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Acute Stroke Research

Ethical considerations

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UW Health *Comprehensive Stroke Program*

Outline

- Background
- Decisional Capacity
- Surrogate Decision-Making
- Exceptions from Informed Consent
  - Clinical context
  - Research context
- Conclusion

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Background

Outdated thinking

- "[R]esearch arguably does not need specific rules for self-regulation because it is, by definition, an activity that routinely monitors itself."

Steneck NH. Introduction to the Responsible Conduct of Research. US Department of Health and Human Services. Office of Research Integrity. 2007.

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Bernhard Walther or Ernst Hofmann or Karl-Friedrich Höcker,
Public domain, via Wikimedia Commons

Alexander Voronzow and others in his group, ordered by
Mikhael Oschurkow, head of the photography unit,
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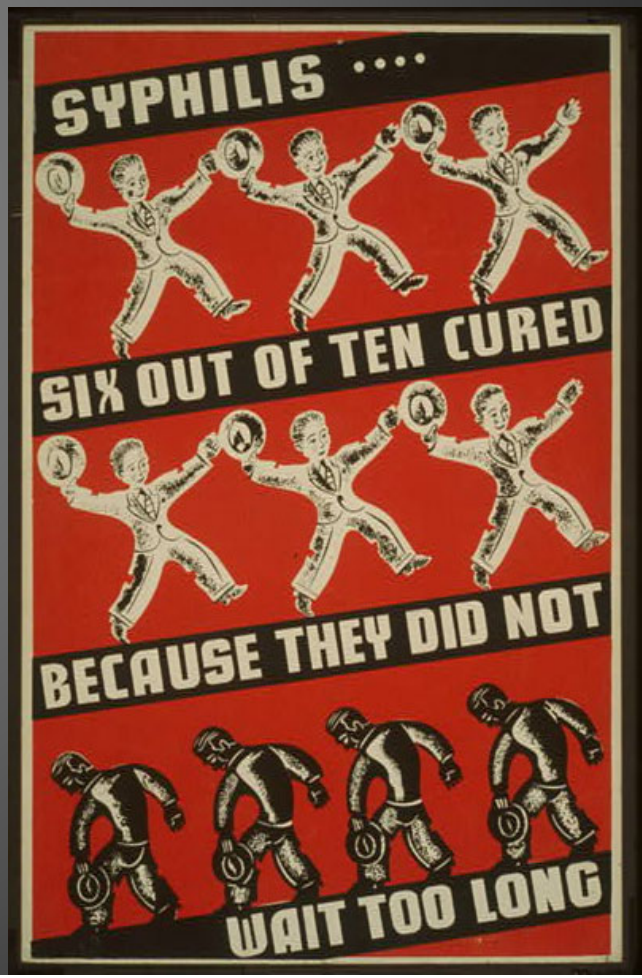
Research Misconduct in the U.S.

https://www.openaccessgovernment.org/modernising-healthcare-nuclear-way/13031/



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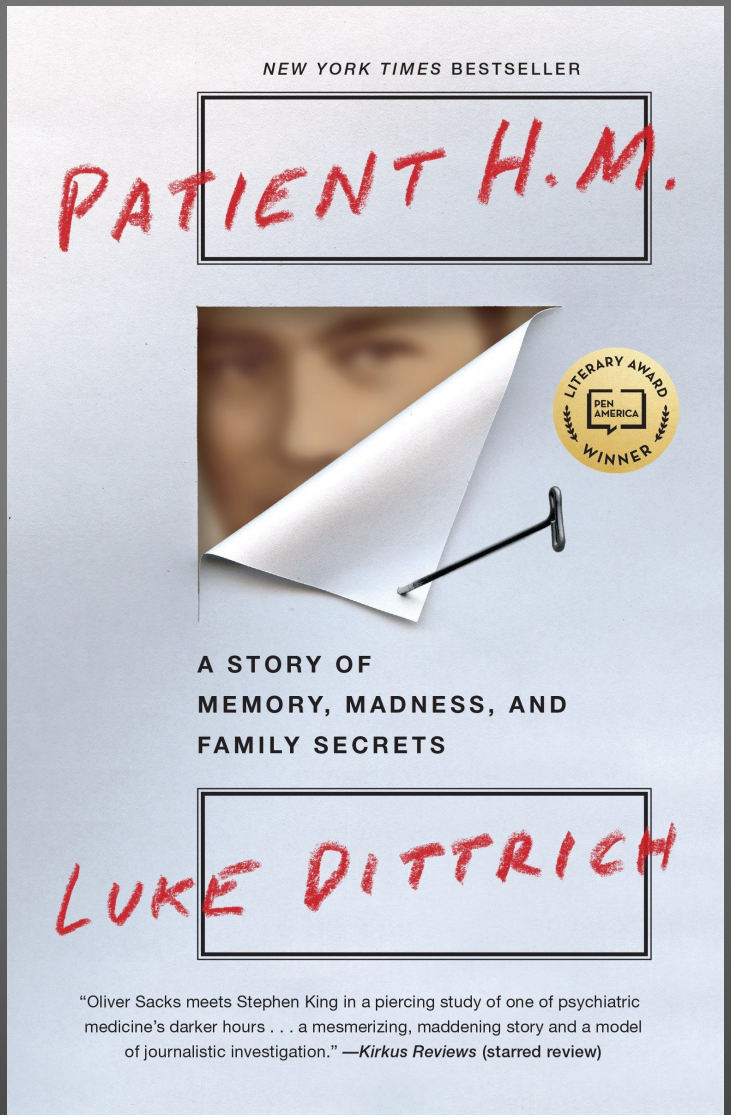
(Alleged) Research Misconduct in the U.S.



Nuremberg Code (1947)
Declaration of Helsinki (1964)

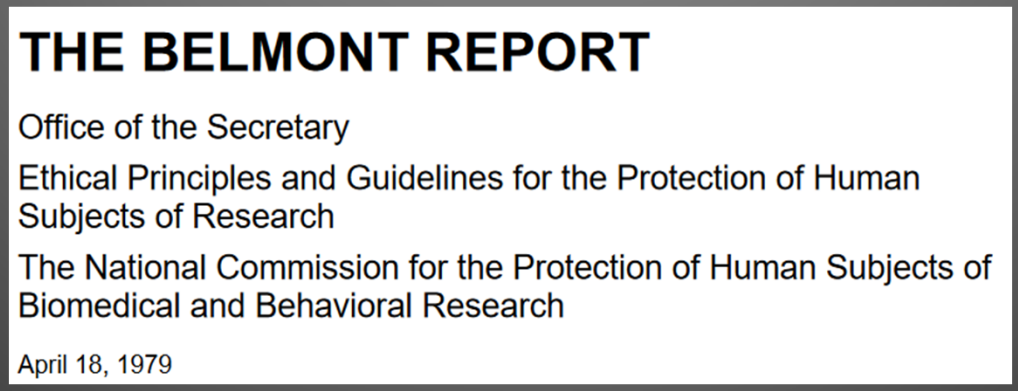
- The voluntary consent of the human subject is absolutely essential.
- The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods . . .

Rudolf Brandt, defendant in the Doctors' Trial. OMGUS Military Tribunal, Public domain, via Wikimedia Commons

Congressional Action (1974)

- Dept. of Health, Education, and Welfare mandated to clarify rules.

- Created a National Commission for the Protection of Human Subjects



THE BELMONT REPORT

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf

Congressional Action (1991)

- 45 CFR § 46
  - Subpart A ("Common Rule")
  - Subpart B: Pregnant women, fetuses, and neonates
  - Subpart C: Prisoners
  - Subpart D: Children

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IRB Role

- Risks to subjects are minimized
- Risks are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative
- Informed consent will be appropriately documented;
- The research plan makes adequate provision for monitoring the data.
- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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When is IRB Approval Required?

- *Human subjects*: Direct interaction or use of identifiable data.

- *Research*: A "systematic investigation . . . designed to develop or contribute to generalizable knowledge"

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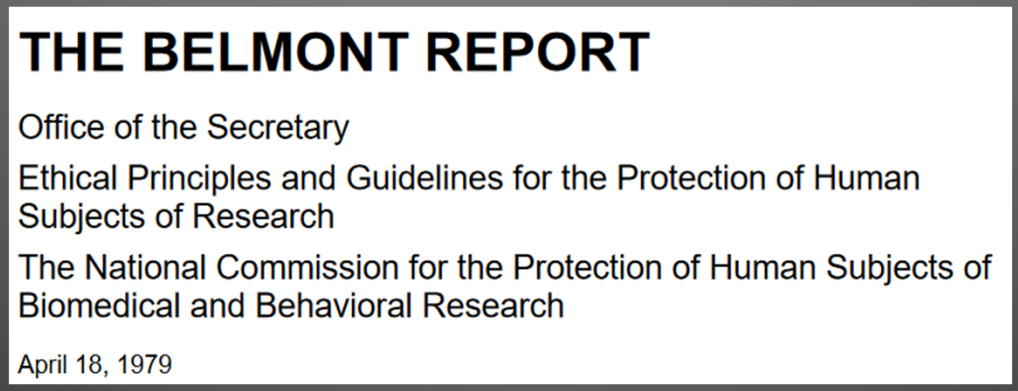
Ethical Principles

- Autonomy (respect for persons)
- Beneficence
- (Non-maleficence)
- Justice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Moral Implications of Autonomy

- Tell the truth
- Respect privacy
- Protect confidential information
- Obtain consent for interventions

Beauchamp TL, Childress JF. Principles of Biomedical Ethics, 7th ed. Oxford University Press; 2013.

Autonomy → Informed Consent

- Disclosure of relevant information
- Recommendation of a plan
- Patient consent (or refusal)
  - In the absence of coercion
  - In a patient with decisional capacity

Beauchamp TL, Childress JF. Principles of Biomedical Ethics, 7th ed. Oxford University Press; 2013.

Autonomy → Informed Consent → Decisional Capacity

- Understanding
- Appreciation
- Reasoning
- Choice

Appelbaum PS, Grisso T. Assessing patients' capacities to consent to treatment. N Engl J Med. 1988;319(25):1635-1638.

Understanding

- A grasp of the basic facts surrounding a decision:
  - The medical condition
  - Proposed intervention
  - Risks
  - Benefits
  - Alternatives

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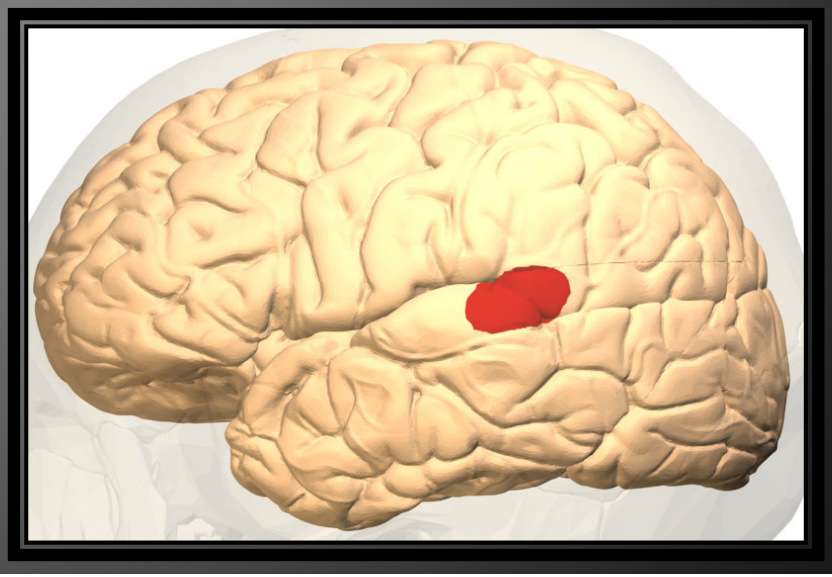
Understanding

- May be assessed via the “teach-back” method.
- May be impaired, e.g., by Wernicke’s aphasia.



Database Center for Life Science(DBCLS)[2]. - Polygon data are from BodyParts3D[1], CC BY-SA 2.1 jp, https://commons.wikimedia.org/w/index.php?curid=32534031

Autonomy → Informed Consent → Decisional Capacity

- Understanding
- Appreciation
- Reasoning
- Choice

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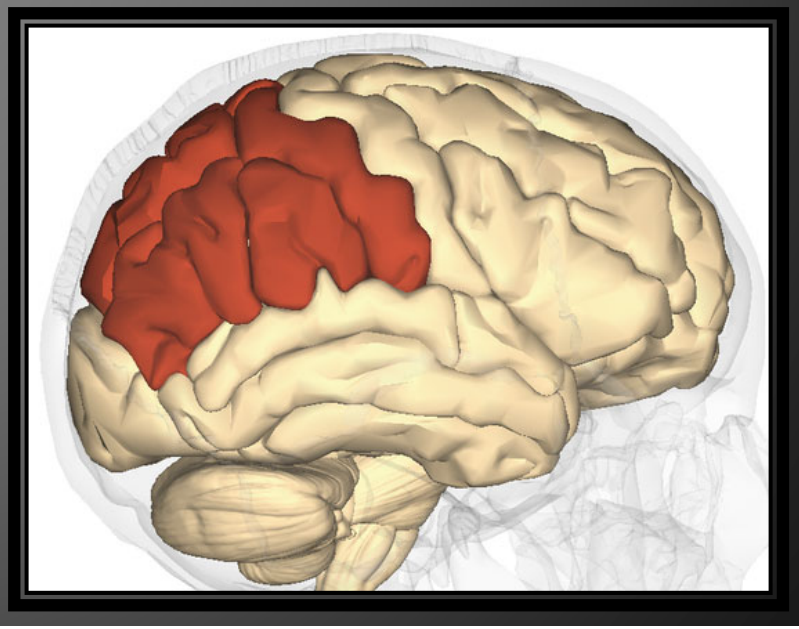
Appreciation

- How the provided information applies to one's own case.
- May be assessed by asking the patient for explanation of why a proposed course of action will or will not benefit them.

Appreciation

- May be impaired in right hemispheric lesions that lead to hemineglect and anosagnosia.



Autonomy → Informed Consent → Decisional Capacity

- Understanding
- Appreciation
- Reasoning
- Choice

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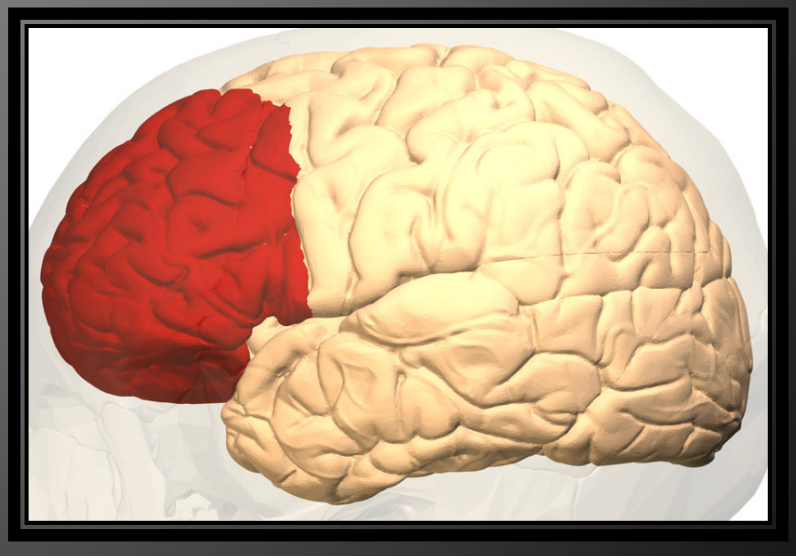
Reasoning

- The ability to compare options and consistently infer the consequences of one's choices.
- May be assessed by asking patients how each of the available options will affect their daily lives.

Reasoning

- May be impaired in the setting of prefrontal or parietal lobe injuries.
- Especially with respect to quantitative and probabilistic risks.



Autonomy → Informed Consent → Decisional Capacity

- Understanding
- Appreciation
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- Choice

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Choice

- Expressing a decision.
- Should be reasonably stable in the absence of new information.

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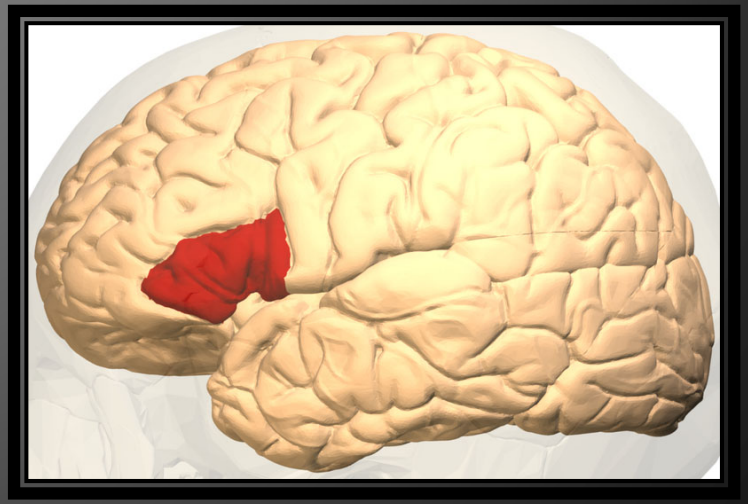
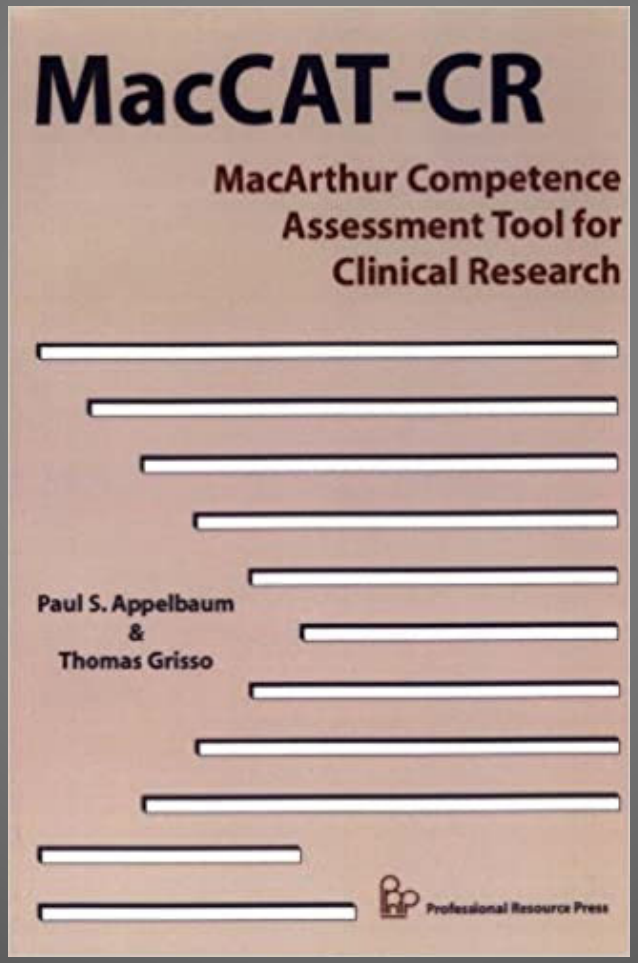
Choice

- Ability to express a choice may be impaired in:
  - Broca's aphasia
  - Reduced consciousness



Assessing Decisional Capacity



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Assessing Decisional Capacity

UCSD Brief Assessment of Capacity to Consent (UBACC)	
1. What is the purpose of the study that was just described to you?	
Response (2 = Study investigational drug for memory)	Score
	0
	1
	2
2. What makes you want to consider participating in this study?	
Response (2 = Improve memory and attention, help others)	Score
	0
	1
	2
3. Do you believe this is primarily research or primarily treatment?	
Response (2 = Research)	Score
	0
	1
	2
4. Do you have to be in this study if you do not want to participate?	
Response (2 = No)	Score
	0
	1
	2

Jeste DV, Palmer BW, Appelbaum PS, et al. A New Brief Instrument for Assessing Decisional Capacity for Clinical Research. Arch Gen Psychiatry. 2007;64(8):966–974.

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Decisional Capacity

Review

- Understanding
- Appreciation
- Reasoning
- Choice

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Outline

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Surrogate Decision-Making

- Guardian (of the person)
- Advance directives
  - Instruction directives
  - Proxy directives
- Next of kin
- Implications for clinical research

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Guardianship in WI

- *Clinical*: May withhold or withdraw life-sustaining treatment ***only*** in cases of chronic vegetative state.

- *Research*: May not provide research consent for wards being treated for mental illness, developmental disabilities, or alcohol or other drug dependencies.

Wis. Stat. § 51.61(l)(j)
Wis. Adm. Code DHS § 94.14

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Surrogate Decision-Making

- Guardian (of the person)
- Advance directives
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Instruction Directives

"Living wills"

- Often too specific, referring only to feeding tubes or CPR, but not stroke treatments.
- Often too vague, referring to "terminal conditions", but not clearly stroke.
- May, but usually don't, mention research

Proxy Directives

HCPOA, DPOAHC

- Surrogates should consider
  - Expressed wishes of the patient
  - Substituted judgement
  - Best interests *(harder to invoke in the research context)*

- POAs for research exist but are uncommon

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Surrogate Decision-Making

- Guardian (of the person)
- Advance directives
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- Next of kin
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Next of Kin

- Laws vary by state.
- WI does not specify a hierarchy; individual hospitals often do. At UW:
  - Court-appointed guardian
  - HCPOA
  - Patient-identified surrogate (verbal or writing)
  - Spouse
  - Adult child(ren)
  - Parents
  - Siblings
  - Close relative or friend

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Surrogate Decision-Making

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Surrogate Consent for Research

NINDS rt-PA example

- 70% of 624 subjects were enrolled via surrogate consent.
- Study would otherwise have taken 12.5 years to complete (instead of 3.8).
- Self-consenting subjects were younger and had milder strokes.

Flaherty ML, Karlawish J, Khoury JC, et al. How important is surrogate consent for stroke research? Neurology. 2008 Nov 11;71(20):1566-71.

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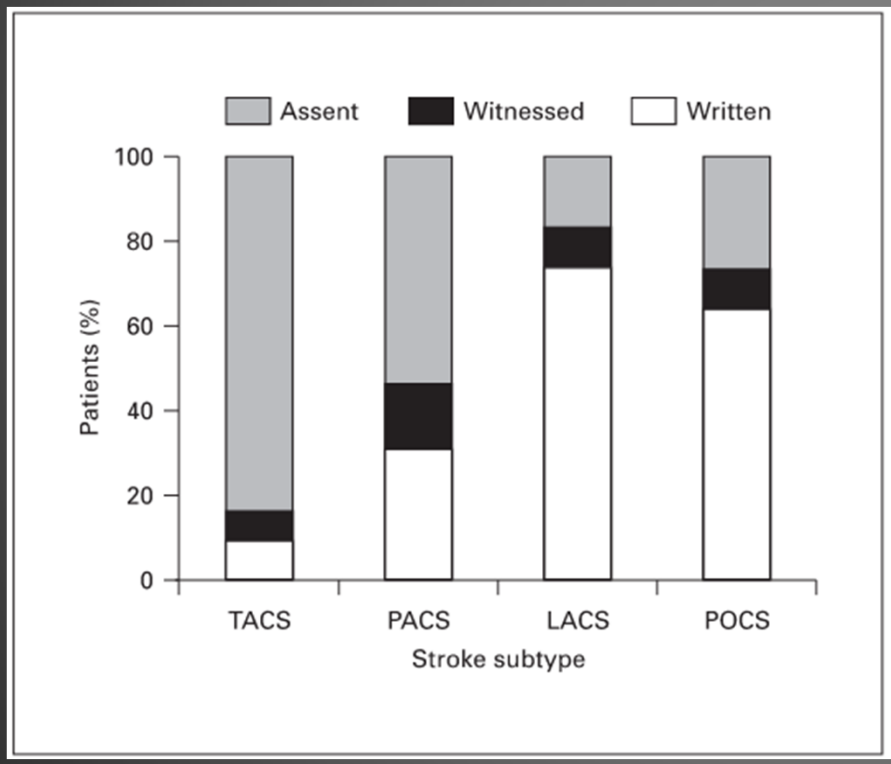
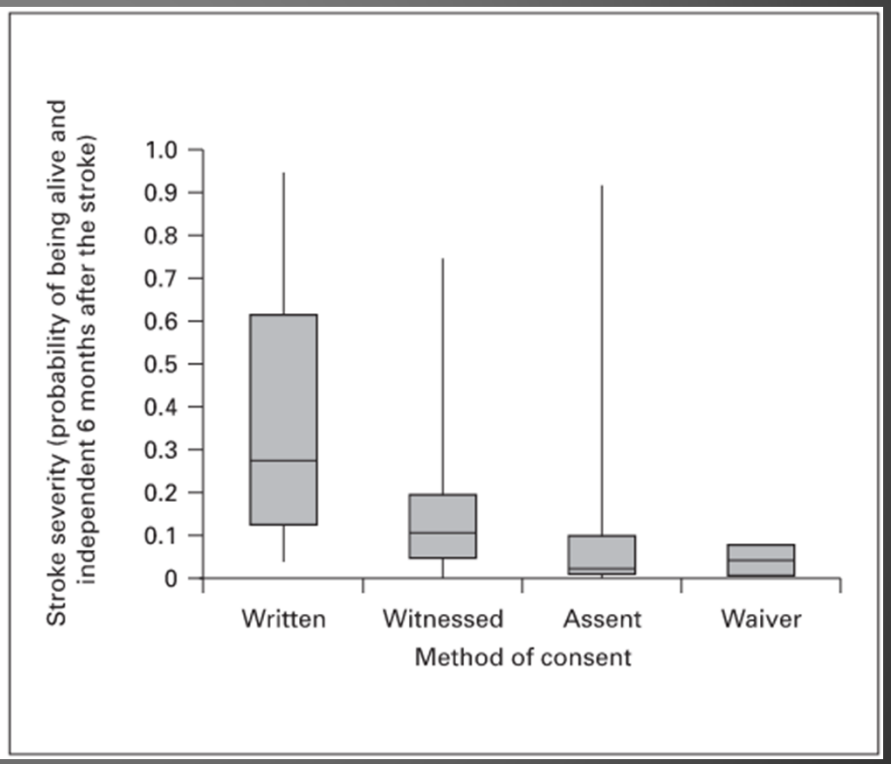
Surrogate Consent for Research

IST-3 example





Kane I, Lindley R, Lewis S, Sandercock P; IST-3 Collaborative Group. Impact of stroke syndrome and stroke severity on the process of consent in the Third International Stroke Trial. Cerebrovasc Dis. 2006;21(5-6):348-52.

Surrogate Consent for Research

Federal Common Rule is broad

- *Legally Authorized Representative*: An "individual . . . authorized under applicable law to consent on behalf of a prospective subject . . ."

45 CFR 46.102(c)
21 C.F.R. 50.3(1)

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Surrogate Consent for Research

State laws vary and are often silent

- In WI, for example, surrogate consent is prohibited for mental health research (only).

Wis. Stat. § 155.20(3)

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Surrogate Consent for Research

Local IRB policies vary

- At UW-Madison, research using surrogate consent must:
  - Be minimal risk; or
  - Hold out the prospect for direct benefit; or
  - Subjects must have signed an advance directive noting that they want to participate in such research.

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Surrogate Decision-Making

Review

- Guardian (of the person)
- Advance directives
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Varieties of Consent

- Expressed
- Implicit / implied
- Tacit
- (Assent)
- Presumed

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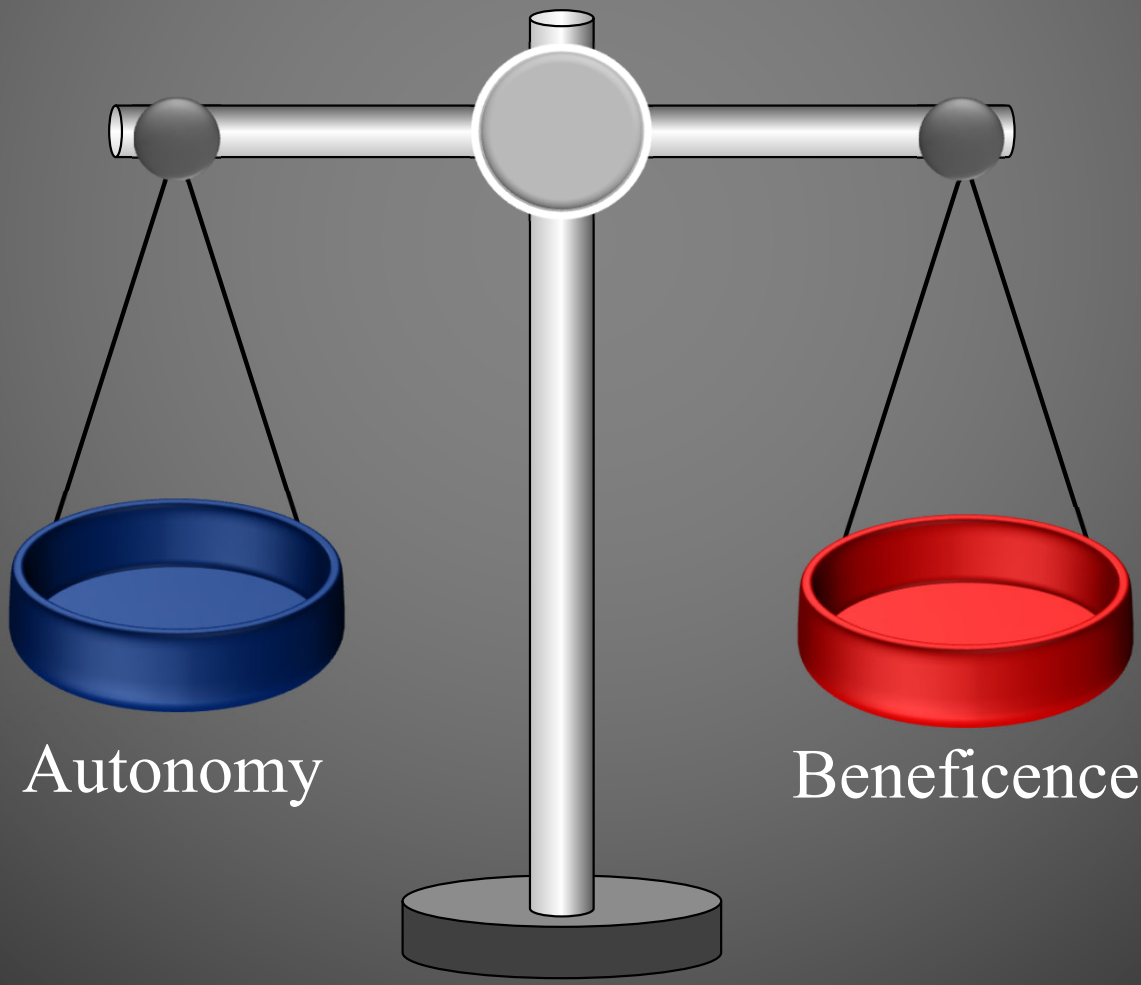
Presumption of Consent

Ethical considerations



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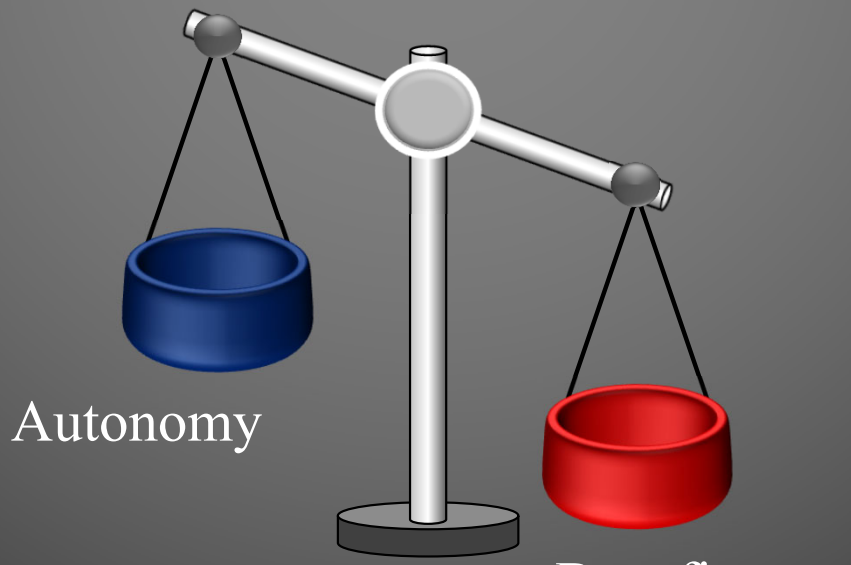
Presumption of Consent

Case 1

- IV alteplase in a patient presenting < 3 hours with severe deficits and no known contraindications.



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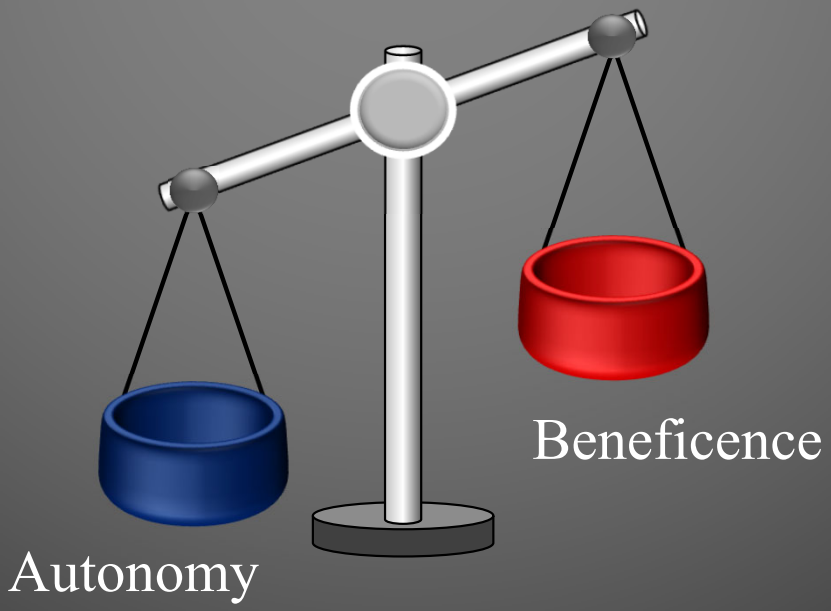
Presumption of Consent

Case 2

- Thrombectomy of an M3 clot in a patient presenting > 24 hours with moderate deficits.



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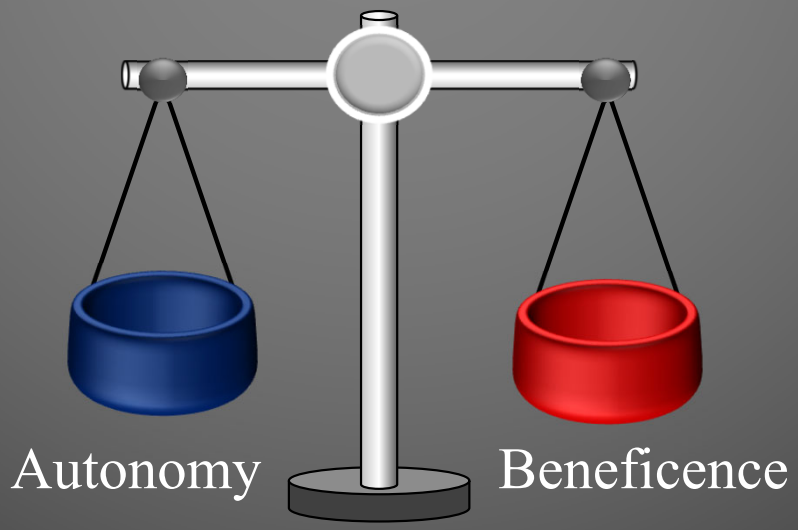
Presumption of Consent

Case 3

- Decompressive hemicraniectomy in an unrepresented 70 year old patient with malignant LMCA infarct.



Consider ethics consult

Presumption of Consent

General approach

- "Standard of care" treatments should be applied.
- The further from standard, the more caution should be exercised in presuming consent.
- If time permits, consider ethics or legal services consultation.

Sattin JA, Chiong W, Bonnie RJ, et al. Consent Issues in the Management of Acute Ischemic Stroke: AAN Position Statement. Neurology. 2022 Jan 11;98(2):73-79.

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Exceptions from Informed Consent

Literature review of justifications

- Decreased data validity and quality
- Distress or confusion of participants
- Practical problems (e.g., time constraints)
- Ethical concerns

Rebers S, Aaronson NK, van Leeuwen FE, Schmidt MK. Exceptions to the rule of informed consent for research with an intervention. *BMC Med Ethics*. 2016;17:9.

Exceptions from Informed Consent

Minimal risk studies

- IRB may alter or waive consent requirements for minimal risk studies:
  - May be applicable to systems-level interventions.
  - Also, e.g., telephone screening pre-enrollment.
  - Not applicable to reperfusion / neuroprotective therapies.

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Exceptions from Informed Consent

EFIC pathway

- For research on emergency treatments for life-threatening, incapacitating, conditions.
  Requirements include:
  - Community consultation during planning
  - Public disclosure (before) and reporting (after)
  - Attempt to contact LAR for written consent, if feasible
  - Attempt to contact family, who may object
  - Patient refusal must be honored
  - Subject / surrogate later informed & may withdraw
  - Independent DMC

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research
Bateman BT, Meyers PM, Schumacher HC, et al. Conducting stroke research with an exception from the requirement for informed consent. Stroke. 2003 May;34(5):1317-23.

Exceptions from Informed Consent

Systematic review of the EFIC pathway

EXHIBIT 1

Key characteristics of exception from informed consent (EFIC) trials involving new drugs or devices, 1996–2017

	Trials ($N = 41$)	
Characteristic	**Number**	**Percent**
CONDITION TREATED		
Cardiac arrest	16	39
Traumatic shock	11	27
Traumatic brain injury	6	15
Status epilepticus	3	7
Respiratory failure	2	5
Ischemic stroke	2	5
Acute coronary syndrome	1	2

Feldman WB, Hey SP, Kesselheim AS. A Systematic Review Of The Food And Drug Administration's 'Exception From Informed Consent' Pathway. Health Aff (Millwood). 2018 Oct;37(10):1605-1614.

Exceptions from Informed Consent

The justice principle as regards EFIC

- Demographic data suggest the need to include more African Americans in the community consultation process.

Feldman WB, Hey SP, Kesselheim AS. A Systematic Review Of The Food And Drug Administration's 'Exception From Informed Consent' Pathway. Health Aff (Millwood). 2018 Oct;37(10):1605-1614.

Exceptions from Informed Consent

EFIC pathway in StrokeNet

http://nihstrokenet.org/fastest/community-resources

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Exceptions from Informed Consent

Deferred consent

- Study procedures commence without consent.
- Once decisional capacity is regained, or a proxy identified, consent must be obtained for study continuation.
- Otherwise, subject may have to be withdrawn.

Kompanje EJO, van Dijck JTJM, Chalos V, et al. Informed consent procedures for emergency interventional research in patients with traumatic brain injury and ischaemic stroke. Lancet Neurol. 2020 Dec;19(12):1033-1042.

Exceptions from Informed Consent

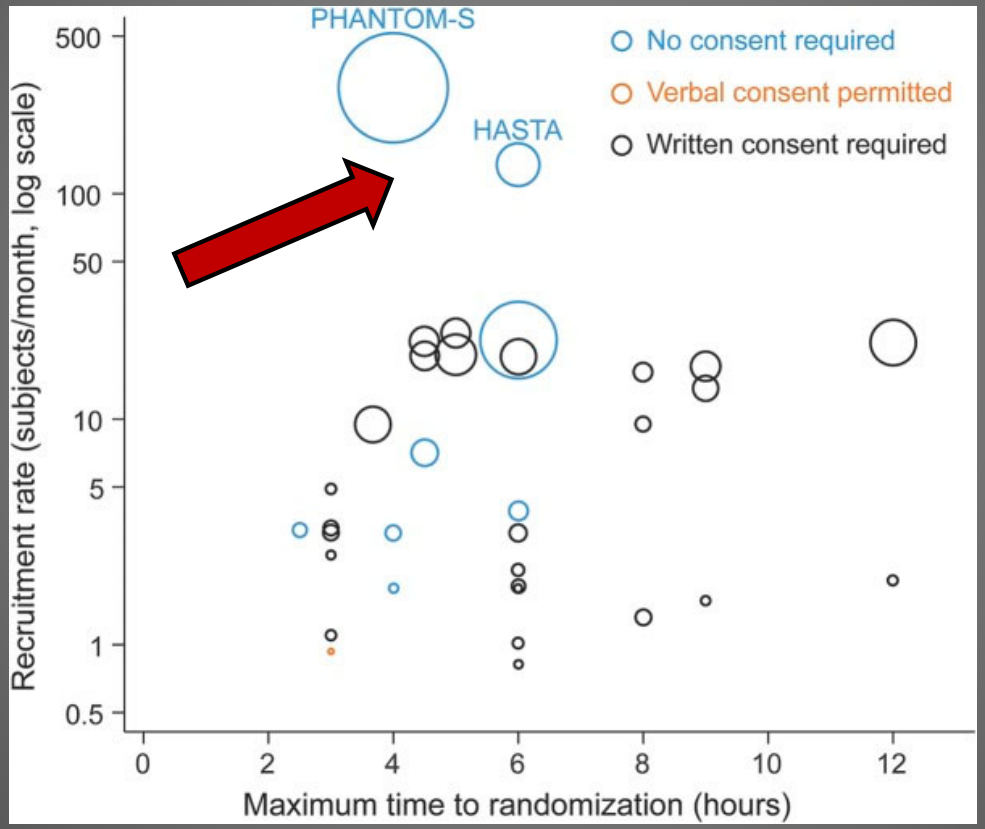
2-Stage pathway: TICH-2

	All	2-stage doctor	2-stage patient	2-stage relative	1-stage patient	1-stage relative	P value
CT to random (min)	75	55	55	69	75	90	< 0.001
Onset to random ≤ 3 hrs.	36%	53%	44%	40%	33%	30%	< 0.001

Law ZK, Appleton JP, Scutt P, et al. Brief Consent Methods Enable Rapid Enrollment in Acute Stroke Trial: Results From the TICH-2 Randomized Controlled Trial. Stroke. 2022 Apr;53(4):1141-1148.

Do Waivers Increase Enrollment?

Probably yes, for systems-level research



Rose DZ, Kasner SE. Informed consent: the rate-limiting step in acute stroke trials. Front Neurol. 2011 Oct 17;2:65.

Feldman WB, Kim AS, Josephson SA, Lowenstein DH, Chiong W. Effect of waivers of consent on recruitment in acute stroke trials: A systematic review. *Neurology*. 2016;86(16):1543-1551.

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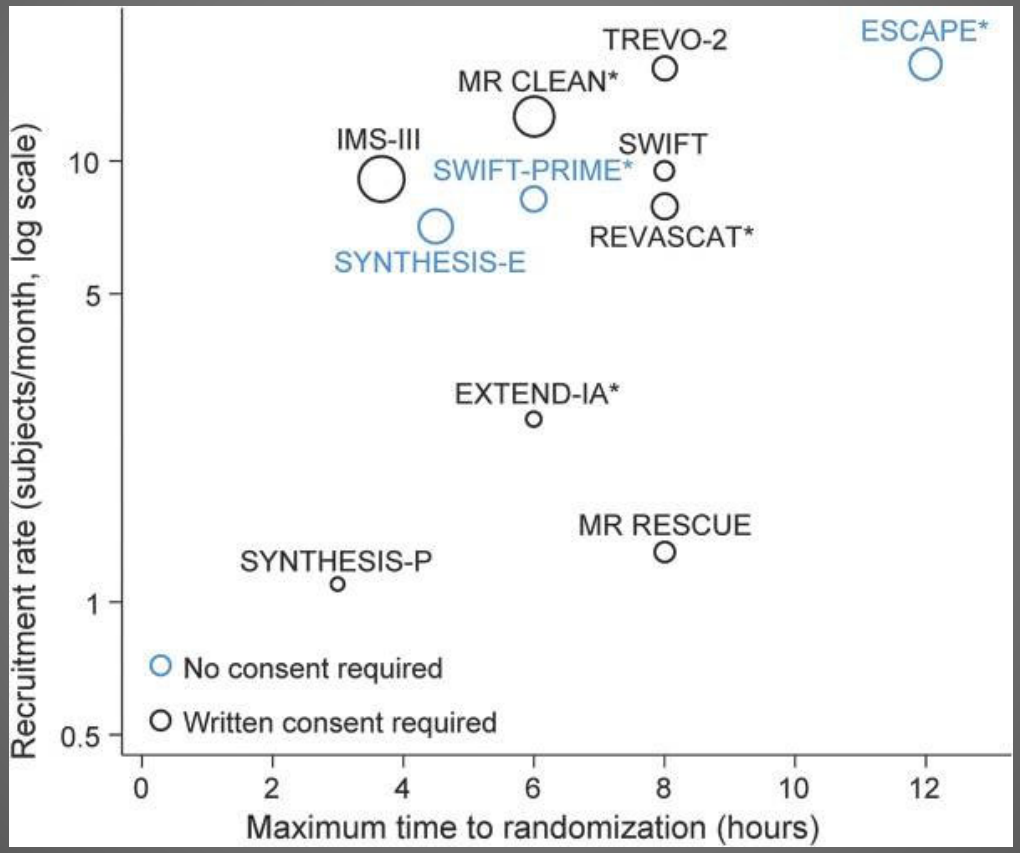
Do Waivers Increase Enrollment?

Possibly not in ED settings



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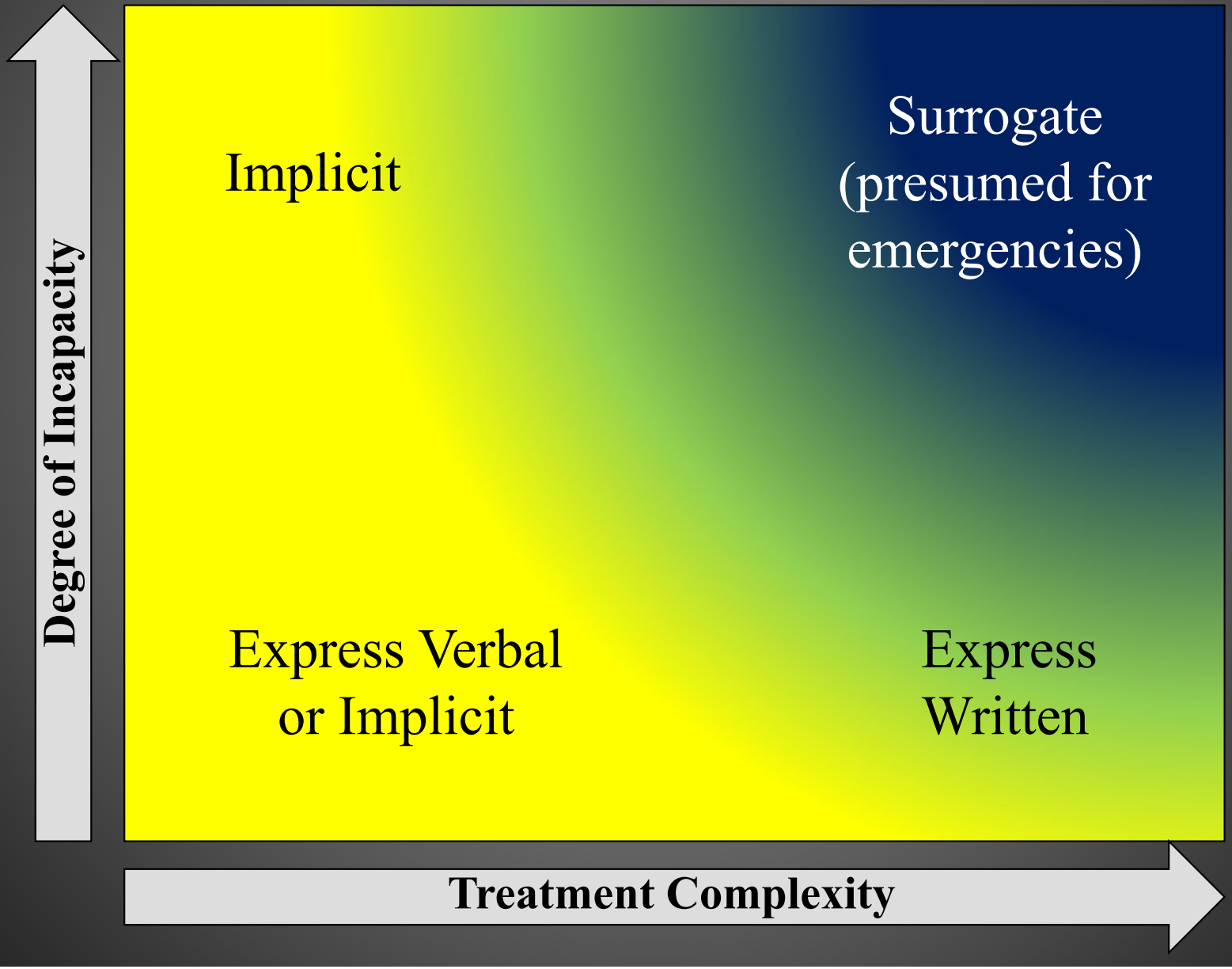
Consent Matrix

Clinical paradigm



Consent Matrix

Simple research paradigm

	Minimal Risk	**> Minimal Risk**
Has Capacity	Written Consent (or waiver)	Written Consent
Lacks Capacity	Waiver	Surrogate Consent (or EFIC)

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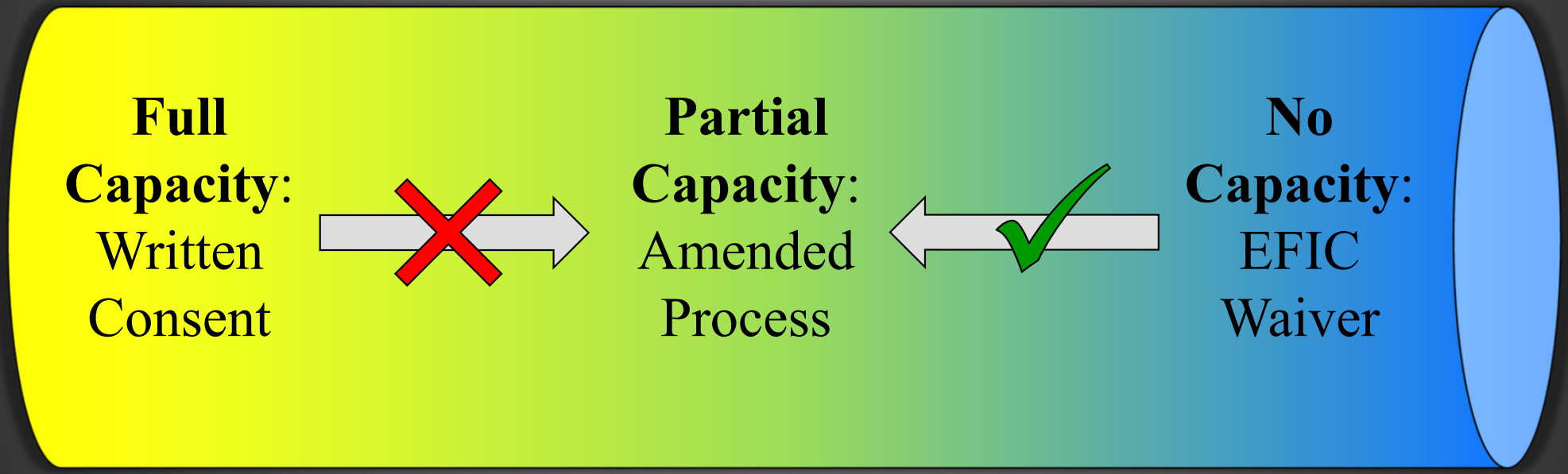
Consent Matrix

Flexible research paradigm



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Comments & Questions!

See chat box for link to bibliography

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