Panel 4:
Vulnerable Populations

Vulnerable Populations in Pragmatic Clinical Trials

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The views expressed are my own.
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Present Focus

- US regulations (state and/or local regulations may also apply)
- Different definitions of vulnerability
- In general: Individuals for whom existing regulations do not provide sufficient protection with respect to a given study

US Regulations

- Rely on consent. Hence, suggest extra protections for those with consent limitations (e.g. mentally disabled and disadvantaged) for 1. IRB membership, 2. Subject selection and 3. Consent

- Mandate extra protections for 3 groups: pregnant women/fetuses; prisoners; children

Two Questions

1. Are the regulations insufficient for some individuals with respect to this study?

2. Are the regulations excessive for some individuals with respect to this study?

Adults Unable to Consent

- US regulations do not include additional protections for adults who cannot consent, other than requiring a legally authorized representative.

- If relevant, consider whether state law allows surrogates to enroll charges in the research and whether any other protections are needed.

Pragmatic Clinical Trials

- The additional protections for pregnant women, prisoners, and children apply to all studies.
- Yet, pragmatic trials evaluating approved interventions may raise no special concerns with respect to these groups.
- What are appropriate responses?

First Option: Irrelevant

If net risks minimal, and no special concerns:

A. Assume attention to vulnerable populations is unnecessary, and

B. Exclude if become aware that a particular individual is pregnant, a prisoner, or a child (both at enrollment and during participation)

SACHRP (Cluster trials)

It is acceptable to not consider vulnerable groups to be included in a given study:

Unless the “investigator or IRB has direct knowledge” of their participation

http://www.hhs.gov/ohrp/sachrp-committee/recommendations/2014-july-3-letter-attachment-c/index.html

Possible Concerns

- Acceptable to OHRP?
- If don't identify and exclude can't collect data on the intervention with respect to that population
- Does not apply to any trials that pose greater than minimal net risks

Second Option: Address

- Design, review, and conduct the study to include the mandated protections for pregnant women, prisoners, and/or children that might be enrolled.

- Can omit protections for any groups that certainly will not be enrolled (e.g. pregnant women in a study comparing treatments for prostatic hypertrophy).

Possible Extra Protections

- IRB membership: If regularly review research with vulnerable subjects consider expert member on IRB
- Selection of subjects: IRBs consider any problems involving vulnerable subjects
- Consent: If some potential subjects likely vulnerable to coercion or undue influence: adopt additional safeguards

Pregnant Women/Fetuses

1. No non-beneficial procedures (risk to fetus from interventions prospect benefit unless data cannot be attained otherwise).

2. Prior data on risks to pregnant women

3. Inform potential subject of risks to fetus

The Two Options

Irrelevant: If notified, exclude

Address (assuming no non-beneficial interventions that pose risks to fetus): 1. Consider whether there are data to assess risk to pregnant women; and 2. Inform any pregnant women of the risks to the fetus

Prisoners

1. At least one member of at least one IRB is a prisoner or a prisoner representative.

2. Notify Secretary that IRB has approved research under prisoner regulations

3. Each prisoner informed participation will not affect parole

The Two Options

Irrelevant: If notified, exclude

Address: 1. Ensure prisoner representative on at least one IRB; 2. Certify to the Secretary that prisoner regulations followed 3. If notified: inform that participation in the research will have no effect on parole

Children

1. Study must be approved in one of the four categories for pediatric research

2. Must obtain assent of the child and parental permission (unless informed consent waived, FDA?)

The Two Options

Irrelevant: If notified, exclude

Address: 1. IRBs determine risk-benefit category; 2. Assuming minimal risk or prospect of direct benefit: obtain the child's assent and the permission of one parent

Summary

- For some studies, it may be appropriate to regard vulnerable subjects as irrelevant and exclude if notified
- In other cases, it may be feasible to prospectively satisfy the regulations on vulnerable populations

Ethical and Regulatory Issues of Pragmatic Clinical Trials Workshop

Vulnerable Populations

Presented by: Susan Huang, MD MPH

May 10, 2016

ABATE Infection Project

Active Bathing to Eliminate Infection Project

Active Bathing to Eliminate Infection

- ABATE Infection Trial
- Premise
  - Hospital-associated infections are common and preventable
  - Most infections arise from bacteria on the body
  - Topical antiseptic soaps and ointment can remove bacteria and prevent infection

Decolonization in Hospitals

- Precedence
  - REDUCE MRSA Trial
  - ICUs – use of chlorhexidine antiseptic soap for bathing and mupirocin nasal antibiotic ointment for all patients in adult ICUs reduced infection
    - ✓ Decreased antibiotic resistant bacteria (MRSA) by 37%
    - ✓ Decreased all cause bloodstream infection by 44%
  - Currently, 70% of U.S. hospitals routinely bathe patients with chlorhexidine in at least one of their ICUs
  - What about outside of ICUs?

ABATE Infection Trial
Active Bathing to Eliminate Infection

Trial Design

- 2-arm cluster randomized trial
- 53 HCA hospitals and 191 adult non-critical care units
- Includes: adult medical, surgical, step down, oncology
- Excludes: rehab, psychiatric, peri-partum, BMT units

Arm 1: Routine Care

- Routine policy for showering/bathing

Arm 2: Decolonization

- Daily CHG shower or CHG cloth bathing routine for all patients
- Mupirocin x 5 days if MRSA+ by history, culture, or screen

Pragmatic Implementation

Purpose

- Assess value of decolonization as a quality improvement (QI) strategy to reduce infections in hospitals
- Effectively, to swap out the current soap in use
- Generalizability

Method

- Leveraged usual QI infrastructure
- No on-site research staff
- Investigators trained sites on protocol
- Training modules, protocols, tools provided

Individual Informed Consent

- **Minimal Risk**
  - Topical, safe, routine pre-op/ICU protocols
  - Already being done under QI protocols in some hospitals
  - Deidentified data
- **Rights and Welfare**
  - Recognizes patients rights in healthcare facilities
  - Able to refuse all forms of medical care
- **Practicality**
  - In usual hospital processes, patients do not select their bathing soap
  - Population approach to reduce contagion
- **Decision** → Waive individual informed consent

Compare and Contrast Vulnerable Population: Pediatrics

Contrasting Example

- Pediatric ICU Trial
- Routine chlorhexidine bathing
- 10 ICUs, 5 academic medical centers
- Randomized cross over design
- IRB required written informed consent

Milstone A et al. Lancet 2013;381 (9872):1099-1106

Pediatric SCRUB Trial

Scrubbing with CHG Reduces Unwanted Bacteria

Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: a multicentre, cluster-randomised, crossover trial

Aaron M Milstone, Alexis Elward, Xiaoyan Song, Danielle M Zerr, Rachel Orscheln, Kathleen Speck, Daniel Obeng, Nicholas G Reich, Susan E Coffin, Trish M Perl, for the Pediatric SCRUB Trial Study Group

Summary

Background Bacteraemia is an important cause of morbidity and mortality in critically ill children. Our objective was to assess whether daily bathing in chlorhexidine gluconate (CHG) compared with standard bathing practices would reduce bacteraemia in critically ill children.

Methods In an unmasked, cluster-randomised, two-period crossover trial, ten paediatric intensive-care units at five hospitals in the USA were randomly assigned a daily bathing routine for admitted patients older than 2 months, either standard bathing practices or using a cloth impregnated with 2% CHG, for a 6-month period. Units switched to the alternative bathing method for a second 6-month period. 6482 admissions were screened for eligibility. The primary outcome was an episode of bacteraemia. We did intention-to-treat (ITT) and per-protocol (PP) analyses. This study is registered with ClinicalTrials.gov (identifier NCT00549393).

Milstone et al. Lancet. 2013; 381(9872):1099-1106

Recruitment by Consent

	Control Arm	Intervention Arm
Eligible	2528	2433
Refused Study Data Consent	3	11
Refused Study Treatment		354
Unable to Consent	0	521
Per Protocol	2525	1547

Nearly 40% loss of enrollment

Impact of Requiring Written Consent

- Unable to pragmatically conduct minimal risk bathing
- Greatly reduced sample size
- Failed to meet primary outcome of reduced bacteremia
- Met secondary outcome of reduced central line infections
- Not widely adopted as standard of care
- Hospitals continue to adopt under QI protocols without definitive science

Milstone A et al. Lancet 2013;381 (9872):1099-1106

ABATE Infection Trial
Permission to Include Prisoners

- ABATE Bathing protocol applies to all
- Prisoners have risks of hospital infection
- Protocol does not explicitly seek out prisoners

- **Prisoner as a subject**
  - Unlikely, but possible
  - Central IRB does not have a prisoner representative

Subpart C Review

- HHS regulations at 45 CFR part 46, subpart C provide additional protections pertaining to biomedical and behavioral research involving prisoners as subjects.
- IRB must satisfy the following requirements of HHS regulations at 45 CFR 46.304(a) and (b):
  - A majority of the IRB (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB.
  - At least one member of the IRB must be a prisoner, or a prisoner representative, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.

ABATE Infection Trial
Permission to Include Prisoners

Decision

- Of HCA IRBs, one had a prisoner representative
- Provided Subpart C review and waived informed consent
- Central IRB relied on that hospital for this requirement (under 45 CFR 46.304(b))

Pre-Planning

- Central IRB anticipated these issues
- Central IRB and HCA compliance team readily identified an IRB that could address this review
- 52 hospitals relied on central IRB, and one hospital asked to independently review to address this issue
- No time delays, but extra planning

California Prisoner Law

- Review of relevant law in California as part of the review of local research contact identified a state law which stated “ Except for specific exceptions, biomedical research may not be conducted on any prisoner in the State of California (PC §3502). Directives from the Secretary of the Youth and Adult Correctional Agency and the Director of the Youth Authority also prohibit the conducting of biomedical research on wards. This applies to research relating to or involving biological, medical, or physical science. The only exceptions are for research that is specifically codified in statute and approved by the Director of the Department, the Secretary of the Youth and Adult Correctional Agency, and the Governor’s Office.
- http://www.cdcr.ca.gov/Reports_Research/rpaguide.html

ABATE Infection Trial: Summary

Vulnerable Populations

- Children and prisoners who are hospitalized experience hospital-associated infections like other patients
- They should not be excluded from studies of minimal risk, routine care activities that could impact a general population
- Differential treatment (requiring consent) makes studies harder to do in these populations and exclusion means applicability of treatments to this population is less well known
- Should these populations always be deemed at higher risk?
- Should review be needed for an intervention that may not have prisoners actually be a part of the study?

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Vulnerable Populations

Ethical and Regulatory Issues of Pragmatic Clinical Trials Workshop

National Institutes of Health
May 10, 2016

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Definition of Vulnerable Persons

Vulnerable Persons: those “who are relatively (or absolutely) incapable of protecting their own interests”

Definitions

- Pragmatic Clinical Trials (PCTs) are trials that:
  - Compare clinically relevant alternative interventions
  - Include a diverse population of participants and heterogeneous practice settings
  - Collect data on a broad range of health outcomes

- PCTs frequently:
  - Randomize at the group level
  - Rely on large data sets
  - Compare approved medical care
  - Frequently meet criteria for minimal risk

Current Considerations of Vulnerability

- Federal Regulations
  - **Pregnant women, fetuses and neonates (45 CFR 46 Subpart B)**
  - **Prisoners (45 CFR 46 Subpart C)**
  - **Children (45 CFR 46 Subpart D & 21 CFR 50 Subpart D)**
  - Persons with Physical / Mental Disabilities
  - Disadvantaged Persons
- Belmont Report
  - Racial Minorities
  - Very sick
  - Institutionalized
- State and Local Laws

Current Considerations of Vulnerability

- Protectionism:
  - Create regulatory and ethical checks
  - Limit participation in many research trials
  - Approach is often to exclude from research
  - Policies developed for traditional clinical trials testing novel products
- Considerations:
  - Is limited participation or exclusion from research a harm?
  - Are the additional protections for vulnerable populations necessary for minimal risk studies?

Ethics for Inclusion

- Principle of Justice
  - inequitable burden of research
  - inequitable access
  - therapeutic orphans
- Principle of Respect / Autonomy
  - vulnerability based on question of ability to provide informed consent
  - minimal risk PCTs may make question less relevant
  - modification of consent

Inclusion

- Exclusion of vulnerable populations may bias study results
- Outcomes may not generalize to vulnerable subjects if they are excluded

Challenge

To identify approaches that support the design and approval of PCTs that include vulnerable subjects while still safeguarding their interests.

Rethink Vulnerability

VIC (very important concept)

Vulnerability is not intrinsic to a certain population…

Rethink Vulnerability

- Transition from viewing vulnerability as membership in a group
- Move to viewing vulnerability as the intersect between the individual, the study characteristics and the circumstances
- Kipnis (2003) identifies seven vulnerability characteristics for pediatric research that can be extended to all populations

Characteristics of Vulnerability

Table I. Individual characteristics of vulnerability to consider by population.

Population	Incapacitational[a]	Juridic[b]	Deferential[c]	Social[d]	Situational[e]	Medical[f]	Allocational[g]
Children	X	X	X	X	X	X	X
Disadvantaged persons			X	X	X		X
Human fetuses	X				X		
Institutionalized	X	X	X	X	X		X
Neonates	X				X		
Persons with physical handicaps/ mental disabilities	X	X	X	X	X		X
Pregnant women			X	Historically and non-US	X		
Prisoners		X	X	X	X		X
Racial minorities			X	X	X		
The very sick	X		X	X	X	X	

Italicized populations are those covered by additional regulations.
Framework adapted from Kipnis:[17]
[a]Lacks "the capacity to deliberate about and decide whether to participate in the study."
[b]"Liable to the authority of others who may have an independent interest in that participation."
[c]"Given to patterns of deferential behavior that may mask an underlying unwillingness to participate."
[d]Belongs "to a group whose rights and interests have been socially disvalued."
[e]"In a situation in which medical exigency prevents the education and deliberation needed to decide whether to participate in the study."
[f]Has "been selected, in part, because of the presence of a serious health-related condition for which there are no satisfactory remedies."
[g]"Lacking in subjectively important social goods that will be provided as a consequence of participation in [the] research."

Rethink Vulnerability

- Incapacitational: lacks the capacity to deliberate and decide about participation
- Juridic: under the authority of others who may have independent interests
- Deferential: behavior may mask an unwillingness to participate
- Social: membership in a group whose rights / interests have been socially disvalued

Rethink Vulnerability

- Situational: medical urgency or need prevents the education and deliberation required to decide
- Medical: the presence of a serious health-related condition for which there are no satisfactory treatments
- Allocational: the lack of important social goods that will be provided by participation in the research

Vulnerability in Study Design

- Early consideration of subject vulnerability
  - Study specific ethical concepts
  - Study specific regulatory issues
  - Design
  - Risk Determination
  - Conduct

Vulnerability in Study Design

- Risk Determination
- Study Population
- Utilization of current regulations
- Investigator / IRB knowledge of intended populations

Summary

- Regulations codify protections for vulnerable populations who participate in research
- Regulations may create barriers for vulnerable populations to participate (Justice)
- Balance protection from harm with importance of inclusion of data
- In all cases a risk / benefit evaluation is required

Summary

- Additional safeguards should be based on the target population of the study
- Evidence is needed to inform the decisions made in clinical practice
- PCTs often help answer real-world questions about current treatments; information from people identified as vulnerable subjects must inform the real-world results

Recommendations

Table 2. Recommendations for vulnerable populations in PCTs.

- When designing a PCT, inclusion of participants who may be members of a vulnerable category should be considered, and how the ethical and regulatory requirements will be assessed and managed should be addressed in the study.
- There should not be a differential burden of research nor differential access to research for one group relative to any other. Therefore, being part of a vulnerable population should not be an exclusion criterion.
- In general, PCTs not targeting vulnerable subjects should not seek to identify vulnerable subjects within the study for the sole purpose to exclude them. This could stigmatize the vulnerable group and risk violating confidentiality and loss of research data for that group.
- PCTs where a vulnerable population is the focus of the study rather than a member of a larger group should address the protections for that group. PCTs where vulnerable subjects are included as part of a larger population should be evaluated based on the level of risk and the characteristics being studied.
- Revisit the regulations to consider the characteristics of the participants and the incremental risk of the research design to determine the need for added protection for vulnerable populations.

Vulnerability in ABATE Design

- Risk Determination
  - Minimal Risk
- Study Population
  - Dedicated units for bone marrow transplant, labor and delivery/post-partum care, psychiatry, acute rehabilitation and pediatrics excluded
- Utilization of current regulations
  - QI determination, FDA consult
- Investigator / IRB knowledge of intended populations

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References

- Levine RJ. Ethics and regulation of clinical research. 2nd ed. New Haven, CT: Yale University Press, 1988
- Tunis et. al. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003; 290: 1624–1632.
- Sugarman J and Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. JAMA 2014; 311:2381–2382.
- Kipnis K. Seven vulnerabilities in the pediatric research subject. Theor Med Bioeth 2003; 24: 107–120.
- Shirkey H. Therapeutic orphans. J Pediatr 1968; 72: 119–120.
- Secretary's Advisory Committee on Human Research Protections. Recommendations on regulatory issues in cluster studies, http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-14/clusterstudiesrecommendations.html
- Caplan AL, et al. Selecting the right tool for the job. *Am J Bioeth 2015 15; 4-10.*

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QUESTIONS
&
DISCUSSION

Questions and Answers

Please submit questions for the panelists to:

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