




# 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  
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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 → Revised Common Rule 2018**

**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 must be focused on disorder causing incapacity.
  - Rarely, OK to involve them, for other reasons (to avoid discrimination)

# Outline

- **Decision-making capacity** and impairment
- Studies with people lacking (or at risk of lacking) decision-making capacity (DMC) are **permissible** in theory.
- But **who should give consent?**
- Should there be **limits to risks** in such research studies?
- What is the **public's (considered) view** and how should it matter?
- What are **additional protections** or safeguards that might be appropriate?



# DECISION-MAKING CAPACITY (DMC) AND IMPAIRMENT

# Lots of terms and definitions...

- Capacity, decisional capacity, mental capacity, competence, decision-making capacity, etc...
- One often hears: “competence is the legal term; capacity isn’t”
  - In fact, MOST laws refer to ‘capacity’ or ‘decision-making capacity’
- Solution is to be aware of the problem and to be clear how one is using the terms.



# Definitions

(DMC=decision-making capacity)

- *Adjudicated DMC/competence*—what a judge determines. Yes/no judgment.
- *DMC/Competence*—a **clinician's approximation** of what the courts might say; usually this carries the day. Yes/no judgment.
- *Abilities* relevant to capacity (e.g., Grisso and Appelbaum 1988). Comes in degrees:
  - 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.

# Decision-Making Capacity (DMC)

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

# ‘Modern’ Functional Model of DMC

- Presumption of capacity
- Cannot be justified by “senile” “unsound mind” etc.
- Actual abilities relevant to the decision must be assessed
- Threshold is affected by context, especially risk-benefit.
- Task/decision specific

# An aside...

- UN Convention [and Committee] on the Rights of Persons with Disabilities, 2008
- CRPD General Comment 1 (2014): Article 12 is said to displace substituted DM with supported DM.
- Rejects functional model of capacity
- This talk assumes sufficient functional loss means loss of legal capacity (reflecting a near universally accepted view).

# Some disorders elevate risk for incapacity

- Cognitive disorders
  - Neurodegenerative—Alzheimer’s Disease, Frontotemporal 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:

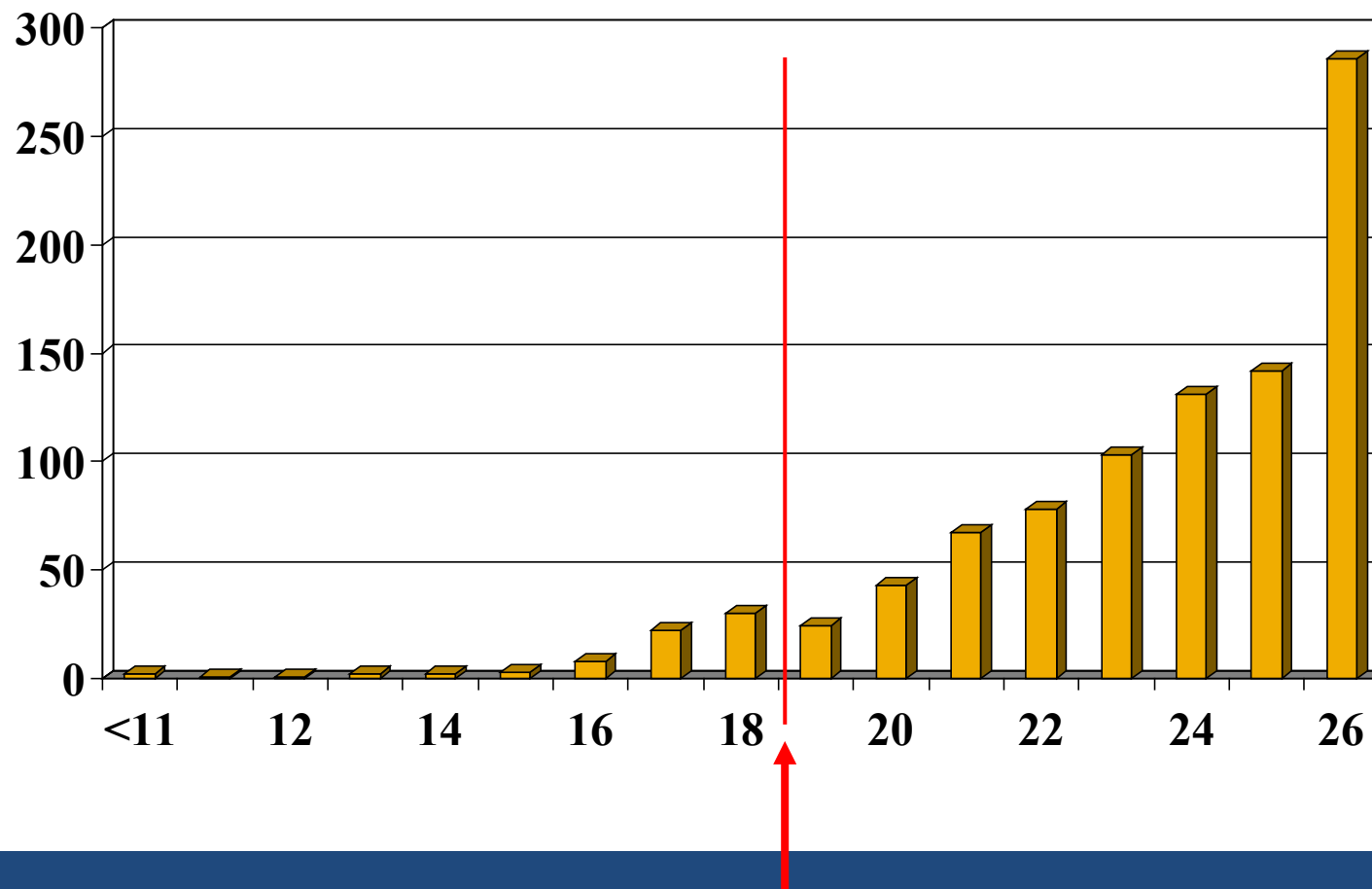
Very rough estimates (Kim, 2010)

- 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%

# Alzheimer's disease

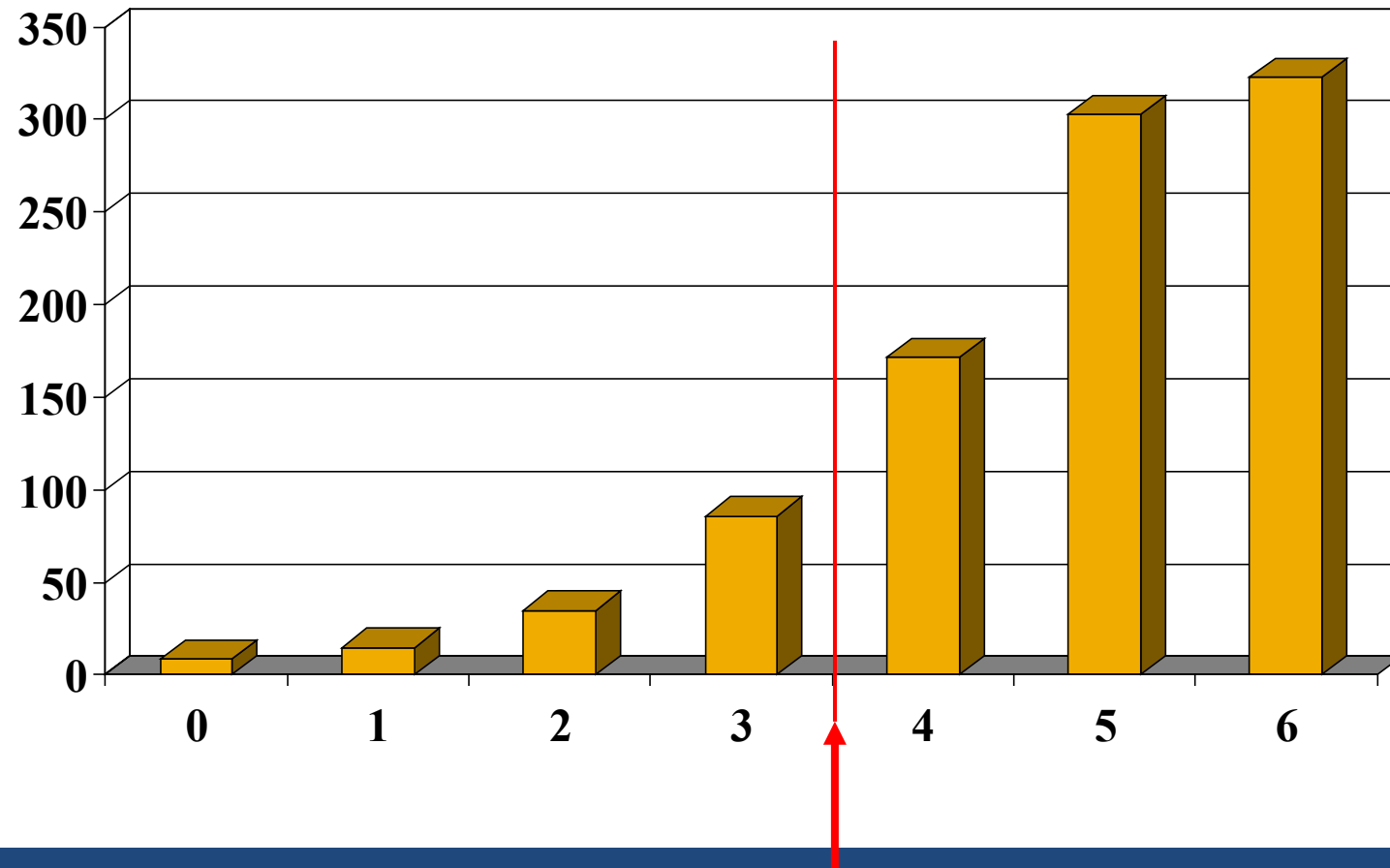
- 40% of pts with even Mild Cognitive Impairment (MMSE  $27.8 \pm 1.8$ ) lack capacity to consent to RCT (Jefferson, JAGS 2008)
- 62-76% of AD patients (MMSE 22-23) in a typical RCT probably lack capacity (Kim, AJP 2001; Warner, JME 2008)
- On the other hand...

# CATIE Schizophrenia Study: Understanding Score Distribution at N=900 (S. Stroup)





# CATIE Schizophrenia Study: Appreciation Score Distribution





**IF STUDIES WITH PEOPLE LACKING (OR  
AT RISK OF LACKING) DMC ARE  
PERMISSIBLE, WHO GIVES CONSENT?**

# Federal regulations allow, in theory...

- Pre-2018, “legally authorized representative” (LAR) (46.102c)
  - “...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.”
  - Deferred to local and state laws to define LAR
- 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)

# 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](http://www.hhs.gov/ohrp/sachrp_20090715letterattach.html))

# Revised Common Rule: when no applicable law, institutional policy can be used

- *Legally authorized representative* 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. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the 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 or history
- Health care proxies (DPOA)
  - Subject’s own choice but must extrapolate to research decision (i.e., appointed for clinical decisions)
- 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

# 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

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



# What proportion of adults prepare an advance directive? (Yadav et al, 2017, Health Affairs)

- Among the 795,909 people in the 150 studies, with data from 2000-2015...
- 36.7 percent had completed an advance directive... [proxy directives are a subset of this]
- Similar across the years reviewed.
- Similar proportions of patients with chronic illnesses (38.2 percent) and healthy adults (32.7 percent) had completed advance directives.
- **Bottom line: only a small minority have DPOA for health care, and this is unlikely to change.**

# So it appears that...

- De facto surrogates will have to be LARs
- This usually means family members
- But is this acceptable? After all, families play key roles in the clinical setting, regarding life/death decisions.



# 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; at NIH, also a higher level of review needed)

# 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.



**HOW DOES THE PUBLIC VIEW FAMILY  
SURROGATE CONSENT IN RESEARCH?**

**AND WHAT LEVEL OF RISK IS ACCEPTABLE?**

# 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]				

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	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
% <u>probably</u> allow	51	19	56	21	46	28	39	27
% <u>definitely</u> 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



# 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...



National Institutes of Health



BIOETHICS AT THE NIH

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SACHRP report URL:

<https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2009-july-15-letter-attachment/index.html>