely allow	33	76	38	76	19	51	17	41

Comments during deliberation….

(De Vries et al. Public's Approach to Surrogate Consent for Dementia Research: Cautious Pragmatism. *Am J Geriatr Psych* 2013)

- 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."

Or as another participants put it…

- “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]?

DD participants after deliberation (N=168)

	LP %	Drug RCT %	Vaccine %	Gene transfer %
No leeway				
Some leeway				
Complete leeway				

How much freedom or leeway would you give [your family member] to go against your preference and instead [do opposite of your current preference]?

DD participants after deliberation (N=168)

	LP %	Drug RCT %	Vaccine %	Gene transfer %
No leeway	24	24	23	29
Some leeway	59	57	61	52
Complete leeway	17	20	15	20

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 POLICY AND PROCEDURES: NEW AS OF SEPTEMBER 14, 2020

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!

LAR type / Risk-Benefit	DPA or Guardian	Concurrent DPA (only if person currently capable of appointing DPA)	De facto (family) surrogate
MR or Prospect of direct benefit	Yes	Yes	Yes (per hierarchy)
No prospect DB and minor increase in risk (for higher risk→ special panel)	Yes	Yes	Yes

Sometimes regulations do get simpler!

Type of LAR / Type of study	Any LAR on list (Guardian, DPA, Family list)
Any type that does not require special NIH panel	Yes