The Ethics & Regulatory Landscape of Including Vulnerable Populations in Pragmatic Clinical Trials

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Conflicts of Interest

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Definition of Vulnerable Persons

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

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

Disadvantaged Populations

- Unique vulnerable population often included in PCTs
- Considerations
  - High copays
  - One arm treatment more costly
  - Difficulty getting to visits
- Approaches
  - Mechanical barriers
  - Trial design
  - Creative funding

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?

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

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

Exclusion

- 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

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

Characteristics of Vulnerability

Table 1. 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."

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

Conclusion

- 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

Conclusion

- 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.

NPRM

- Notice of Proposed Rule Making
- Published September 8, 2015
- To strengthen the effectiveness and efficiency of the oversight system by making the level of review more proportional to the seriousness of the harm or danger to be avoided
- “Final Rule” to be published this fall

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Questions / Discussion