Let Their 'Yes' be 'Yes' and Their 'No' be 'No': Understanding Assent in Clinical Research

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HEALTH SCIENCES

SCHOOL OF MEDICINE

July 4th, 1885
Paris, France
8 am

- Joseph Meister, 9 years old, is playing outside of a grocers' in Paris
- A possibly rabid dog appeared outside the store, and attacked the grocer, a Mr. Theodore Vone
- The dog then saw Joseph and jumped on him, knocking him to the ground

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773

July 4th, 1885
Paris, France
8 am

- Per report of eyewitnesses, he was bitten extensively on the hand, legs and thighs
- Bystanders run to help
- While pulling Joseph out from under the dog, he is noted to be covered with dog saliva and blood
- The dog is eventually caught and killed

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773

July 4th, 1885
Paris, France
8 pm

- An autopsy is performed on the dog
- Bits of wood, grass and straw are found in the stomach, and the dog is diagnosed with rabies

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773

July 6th, 1885
Paris, France

- Joseph is taken to see Dr. Louis Pasteur, who at that time was working on an experimental rabies vaccine

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773

- Pasteur had been waiting to test the vaccine in human subjects, and felt his studies had advanced to the point that human trials were warranted

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773

July 6th, 1885
Paris, France

- Dr. Pasteur had utilized an experimental vaccine in 50 dogs with success, but never in a human
  - "…I decided, not without deep and severe unease…to try on Joseph Meister the procedure which had consistently worked in dogs."

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773

July 6th, 1885
Paris, France
8:00 pm

- At 8:00 pm on July 6th, 1885, Dr. Pasteur injects Joseph with the experimental vaccine
- He ultimately injects Joseph 13 times over 10 days, because "…in this first trial (in a human) I had to be especially cautious".

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773

Joseph Meister never developed rabies

- He was also never asked by Dr. Pasteur if he wanted the vaccine

- He was also never asked by Dr. Pasteur if he wanted the vaccine
- His parents were asked, but not Joseph

- It is possible he may never have developed rabies
- He may have suffered serious or deadly side effects from the experimental vaccine

- It is also possible Joseph would not have been old enough to understand the high risk of death from rabies, and that perhaps he may have focused only on the need for the 13 shots

Outline

- 1.) Vignettes
- 2.) What is Assent? A History of the Process
- 3.) Federal Regulations
- 4.) NM State Law
- 5.) Pediatric Assent
  - a.) Neurodevelopmental Concepts
  - b.) Adolescents
  - c.) Younger Children
- 6.) Assent with Cognitively-Impaired Adults
- 7.) Vignettes re-visited
- 8.) Conclusion

Vignette 1

- You are about to approach the family of a diabetic 8-year-old girl regarding consent and assent to participate in a randomized controlled trial of a new long-acting insulin

Vignette 1

- The drug may mean less insulin injections per day for a subject
- However, it will require more frequent finger-stick blood measurements, multiple outpatient visits in the CTSC clinic, a daily meal diary and a brain MRI

Vignette 1

- The family is on board with the study
- The child is not paying much attention to your talk, and is watching ‘Paw Patrol’ on TV and intermittently snacking on miniature ‘Chips Ahoy’ cookies

Vignette 1

- You turn off the TV and go over the protocol with her in language appropriate for an 8-year-old
- When you ask if she wants to participate, she continues eating and quickly responds “So I get less insulin shots? Sure!” and then picks up the TV remote to turn the cartoon back on

Vignette 2

- You are about to enter the clinic room of a 16-year-old young woman with rare variant of Pfeiffer syndrome, a genetic condition which presents with severe craniofacial deformities
- You explain that the genetic testing study for which she consented to last month was a major breakthrough, and researchers have now found a gene they believe is responsible for her form of the disease

Vignette 2

- You explain that to complete the study per protocol, they now need to take a photo of her (with her eyes blacked out, and completely unidentifiable) to go along with the genetic information

Vignette 2

- Her parents readily consent to this, still chatting excitedly about how happy they are that their daughter's blood resulted in the discovery of this gene

Vignette 2

- Looking across the room, you see that the patient is less happy
- She is staring at the floor and not speaking

Vignette 2

- When you ask what is wrong, she says “I’ve changed my mind about participating in this study. All my life, people have made fun of my appearance. Now, all people care about is my blood and a picture of my face---like I’m some kind of freak or a ‘commodity’ to be used. I’m tired of it. I just want to be a normal person, not a scientific breakthrough, not a freak, not a picture or a string of genetic information in a journal. Just a teenager.”

Vignette 2

- She goes on: “I know its de-identified, and my eyes are blacked out, but just knowing it’s out there, and that people are looking at it---it bothers me. I…I…I think I want to withdraw my assent for this study. I read in the consent form last night that I’m allowed to do that---you guys haven’t taken the picture yet, and you still have the blood. I think that’s what I want to do.”

Vignette 2

- Her mother comes over to her, and puts a hand on her shoulder
- She says “Sweetheart, I know this I really hard for you. But think of all the kids you could help with this…”
- After a long pause, still staring at the floor, she nods her head ‘yes’ and agrees to continue in the trial

Vignette 3

- You enter the ED to approach the family of an elderly man for consent and assent to participate in a study.
- The study involves collection of 3 blood specimens over several hours for a study on heart failure---a condition with which the gentleman is presenting
- A research echocardiogram (an hour longer than the standard of care echocardiogram) will also be collected, as well as a timed-walk

Vignette 3

- The study has a legally-authorized representative (LAR) provision, and an acceptable LAR is available at the bedside in the form of his daughter
- Assent from the subject is to be attempted per protocol

Vignette 3

- You learn quickly that the potential subject has early-onset Alzheimer's disease, and that his wife died of heart failure several months ago

Vignette 3

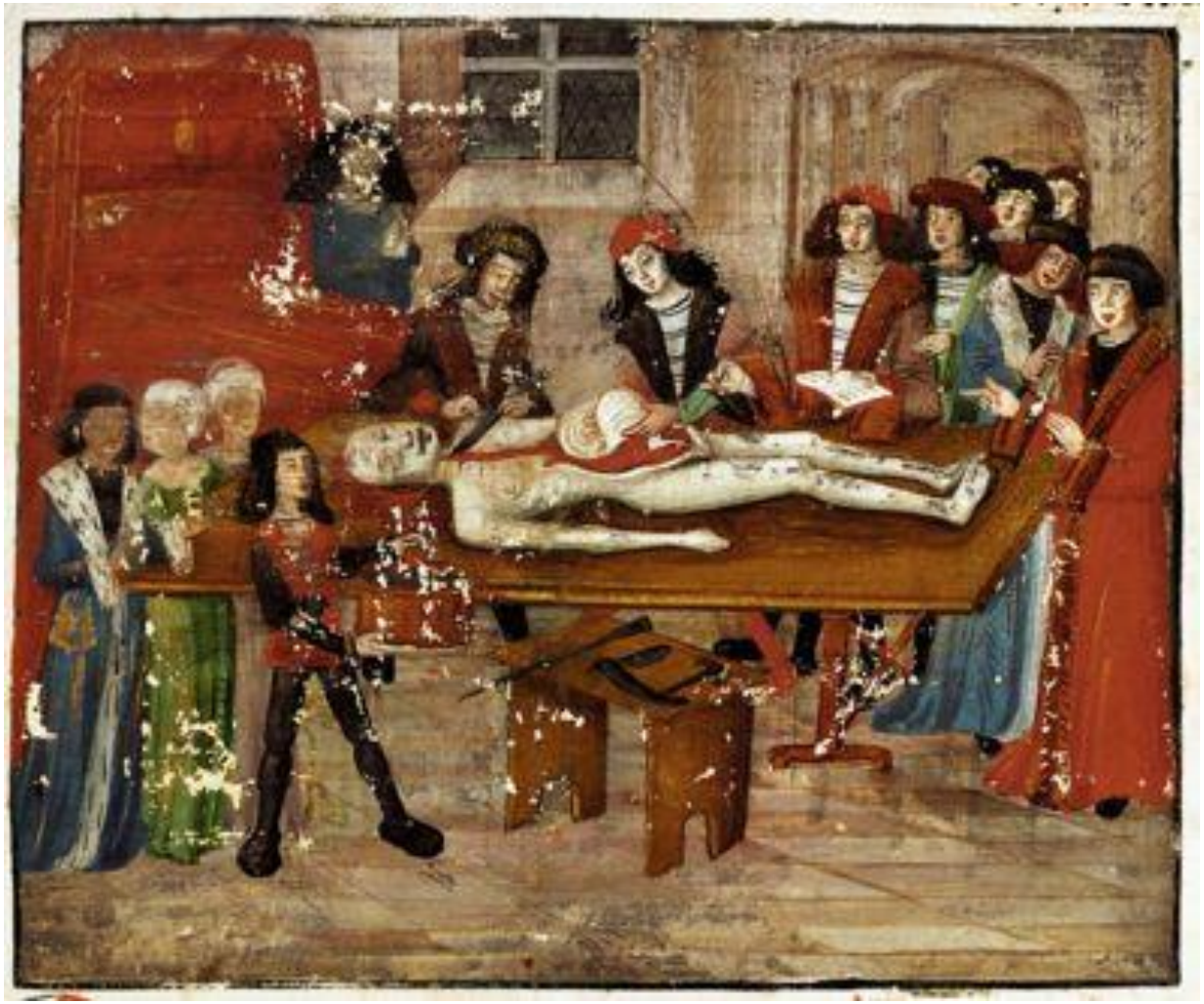
- You explain the study in detail to his daughter and to him (with varying language complexity)
- With a teach-back approach, he sometimes seems to forget what he is signing up for, and keeps saying “As long as it helps people like my wife, I’ll do it---she had heart failure too you know.”
- He gets some points right, but forgets others

Vignette 3

- You get the impression he has a general idea of what he is signing up for, and he is willing to sign the assent form.
- His daughter says it is fine with her, but ultimately won't sign the consent form '…unless Dad is OK with it.'

2.) History of Assent in Research

The Middle Ages:
Not alot of IRB Approved Research Going on...



The Middle Ages:
HIPAA Not Yet Up and Running...

The Nuremberg Code
1947

The Nuremberg Code 1947

- "The voluntary consent of the human subject is absolutely essential. This means that the person should have legal capacity to give consent."

Carroll TW, et al. *J Hist Medicine All Sci*. 2010;66(1):82-116.

The Nuremberg Code 1947

- **Many bioethicists concluded that this effectively excluded children from research**
  - "It is to treat him as if he were a joint adventurer in the common cause of medical research." Paul Ramsey.

Carroll TW, et al. *J Hist Medicine All Sci*. 2010;66(1):82-116.

Post-WWII

- **Conversely, many unethical studies in children DID occur during the post-WWII time period**
  - 1956-1971 Willowbrook hepatitis studies
    - Exposure of healthy children 3 to 11 years old to active hepatitis viruses to study the disease course

Carroll TW, et al. *J Hist Medicine All Sci*. 2010;66(1):82-116.

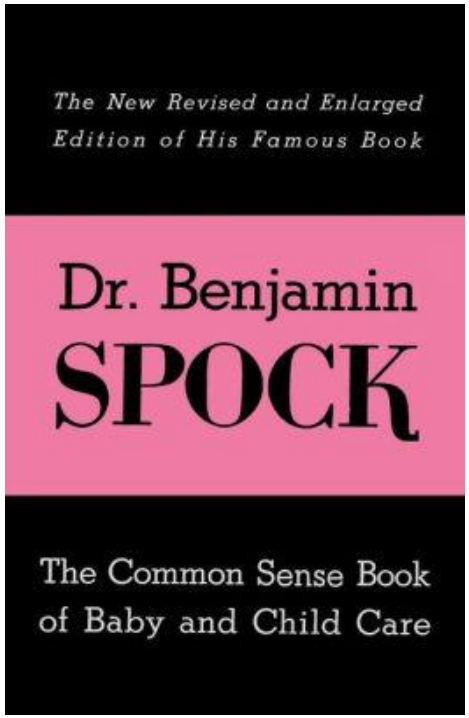
Post-WWII

- But how to justify potentially ethical research without a clear benefit to the individual child but to society?

Carroll TW, et al. *J Hist Medicine All Sci*. 2010;66(1):82-116.

Post-WWII

- An increasingly child-centered American culture emerging



Carroll TW, et al. *J Hist Medicine All Sci*. 2010;66(1):82-116.

Post-WWII

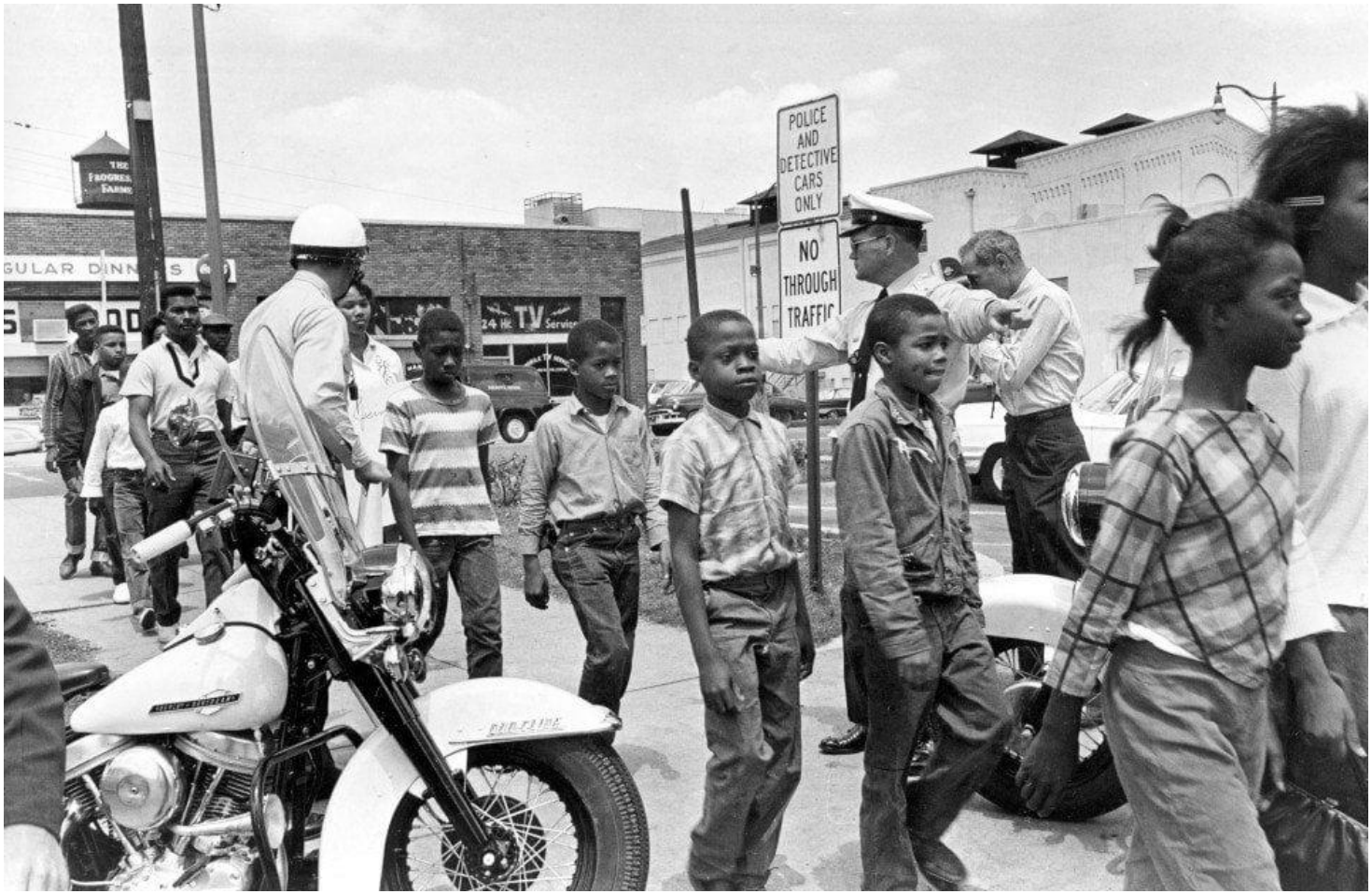
- **Polio Vaccine Trials of 1954:** Successful Pediatric participation in clinical research

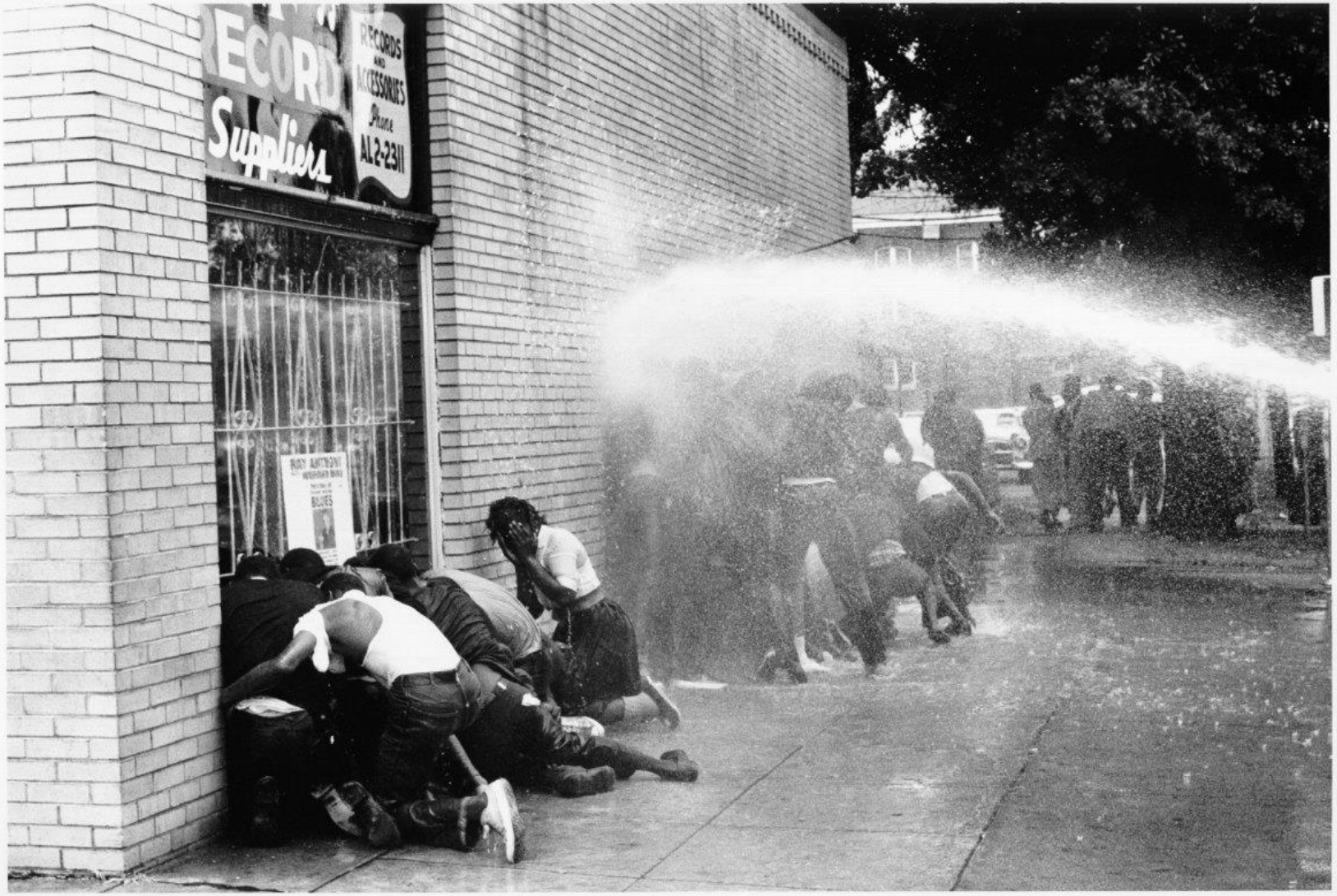
Carroll TW, et al. *J Hist Medicine All Sci*. 2010;66(1):82-116.
Oshinsky D. Polio: An American Story. New York. Oxford University Press, 2005.

- March of Dimes head Basil O'Connor called upon families to participate in the polio vaccine tests
- After their success, they '...instilled a lasting faith in the power of medical research to eradicate children's diseases.'

Carroll TW, et al. *J Hist Medicine All Sci*. 2010;66(1):82-116.
Oshinsky D. Polio: An American Story. New York. Oxford University Press, 2005.

Alabama, 1963
Schoolchildren Confront Bull Connor

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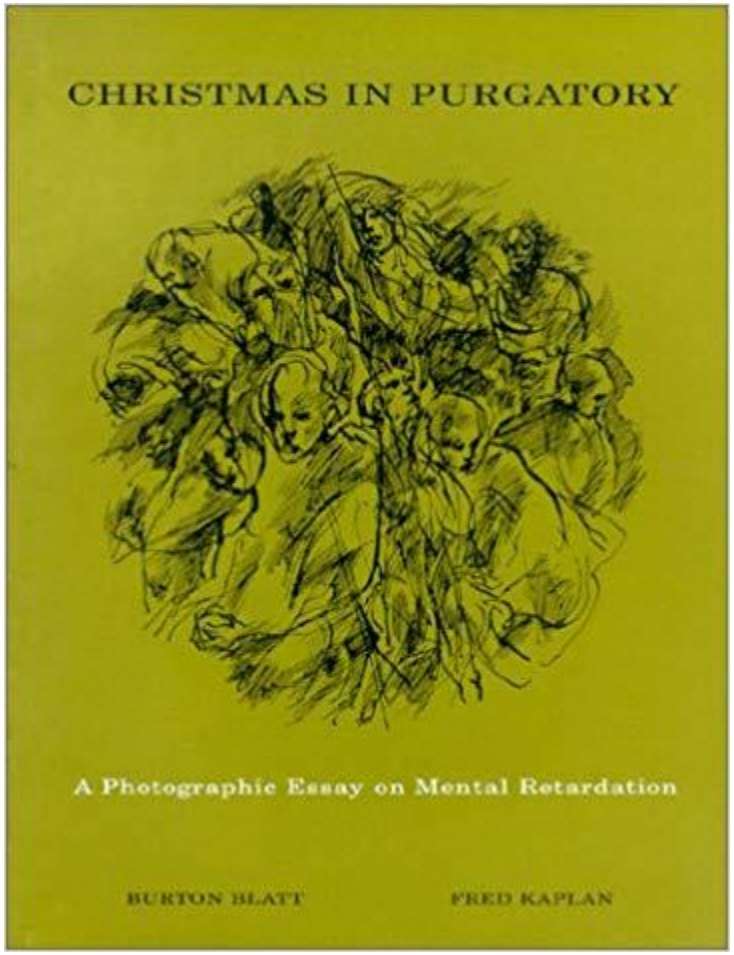
JOCKEY BOY
RESTAURANT
Coca-Cola

Tinker vs. Des Moines, United States Supreme Court 1969

- Children were allowed to protest the Vietnam war by wearing arm bands to school
- Ruling the first amendment applied to children

Boston, 1974
African American Children Fight Segregation in Boston's all-White Schools

Growing Respect for Children's Autonomy, Increasing Demand for Protection of those Incapable of Consent



Blatt B, Kaplan F. Christmas in Purgatory: A photographic essay on mental retardation. 1966.

Brooklyn Jewish Chronic Disease Hospital

- Physician-researcher injected cancer cells into elderly residents without consent, assent or assessment of comprehension

Skloot, R. The Immoral Life of Henrietta Lacks. 2010
Mulford, RD. Experimentation on Human Beings. Stanford Law Review. 1967.

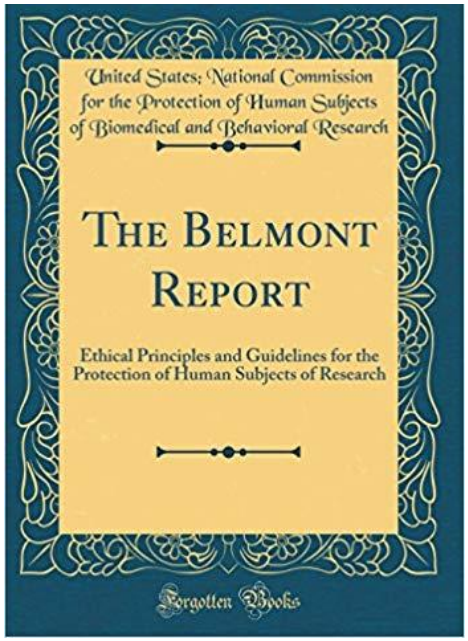
THE BELMONT REPORT

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



Department of Health, Education and Welfare. 1979

The Belmont Report

"Even for these persons [infants and young children, mentally disabled patients]...respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored..."

Department of Health, Education and Welfare. 1979

The Belmont Report

- A nod to adults incapable of providing consent was also present:

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Department of Health, Education and Welfare. 1979

- Vague mention of assent in the first American Academy of Pediatric guidelines on Pediatric Research (1976)

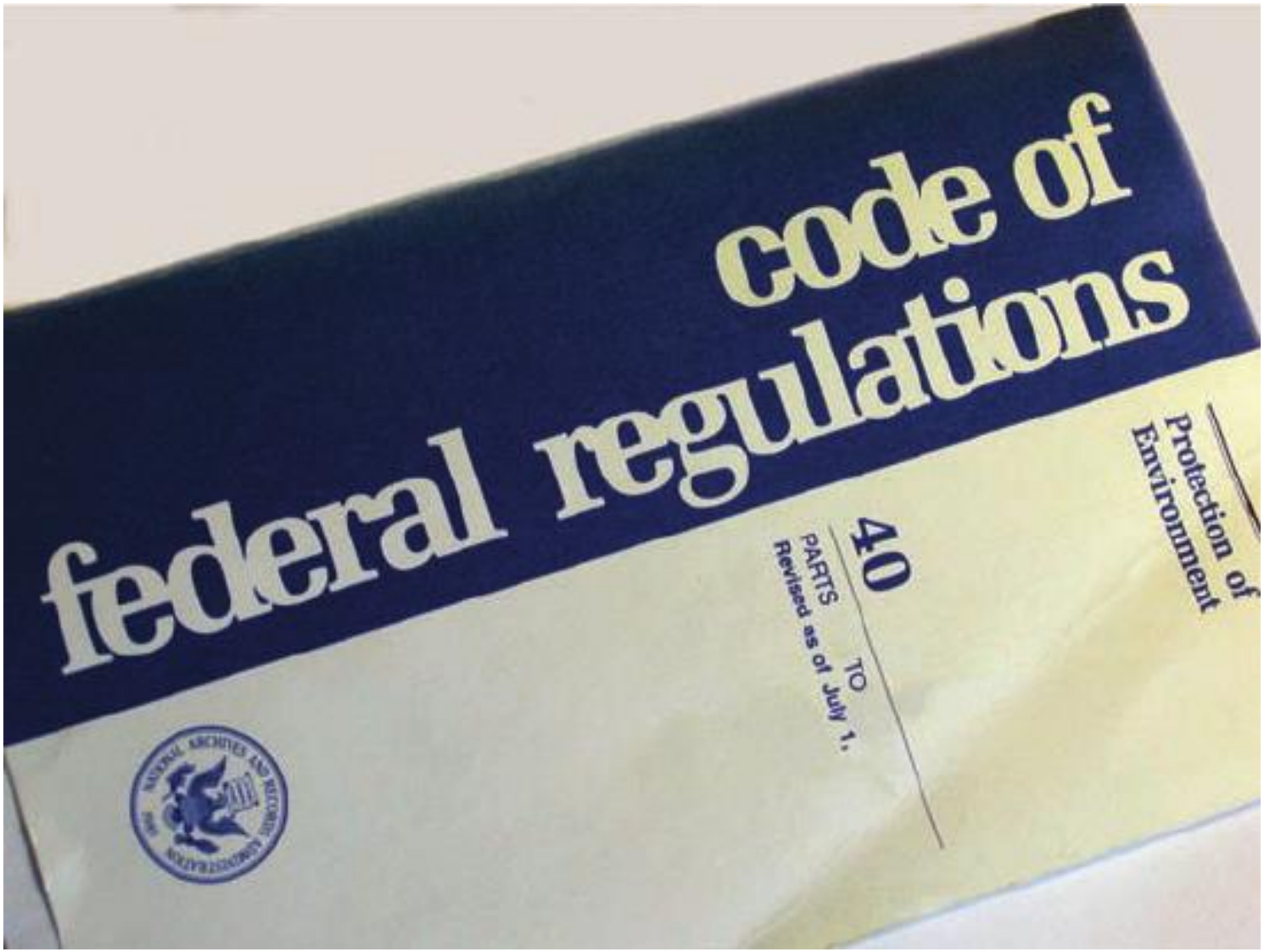
PEDIATRICS, Volume 57, Number 3: Pages 414-416,
March 1976.

- “It is also wise to include a provision that the procedure will be verbally explained to the minor and his wishes respected.”
- “...a study not specifically essential to the child will be discontinued if the child exhibits fear or resistance.”

PEDIATRICS, 1976;57(3):414-416

- **Convention on the Rights of the Child**
  - U.N. General Assembly, December 12, 1989
  - Article 12
    - “States parties shall assure to the child who is capable of forming his or her own view the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child.”

3.) Federal Regulations



1981
What Does The Common Rule Say About Pediatric Assent?

(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

1981
What Does The Common Rule Say About LAR's for Adults

- Mentioned as an option with adult research subjects

4.) NM State Law

Legally Authorized Representative---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. 45 C.F.R. § 46.102(c)

4.) NM State Law
Who can be an LAR?

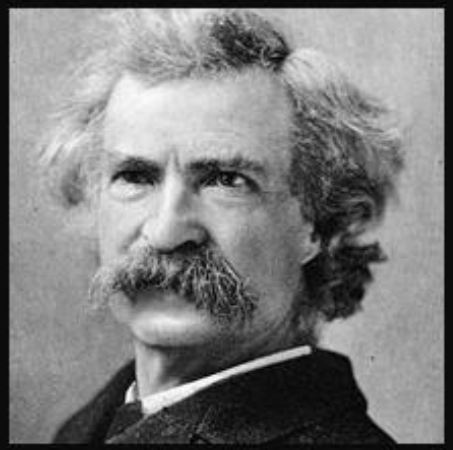
- **For research as part of health care treatment (in descending order of priority)**
  - Spouse
  - Person in a long-term relationship
  - Adult child
  - Parent
  - Adult sibling
  - Grandparent
  - Adult with special knowledge of the person or who has provided care

4.) NM State Law

- Pediatric assent not discussed in NM state law

5.) Pediatric Assent
a.) Neurodevelopmental Issues

Mark Twain



When I was 17, my father was so stupid, I didn't want to be seen with him in public. When I was 24, I was amazed at how much the old man had learned in just 7 years.

AZ QUOTES

Why Age 7 for Assent?

- A.) No clear reason
- B.) 7 is a lucky number
- C.) There are 7 days in a week
- D.) Mickey Mantle wore #7, and he was a really good baseball player
- E.) Children become cognitively capable of providing assent at the age of 7

Why Age 7 for Assent?

- A.) No clear reason

Why Age 7 for Assent?

- American Academy of Pediatrics recommends age 7
- **Cardwell vs. Bechtol, Tennessee Supreme Court ruling (1987)**
  - Ruled that children under 7 years of age had a lack of capacity to assent/consent
  - No biological basis for this

Cardwell v. Becthol, 724 SW 2d 739, 745 (Tenn 1987)

- MRI studies show the gray matter volume and myelination patterns in the brain continue to mature until the 3rd decade of life
- The pre-frontal cortex (balances risks/rewards) is one of the last areas of the brain to mature (into young adulthood)

Katz AL, et al. Pediatrics. 2016;138(2)

Brain Maturation Over Time

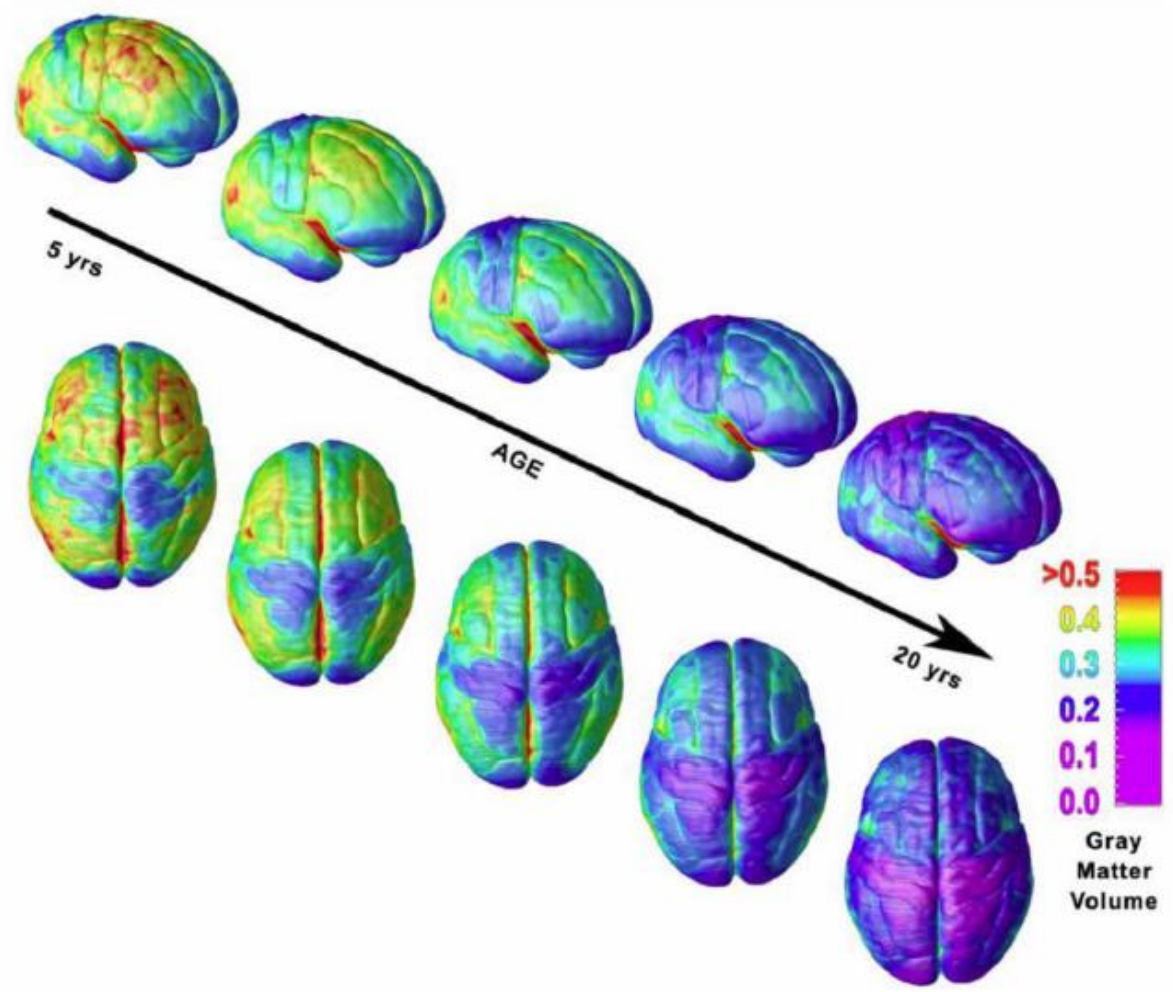


Figure 1. Right lateral and top views of the dynamic sequence of gray matter maturation over the cortical surface.

Colver A, et al. Arch Dis Child. 2013;98(11):902-907.

5.) Pediatric Assent
b.) Adolescents

Teens Have Been Known to Make Bad Choices from Time to Time

What About Assent for Research Participation?

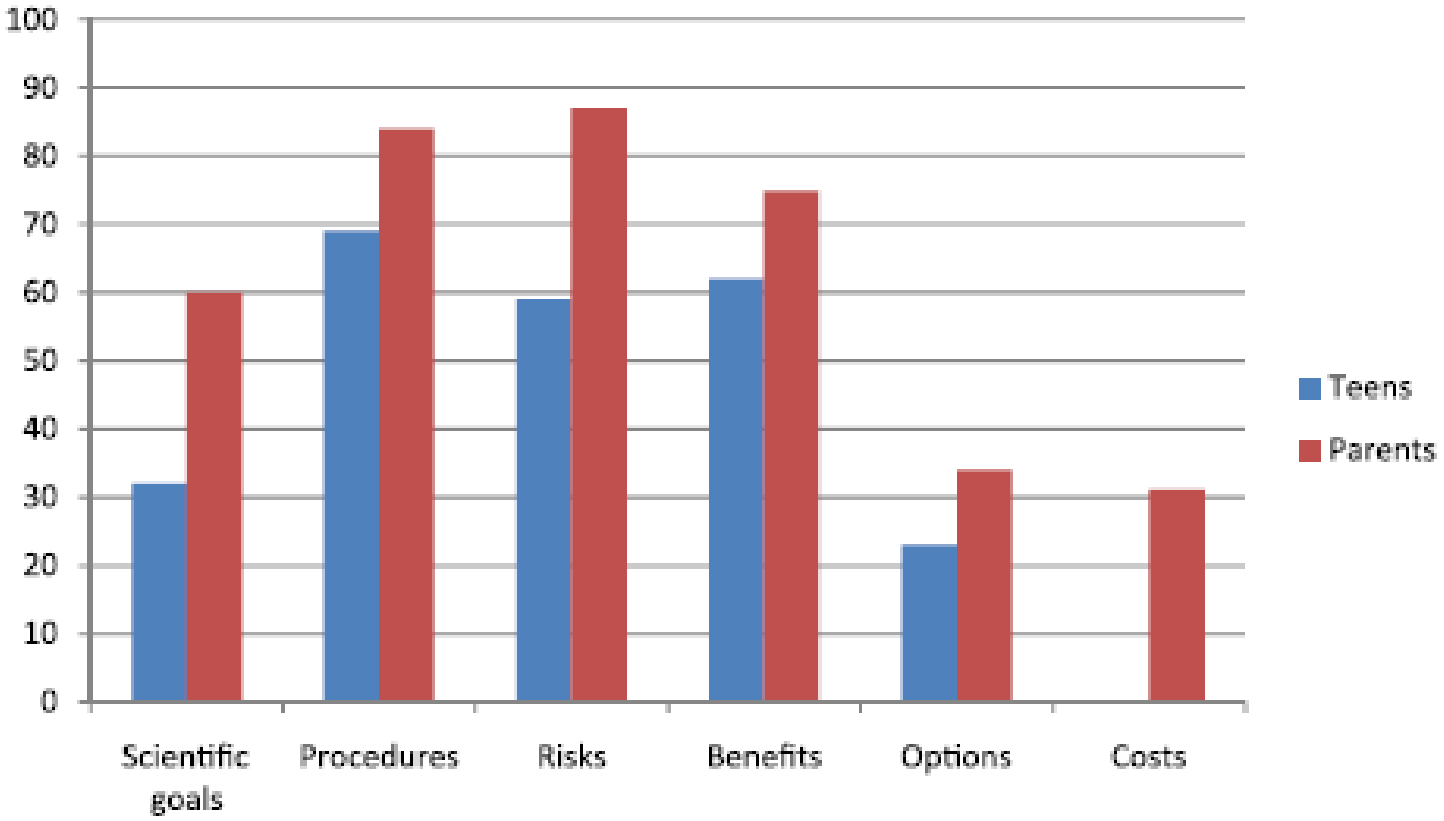
- When presented with 9 hypothetical trials of increasing risk, teens were nearly **twice as likely** as parents to agree to participate in the most risky trials

Brody JL, et al. J Adolesc Health. 2005;37:229-235.

- The teens were more concerned about the ‘hassles’ of the study
- **Only 10% of teens mentioned risk as a concern of enrollment**

Brody JL, et al. J Adolesc Health. 2005;37:229-235.

What do Teens Want to Know about a Study?



Grady C, et al. J Adolesc Health. 2014;54:515-520.

Teens and the Assent/Consent Form

- **Multi-site study of 177 adolescents enrolled in clinical research at U.S. sites**
  - What percentage did not read the assent/consent form at all or very carefully?
  - What would you guess?

32%

Pressure to Enroll? The Role of Undue Influence

- Structured interview of 177 teens enrolled in clinical research at the NIH or Seattle Children's Hospital

Grady C, et al. J Adolesc Health. 2014;54:515-520.

Teenager's and Parent's Perceptions of Pressure to Enroll in a Study

Statement	% Teen's Agreement with Statement	% Parent's Agreement with Statement
Felt pressure or 'could not have refused to enroll'	37%	N/A
Would have been 'difficult' or 'very difficult' to refuse	28%	N/A
Parents would have tried 'hard' to convince a teen to enroll	N/A	45%

Grady C, et al. J Adolesc Health. 2014;54:515-520.

How to Deal with Teenage Subjects: Separating Teens from Parents for Assent

- Randomized, controlled trail of separating adolescents from parents during assent vs. assent in the same room as parents
- Pre-post test of knowledge of the study

Annett RD, et al. AJOB Empir Bioeth. 2017;8(3):189-197

- Teens undergoing assent **separately** exhibited **significantly higher** post-test scores on knowledge of risks, benefits, research processes and details of the study than those undergoing assent with parents in the room

Annett RD, et al. AJOB Empir Bioeth. 2017;8(3):189-197

5.) Pediatric Assent:
c.) Younger Children

- Many studies have suggested that comprehension of key concepts in assent is limited in children under the age of **10 years**

Bruzzese JM, et al. Appl Dev Sci. 2003;7(1):13-26.
Burke TM, et al. J Med Ethics. 2003;31(12):715-720.

5.) Pediatric Assent: Younger Children

- **Ondrusek, et al**
  - Looked at children involved in a nutrition study with blood work, CO2 collection
  - **NONE** of the children under age 9 were able to describe why the study was being done
  - **NONE** were aware the study had no benefit to them
  - 75% of kids under age 10 were **unaware they could withdraw** from the study
  - 90% over age 10 **were aware** the could withdraw from the study

Ondrusek N, et al. J Med Ethics. 1998;24(3):158-165

5.) Pediatric Assent: Younger Children

- Multi-site, 2-year study of 161 children in the inpatient setting
- Assessed competence to give informed assent with a validated assessment tool
  - **Children under 10 years of age were most likely to be unable to give informed assent (81% sensitive, 84% specific)**

Hein IM, et al. JAMA Pediatr. 2014;168(12):1147-1153

Not a New Finding...

- **Schwartz, et al**
  - 36 hospitalized children in 1972 enrolled in a research study
  - **No child under 11 years of age was aware that they were enrolled in a research study**, nor were able to differentiate between medical care and the research study
  - Similar results in many other studies over the decades

Ondrusek N, et al. J Med Ethics. 1998;24(3):158-165
Hein IM, et al. JAMA Pediatr. 2014
Schwartz AH, et al. N Engl J Med. 1972;287(12):589-592

5.) Pediatric Assent: Younger Children

- Children in this age range may have a difficult time separating treatment from research, and were at high risk of **therapeutic misconception**
- Difficulty with **magnitude or risk vs. probability of risk**

Unguru Y, et al. Pediatrics. 2010;25(4):e876-e883
Wagner KD, et al.
Reynolds WW, et al. Soc Sci med. 2007;65(10).

What do Kids Want from Assent?

- **Focus groups with 37 children enrolled in oncology trials**
  - 87% wished someone would have explained WHY research in general is done before explaining the study to them
  - 75% wanted to speak with other children enrolled in a research study prior to making a decision

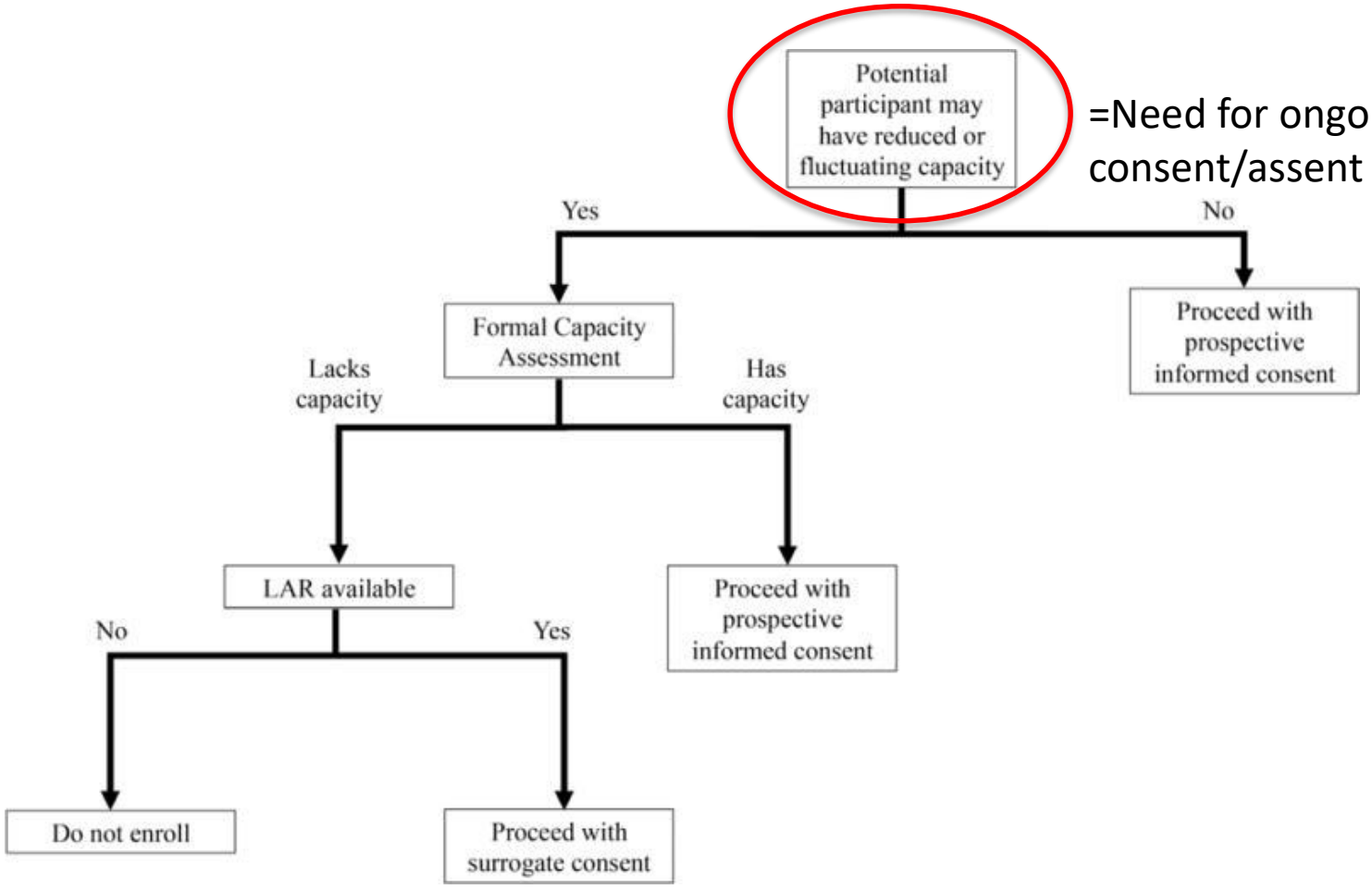
Unguru Y, et al. Pediatrics. 2010;125:e876-e883

Altruism

- 73% of children enrolled in Oncology trials did so out of altruism ('...to help other kids...')
- This was more than for personal benefit (60%)

Unguru Y, et al. Pediatrics. 2010;125:e876-e883

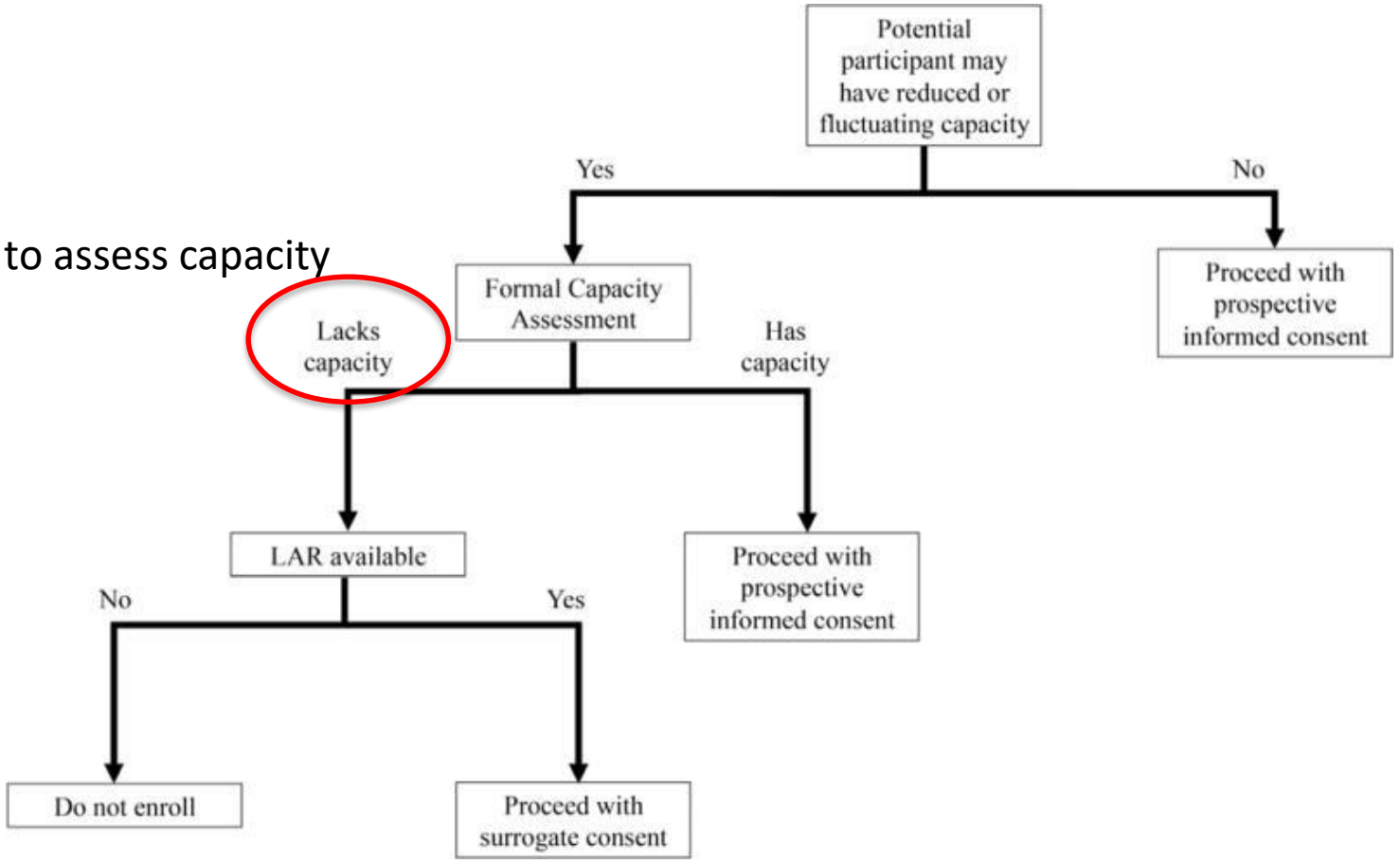
6.) Cognitively-Impaired Adults



=Need for ongoing consent/assent assessment

6.) Cognitively-Impaired Adults

=Need to assess capacity



- Several tools for assessing research decisional capacity exist (e.g. MacArthur Competence Assessment Tool or MacCAT-CR)
  - Assesses 4 thought domains
  - Assesses understanding of the study, how participation may affect them, the ability to compare alternatives, etc.
  - The investigators can assign different weights to each domain depending on the study

- Even if an individual requires an LAR, assent may still be considered

Considerations

- Limiting enrollment of cognitively impaired adults in research may limit medical advances into the diseases causing the cognitive impairment (e.g. Alzheimer's disease)=**Justice**

Problems

- Not all states clearly define who can serve as an LAR for medical research purposes
- Appropriate LAR candidates may not be available for all potential subjects

Oruche, UM. J Nursing Law. 2009;13(3):73227162

Problems

- Assessment tools are often unvalidated and users may be inexperienced in their use and interpretation

Problems

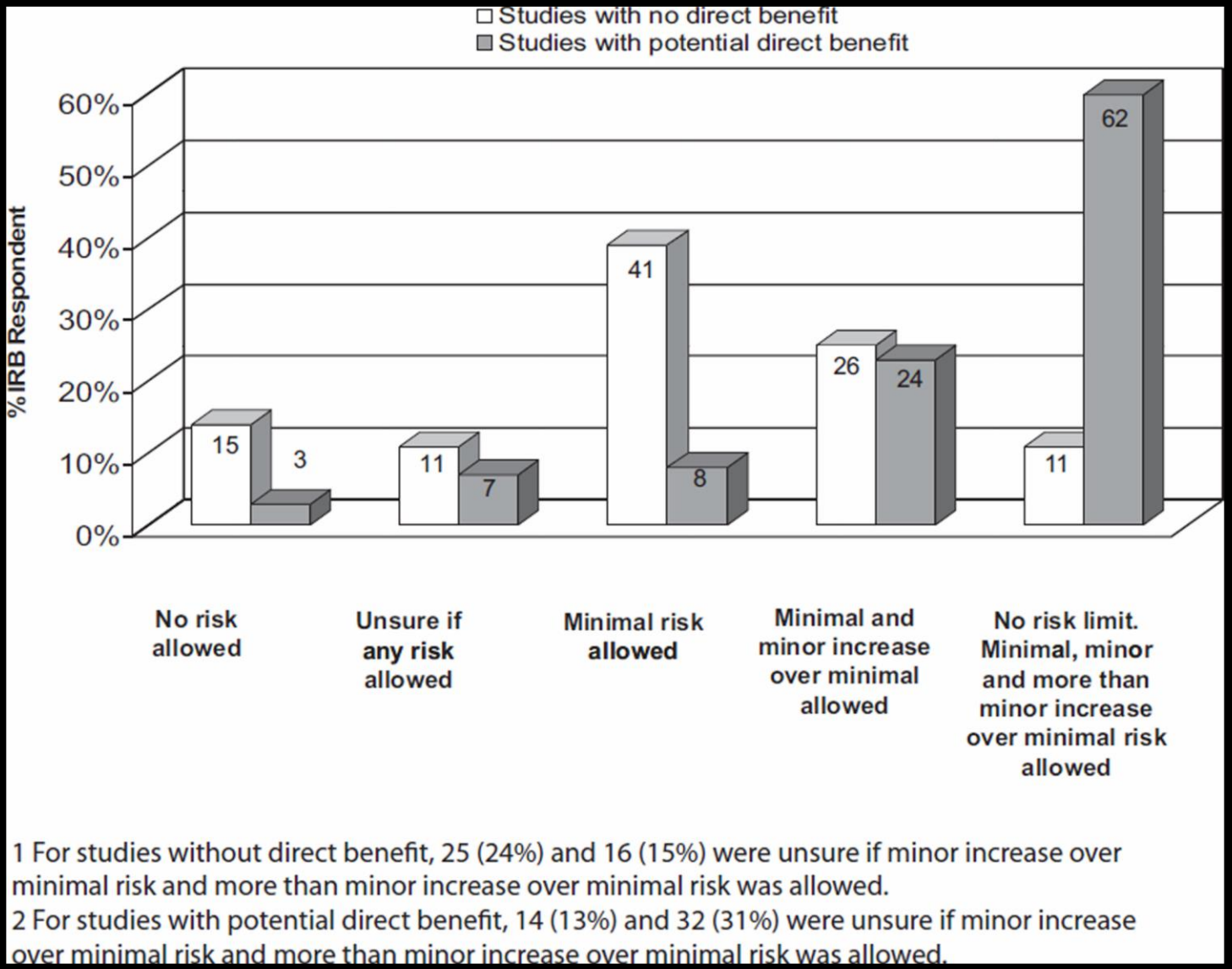
- Cognitive ability may **wax and wane or progressively decline** over the course of a study
  - e.g. a subject who previously consented to participation in a trial, but is now cognitively impaired

Problems

- **IRB practices may vary...**
  - Survey of 104 IRB's across the United States

Gong MG, et al. Crit Care Med. 2010;38(11):2146-2154

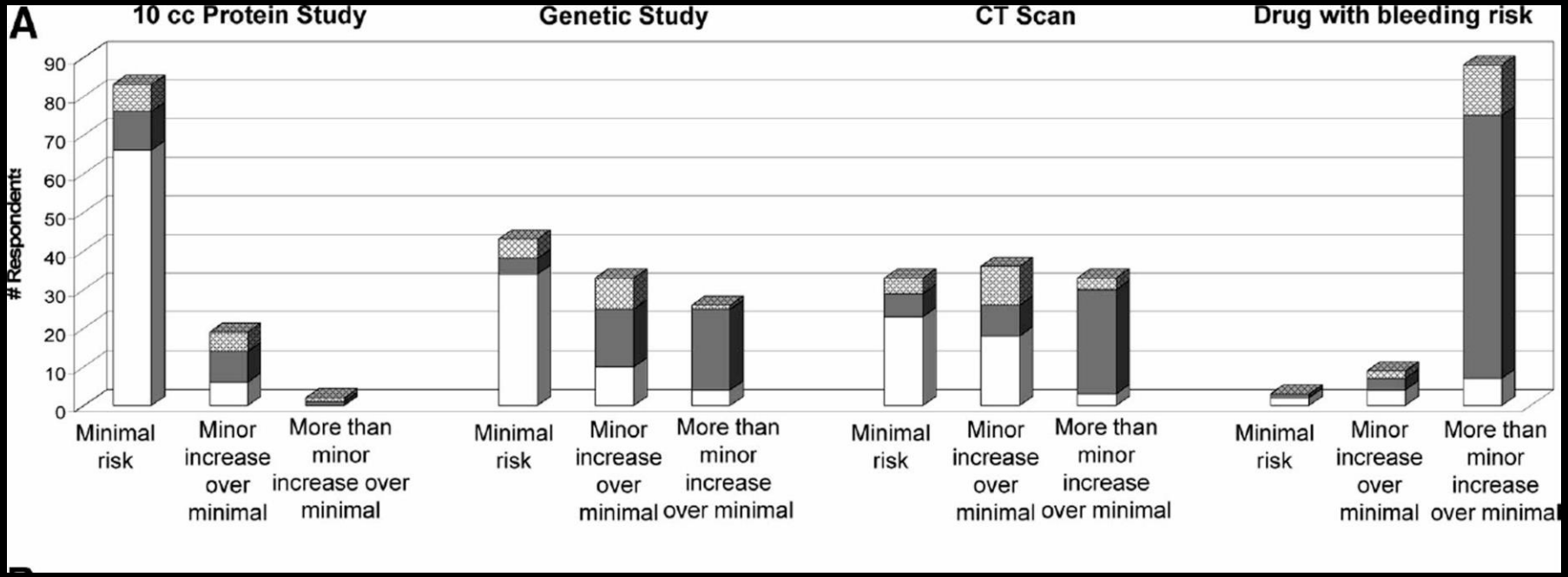
Level of Risk Tolerated by IRB's with Use of an LAR



1 For studies without direct benefit, 25 (24%) and 16 (15%) were unsure if minor increase over minimal risk and more than minor increase over minimal risk was allowed.
2 For studies with potential direct benefit, 14 (13%) and 32 (31%) were unsure if minor increase over minimal risk and more than minor increase over minimal risk was allowed.

Gong MG, et al. Crit Care Med. 2010;38(11):2146-2154

IRB Categorization of Risk and Permissiveness of Hypothetical Studies with an LAR: Assuming No Benefit



White=allowed the study
Grey=rejected the study
Hatched=Unsure

Who Would IRB's Would Allow to Act as an LAR?

Potential Surrogate	Yes (%)	No (%)	Unsure (%)
Spouse	83%	14%	1%
Parent	78%	13%	7%
Adult Child	68%	18%	12%
Adult Sibling	55%	32%	12%
Other Adult Family Member	31%	46%	21%
Friend	14%	73%	11%

Table adapted from: Gong MG, et al. Crit Care Med. 2010;38(11):2146-2154

Summary

Key points discussed thus far (kids)

- 1.) Children under 10 may not fully grasp what is being discussed
- 2.) Kids tend to be more altruistic than you might think
- 3.) Consider separating teens and adults for assent
- 4.) Explain what research is in general and why we do it
- 5.) Is there a risk of undue influence?
- 6.) Would a child like to speak with another child who has been in a research study?
- 7.) Kids continue to develop throughout their teenage and early adult years
- 8.) Teens may underestimate risk
- 9.) Kids may have difficult times with the probability of risk vs. the magnitude of risk

Summary

Key points discussed thus far (adults)

- 1.) Cognitive impairment may wax and wane
- 2.) Utilize validated, customizable tools for assessment of decision-making capacity and have proper training in their use and interpretation
- 3.) Be aware of state laws regarding LAR use
- 4.) Recognize there is tremendous variability amongst IRB's and how they interpret risk and LAR use
- 5.) Recognize the differences between no greater than minimal risk and greater than minimal risk studies with and without benefit

7.) Back to the Vignettes…

- Using what we have learned and discussed, let's re-visit the four vignettes again

Vignette 1

- 8-year-old girl very accepting of the new long-acting insulin despite a very involved protocol, focusing on “I get less insulin shots?”

Vignette 2

- The teenager with the inherited craniofacial abnormality wanting to withdraw assent because she is tired of being treated like '…a scientific commodity.'

Vignette 3

- The elderly man with early-onset Alzheimer's disease whose wife recently died from heart failure, wanting to enroll in a heart failure study altruistic reasons---and with limited understanding of the study

8.) Conclusion: What Became of Joseph Meister?

- Joseph Meister ultimately became curator of the Pasteur institute in Paris
  - Dr. Pasteur was buried in a crypt underneath the institute

June 20, 1940
Paris, France

- In June of 1940, German forces officially began the occupation of Paris
- On June 20th, Nazi officers entered the Pasteur Institute

Courtesy New York Times, June 1940

June 20, 1940
Paris, France

- A staff official ran into the office of Joseph Meister to inform him of these developments
- Joseph Meister ran out of his office to investigate, and ultimately found German officers ransacking the Crypt in which Dr. Pasteur was buried

Courtesy New York Times, June 1940

June 20, 1940
Paris, France

- Meister asked the officers to stop
- They responded harshly, and told him that he must leave the crypt or he would be killed

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773

June 20, 1940
Paris, France

- Joseph Meister refused to leave, and was subsequently shot to death in the the crypt

Bulletin de l'Academie des science. October 26, 1885. Pg 765-773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The New York Times

Late Edition

CRYPT OF HONORED SCIENTIST DESECRATED

HEATHER PRATT

PARIS – 20, June 1940 German occupiers of Paris violate the resting remains of Louis Pasteur, the father of Microbiology (2).

Joseph Meister, the first person to ever receive a Rabies vaccine by Pasteur and gatekeeper to the Institut Pasteur, defended Pasteur's crypt. When faced with death by the NAZIS,

scare of the past, and hospitals are cleaner and safer than ever!

WHO WAS PASTEUR

Louis Pasteur was raised a poor child. His father worked as a tanner in Louis' childhood hometown near Arbois, France. Pasteur was an average student during his elementary education who preferred fishing and drawing to scientific studies. In college he continued to