Ethical issues in aging research with emphasis on research involving older participants with diminished capacity to consent

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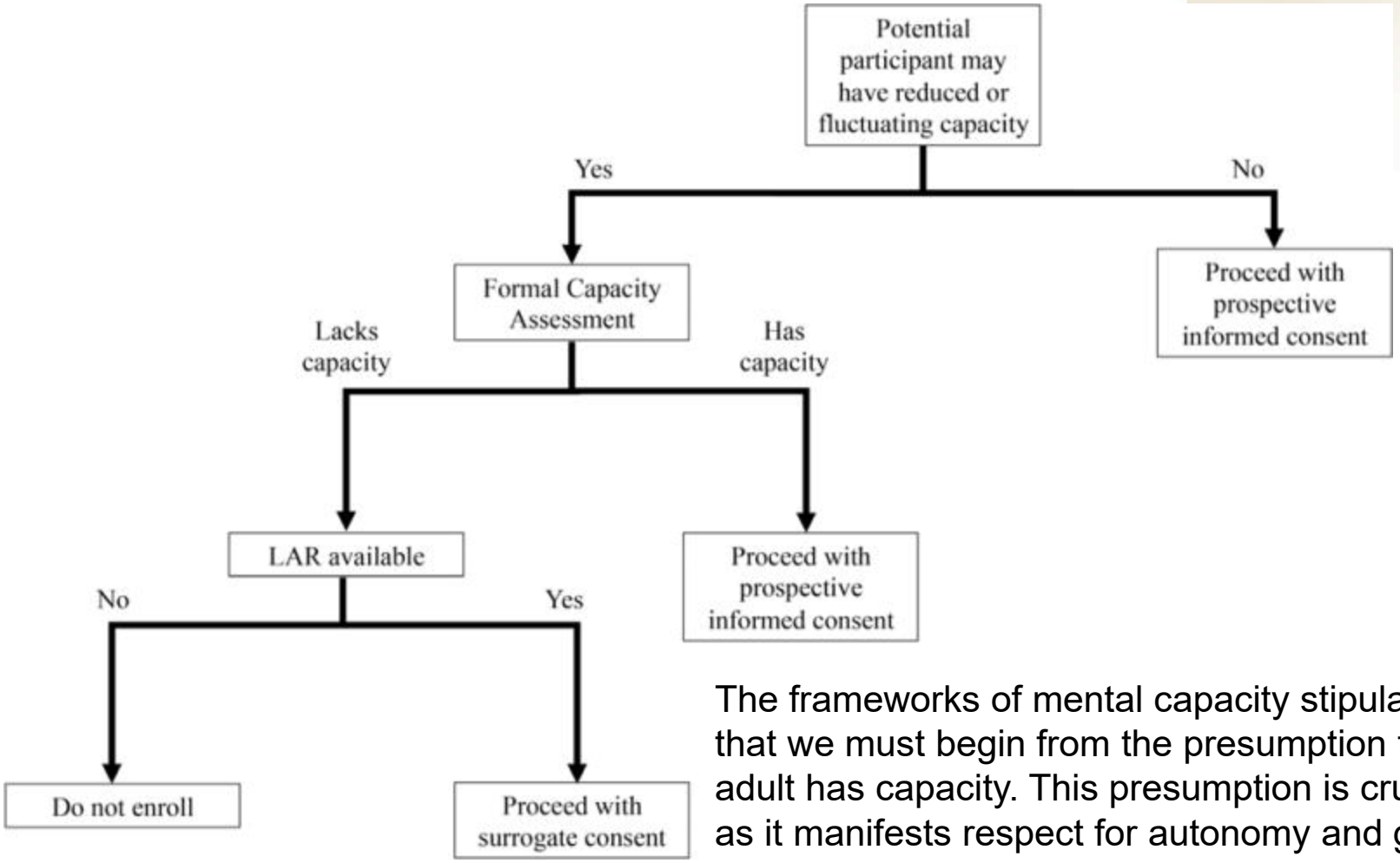
Introduction

- Research protocol cases
- Brief clinical overview Alzheimer Disease (AD)
- Assessment of decision making capacity
- Legally authorized representatives (LAR) and importance of dyad in AD research
- Substituted judgment and best interests
- Challenges of anti-aging research
- Recommendations

- For each of the subsequent cases, consider:
- How will the capacity to provide consent or assent be assessed?
- How will informed consent be obtained?
- Who will provide informed consent? Assent?
- Are there additional issues or safeguards that need to be considered to protect the subjects?

Approach algorithm



The frameworks of mental capacity stipulates that we must begin from the presumption that an adult has capacity. This presumption is crucial, as it manifests respect for autonomy and guards against prejudice and paternalism on the part of the evaluator

Why are the elderly a vulnerable population?

- Advancing age, and age-associated comorbidities may place older individuals at increased physical, cognitive or financial risk for participation in research
- When older people are cognitively impaired or institutionalized, the same protections apply to them as to younger persons with decisional impaired/incapacity or children

Nursing home patients (1)

- Historically there have been abuses where individuals in nursing homes have been used as subjects merely because they provided a convenient sample. Some of these studies were performed without informed consent.
- This violates the principle of justice, the equitable distribution of research burdens and benefits

Jewish Chronic Disease Hospital, Brooklyn NY

Nursing home patients (2)

- Institutional settings increase the chances for coercion and undue influence because of the lack of freedom inherent in such situations.
- Research in institutional settings should be avoided, unless:
  - the involvement of the institutional population is necessary to the conduct of the research (e.g., the disease or condition is endemic to the institutional setting, persons who suffer from the disease or condition reside primarily in institutions)
  - or the study focuses on the institutional setting itself

Case 1

- Patients with mild to moderate Alzheimer's Disease (AD) are being recruited into a VA sponsored cooperative study examining whether memantine in combination with vitamin E would result in clinical improvement on cognition, ADL and other outcome measures versus memantine alone, vitamin E alone or placebo
- Caregiver provides team with their periodic assessment of subject's cognition, activities of daily living (ADLS), instrumental activities of daily living (IADLS) and other measures
- We were one of the sites (JAMA. 2014;311:33-44)

Alzheimer Disease (AD)

- Alzheimer Disease is a neurodegenerative disorder and is the most common cause of dementia
- Clinical features
  - Memory impairment
  - Language: verbal fluency and anomia
  - Loss of visuospatial skills
  - Reduced insight
  - Apraxia: difficulty learning and performing motor tasks
  - Impaired executive function: planning, poor insight
  - Neuropsychiatric symptoms

Decision-making Capacity and Competency

- *Competency* is a legal determination, made by a court of law, that a patient has the requisite capacities to make a medical decision.
- This is in contrast to *decision-making capacity* which is a clinical determination made by the clinician or investigator

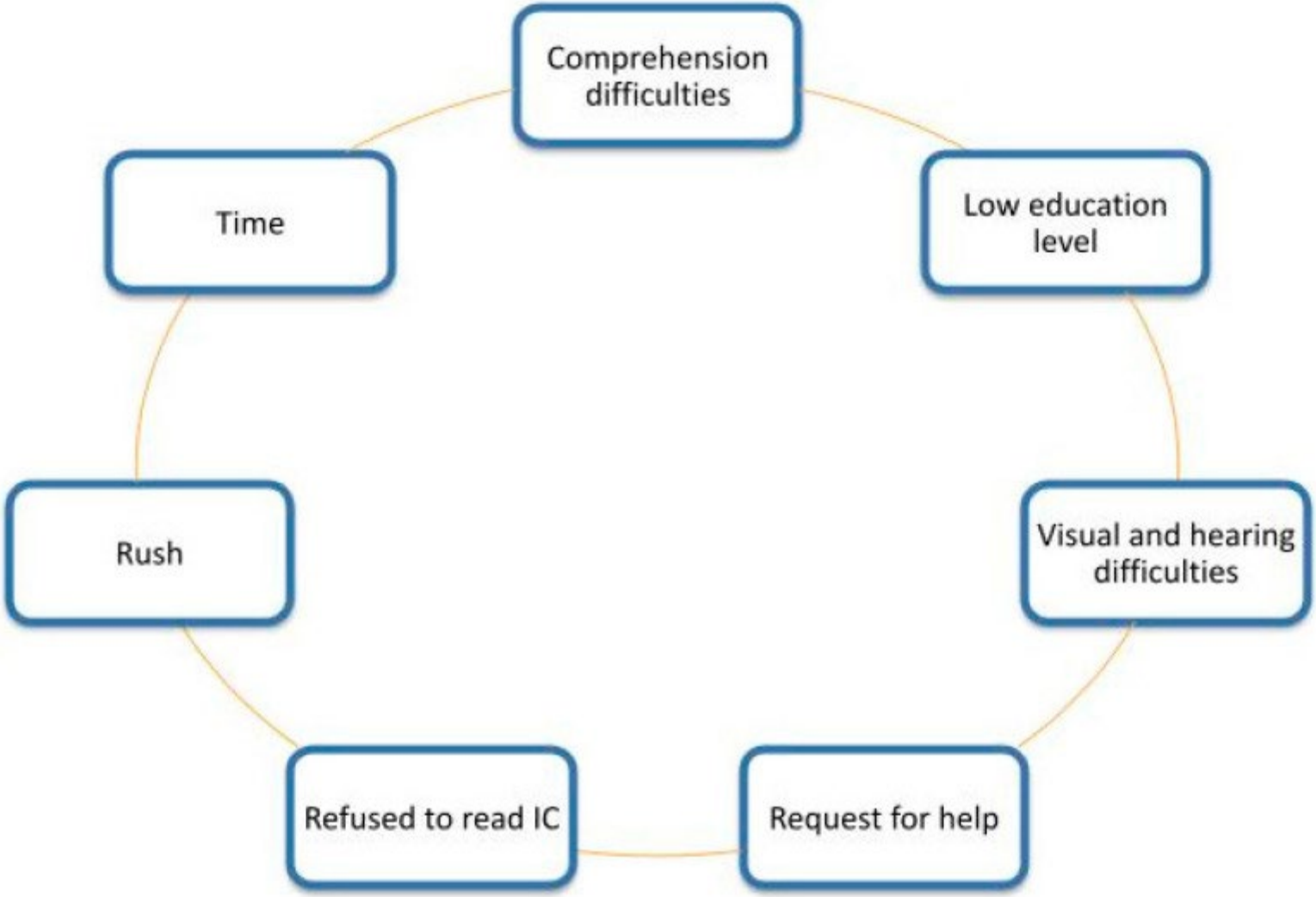
Decision-making Capacity
(VAMCHC Policy Memorandum 512--14/RM)

- 4 components: understanding, appreciating, formulating, communicating.
- The patient needs to *understand* and *appreciate* the nature and expected consequences of participation including risk and benefits and alternative to participate.
- The patient must have the ability for *formulate* a judgment and *communicate* this decision

Decisionally Impaired or Incapacitated

- Respect for persons requires special protections for decisionally impaired or incapacitated
- No specific federal guidelines for assessing capacity
- 3 categories of individuals whose decision-making capacity is in question
  - Capacity to provide consent
  - Capacity to provide assent or dissent
  - No capacity to provide assent or dissent where legally authorized representative provides consent

Age and the ability to provide informed consent. Some issues identified with obtaining informed consent for a RCT in adults over 65 years.



López-Parra Met al. Patient Information and Informed Consent for Research in the Elderly: Lessons Learned from a Randomized Controlled Trial. Healthcare (Basel). 2022 Jun 2;10(6):1036. doi: 10.3390/healthcare10061036. PMID: 35742087; PMCID: PMC9222813.

How does one assess decision-making capacity? (1)

- Assessment of cognitive function using Mini-mental status examination (MMSE) (Folstein J Psychiatr Res 1975;12:189)
  - Widely used in routine clinical practice
  - Scores range from 0 to 30, with “normal” 26-30
  - dementia < 24; adjusted for education < 21
  - Has been criticized for lack of sensitivity in detecting mild cognitive impairment
  - Instrument only tests limited number of cognitive domains

How does one assess decision-making capacity? (2)

- Multiple other instruments to assess cognitive function
  - Montreal cognitive assessment (MOCA). Particularly useful for detecting mild cognitive impairment
  - Mini-Cog
  - Mini-CEX

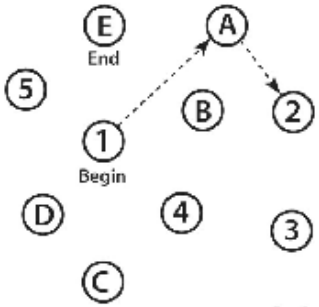
  It may be necessary to perform disease specific assessments, such as looking for aphasia in stroke patients

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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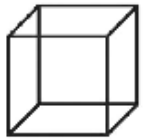


[ ] [ ]

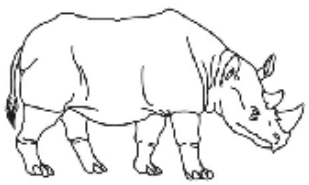
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING

[ ]



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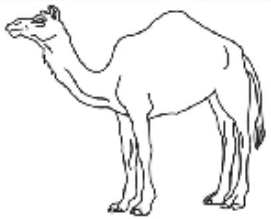


[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.): Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange – fruit [ ] train – bicycle [ ] watch – ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

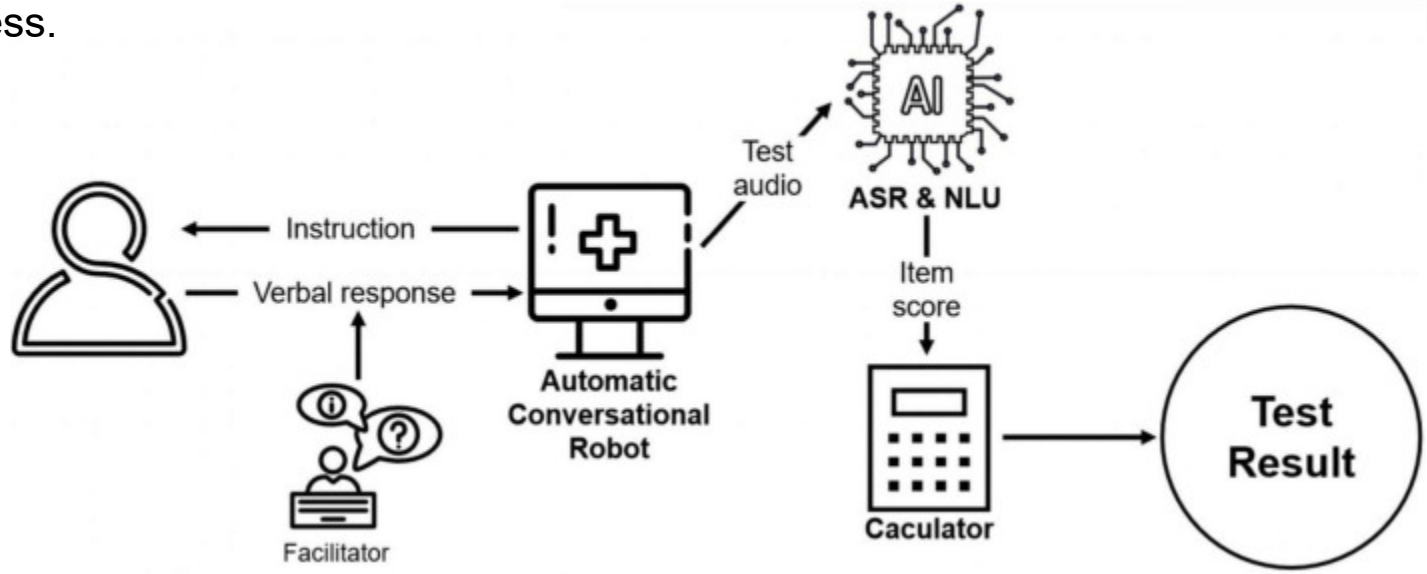
Normal ≥ 26 / 30

TOTAL __/30

Add 1 pt if ≤ 12 yr edu

Administered by: _____

The Digital Cognitive Screening (DCS) platform is a semi-automatic conversational robot that using voice-recognition technology, the platform initiates a conversation by asking the questions and cuing participants to answer verbally. After the test is finished, the platform automatically scores the participants' performance based on their verbal response. The automatic speech recognition (ASR) converts the test audio into text, and subsequently, natural language understanding (NLU) is used to extract key information from the text data and assess its correctness.



The DCS included the following cognitive test items: (1) Memory: 5-word (face, silk, chrysanthemum, hotel, red) delayed memory test with a total score of 5; (2) Orientation: 6-item orientation task (year, month, week, date, city, address) with a total score of 6; and (3) Executive function: animal fluency test with a score of 1 if participants speak out more than 11 animals. Zhao X, et al. A voice recognition-based digital cognitive screener for dementia detection in the community: Development and validation study. Front Psychiatry. 2022 Jul 22;13:899729. doi: 10.3389/fpsyt.2022.899729. PMID: 35935417; PMCID: PMC9354045.

(slide for information purposes)

How does one assess decision-making capacity? (3)

- MacArthur Competency Assessment tool for Clinical research (MacCAT-CR)
  - MacCAT-CR must be adapted for each research scenario, in keeping with the decision-specific nature of capacity.
- Clinical Dementia Rating (Neurology 1993;43:2412)
- Assess for delirium (fluctuating level of consciousness) using clinical judgment and the confusion assessment method (CAM)

Orientation to Person, Place and Time is not Adequate to Determine Capacity to Consent

- Subjects must show that they understand the elements of the research
- Formal assessment of study specific knowledge
  - Can they name the risks, benefits, if participation is voluntary, etc.
  - Based on this test, investigator can propose specific criteria for whether the subject can provide their own informed consent, or whether consent from legally authorized representative (LAR) is required

EVALUATION TO SIGN CONSENT FORM (recommended UMB HRPO tool, investigators can make their own)

Make a subjective judgment regarding item 1 below. Ask the patient questions 2-6. The evaluator may select the language to use in asking the questions in order to help the patient understand them.

1. Is the patient alert and able to communicate with the examiner?
yes = 2 no = 0
2. Ask the patient to name at least two (2) potential risks incurred as a result of participating in the study. 0 = unable to list potential risks, 1 = can list one risk, 2 = can list two risks
3. Ask the patient to name at least two (2) things that will be expected of him/her in terms of patient cooperation during the study. 0 = not able to list expectations, 1 = able to list one expectation, 2 = able to list two expectations
4. Ask the patient to explain what he/she would do if he/she decides that they no longer wish to participate in the study. 0 = doesn't know, 1 = answers but not the most appropriate response, 2 = talk to any staff member
5. Ask the patient to explain what he/she would do if he/she is experiencing distress or discomfort. 0 = doesn't know, 1 = answers but not the most appropriate response, 2 = talk to any staff member
6. Ask the patient to explain how medications (or treatments) are assigned during the study. 0 = doesn't know, 1 = answers but not the most appropriate response, 2 = correct answer

Evaluator

https://www.umaryland.edu/media/umb/oaa/hrp/documents/study-tools-docs/eval_consent.pdf

Problems with Assessment of Capacity

- Mild to moderate inter-rater reliability of assessment of decision-making capacity even in experienced psychiatrists based on patient interviews (Kim 2011)
- Use of the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) understanding subscale had moderate-high rate of agreement (Karlawish 2008)

Categorical Capacity Status of Participants as Determined by 5 Expert Judges

Table 3. Categorical Capacity Status of Participants as Determined by 5 Expert Judges[a]

Determination	Capacity to Appoint Research Proxy (n=188)		Capacity to Consent to Drug RCT (n=181)		Capacity to Consent to Neurosurgical RCT (n=186)	
	No. (%)	Mean (SD) MMSE Score	No. (%)	Mean (SD) MMSE Score	No. (%)	Mean (SD) MMSE Score
Capable	**116** (61.7)	22.9 (3.3)	**75** (41.4)	23.7 (3.1)	**29** (15.6)	25.0 (2.8)
3 Judges agree	32 (17.0)	21.8 (3.0)	20 (11.0)	22.7 (3.6)	8 (4.3)	24.0 (1.9)
4 Judges agree	27 (14.4)	22.2 (3.3)	30 (16.6)	23.0 (2.8)	14 (7.5)	25.1 (2.8)
5 Judges agree	57 (30.3)	23.8 (3.3)	25 (13.8)	25.3 (2.4)	7 (3.8)	26.0 (3.6)
Incapable	**72** (38.3)	17.3 (5.3)	**106** (58.6)	18.9 (4.9)	**157** (84.4)	20.1 (4.8)
3 Judges agree	23 (12.2)	18.8 (5.4)	21 (11.6)	21.2 (4.3)	19 (10.2)	23.0 (2.6)
4 Judges agree	26 (13.8)	17.8 (4.3)	29 (16.0)	19.3 (4.2)	34 (18.3)	22.4 (3.1)
5 Judges agree	23 (12.2)	15.3 (5.7)	56 (30.9)	17.7 (5.2)	104 (55.9)	18.8 (5.1)

Abbreviations: MMSE, Mini-Mental State Examination; RCT, randomized clinical trial.

[a]A total of 188 participants completed the first interview, which included the Capacity to Appoint a Proxy Assessment (CAPA) and either the drug RCT or the neurosurgical RCT MacArthur Competence Assessment Tool–Clinical Research (MacCAT-CR)(decided randomly) as well as the Mini-Mental State Examination (MMSE). One person finished CAPA during the first interview but did not finish MMSE or MacCAT-CR; and this person declined the second interview as well. This person is 1 of 8 who declined the second interview. The remaining 7 of 8 persons who declined the second interview did finish the CAPA, MMSE, and 1 of 2 MacCAT-CRs, but are missing the second MacCAT-CR.

Kim, S. Y. H. et al. Arch Gen Psychiatry 2011;68:214-219.

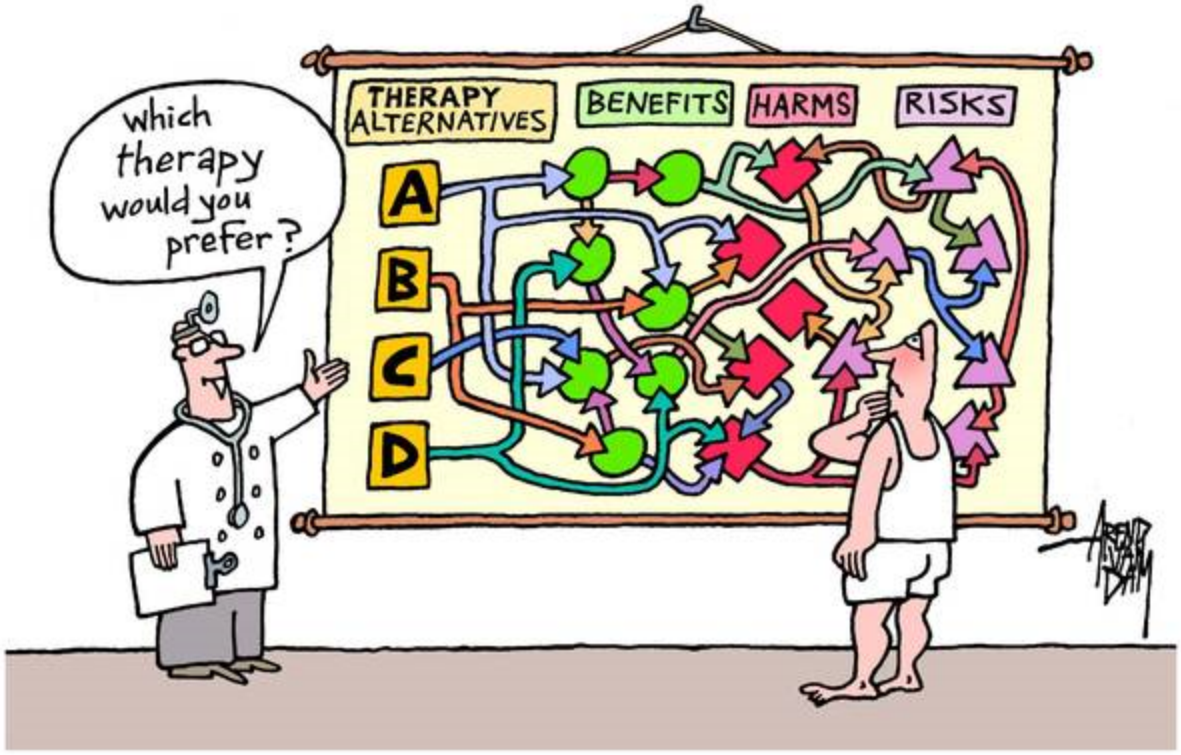
ARCHIVES OF GENERAL PSYCHIATRY

Problems with Assessment of Capacity

- Inherent limitations in the use of the instruments, particularly the MMSE as it only assesses limited number of cognitive domains
- Lack of discriminatory power to identify mild cognitive impairment (MCI)
  - Montreal Cognitive Assessment (MoCA) now more widely used in clinical practice to identify MCI
- A person's capacity to perform to perform one function cannot be presumed to be equivalent to his or her capacity to perform other functions.

If There is Evidence of Decisional Impairment or Incapacitation (1)

- PI must provide the IRB with a plan for assessing patient's ability to assent/dissent
- This is modeled after the approach in children
- Approach in individuals with mild to moderate cognitive impairment (MMSE 16-21) is to obtain their assent
- The threshold for transition to loss of capacity for medical decision making occurs ~MMSE score of 18 to 20 (Pucci, Hirschman)
  - Very mild to mild AD can provide consent (principle of double consent often employed)
  - Mild to moderate AD can provide assent



informed consent

From: **Assessment of Length and Readability of Informed Consent Documents for COVID-19 Vaccine Trials**

Table 1. Characteristics of the Phase III COVID-19 Vaccine Randomized Clinical Trial Informed Consent Documents[a]

Metric	Pfizer	Johnson & Johnson	Moderna	AstraZeneca	Mean	Proposed alternative
Length, pages, No.	25	25	20	17	21.8	10
Document reading time, min						
175 wpm (lower bound)	44.7	47.7	53.4	44.7	47.6	16.9
240 wpm (mean)	32.6	34.8	38.9	32.6	34.7	12.3
300 wpm (upper bound)	26.1	27.8	31.1	26.1	27.8	9.9
Word count, No.						
Whole document	7828	8341	9340	7821	8333	2960
Risk section	884	989	1445	977	1074	200
Privacy section	2478	1955	1280	1750	1866	778
Reading grade level						
Whole document	9.8	8.8	9.6	11.3	9.9	7.6
Risks section	9.5	8.5	9.4	11.2	9.7	6.1
Privacy section	11.7	10.7	11.5	13.1	11.8	9.6
Reading ease[b]						
Whole document	52.2	56.8	51.1	49.6	52.4	61.8
Risks section	58.8	56.8	54.8	46.9	54.3	71.2
Privacy section	39.8	48.7	40.3	41.0	42.5	53.8

Abbreviation: wpm, words per minute.

[a] Range, 0 to 100, with 100 indicating easiest to read and scores less than 60 considered difficult by the Department of Health and Human Services.

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Need to write better consent forms! Look at the very long reading times!!

- Reinforcement (multiple sessions) and use of novel procedures (video, story book, simplified CF, etc.) may improve comprehension (empiric evidence supporting this is weak)

Risk-sensitive Decision Making Capacity assessment (RS-DMC) the "Sliding Scale" Approach"

- Some advocate that thresholds for "competence" to make decisions (DMC or decision making capacity) about enrolling in a study are a sliding scale, depending in part on the complexity of the study, and risks to subjects
  - The greater the net risk to the subjects, the stricter the requirement for capacity to provide consent

If There is Evidence of Decisional Impairment or Incapacitation (2)

- Family member or other legally authorized representative is asked to make the decision to participate
- Hierarchy of decision making determined by state law (if there is one)
- Federal guidelines for VA studies

There are three kinds of health care proxies: Health Care Agent, Surrogate & Guardian.

https://www.marylandattorneygeneral.gov/Health%20Policy%20Documents/ProxyHandbook.pdf

- A health care agent is a person chosen to make medical decisions for another, should a severe illness or injury occur that makes communication impossible. The document that grants this decision-making power to the person selected is called a medical power of attorney.
- A health care agent may also be called a health care proxy or surrogate or an attorney-in-fact.

Legal surrogate

- Even when nobody has been named as a health care agent, a person may still be asked to make medical decisions for someone else. If you are a family member or possibly a close friend, under Maryland law you can make health care decisions if the person no longer can, and you are the closest relative or friend available. In Maryland, you would be called a surrogate.

Guardian

- A court may appoint a guardian to make health care decisions for someone else. A guardian is directly answerable to the court.

Legally authorized representative

- A legally authorized representative means an individual or other entity authorized under state law to consent on behalf of the research participant. Maryland law does not specify who may consent to research participation on behalf of an incompetent adult; however, Maryland law does indicate who may consent to medical care on behalf of an incompetent adult.
- Prior opinions from the Attorney General were that the same hierarchy applies to research

Maryland Hierarchy (slight difference for VA)

https://www.marylandattorneygeneral.gov/Health%20Policy%20Documents/ProxyHandbook.pdf

- (1) a health care agent appointed by the adult before becoming incompetent
- (2) a legal guardian appointed by the court
- (3) a spouse
- (4) an adult child
- (5) a parent
- (6) an adult sibling
- (7) a friend or other relative.

- For individuals who know that they may lose capacity to provide consent during the course of the study, PIs should provide participants the opportunity to appoint a “research agent” who may provide consent on the participant’s behalf after the participant loses capacity to consent for him/herself.

Challenges Informed Consent LAR

- Identification of proper LAR
  - Care giver often not LAR
  - State law: If present for decision making in clinical care, does it apply to research?
  - VA handbook 1200.05 hierarchy
- Informed consent from LAR not always an option

Importance of the Dyad in AD Research

- Caregiver often has to provide information on subject
  - Dyad (Subject with Alzheimer disease and caregiver)
  - In clinical trials caregivers are typically research subjects and also have to provide informed consent.
- Many clinical trials require AD subject-caregiver dyad as part of eligibility criteria
  - Under-representation of demented subjects residing in nursing homes and assisted living facilities in clinical trials of AD drugs in part due to lack of dyad (Hanson 2010)

How do you assure that LAR understands their responsibilities?

- Older caregivers may have subclinical cognitive impaired and difficulty comprehending consent form
  - How do you assure that LAR can provide valid informed consent?
  - Is team obligated to perform assessments of cognitive status of elderly spouse who serves as LAR?
  - What level of documentation is required of informed consent process with LAR?

LAR Challenges in Long-term Studies

- LAR may change during the course of the study
  - Death of spouse (initial LAR)
  - Court appointed guardian, durable power of attorney that may be different than the initial LAR
- How is research team informed of these changes?
- If new information comes to light after the completion of the study that impacts on subjects, who gets notified? Original LAR? “next of kin”?

Surrogate Decisions

- Based on “substituted judgment” – what the person said before they lost capacity (e.g. “I don’t want to be a vegetable.”.”)
- Based on “best interests” – what decision leads to the outcome an objective observer would think is best
- What do these concepts mean when it comes to the decision to participate in research?

Assent from subject

- A common problem in IRB submissions is that the PI hasn't provided enough information on subject assent
- Type of assent: verbal versus written
- Simplified assent form modelled after approach in pediatric studies rarely used
- Which subjects will provide assent? All? Only those who can?

LAR Documentation

- You are required to completed the Legally Authorized Representative Identification Form Adult Subjects
- https://www.umaryland.edu/media/umb/oaa/hrp/documents/study-tools-docs/LAR_1-16-14.pdf

Options Proposed to Further Protect Rights of Cognitively Impaired

- Capacity to provide informed consent assessed by an individual independent of the research team
- Independent person who obtains informed consent with the focus on whether the patient understands risks and benefits
- Independent participation monitor (VA or HRPO Research Subject Advocate, etc.)
- Prospective authorization
- Periodic re-consenting

Case 1: Known decisional impairment

- Study is greater than minimal risk with prospect of direct benefit
- Consent from LAR
- Assent from subject
- Consent from caregiver for their own participation in study (since they are providing information)

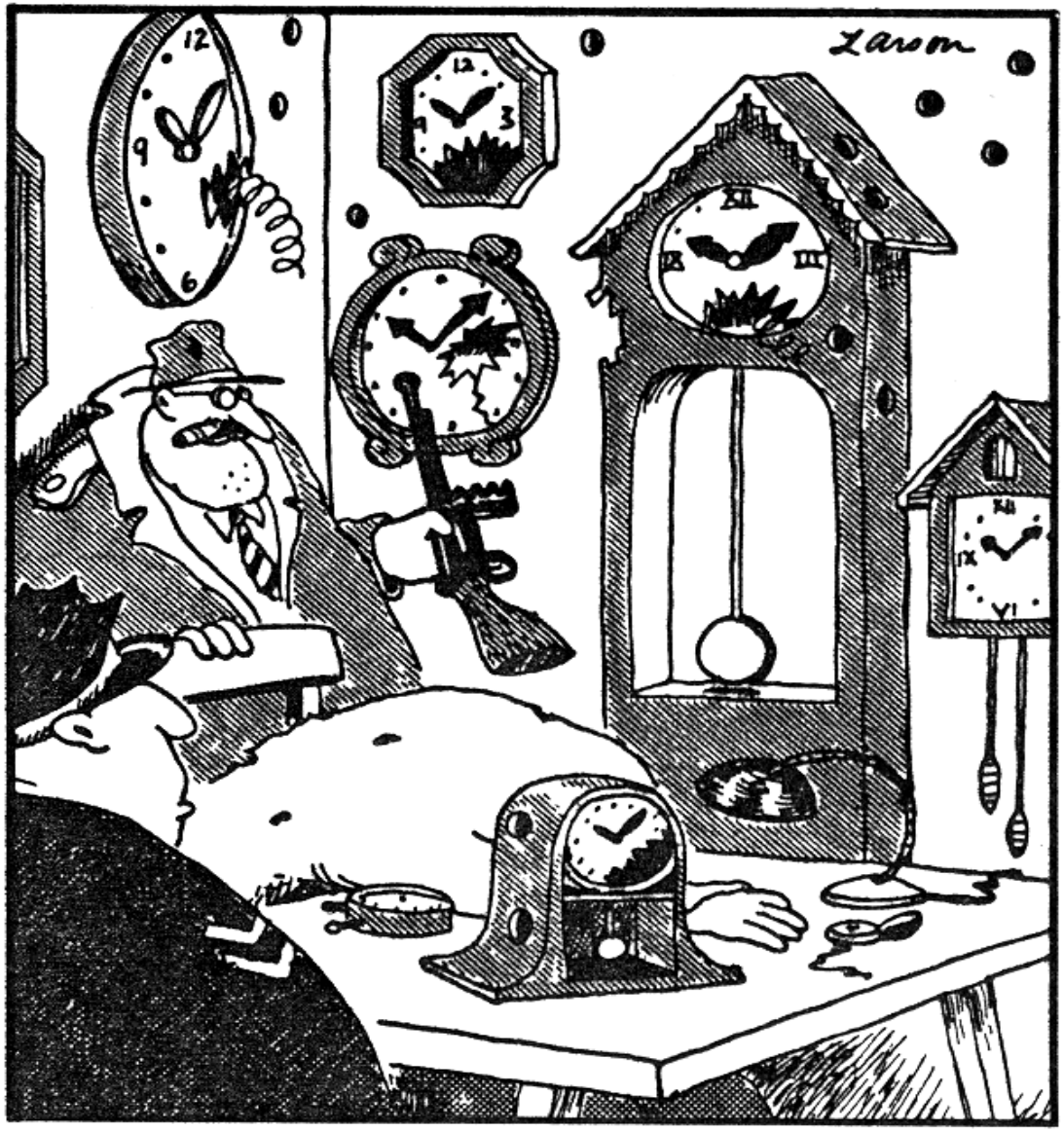
Case 2

- Older adults who have suffered an acute hip fracture and awaiting elective surgery are being recruited into a longitudinal study examining the recovery of physical functioning and its relationship to blood markers of inflammation post-surgery. Subjects will be assessed the day of surgery, 1,2,3 days post-operatively, at time of discharger from the hospital and then monthly for a year.

Anticipated vulnerable subject characteristics

- Delirium is defined as a fluctuating level of consciousness
- Investigators (and IRB) need to consider potential for delirium at time of enrollment or subjects becoming delirious during the course of the study (case 2)
  - Elderly postoperative subjects
  - Older adults with sepsis
  - >30% of ICU patients have delirium

DELIRIUM IS OFTEN UNRECOGNIZED



"We've got the murder weapon and the motive ...
now if we can just establish time-of-death."

Anticipated vulnerable subject characteristics

- Transient or temporary loss of capacity
  - Planned surgical intervention
  - Intensive care unit on ventilator
  - Trauma or other acute medical event
  - Planned emergency research (not allowed for VA research)

SIMPLIFIED DIAGNOSTIC CRITERIA

-- Uses 4 criteria assessed by CAM:

(1) acute onset and fluctuating course

(2) inattention

(3) disorganized thinking

(4) altered level of consciousness

-- The diagnosis of delirium requires the presence of criteria:

(1), (2) and (3) or (4)

- Study is minimal risk, no benefit study
- Prospective study: Feasible to obtain consent/assent from all subjects as clinical team will be obtaining informed consent for surgical procedure
- Not a VA study (VA additional criteria do not apply)

Case 3

- An investigator wants to examine the pattern of methicillin antibiotic resistant staph aureus in elderly nursing home patients. Nasal and rectal swabs will be performed upon admission to the nursing home and every month for 3 months. Subjects found to be carriers of the pathogen will be treated by standard of care antibiotics.

- Many of the subjects will have known dementia, many others with delirium or other evidence for cognitive impairment
- Scientific validity of study requires sampling all subjects in nursing home and all new subjects upon admission to nursing home
- Minimal risk study with potential prospective of direct benefit

Waiver of informed consent 45 CFR 46.116 d

- An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
  - (1) the research involves no more than minimal risks;
  - (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
  - (3) the research could not practicably be carried out without the waiver or alteration; and
  - (4) whenever appropriate, the subjects will be provided with additional information after participation.

- Study was granted waiver of written informed consent and HIPAA authorization as this is a minimal risk study, need data on 100% of subjects for scientific validity, and it was not practical to obtain informed consent and HIPAA on all the subjects
- IRB minutes/letter to investigator need to document rationale behind waivers

Case 4: Challenges in doing long-term studies: Huntington's Disease

- HD is an autosomal dominant inherited neurodegenerative disorder cause by excessive trinucleotide repeats in the HTT gene that is characterized by progressive motor dysfunction, emotional disturbances, dementia, and weight loss
- The average age of clinical onset is about 37 years of age; however the range is from infancy into the 80's.
- Affected individuals are disabled by early functional decline and require care and supervision for another 15-25 years before succumbing to the effects of severe physical and mental deterioration.
- There is no therapy proven to delay onset or slow progression. Drugs currently only treat symptoms such as chorea and psychiatric issues

Case 4 (continued)

- An investigator is proposing a RCT of the effect of a nutraceutical versus placebo on the decline in functional performance and cognition in subjects with mild Huntington's Disease
- Subjects will be followed for three to five years
- Upon entry into the study, the subjects will have a Huntington Study Group Total Functional Capacity (TFC) score >7 and will be able to provide their own informed consent

Informed consent issues

- Some of the subjects are expected to lose capacity during the course of the study.
- The phenotypic decline will occur at a variable and unpredictable rate
- What additional steps need to be take to protect these vulnerable subjects?

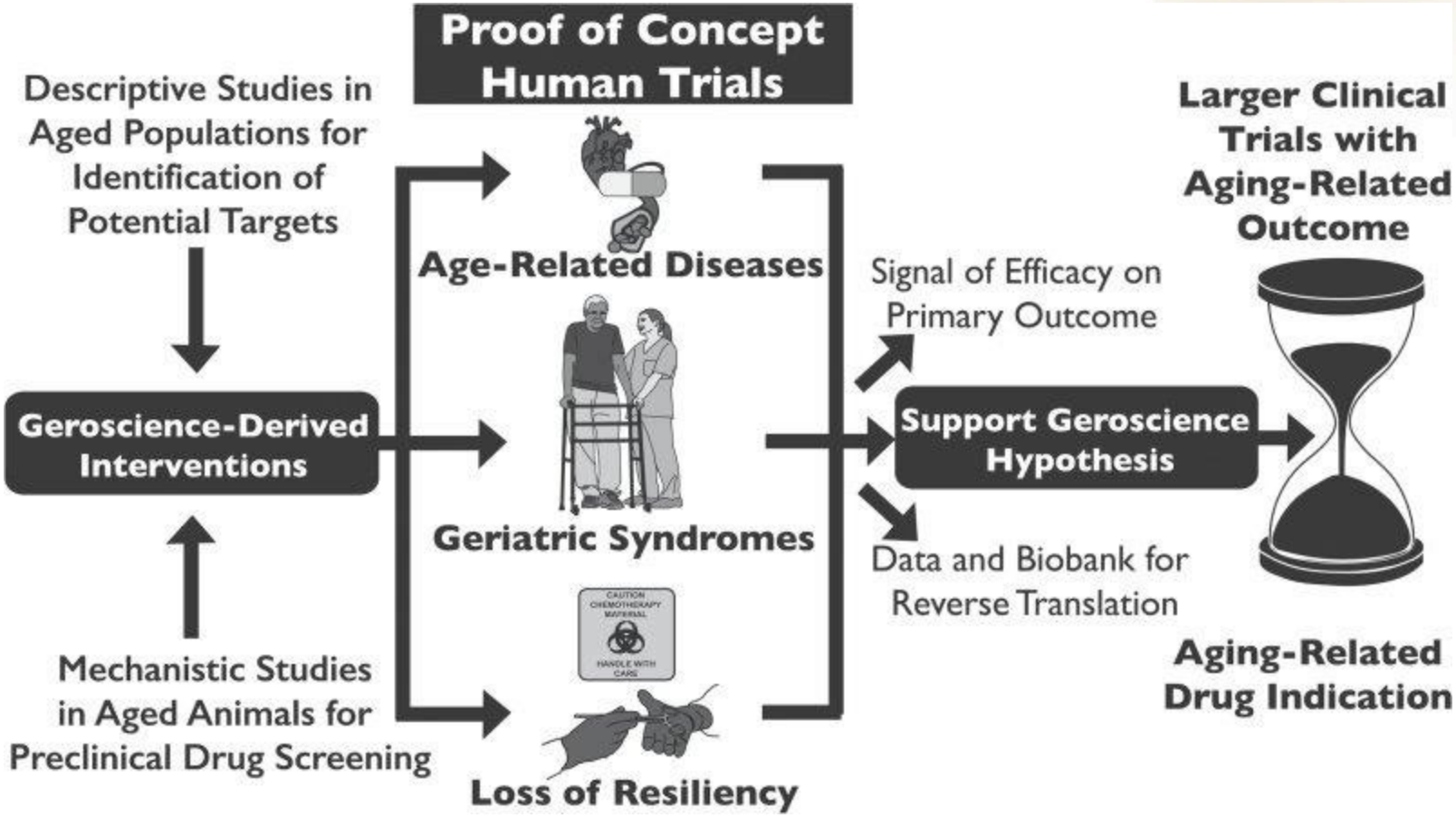
- The subject will be asked to name a legally authorized representative (LAR) upon entry into the study.
- Subjects will sign a separate consent form that discusses the need and responsibilities of the LAR and this document will contain the name of the LAR and their relationship to the subject
- Subjects can however enter the study even if they do not name an LAR

- During the study, if the PI feels that the subject has had a significant cognitive decline (a score of 60% or less on the UHDRS Independence scale), they will conduct a capacity assessment, including discussion of the study purpose, differences between research and clinical assessments and the risks of study participation.

- If the subject has lost the capacity to provide informed consent, the LAR will be asked to provide written informed consent and the subject, assent
- If no LAR has been identified, or if the LAR does not want the person to continue in the study, or if the subject withholds assent, the subject will be withdrawn from the study

Case #5: Targeting Aging with Metformin (TAME) study

- Hypothesize that metformin will delay the onset of several major age-related diseases, thereby indicating its potential to extend health span and increase active life expectancy
- The TAME study is planned as a double-blind, placebo-controlled multicenter trial, enrolling approximately 3,000 individuals aged 65 years and older and will exclude variety of pre-existing conditions.
- The primary outcome for this trial is the time to occurrence of any component of a multimorbidity composite, which includes coronary heart disease, stroke, congestive heart failure, peripheral arterial disease, cancer (driven mainly by breast, colorectal, prostate, and lung), T2DM, cognitive impairment, and mortality.
- The study proposes to use a metformin dose of ~1,500mg per day. It is designed as a 6-year study, with a mean follow-up time of more than 3.5 years.

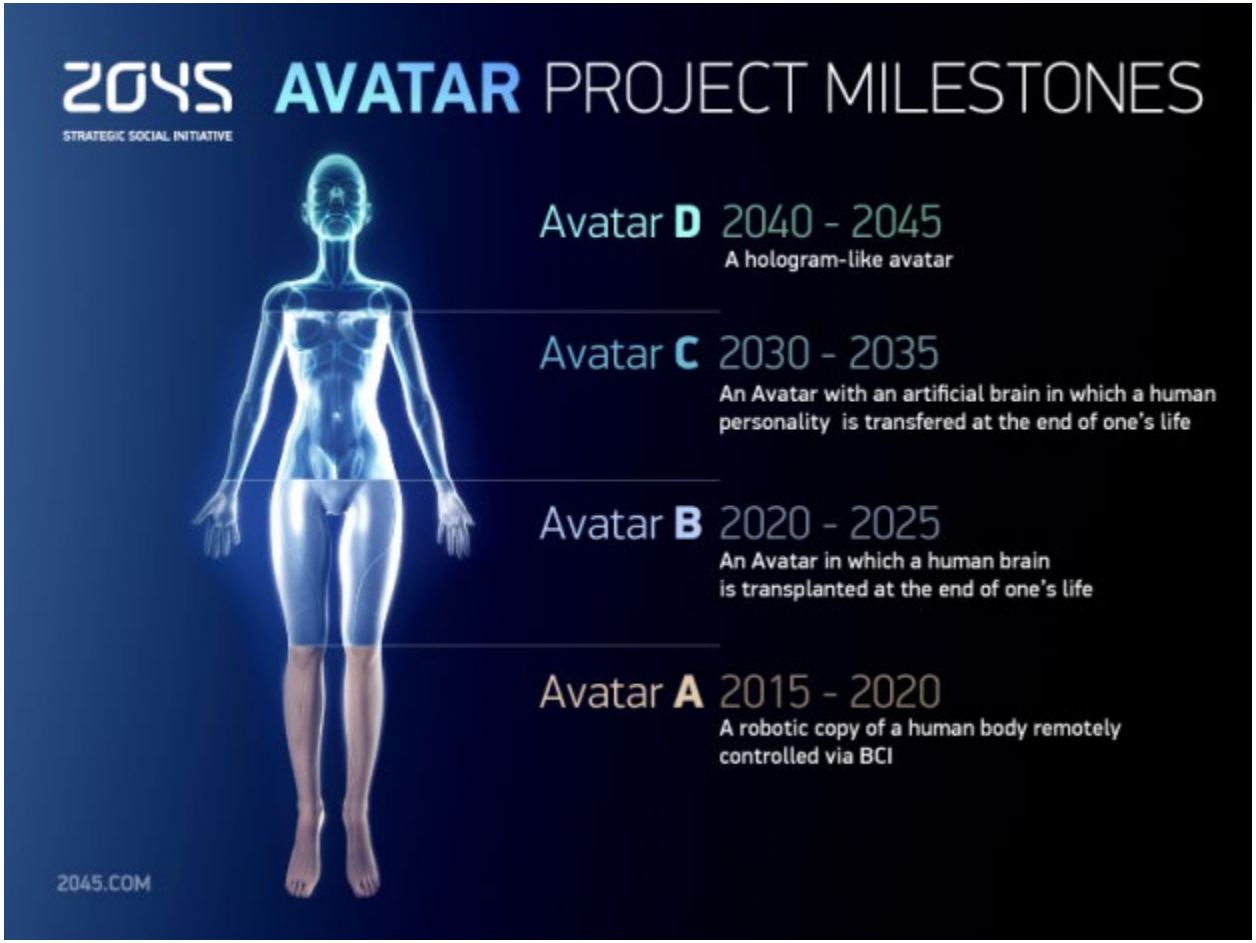


Senolytics: targeting senescent cells for age-associated diseases

The Immortality Financiers: The Billionaires Who Want to Live Forever

- Google has been experimenting with "life extension" through an independent company called Calico (https://www.calicolabs.com/) . Calico operates from a $1.5 billion research center in San Francisco with the aim of developing "life-enhancing therapies for people with age-related diseases. In 2021 in their continued partnership with AbbVie they committed another billion to this research.
- Google isn't the only company fighting back the years. Other Silicon Valley types including Peter Diamandis' Human Longevity Inc (https://www.diamandis.com/human-longevity-inc) and Ray Kurzweil are also looking into the realms of life-extension research.
- Kurzweil has predicted that machines and humans would merge in 2045 (“singularity”) (The Singularity Is Nearer When We Merge with AI).

Dmitry Itskov, a Russian billionaire has created the “2045 Initiative" which “aims to create technologies enabling the transfer of an individual’s personality to a more advanced non-biological carrier, and extending life, including to the point of immortality".



Likelihood of increasing health disparities between rich and poor, young and old as costly anti-aging technology and therapies become reality

In “Elysium” set in the future, the rich live in satellites in outer space where disease largely conquered, benefit from anti-aging technology where the poor minions live in squalor

Ethical issues for discussion

- Extending life span is generally not felt to be a worthy goal unless health span is improved and extended in parallel.
- Social, economic and ethical aspects of applying the healthspan- and lifespan-extending interventions should however be comprehensively debated prior to their implementation in public health practice.

Summary of cases

- Known cognitive impairment:
  - Research protocol is targeting subjects with dementia to specifically study a question that can only be answered by enrolling them as subjects (case 1).
- High likelihood of dementia and delirium:
  - Study being performed in setting or enrolling from population enriched in subjects with dementia or likely to have dementia; i.e. subjects residing in nursing homes, assisted living, etc (cases 2, 3).

- Enrollment of subjects who will lose capacity overtime (case 4)
  - Team must anticipate the need for continual assessment of capacity with clear guidelines for loss of capacity
  - Prospective identification of LAR (if possible)
  - Recognizes that LAR may change over the course of the study

- Case 5 rapidly evolving field of senolytics with its own set of challenges

Recommendations

- Assessment of capacity to provide informed consent should be tailored to the study population
- Investigators should employ specific assessments relevant to the protocol
  - The subject must demonstrate study specific knowledge, *understand* and *appreciate* the nature and expected consequences of participation including risk and benefits and alternative to participate and have the ability to communicate this decision to the team.

Greater the net risk to the subjects:

– Stricter requirement for capacity to provide consent by the subject
– Greater demands and responsibility on the LAR to represent the best interest and or substituted judgment on behalf of the individual with diminished capacity

You never know what will happen. Woman, 104, dies days after making a skydive