Research Risk for Vulnerable Populations
2017 IRB Annual Retreat

Wednesday Morning, February 15, 2017
Rizzo Conference Center

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Housekeeping Announcements

1. WiFi name: RizzoRoadRunner
2. No Password needed
3. Restrooms out the door, on the left before you get to the stairs.
4. Lunch at the Dubose Home, exit the room, go right, cross the street and follow the walkway
5. Please complete the evaluation survey that will be emailed to you.

WELCOME

Robin Cyr, PhD

Associate Vice Chancellor for Research &
University Research Compliance Officer

Robin Cyr, PhD

Associate Vice Chancellor for Research and serves as the University Research Compliance Officer which includes leading the Research Compliance Steering Committee composed of directors of units responsible for research compliance operations across campus. Robin is responsible for developing policies, training resources, guidance materials, and processes regarding fiscal compliance with regard to grants and contracts, human subjects protections, animal welfare, responsible conduct of research, conflict of interest, and other federal regulations governing sponsored research. She leads and/or supports investigative and regulatory site visits, including FDA, CMS, CDC, and OIG inquiries and audits as well as site visits requested by research sponsors. Robin represents the University as the administrative representative for the Federal Demonstration Partnership (FDP) and the Council on Government Relations (COGR) and serves on the COGR Research Regulatory Reform Committee. Cyr oversees the Conflict of Interest Program, Office of Human Research Ethics and the Office of Animal Care and Use.

The Office of Human Research Ethics: An Update and Progress Report

February 15, 2017

Elizabeth Kipp Campbell, Ph.D., CIP
Director

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Elizabeth Kipp Campbell, Ph.D., CIP

began her career as a researcher, obtaining her Master's and Doctoral degrees from the Pennsylvania State University where her research focus was on stress, illness and immune functioning in children. While an NIH post-doctoral fellow at the University of Minnesota, she became interested in the ethics of human research and was recruited to serve on the Institutional Review Board (IRB) there. She left academia to pursue a career full-time in this area, serving as the Director of the IRB at Children's Hospitals and Clinics of Minnesota and also volunteering as an Assistant Chair/Chair of a Biomedical panel on the University of Minnesota's IRB for 14 years. In 2010 she came to Purdue and served as the first Director of the Human Research Protection Program. Elizabeth left Purdue in 2015 to become the Director of the Office of Human Research Ethics at the University of North Carolina at Chapel Hill.

Topics of Discussion

1. Staffing of the OHRE
2. IRB Committees: Continued Refinement of Structure and Function
3. Educational Opportunities
4. Metrics of IRB Activity
5. 2016 Achievement Highlights
6. 2017 Opportunities and Challenges

Current OHRE Staff

There are currently 21 staff members

These include: Director, 5 Management level staff, 5 Administrative staff, 1 Business services coordinator, 2 Senior IRB Analysts, and 7 IRB Analysts.

There are currently 7 staff members who are certified as IRB Professionals (CIP). Three more staff are taking the next CIP exam.

Reorganization of the OHRE Staff

Five new Analysts and 2 new Admins joined the staff in 2016.

Sr. Analyst positions created and filled from within.

We are now FULLY STAFFED with Analysts!

Currently interviewing for an IRB Compliance Reliance Manger, particularly with NIH sIRB mandate.

Still need to fill the Assistant Director position.

Refinement and Expansion: IRB Committees

1. Added 2 Vice-Chairs: continue succession planning
2. Implementation and refinement of training program for new Chairs and Vice-chairs
3. Continuing to add expertise across all committees
4. Continued refinement of IRB full board review process
5. Developed and implemented on-boarding process for new IRB members
6. Still working to develop an annual evaluation process for IRB Chairs and members to implement in mid 2017

Educational Opportunities

Instituted and completed EROC requirement for all IRB members

Implemented specialized training sessions for non-scientist members and continued education sessions at IRB meetings

Sent 9 staff, IRB members and chairs to the 2016 national Advancing Ethical Research (AER) Conference

Participated in numerous Webinars from FDA, OHRP, PRIM&R, AAHRPP and others

OHRE IRB Metrics

- Total volume continues to increase, averaging about 5% per year over the past 5 years
- Over 5600 open studies and took over 14,000 actions this past year
- The largest portion of reviews is Expedited, followed by NHRS, Exempt, and then Full Board
- Complexity overall, particularly of Full Board studies, continues to increase

2016 Achievement Highlights

1. Review of IRBIS electronic system
2. Faculty Advisory Committee Implementation
3. IRB Pop-ups instituted
4. Completed 3 Federal audits with no findings

2016 Achievement Highlights

5. HRP Consulting Site Visit
6. Fully staffed with Analysts
7. Non-full board 1st review at 5 or fewer business days!
8. All SOPs revised and updated to best practices

2017 Opportunities and Challenges

- Campus Communication and Education regarding new and revised SOPs
- AAHRPP re-accreditation and site visit
- NIH requirement for Single IRB of record
- New Common Rule ?????

CHILDREN'S CAPACITY TO MAKE RESEARCH DECISIONS

Steven Joffe, MD, MPH, Emanuel and Robert Hart Associate Professor of Medical Ethics and Health Policy at the University of Pennsylvania Perelman School of Medicine;

Vice-Chair of the Department, leading the medical ethics division;

directs the Penn Fellowship in Advanced Biomedical Ethics;

Associate Professor of Pediatrics at the Perelman School of Medicine.

Steven Joffe, MD, MPH

is the Emanuel and Robert Hart Associate Professor of Medical Ethics and Health Policy at the University of Pennsylvania Perelman School of Medicine. He serves as Vice-Chair of the Department, leading the medical ethics division, and directs the Penn Fellowship in Advanced Biomedical Ethics. He is also Associate Professor of Pediatrics at the Perelman School of Medicine.

Dr. Joffe attended Harvard College, received his medical degree from the University of California at San Francisco (UCSF), and received his public health degree from UC Berkeley. He trained in pediatrics at UCSF and undertook fellowship training in pediatric hematology/oncology at the Dana-Farber Cancer Institute and Boston Children's Hospital.

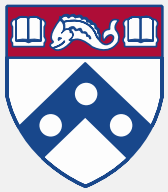
Dr. Joffe's clinical work is in the area of stem cell transplantation in children. His research addresses the many ethical challenges that arise in the conduct of clinical and translational investigation, both in pediatric oncology and other areas of medicine and science. He has been the principal investigator (PI) of NIH, PCORI and foundation-funded studies that examine the roles and responsibilities of PIs in multicenter randomized trials, accountability in the clinical research enterprise, governance of learning activities within learning healthcare systems, return of individual genetic results to participants in epidemiologic cohort studies, and the integration of genomic sequencing technologies into the clinical care of cancer patients. He currently serves as Chair of the Children's Oncology Group Bioethics Committee and as a member of the U.S. Food and Drug Administration's (FDA) Pediatrics Ethics Subcommittee.

Children's Capacity to Make Research Decisions

Institutional Review Board Retreat
UNC-Chapel Hill
Chapel Hill, NC

Steven Joffe, MD, MPH
Emanuel and Robert Hart Associate Professor
Department of Medical Ethics & Health Policy

February 15, 2017



Perelman School of Medicine
University of Pennsylvania

Disclosures

- I have no financial relationships to disclose
- I will not be discussing off-label use of specific medications

Objectives

- Define the concept of assent to participation in research
- Describe when children acquire the capacity to make research decisions
- Discuss the relationship between capacity and the right to assent

But first, a story…

Understanding the concept of assent

Several parties must authorize a child's participation in research

Child assent

- "…the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent."

§ 46.408(a)

Definition of assent

"…a child's ***affirmative agreement*** to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent."

45CFR46 § 408(a)

Waiver of assent due to benefit to child

- Assent not required if IRB finds that
  - "research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research"

45CFR46 § 408(a)

Waiver of assent due to lack of capacity

- “if the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted…the assent of the children is not a necessary condition for proceeding”
- “in determining whether children are capable of assenting, the IRB shall take into account the ages, maturity & psychological state of the children involved”

45CFR46 § 408(a)

Practical implications of requiring assent: child veto

		Child Assent	
		Yes	No
Parental Permission	Yes	Enroll	Don't enroll
	No	Don't enroll	Don't enroll

Objectives

- ✓ Define the concept of assent to participation in research
- Describe when children acquire the capacity to make research decisions
- Discuss the relationship between capacity and the right to assent

What abilities should the child have if s/he is to be asked to assent?

The National Commission's perspective

- "The Commission believes that children who are seven years of age or older are generally capable of understanding the procedures and general purpose of research and of indicating their wishes regarding participation. Their assent should be required in addition to parental permission…. The objection of a child of any age to participation in research should be binding…."

Research Involving Children, 1977, p. 16

The basis for National Commission's conclusions was thin

JOURNAL OF SOCIAL ISSUES
VOLUME 34, NUMBER 2, 1978

The Competence and Freedom of Children to Make Choices Regarding Participation in Research: A Statement

Lucy Rau Ferguson

Michigan State University

The basis for National Commission's conclusions was thin

"Research on cognitive development…suggests that a number of critical shifts in cognitive capacities occur around the age of seven. At this point the child's perspective becomes less egocentric, s/he is capable of conceiving a problem to some degree from the other person's perspective and of understanding the consequences of his/her actions for others."

Ferguson LR, Journal of Social Issues 34:114, 1978

The basis for National Commission's conclusions was thin

"The capacity for understanding simple scientific principles is evident, as well as capacity for social role taking. The child is often willing to engage in altruistic or other prosocial forms of behavior, even at some cost to the self. Thus both from a cognitive and a motivational point of view, considerable capacity for self-determination can be said to be present in the school-age child."

Ferguson LR, Journal of Social Issues 34:114, 1978

The basis for National Commission's conclusions was thin

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VOLUME 34, NUMBER 2, 1978

The Competence and Freedom of Children to Make Choices Regarding Participation in Research: A Statement

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REFERENCE NOTES

1. National Commission for the Protection of Human Subjects. *Children and the mentally disabled as research subjects* (Staff Rep.). Washington, D.C.: National Commission, October 1975.
2. Levine, R. J. *The nature and definition of informed consent in various research settings.* Washington, D.C.: National Commission for the Protection of Human Subjects, December 1975.

REFERENCES

Kelman, H. C. Human use of human subjects: The problem of deception in social psychological experiments. *Psychological Bulletin*, 1967, 67, 1–11.

Mussen, P. H. (Ed.) *Carmichael's Manual of child psychology* (3rd ed.; Vol. 1). New York: Wiley, 1970.

Others took a different view

"…there is little evidence that minors of age 15 & above…are any less competent to provide consent than are adults."

Grisso T, Vierling L. Prof Psychol 9:412, 1978

Others took a different view

"In the age range of 11-14 years, existing research suggests caution regarding any assumptions about these minors' abilities to consider intelligently the complexities of treatment alternatives, risks, and benefits, or to provide consent that is voluntary."

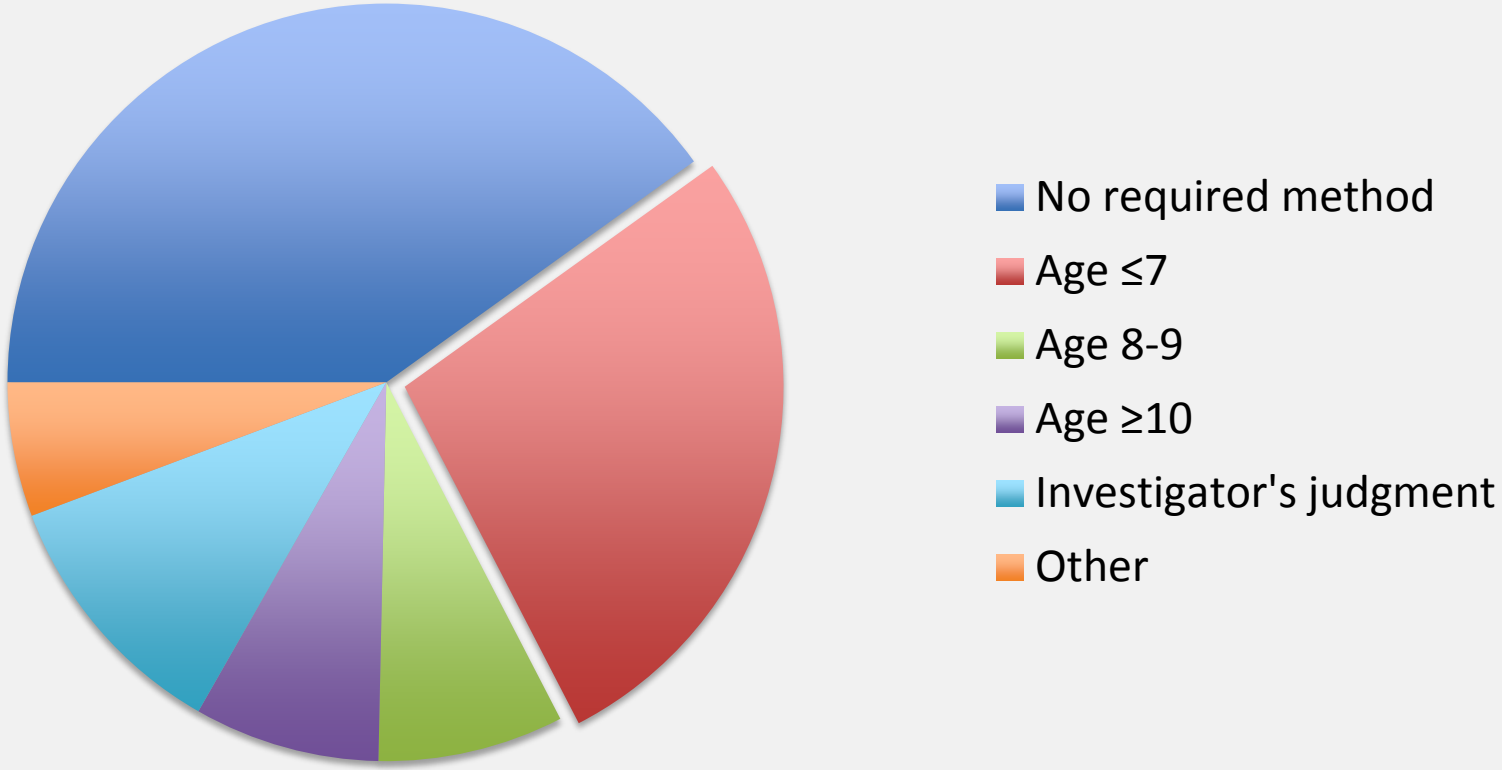
Grisso T, Vierling L. Prof Psychol 9:412, 1978

Others took a different view

"…Most research suggests that minors below age 11 generally do not have the intellectual abilities or are too prone to deferent response to satisfy a psychological interpretation of the legal standard for competent consent."

Grisso T, Vierling L. Prof Psychol 9:412, 1978

IRBs vary in their approach to child assent



(based on survey of Chairs of 188 U.S. IRBs)

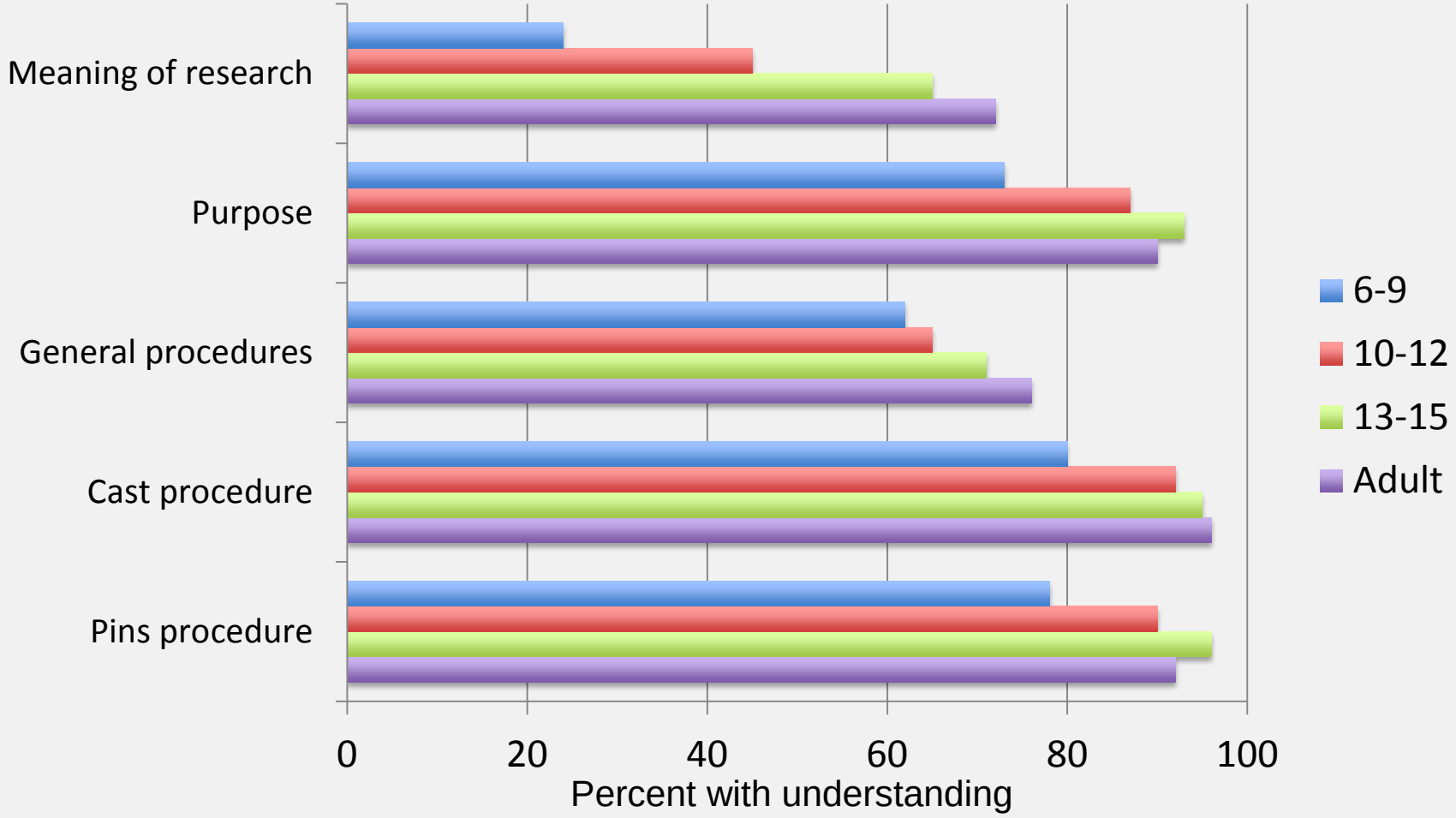
Pediatrics 113:1741, 2004

What do the data on children's capacity show?

- Burke et al presented 251 children ages 6-15, and 237 adults, with one of six hypothetical randomized trials regarding casting vs. pinning for fixing a fracture
  - Interviewer asked structured questions about study
  - Interviewer then coded responses as indicating understanding or lack of understanding

J Med Ethics 31:715, 2005

What do the data on children's capacity show?



J Med Ethics 31:715, 2003

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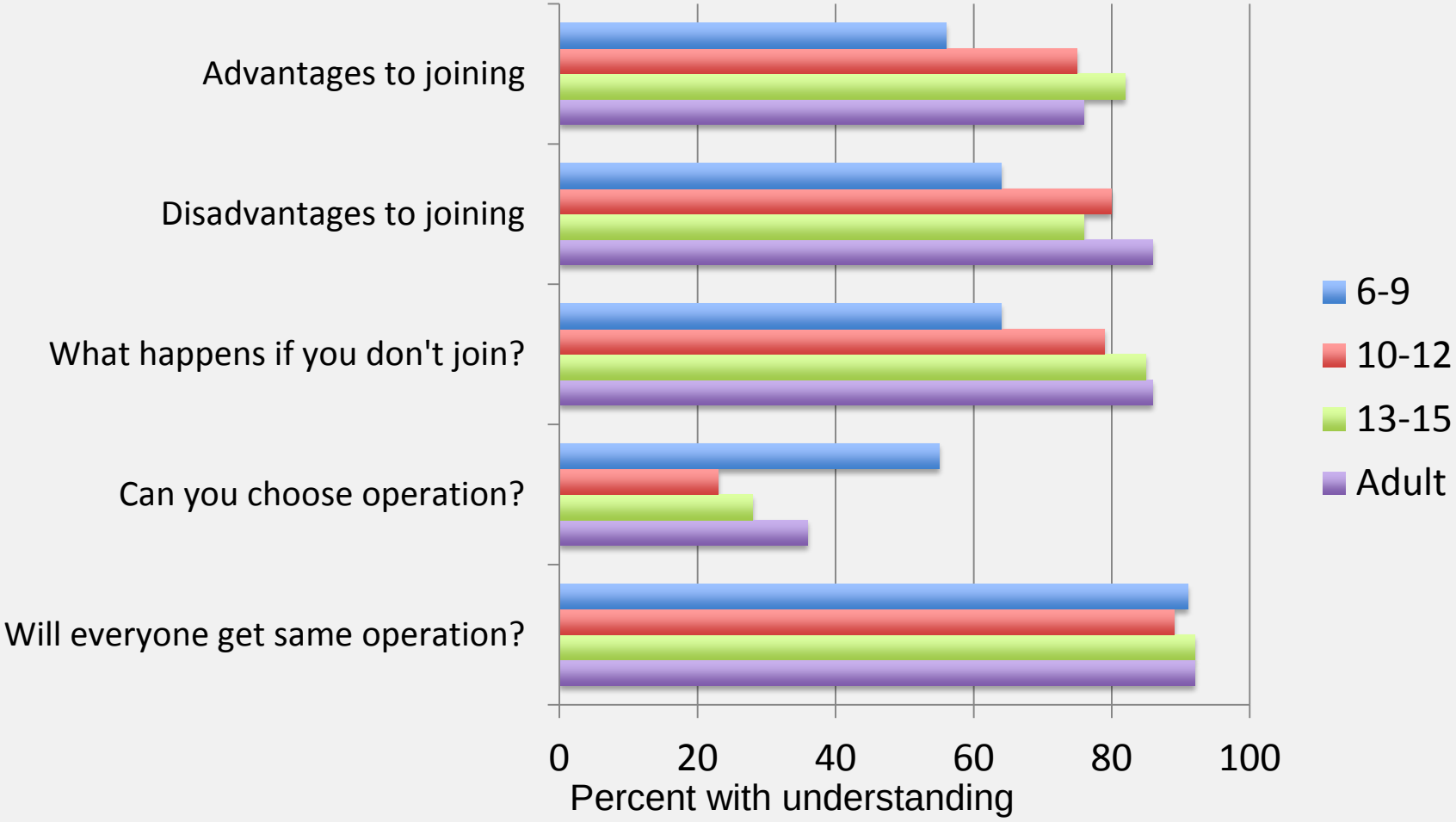


J Med Ethics 31:715, 2003

What do the data on children's capacity show?

- Tait et al presented a hypothetical study regarding control of postoperative nausea to 190 hospitalized children ages 7-17
  - Randomized to standard or modified information form
  - Information also read to all children

Anesth Analg 105:358, 2007

Figure 1. An excerpt from the modified form.

Why we are doing this study:

Many children feel sick to their stomachs (nauseous), and often throw up (vomit) after having surgery.

This study wants to find out if the drug, dolasetron (doh-las-etron), will help. Right now, dolasetron is approved by the FDA (Federal Drug Administration) for use in adults after surgery. This study will find out if this drug will help children feel less sick and throw up less often after their surgery.

Who can be in the study?

- ☺ 140 children under 18 years old
- ☺ Children having anesthesia and surgery

Who can not be in the study?

- ☹ Children with motion sickness
- ☹ Those with liver, kidney, heart or nervous system problems

Risks or side effects:

The side effects of dolasetron are similar to side effects of other medicines used to prevent or treat stomach upset after surgery.

These are:

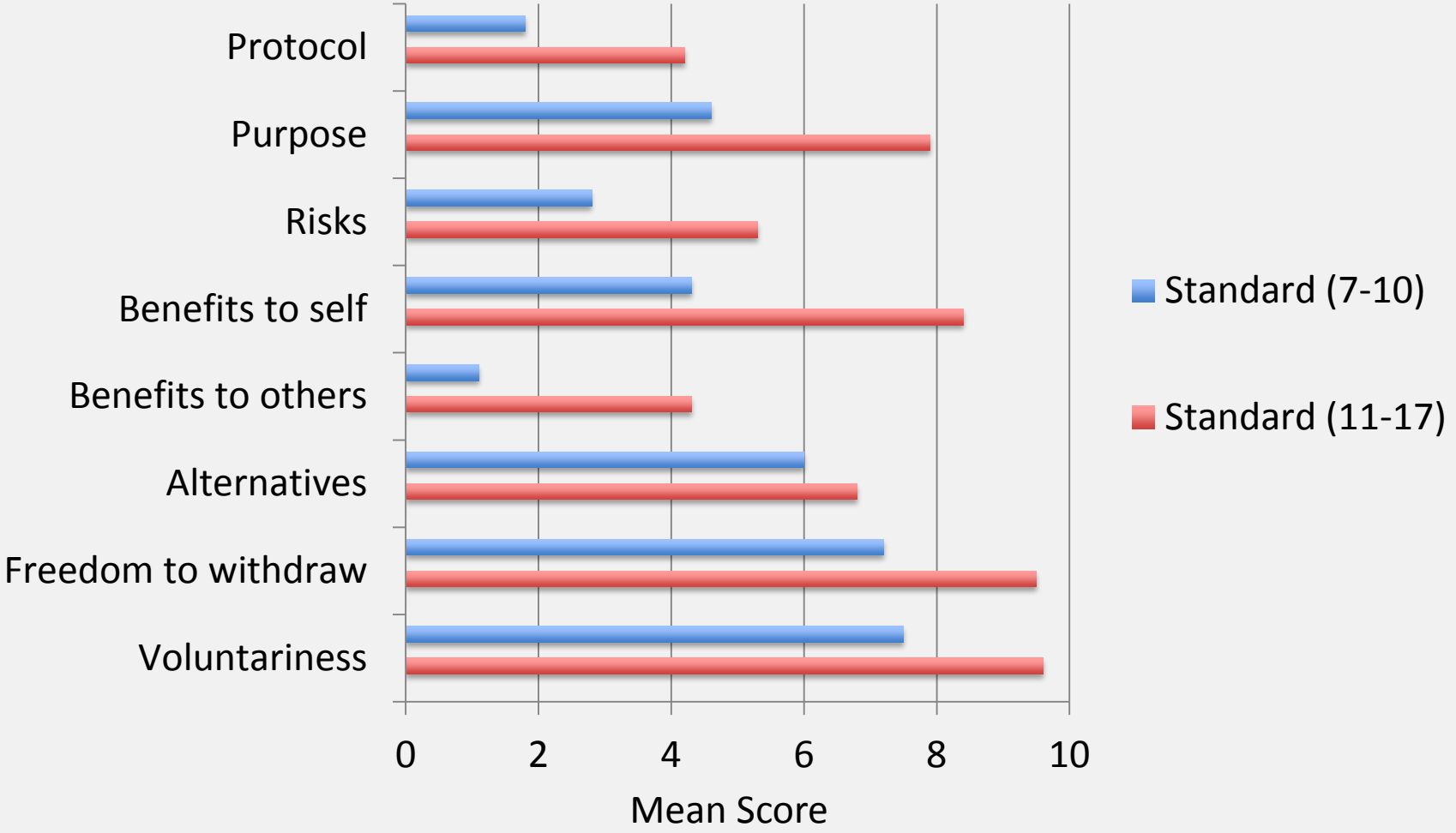
- ☹ Headache
- ☹ Stomach cramps
- ☹ Dizziness
- ☹ Rash

Tait A R et al. Anesth Analg 2007;105:358-364

ANESTHESIA & ANALGESIA

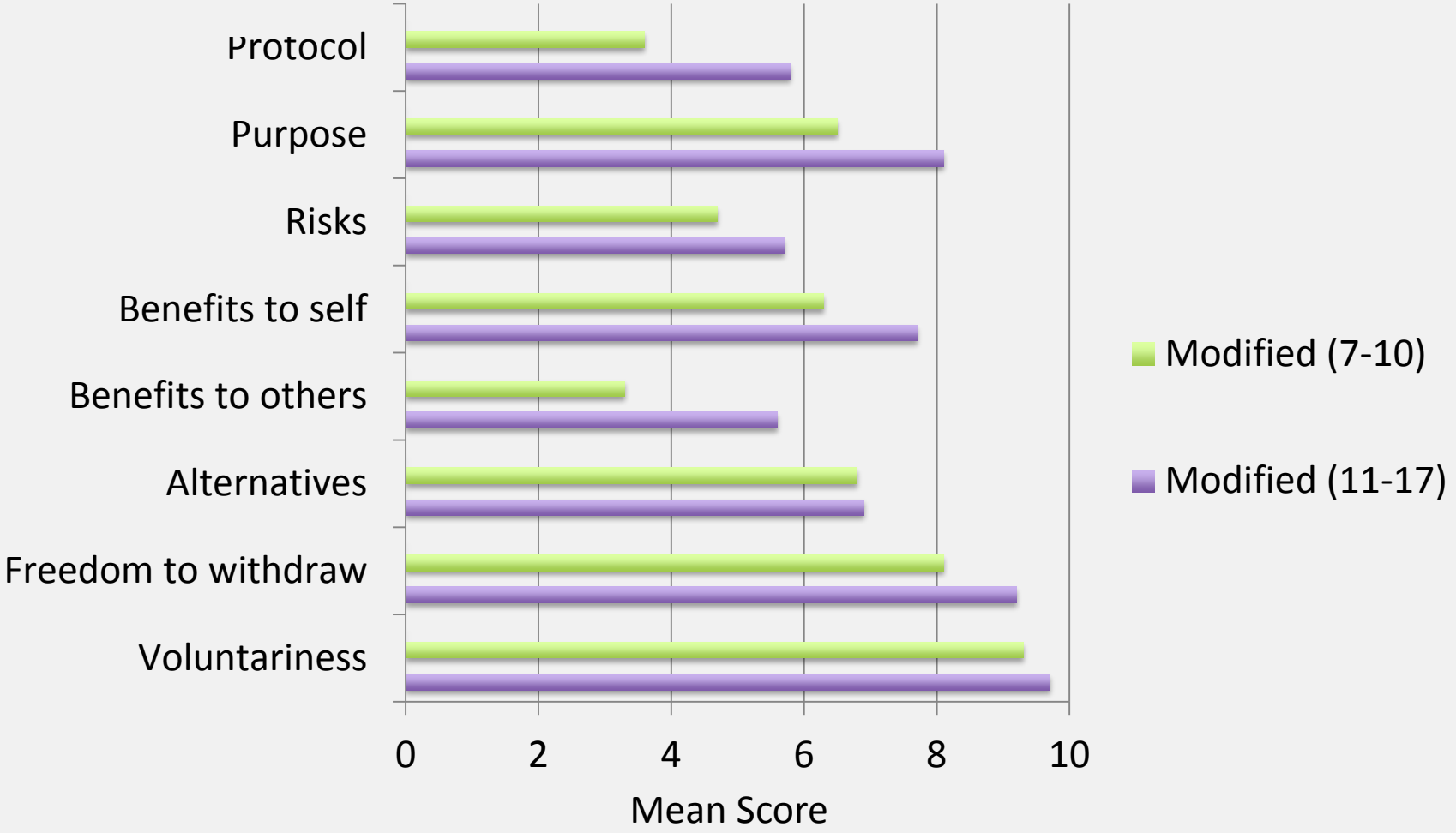
©2007 by Lippincott Williams & Wilkins

Using standard form, understanding varied considerably by age



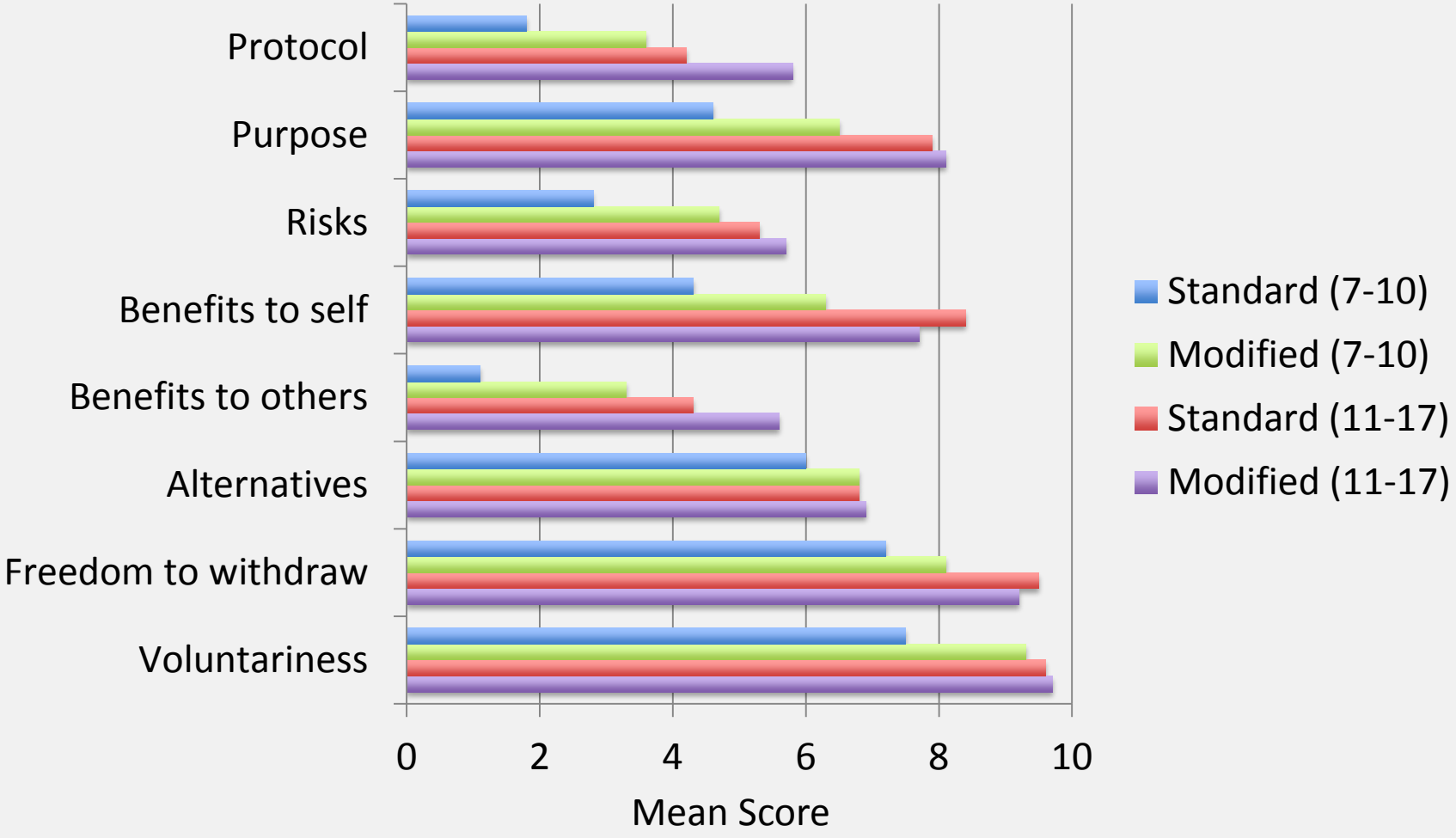
Anesth Analg 105:358, 2007

Using an improved form reduce misunderstanding among younger kids



Anesth Analg 105:358, 2007

Understanding by Age and Form



Anesth Analg 105:358, 2007

The importance of having a map when navigating new territory

Maturity of judgment: the missing dimension in assessing capacity?

- Are abilities to understand and to reason all that matters?
  - "There is good reason to believe that many of the executive processes that govern such phenomena as impulse control, foresight, planning, and the like are still maturing well into middle and late adolescence, if not into young adulthood."
  - e.g., responsibility, temperance, perspective

Law Hum Behav 20:24, 1996
Ann N Y Acad Sci 1021:51, 2004

Objectives

- ✓ Define the concept of assent to participation in research
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Is capacity all that matters?

The National Commission's view

- "The Commission believes that children who are seven years of age or older are generally capable of understanding the procedures and general purpose of research and of indicating their wishes regarding participation. *Their assent should be required in addition to parental permission.*"

National Commission. *Research Involving Children: Report and Recommendations*. Washington, DC: DHEW Publication No. (OS) 77-0004; 1977, p. 16.

Potential objections to Commission's view

1. 7-year olds are not necessarily capable of "understanding the procedures and general purpose of research and of indicating their wishes regarding participation" for most studies.

2. Capacity requires more than just the ability to understand the procedures & general purpose of research and to indicate one's wishes.

3. Other considerations, besides capacity, matter in deciding whether a child should have authority to veto her parents' decision about participation in research.

Two views of parental authority

1. Parents' authority to make decisions for their children fills a void created by children's lack of capacity to make decisions for themselves
   - As child develops capacity, parents' authority shrinks

Two views of parental authority

2. Parents' authority to make decisions for their children rests (partly) on moral grounds that are independent of capacity, e.g.,
   - because parents are responsible for raising and providing for their children
   - because parents should define and pursue child's best interests as parents see them
   - because parents should decide what ends child should pursue
   - because families deserve a zone of privacy free from interference by the state

Hastings Cent Rep 47(1):32, 2017

Ross LF. *Children, families, and health care decision making*. Oxford: Clarendon Press; 1998.

Back to the case…

Summary

- The concept of assent is clear in regulations, but its ethical basis and practical application are disputed
- Although there is no single “age of assent,” the relevant abilities likely come on line between 9-14
- Nevertheless, capacity alone should not determine whether and when children acquire the right to assent

Thank you

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AREN'T ALL RESEARCH SETTINGS THE SAME? WHAT SHOULD IRBS BE AWARE OF WHEN REVIEWING INTERNATIONAL RESEARCH?

Joanna "Asia" Maselko, ScD

ASSOCIATE PROFESSOR

Department of Epidemiology, UNC-CH

Joanna "Asia" Maselko, ScD

ASSOCIATE PROFESSOR Department of Epidemiology, UNC-CH, is a social and psychiatric epidemiologist. She studies the mechanisms through which the social environment shapes the risk for common mental disorders. Anchored in a life-course framework, a large portion of her research focuses on the intergenerational transmission of risk and the role of the environment in altering socioemotional developmental trajectories in children.

Dr. Maselko currently is the PI of the SHARE CHILD study, a cluster RCT set in rural Pakistan, which investigates mechanisms through which maternal depression impacts early child development.

The study also examines the role of social contextual factors such as socioeconomic status, family composition and parenting. In another research project in Sri Lanka, Dr. Maselko studies caregiving provided by grandparents and its impact on the health of both grandparent and grandchild.

Dr. Maselko aims to understand the effects of mental health on the effectiveness of interventions aimed at improving population health and other social outcomes. For example, by how much would we expect the effectiveness of a breastfeeding promotion program to be reduced if 25 percent of the target population is depressed? Empirical evidence about the impact of mental health on program up-take and success can help improve program design and implementation.

In a separate line of research, Dr. Maselko has studied the relationship between religious engagement and health, focusing on how gender, race/ethnicity and socioeconomic status affect this relationship.

ScD, Social Epidemiology, Harvard University, 2004; SM, Health and Social Behavior, Harvard University, 2000; BS, Biological Sciences, University of Alaska-Anchorage, 1996

Aren't all Research Settings the Same? What Should IRBs Be Aware of When Reviewing International Research?

Joanna ("Asia") Maselko

Associate Professor

Dept. of Epidemiology

Why is this an issue?

- Larger imbalance of power and resources
  - Overall
  - Access to healthcare

- Larger differences in cultural norms
  - Expectations for how individuals relate to each other

Overview

1. Justice
    1. Benefits for participating
    2. Benefits from knowledge gained
2. Autonomy
    1. Informed Consent
3. Working with local IRBs and conclusions

Starting point

- *From Association for Accreditation of Human Research Protection Programs (AAHRPP)*
  - The researcher must provide the same *or equivalent* protections to human subjects in research conducted in other countries.
    - The protections need not be identical to those provided in the U.S. but must be equal in function or effect.
    - Subject autonomy and dignity should be respected.
    - Protections should encompass the ethical principles of respect for person, beneficence, and justice.
  - The researcher must be familiar with and comply with local laws, regulations, political and socio-economic factors, and cultural context in all locations where the research is conducted.
  - The researcher must have sufficient knowledge of the local context, which may impact all aspects of the research design, and in particular, the protection of the rights and welfare of subjects.

https://www.seattleu.edu/irb/policies/submissions/international/

Active area of research and scholarship

- WHO and Council for International Organizations of Medical Sciences (CIOMS) guidelines
- Other documents specific to international research, mostly focused on HIV research

1. Justice

- The study participants are giving the researcher something, what do they get in return?

Who benefits from the research participation and knowledge gained?

1. What are the benefits of participating in the research project?
   - 'for the good of science'
   - Participants want to know first how they will benefit?
   - Compensation for 'time'; a small gift – what is fair?
   - the idea that you are a health person/doctor and might give them 'nothing' is not well understood, especially if it's a trial

   - Ancillary care….

Potential risks of participating in research

- Loss of privacy/confidentiality
- Requests for assistance

Benefiting from knowledge gained

2. Who will benefit from the ultimate knowledge gained?

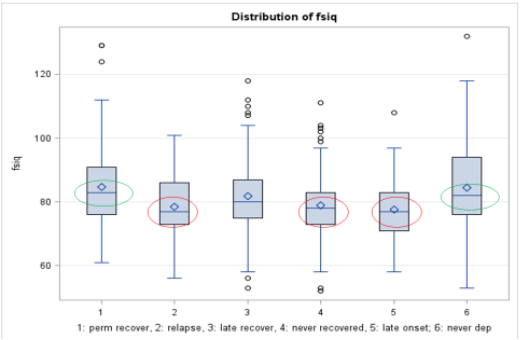
    -this same community, at a later time?

    -similar communities, elsewhere?

    -'science'

What are the responsibilities of the researcher?

RESULTS



Most common benefits after intervention study

- Effective intervention (either currently proven one or another one)
- Technology transfer (e.g., license to manufacture a drug)
- Health services (e.g., maintenance of a primary care clinic)
- Capacity building (applicable to most types of research)

- Applies both to research participants as well as ‘community’

2. Informed Consent

- What is ‘informed’?
- Bad in US, worse in LMIC

- A) explaining the study
- B) the document itself
- C) the act of consenting

A. Process of explaining the study

- How will you explain what are the incentives to participation?
- Language issues
- Belief systems
  - Is it ok to withhold information?
  - Absolute trust in clinician to make decision

Understanding biomedical research terms

- Research
- Intervention vs. observation
- Placebo
  - A ‘fake’ medicine
  - Active control best
- Randomization
  - A lottery
  - If I don’t get the intervention now, will we get it later?

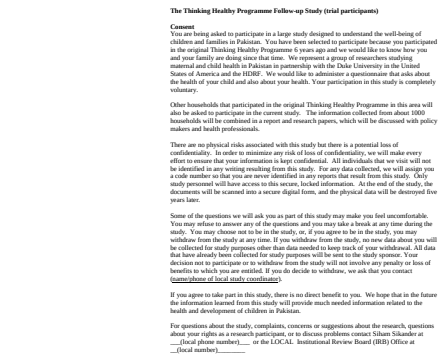
Understanding Privacy

- Notions of privacy differ dramatically cross-culturally
- Consent forms usually have a lot of language about privacy, how identifiable information will be handled
  - In terms of data collection procedures (privacy during interviews)
  - In terms of the data itself that is collected
- Private interactions may be considered more ‘risky’ to the participant
- May not get full privacy but need to then create safe space, context dependent

Consent as social process: Group models of explaining study

- Group conversation about the project, with family members or peers
  - Flipcharts, drawings
- followed by an individual consent procedure.
- May begin with a community leader who comes and facilitates the conversation (Mystakidou et al 2009)
- Might need ‘permission’ from community leaders as individuals look to the leaders for clues

B. The document itself



The Thinking Healthy Programme Follow-up Study (trial participants)

Consent

You are being asked to participate in a large study designed to understand the well-being of children and families in Pakistan. You have been selected to participate because you participated in the original Thinking Healthy Programme 6 years ago and we would like to know how you and your family are doing since that time. We represent a group of researchers studying maternal and child health in Pakistan in partnership with the Duke University in the United States of America and the HDIF. We would like to administer a questionnaire that asks about the health of your child and also about your health. Your participation in this study is completely voluntary.

Other households that participated in the original Thinking Healthy Programme in this area will also be asked to participate in the current study. The information collected from about 1000 households will be combined in a report and research papers, which will be discussed with policy makers and health professionals.

There are no physical risks associated with this study but there is a potential loss of confidentiality. In order to minimize any risk of loss of confidentiality, we will make every effort to ensure that your information is kept confidential. All individuals that we visit will not be identified in any writing resulting from this study. For any data collected, we will assign you a code number so that you are never identified in any reports that result from this study. Only study personnel will have access to this secure, locked information. At the end of the study, the documents will be scanned into a secure digital form, and the physical data will be destroyed five years later.

Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions and you may take a break at any time during the study. You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes other than data needed to keep track of your withdrawal. All data that have already been collected for study purposes will be sent to the study sponsor. Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled. If you do decide to withdraw, we ask that you contact (name/phone of local study coordinator).

If you agree to take part in this study, there is no direct benefit to you. We hope that in the future the information learned from this study will provide much needed information related to the health and development of children in Pakistan.

For questions about the study, complaints, concerns or suggestions about the research, questions about your rights as a research participant, or to discuss problems contact Siham Sikander at ___(local phone number)___ or the LOCAL Institutional Review Board (IRB) Office at ___(local number)_____

- What goes into the document?
  - Who is paying/sponsoring the study.
- Legal/university requirement vs. a meaningful document for the study participant
- Individuals may fear the document itself

2. Act of consenting

- Who is involved in the decision?

- <u>Imbalance of power</u>
  - Between researcher and participant is one of the reasons why participants bring in family members – to help decide and to help say ‘no’ if needed
  - Between family members and participant

- Group processes are helpful
  - Cultural accommodation good but participant only can make decision
- Collaboration and trust established

Documenting consent

- Our default is to sign
- Literacy
- Signing might put some vulnerable persons at risk
- Word may be stronger than the signature

3. Working with local IRB

- Important for investigator to know local IRB climate and infrastructure
  - Many countries have existing guidelines
- Caution:
  - Training might be very weak, get critique on research design
  - some bureaucracies are counterproductive (eg. India)
  - Conflict between IRBs
  - Sometimes there is zero infrastructure so requiring local IRB approval challenging

4. Conclusions: what should the IRB know?

- Be flexible, talk with the investigator,
  - a lot of the issues are not clear from the form
- For many of these difficult issues, it's important to lay them out and discuss with the local team leads, so that it's understood and answer can be agreed on
  - Create safe spaces to discuss issues

- Want to know how familiar is investigator with the country, if not them, who are their local partners?
- Be more collaborative

Oregon State University example

OSU IRB Asserts that relevant local context information should be included in the IRB protocol.

- *This includes, but it not limited to, the following:*

  - A description of the research team's knowledge of or experience in the host country as well as any relevant qualifications for conducting the proposed research within the international setting should be included in the Investigator Qualifications and/or Training and Oversight sections of the IRB protocol.
  - Cities, regions countries where research will be conducted
  - Scientific/ethical justification for conducting the research in an international setting
  - Economic status of the country/community
  - Current events or socio-political environment in the country that may impact research conduct or alter the risks or benefits to subjects
  - Societal and cultural beliefs in the country that may impact research conduct or alter the risks or benefits to subjects
  - If women and children are part of the subject population, their role in the society, including their autonomy and legal capacity to make decisions.

Many other resources

- Fogarty center: https://www.fic.nih.gov/ResearchTopics/Pages/Bioethics.aspx

15 MINUTE BREAK

10:00 – 10:15

Vulnerability: Rising Above the Floor of the Subparts

Jeremy Block PhD, MPP

Managing Partner, Venture Catalyst

Co-I, MSKCC | Clinical Genetics Service

Adjunct Prof. Public & International Affairs, Baruch College CUNY

Jeremy Block PhD, MPP

JEREMY BLOCK is the Managing Partner of Venture Catalyst, working with investors and venture-backed companies to maximize the odds of venture success. Dr. Block is also an adjunct professor of public and international affairs at Baruch College. Jeremy is currently a Co-Investigator and study director of a digital health trial focusing on population screening of genetic founder mutations at Memorial Sloan Kettering Cancer Center. Previously, Dr. Block was an Assistant Professor of Population Health Science & Policy at the Icahn School of Medicine at Mount Sinai where he was also an IRB Chair at hospitals within the Mount Sinai Health System. Jeremy is primarily interested in the intersection of science and technology with society, public policy, and business. His background includes advising at the federal, state, and local level on a variety of science and technology relevant fields include; green procurement, human research subject protections, chemical & biological weapons, emerging properties and markets with science and technology components, and research systems at public & private universities. In addition Jeremy has been involved in technology development in the areas of virtual reality and also digital & mobile health applications. He has a background in teaching ethics in public policy, bioethics, and science and technology policy at both the undergraduate and graduate level.

He holds a Bachelors in Chemistry & Biology, Masters in Public Policy, and Ph.D. in Biochemistry from Duke University.

What does vulnerability mean?

ICH-GCP, section 1.61 **'Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate**	**Belmont Report** **"persons with diminished autonomy are entitled to protection"** **"Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them … The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit."**	**NBAC 2001** **"In general, persons are vulnerable in research either because they have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity … or situational circumstances …, or because they are especially at risk for exploitation."**
Declaration of Helsinki, Paragraph 9 'Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence'	CIOMS, Commentary on Guideline 13 'Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interest'	45 CFR 46 (DHHS Regulations) Subpart B – women & fetuses Subpart C – prisoners Subpart D – children

Vulnerability Effects

Physical Control - subjects have been physically forced to participate in research at times. This represents a complete lack of voluntariness. A classic example is the use of prisoners of the Nazi Holocaust camps in research with an endpoint of subject death, such as the hypothermia studies. The subjects had no choice about whether or not to participate, and were under the complete physical control of the investigators.

Coercion - The use of a credible threat of harm or force to control another person. An example could be the threat of losing your job if you refuse to participate in research.

Undue Influence - The misuse of a position of trust or power to influence a decision someone would not otherwise make.. An example would be to offer a substantial amount of money to people of low economic status to participate in a research study.

Manipulation - Deliberate management of conditions or information to lead someone to make a decision they would not otherwise make. Examples of information manipulation include lying, deception, withholding information, and exaggeration.

Vulnerability

- "When some or all of the subjects are likely to be vulnerable to coercion or undue influence … additional safeguards have been included in the study to protect the rights and welfare of these subjects."

45 CFR 46.111(b)

Vulnerability

- "persons with diminished autonomy are entitled to protection"
  - "Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them … The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit."

National Commission for the Protection of Human Subjects Belmont Report (1979)

Vulnerability

- "In general, persons are vulnerable in research either because they have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity … or situational circumstances …, or because they are especially at risk for exploitation."

National Bioethics Advisory Commission
"Research Involving Human Participants", 2001

Vulnerability

- Vulnerable group-based approach
  - Pregnant women and fetuses
  - Prisoners
  - Children
  - Cognitively impaired
  - …

Vulnerability

- Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D - Additional Protections for Children Involved as Subjects in Research

Vulnerability

- Groups may not be the best way to look at vulnerability …
  - Group-based approach classifies certain persons as vulnerable, rather than classifying situations in which individuals might be considered vulnerable
    - Acutely ill

Vulnerability

- Analytic approach (NBAC)
  - Cognitive or communicative – diminished capacity to understand or communicate
  - Institutional - subject to the formal authority of others
  - Deferential - informal subordination to others (gender, race or class inequalities; inequalities of power & knowledge)
  - Medical – serious health conditions
  - Economic and/or Social - disadvantaged in the distribution of social goods and services, or belonging to an undervalued group

Vulnerability

- Represent potential violations of the "deal" – that persons may participate in research as long as R/B acceptable, risks minimized and informed consent obtained
  - Consent-based vulnerabilities – create or exacerbate barriers to informed consent
  - Risk-based vulnerabilities – increase the level of risks associated with a subjects' participation
  - Justice based vulnerabilities – raise concerns about distribution of benefits and burdens
- While consent based vulnerabilities can be remedied by eliminating barriers to voluntariness or enhancing comprehension, risk and justice based vulnerabilities persist even if subjects voluntarily consent

Coleman: J Law Med Ethics 37:12, 2009

What does vulnerability mean?

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Beyond the Subparts

Vulnerability as a concept isn't defined by the subparts of 45 CFR 46…

- An expanded view of vulnerability
  - Group based vulnerability is not the whole picture

"In general, persons are vulnerable in research either because they have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity … or situational circumstances …, or because they are especially at risk for exploitation."

National Bioethics Advisory Commission
"Research Involving Human Participants", 2001

Beyond the Subparts

"Vulnerable groups" may not be the best way to look at vulnerability.

- Multiple vulnerabilities?
  - Pregnant minors
  - Homeless people who are mentally ill
  - HIV+ Gay men

A group-based approach classifies certain persons as vulnerable, rather than classifying situations in which individuals might be considered vulnerable.

Beyond the Subparts

Research Targeting a Vulnerability

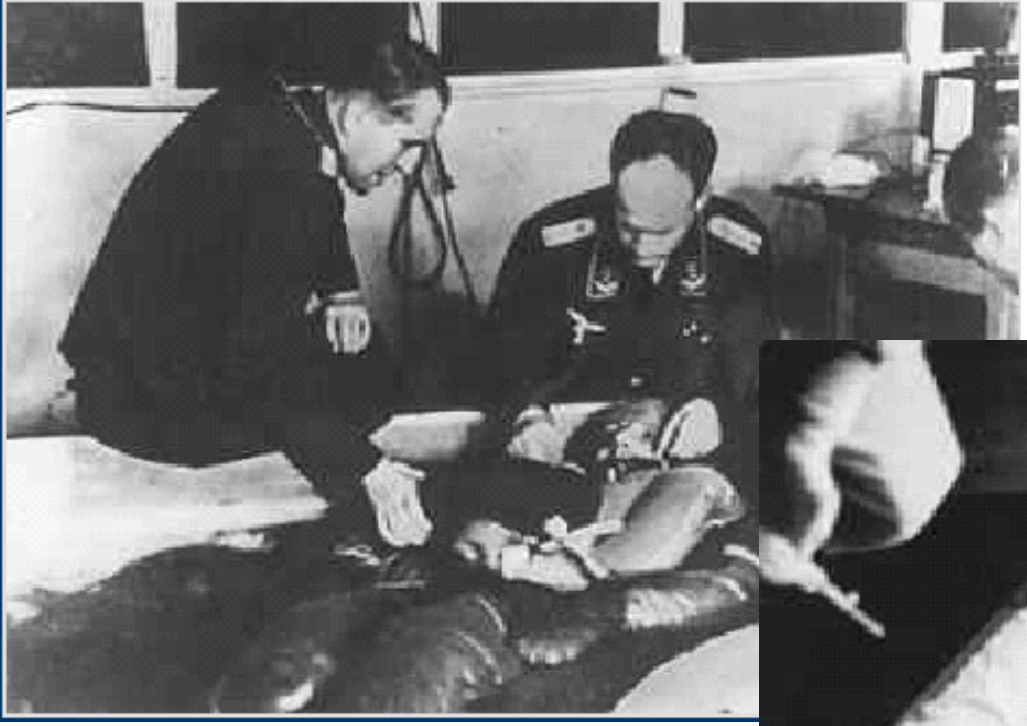
Targeted: The research study is geared towards a vulnerable group or situation.

Un-Targeted: The study is not geared towards a vulnerable group or situation.

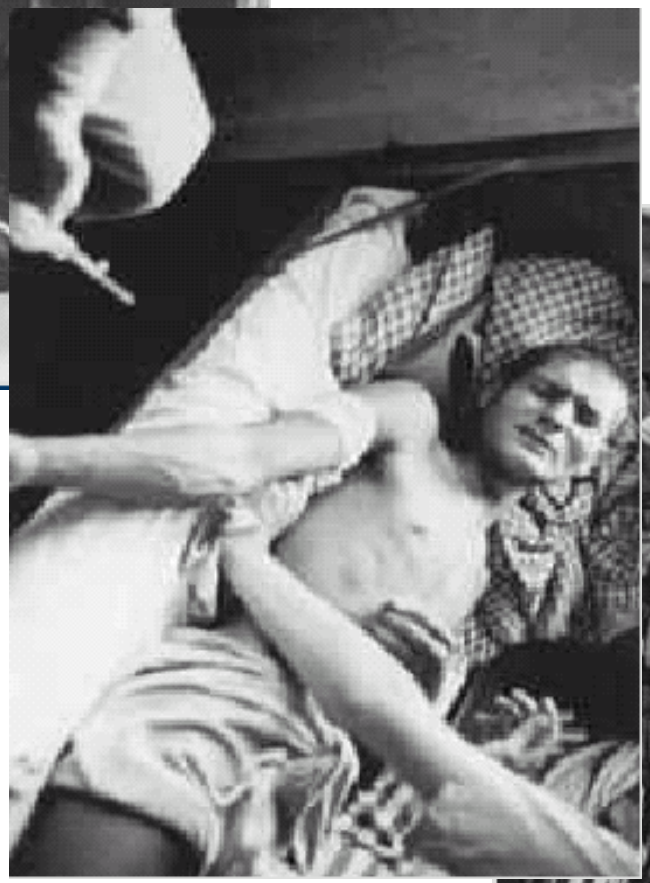
Vulnerable Populations: Responses to Scandals & Mad Scientists Create a Research Ethics Regulatory Environment

Much of the regulations and discussions in bioethics surrounding protecting human subjects in research are reactions to cases of what we now classify as misconduct. Many of these cases involved mistreatment of individuals or groups of individuals we now call vulnerable populations.

German Experiments



Freezing Experiments



Salt Water

High Altitude

Performed by Nazi Doctors

Part of a larger Eugenics program
In full swing by 1939

Included a Euthanasia program, where weak and disabled should get a ‘merciful death’

The New England
Journal of Medicine

Copyright, 1966 by the Massachusetts Medical Society

Volume 274 JUNE 16, 1966 Number 24

Reprinted from pages 1354-1360.

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON

The New York Times

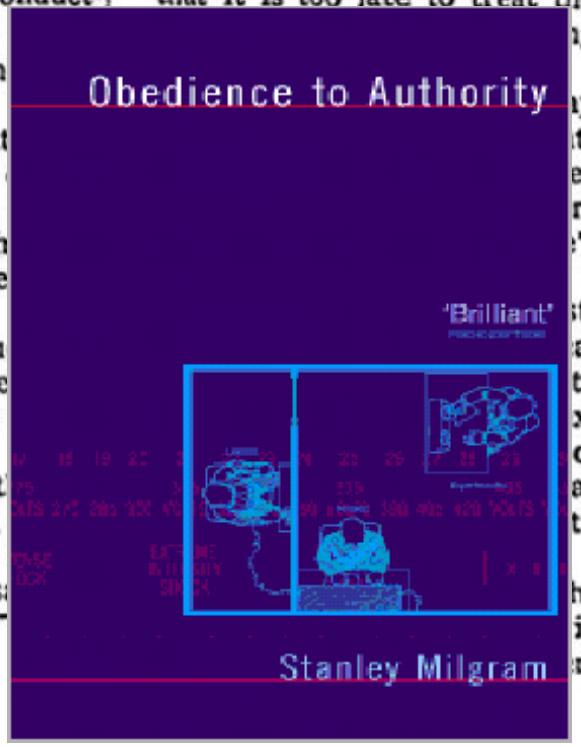
Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which beings with syphilis, wh induced to serve as ve gone without tment for the few have died cts, even though herapy was eve ed. udy was condu e from autopsie ase does to the

ls of the healt initiated the ment have long since Current officials, who s

have serious doubts about the morality of the study, also say that it is too late to treat the ng ny t- es rs 's t- a- th x- of as ti- he in n,

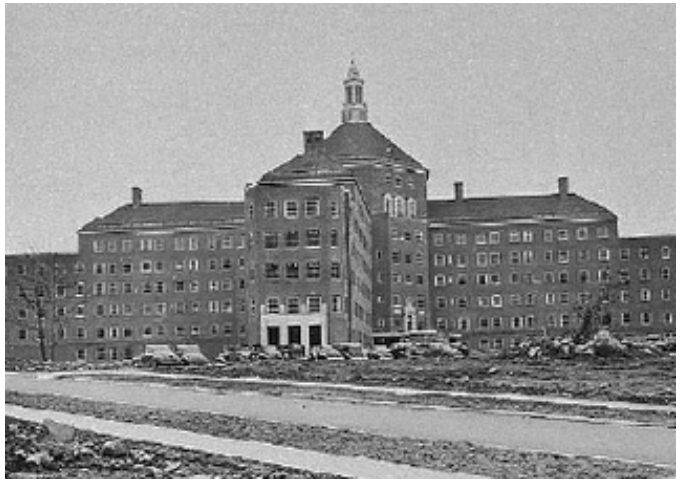


Includes examples of 22 unethical research studies.

(1963) Dr's. Southam & Mandel found guilty of fraud and misconduct

injecting liver cancer cells into hospitalized elderly patients without consent.

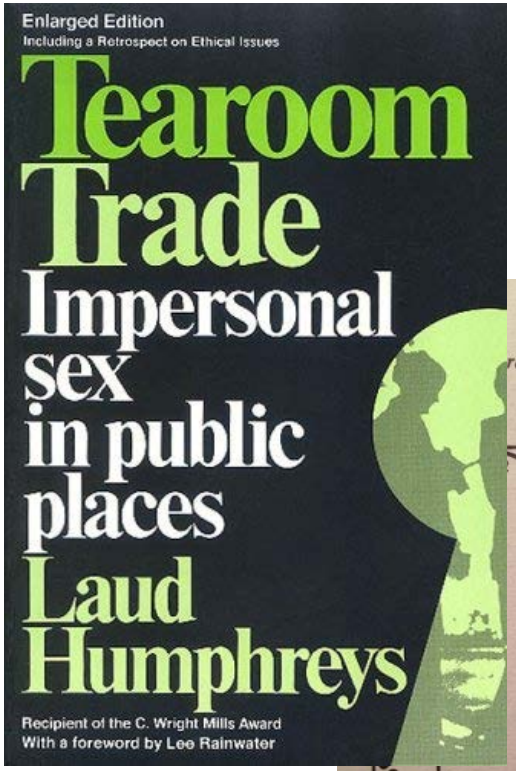
Saul Krugman
New York University
School of Medicine

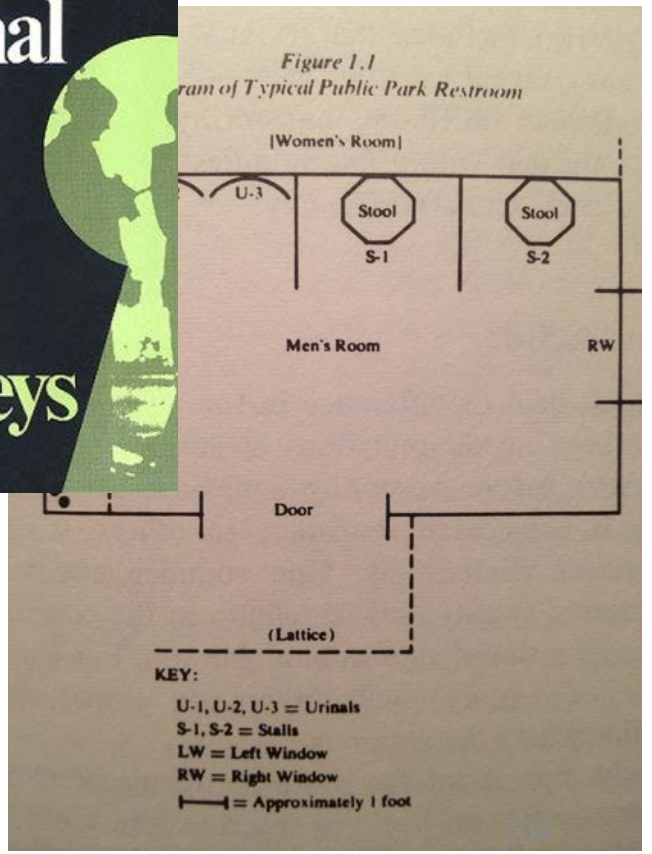


Willowbrook: Saul Krugman: Argued that since they would become infected anyway, it is ethical to inject them with hepatitis in a controlled fashion in order to study it.

Tearoom Trade Study: 1970

- Sociological Study (Ph.D. dissertation) of Gay Men by Laud Humphreys, a social demographer.
- Observation in Public Restrooms as a ‘watch queen.’
- Obtaining name and addresses through license plate identification
- In-home interviews pretending to be someone else.

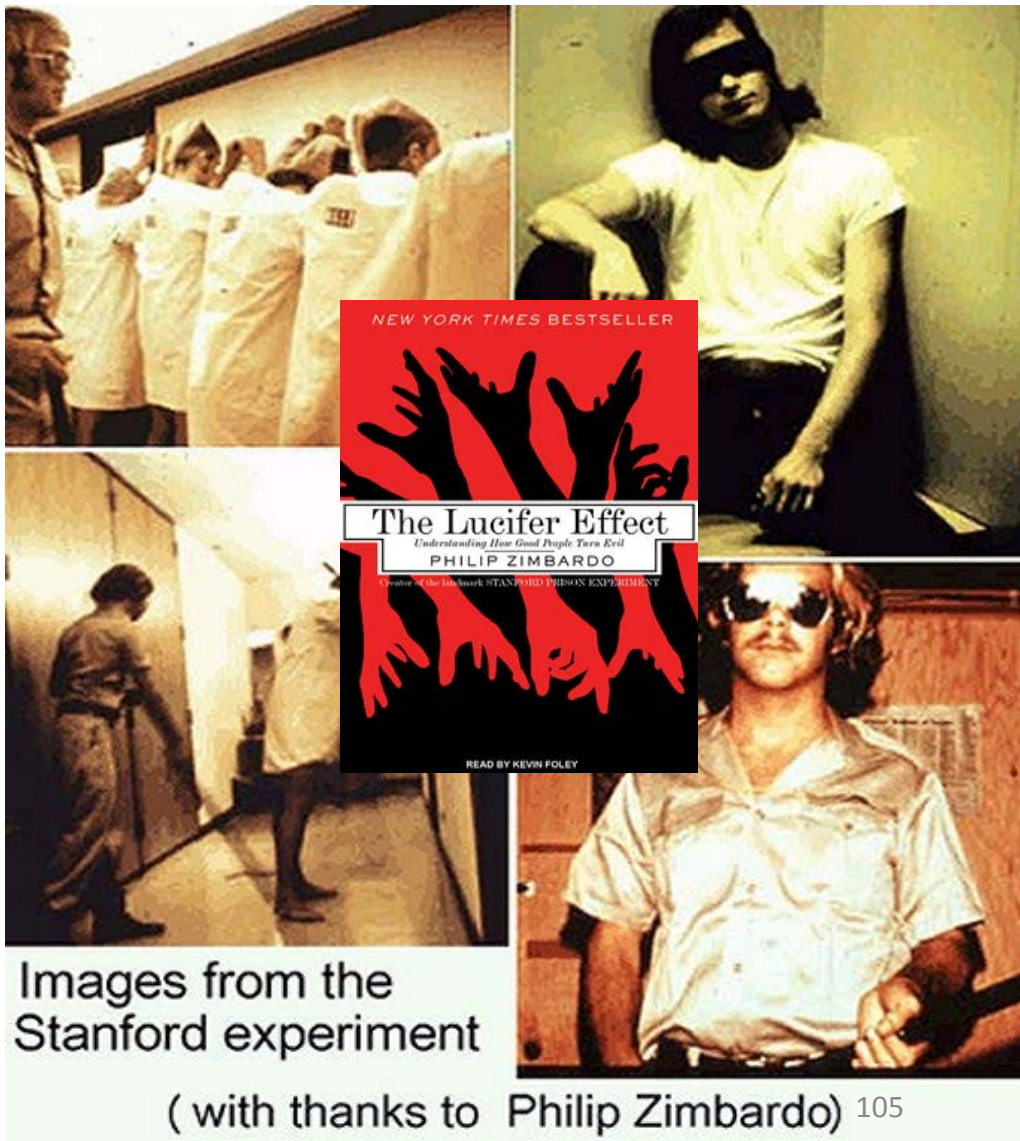




Stanford Prison Experiment

- Twenty four male students were randomly assigned to be either prisoners or guards.
- Conducted in the basement of the Stanford psychology building
- Funded by the US Office of Naval Research
- The participants created an authoritarian regime, and subsequently tortured their fellow students.
- Many prisoners accepted the abuse, and even willingly harassed other prisoners.
- The experiment was stopped after six days.

Hypothesis: Inherent traits of prisoners and guards causes abusive behavior.



Oversight & Response

- Nuremberg Code (1947)
- Declaration of Helsinki (1964)
- NIH Policy (1966)
- National Research Act (1974); created 45CFR46, formalized IRB's, created 'National Commission' - later became NBAC then Presidents Council.
- Belmont Report (1979) –
  Autonomy | Risk:Benefit | Justice
- Declaration of Helsinki - amended (1989)
- Common Rule (1991)
- HIPAA (1996)

earliest example I've found…

Spanish American War "Immunes": Army's four black regiments–the 9th and 10th Cavalry and 24th and 25th Infantry. Recruited blacks and experimented by having them exposed to and fight in Cuba and other areas with yellow fever

"Although neither black nor white Immune regiments had shown any immunity to diseases–a total of seven officers and 241 enlisted men had succumbed to them–it was still commonly believed that black soldiers performed better than white troops in tropical climates"
- The Black "Immune" Regiments in the Spanish-American War.

Some of our brave colored Boys who helped to free Cuba.

The Washington Post "Among all the fallacies and crack-brained nonsense bred by the war, we know of none so extravagant as the 'immune regiment.'

Soldiers given a gold medal & lifetime pension...

A few current topics

- Digital Health
- Undocumented individuals

Digital Health Call to Action

(the most important slide to remember)

We have a moral obligation to act and do our part to ensure the upstream research and development in digital health that redefines healthcare does not recreate the same problems that do not serve the vulnerable amongst us. To do so robs people of dignity and autonomy, places them at an institutionalized increased risk compared to others, and unjustly excludes them or places them last in line to reap the rewards of new research & developments.

Risk | Benefit
Vulnerable Populations

<u>Group</u>

- Children – tech adoption higher, generational knowledge of risks shows big differences
  - Cyber-bullying
  - Sharing practices very different

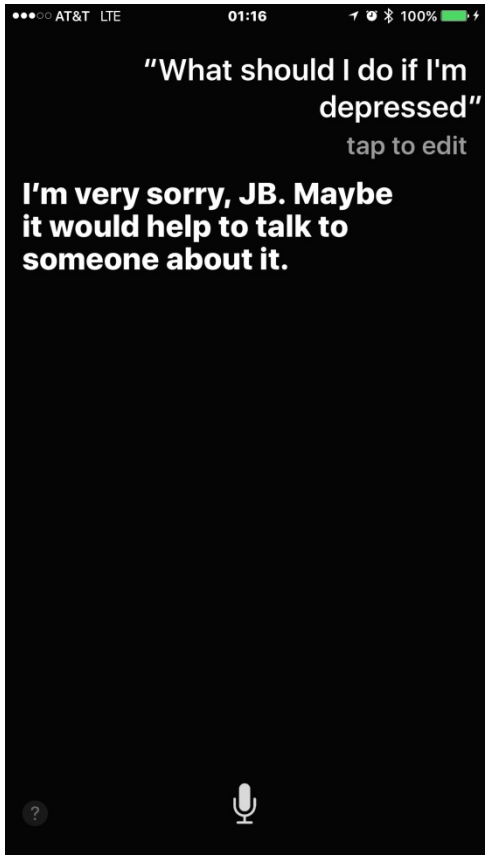
- Prisoners – generally they have extreme limitations of access to technology

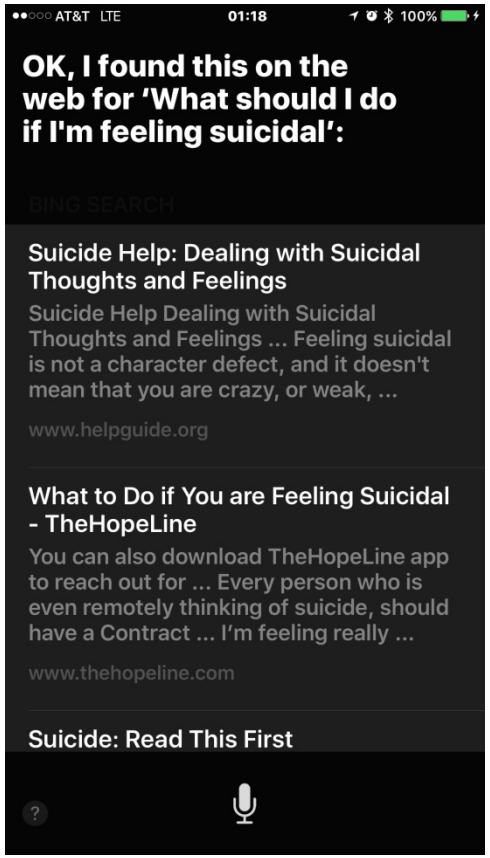
<u>Situational</u>

- School environment (FERPA & DOE)
- Catastrophes & Disasters
  - Remember what happened to the disabled during Katrina…
- In public
  - Inadvertent disclosures

Risk | Benefit
Vulnerable Populations

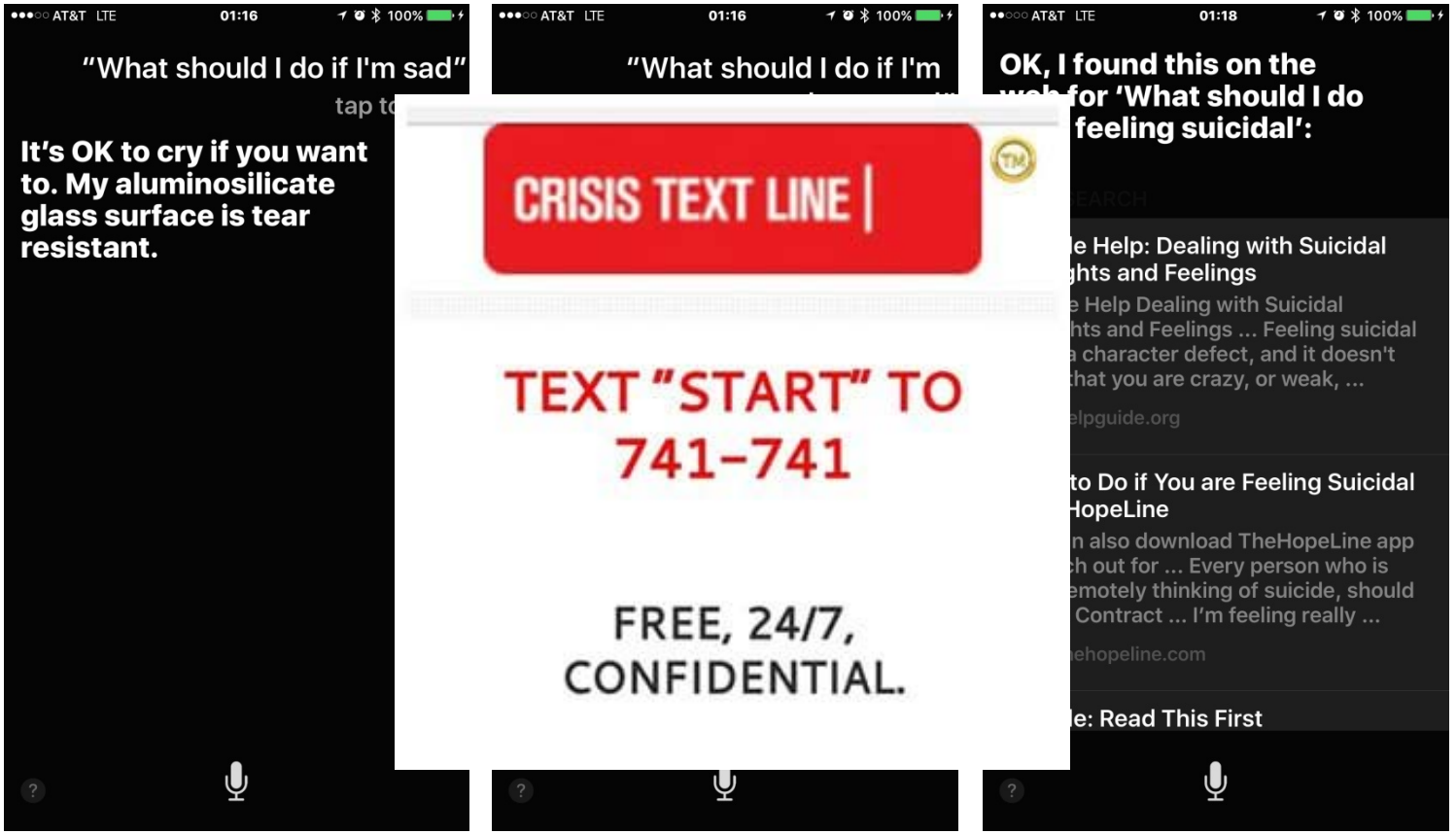
doing nothing, or doing something





Risk | Benefit
Vulnerable Populations

doing nothing, or doing something



Undocumented Individuals

"Donald Trumps Immigration Ban Sows Chaos" Jan 20, 2017, Wall Street Journal

"Living in fear of deportation is terrible for your health" Feb 10, 2017, Washington Post

- What are the particular risks?
  - Legal
  - Social
  - Health
- What specialized protections might you include?
  - Confidentiality, Privacy, Data Security

Special Considerations: Undocumented Individuals

- Waivers Waive as much documentation as possible
- CoC Get a certificate of confidentiality
- Subject Removal: Consider letting an investigator remove individuals from a study if they think the person is at particular risk of harm.
- Not Collected Unless: Limit the identifying information of individuals in study records, and craft procedures for anonymization.
- "Nuclear Option" – (1) include process where investigator has authority to expunge all research data if a threat to the subjects is identified. (2) consider inclusion of deterrence measures.

Thank You!

- Feel free to be in touch:
  jeremy@venturecatalyst.nyc
- Special thanks to …
  Bruce Gordon MD, Univ of Nebraska
  Charlotte Coley MA, Univ of North Carolina