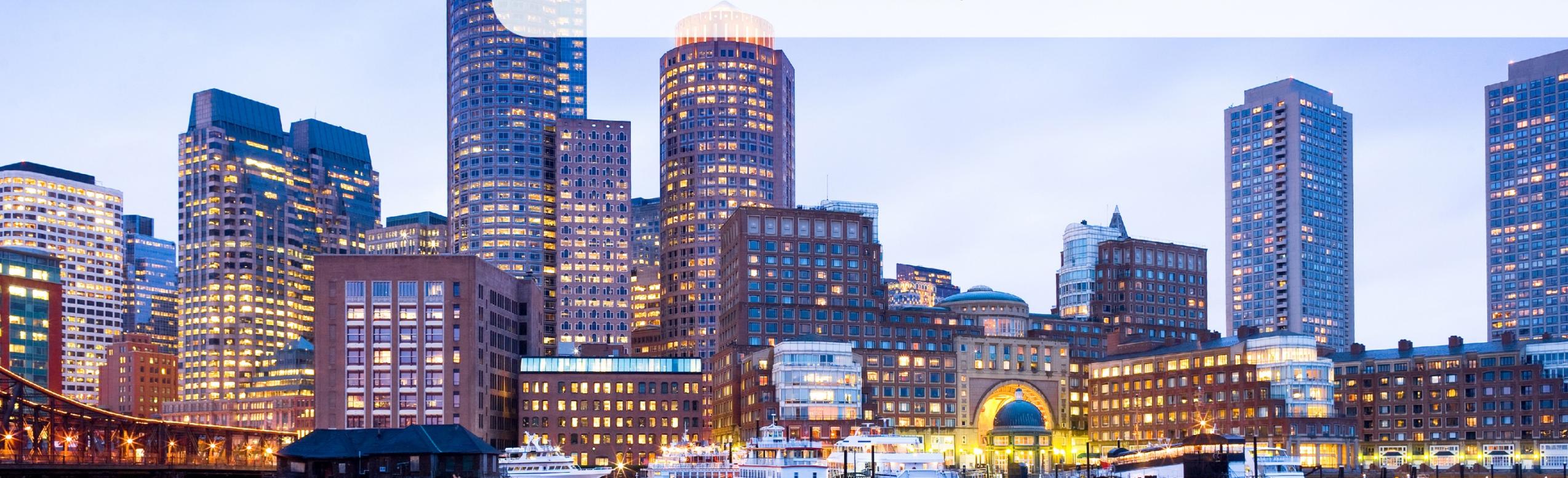


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# Vulnerability Explored: Concepts and Applications

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# Disclosure: Bruce Gordon, MD

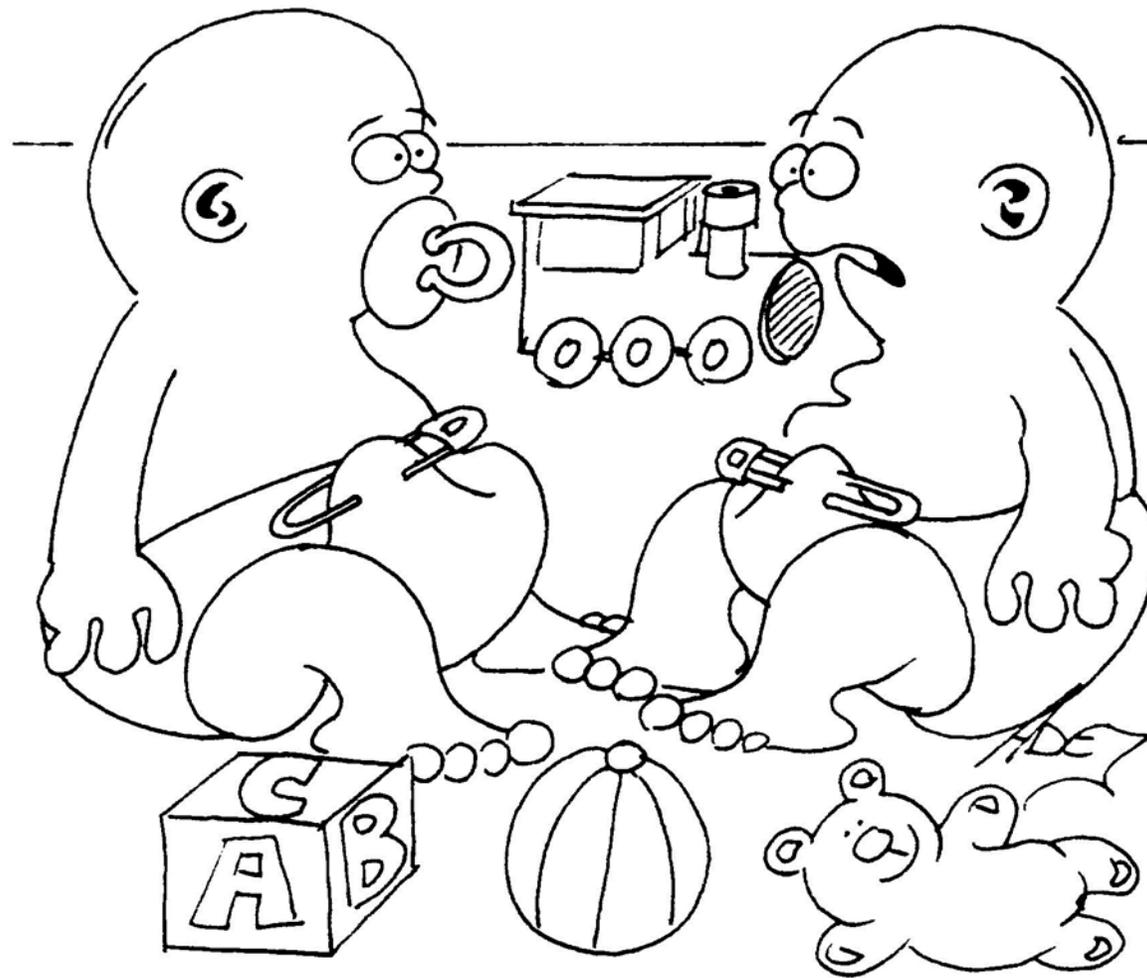
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However,  
sometimes I don't recycle ...



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Fat, bald and incontinent. Life seems to have dealt us a glancing blow."

# 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

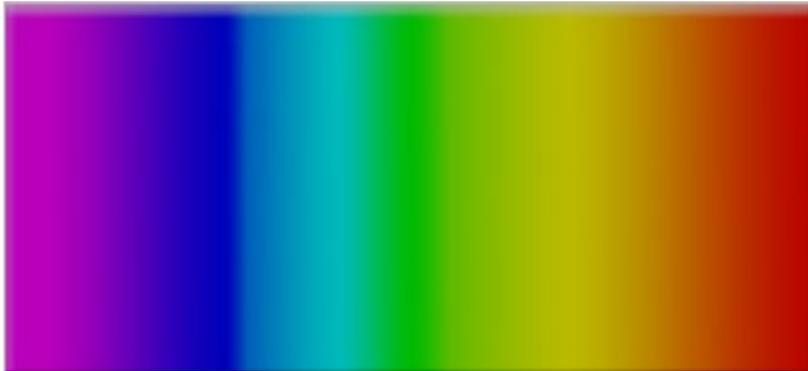
# Vulnerability

- 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"

# What are vulnerable subjects actually vulnerable to?

- Risk of some sort of harm beyond that of others ...
  - "the root of the concept of vulnerability lies in the possibility of physical harm." (Levine)
  - open to "an assault" on their "respect, health, or rights" (Leavitt)
  - heightened risk of experiencing a wrong ... ranging from physical harm to breach of confidentiality to not "getting fair consideration in resource allocation." (Hurst)
  - at risk of being enrolled in research in violation of one or more of premises of the basic "deal" [risks are reasonable in relation to anticipated benefits; risks have been minimized; voluntary informed consent] (Coleman)

# Vulnerability



- Vulnerability is not all or none ...
  - a particular situation or a particular characteristic may place a particular person at greater (or lesser) risk of "harm"
  - to the extent that the situation or characteristic places that person at risk that person is made more (or less) vulnerable

# Vulnerability

- "Additional safeguards" included to protect the rights and welfare of these subjects must reflect the particular vulnerability of the specific subject (or subject population)
  - One size may not fit all ...

# Who is 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

# Who is vulnerable?

- 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

- "Vulnerability is sensitive to context, and individuals may be vulnerable in one situation but not in another."

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

# Taxonomy of Vulnerability (NBAC)

- Types of vulnerability
  - **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)
  - **Medical** – serious health conditions
  - **Economic and/or Social** - disadvantaged in the distribution of social goods and services, or belonging to an undervalued group

# Vulnerability

- Basic approach to consideration of inclusion of vulnerable subjects
  - Is inclusion necessary?
  - If inclusion is necessary, are protections adequate?

# Is Inclusion Necessary?

- Competing ethical imperatives
  - Respect for persons → protect those with limited autonomy
  - Beneficence, Justice → do good (provide benefits of research); distribute benefits of research fairly



# Is Inclusion Necessary?

- Are there less vulnerable populations which could answer the same scientific questions?
  - Phase II study of investigational drug for depression. Target population is inhabitants of a homeless shelter who have moderate to severe depression
  - Phase II study of an investigational antibiotic for hospital acquired pneumonia. Target population includes **children, adolescents** and adults.



# Is Inclusion Necessary?

- "The argument in favor of conducting research involving children rests on ... **the consequences of not conducting research** involving children in those instances. Such consequences might include the perpetuation of harmful practices, the introduction of untested practices, and the failure to develop new treatments ..."

National Commission Report on  
Research Involving Children (1977)

# Is Inclusion Necessary?

## THE GASPING SYNDROME AND BENZYL ALCOHOL POISONING

JUAN GERSHANIK, M.D., BETTY BOECLER, R.N., M.N.,  
HARRY ENSLEY, PH.D., SHARON McCLOSKEY, B.S.,  
AND WILLIAM GEORGE, PH.D.

**B**ENZYL alcohol is commonly used as an antibacterial agent in a variety of formulations, including bacteriostatic sodium chloride and bacteriostatic water, that are intended for intravenous administration. Although benzyl alcohol toxicity has been recognized, the concentration that is necessary for antibacterial action appears to be much lower than the concentration that would be dangerous to adults.<sup>1,2</sup> Little, if anything, is known about the possible toxic effects of benzyl alcohol in neonates.

Ten premature infants in our neonatal intensive-care unit developed similar clinical syndromes characterized by the deterioration of multiple organ systems and eventual death, which we believe were the result of benzyl alcohol poisoning. In a preliminary report we have referred to this clinical pattern as the "gaspingsyndrome."<sup>3</sup> All the infants had originally presented with respiratory distress requiring mechanical ventilation and umbilical arterial catheterization for frequent

- Benzyl alcohol poisoning (Gaspingsyndrome 1982)
  - decreased mortality rate (81% vs 46%) in infants <1000 g after removing benzyl alcohol (Pediatrics 77:500, 1986)

# The New England Journal of Medicine

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## INFECTIOUS HEPATITIS\*

### Studies of Its Natural History and Prevention

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NEW YORK CITY

**T**HE control of viral hepatitis in both military and civilian populations presents one of the foremost problems in preventive medicine. The adaptation of the etiologic agent or agents to a laboratory animal or to tissue culture and the development of a specific immunologic test would provide tools to speed the solution of the problem. Neither tool is available at present. Man still remains the only established susceptible host. The clinical diagnosis of viral hepatitis

were exposed to hepatitis virus and that subclinical infection followed by active immunity developed. He suggested this mechanism of "passive-active immunity" to explain the prolonged protective effect.

The present report is concerned with an attempt to control the high prevalence of infectious hepatitis in an institution for mentally defective patients. Its purpose is threefold: to describe the circumstances under which the disease occurred, and the effect of

# Are Protections Adequate?

- Do prospective subjects have difficulty providing voluntary, informed consent?
  - Are there decisional issues?
  - Are there communication issues?
  - Are there social conditions which limit the subject's options?
  - Might the subject's hope for medical benefit influence judgment?
  - Can the subject consent for himself?
- How might informed consent be facilitated?

# Are Protections Adequate?

- Are conditions for informed consent satisfied?
  - Is information presented in an **understandable** manner?
  - Do subjects **comprehend** the details of the research and their rights as research subjects?
  - Is the process of consent conducive to true **voluntariness**?

# Are Protections Adequate?

- Remember the "definition" of vulnerability:
  - "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.**" (NBAC)
- Informed consent does not necessarily eliminate vulnerability

# Vulnerability

Coleman: J Law Med Ethics 37:12, 2009

- 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

# Are Protections Adequate?

- Are prospective subjects at risk for exploitation?
  - Is there a power differential?
  - Are there economic issues which might place subject as risk for undue inducement?
  - Is the recruitment process acceptable?
  - Are payment arrangements acceptable?
- How might these risks be minimized?

# Are Protections Adequate?

- "... the more reliable safeguard is provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator."

Henry Beecher 1966

# Thank You

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**Research with the Vulnerable: The Basics and Beyond**  
Corinne Rogers, MS, CIP  
IRB Director, NSYPI IRB

# Disclosure: [Corinne Rogers, MS, CIP]

*I have no relevant personal/professional/financial relationship(s) with respect to this educational activity*

*New York State Psychiatric Institute, IRB Director*

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# Vulnerable Populations: Beyond the regulations

## **New York State Psychiatric Institute, Institutional Review Board (NYSPI-IRB)**

- Reviewing IRB for protocols emanating from NYSPI, Research Foundation for Mental Hygiene, Columbia University Department of Psychiatry, several NYS OMH facilities
- Approximately 200 new studies submitted per year
- 30 IRB members (including alternates) from diverse psychiatric backgrounds and disciplines
- All protocols involve psychiatric populations – thus, we extend the notion of vulnerability beyond those defined in the regulations

# Beyond the regulations

- Individuals with Psychiatric disorders
  - Schizophrenia/psychosis
  - Depression
  - Substance Use Disorders
  - Eating Disorders
- Individuals in a dependent relationship with the investigator such as students or employees. Or investigator's own patients. We prohibit physicians from enrolling their own patients.
- Members of the LGBTQ community. Heightened issues of confidentiality and ways we try to minimize this risk.

# Beyond the regulations

- Schizophrenia/psychosis
  - Independent assessment of capacity by a clinician who is not part of the research team – required for all more than minimal risk studies
  - Assessment of understanding of consent for minimal risk studies
  - Assessment should be ongoing

# Beyond the regulations

- Schizophrenia/psychosis
  - Verbal re-consent at a certain interval for long trials (also do this for research on depression)
  - “Study Buddy”

# Beyond the regulations

- Depression
  - For experimental medication studies: Participants must have had a least one failed trial of an effective medication at an adequate dose for an adequate duration. Treatment naïve are not permitted.
  - Can't take someone off of an effective medication to participate in an experimental treatment trial

# Beyond the regulations

- Depression
  - Require operationalized drop-out criteria for worsening – for both the trial and wash-out period if there is one.
  - Verbal re-consent at a certain interval for long trials
  - Treatment and/or referrals provided post participation

# Beyond the regulations

- Substance Use Disorders
  - Enrollment in substance/alcohol administration studies limited to non-treatment seekers.
  - Must be clear in the CF that participants can stop and request treatment at any time.
  - CF does not need to identify why participants are being asked to participate (eg., "...because you use cocaine"). This is not limited to SU studies (e.g., HIV studies, LGBTQ research, etc.)
  - Treatment and/or referrals provided post participation.

# One last thought

“No matter how many regulations are put in place or guidelines are written, and no matter how intense the scrutiny by IRBs or other authorities, there can be no substitute for the ***ongoing commitment*** by researchers and the institutions in which they work to ethically appropriate behavior throughout the research process.”

# Questions?

# Thank You