Challenges in regulatory oversight of cluster randomized trials

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My conflicts of interest

- Ethics Advisory Committee, Roche
Topics to discuss

- Applying and interpreting 45 CFR 46
- Conceptual challenges
- Practical challenges
- Communicating guidance effectively
Are IRB review and informed consent required?

- Is the activity research?
- Does it involve human subjects?
- Is it exempt?
  - Existing data, records
  - Surveys and interviews
  - Subjects cannot be identified
Case: Reducing obesity

- Multi-pronged intervention
- Randomization by school
- Outcome is change in BMI on required annual physical exam
- Leave aside Subpart D, Family Educational Rights and Privacy Act
Multi-pronged obesity interventions

- Nutritional labeling and placement of healthy foods in cafeteria
- Dietary counseling for athletic teams
- Nudges drawing on peer pressure
  - Tweet from peer leaders: “The football team is choosing healthy foods and snacks”
Is it human subjects research?

- Local or generalizable knowledge?
- Apply for research grant?
- How described in project documents?
  - Characteristics of activity not name
- Intend to publish?
- Multiple, mixed intentions
Waiver of consent

- No more than minimal risk
- Not adversely affect rights and welfare of subjects
- Could not be practicably carried out
- Additional pertinent information
Minimal risk

- “Not greater ... than those ordinarily encountered in daily life or during performance of routine physical ... examinations or tests”
Which interventions are minimal risk?

- Nutritional labeling and placement of healthy foods in cafeteria
- Dietary counseling for athletic teams
- Nudges drawing on peer pressure
  - Tweet from peer leaders: “The football team is choosing healthy foods and snacks”
What counts as adverse effect on rights and welfare?

- Stigmatize persons who are obese, eat “unhealthy” diet?
  - What if target tweets to obese students?
  - Disproportionally certain populations
  - Aim to leverage group norms
  - Assume that individual controls weight

- Significant vs. any effect?

- Many vs. any participants?
Conceptual challenges in applying regulations

- Key regulatory terms require interpretation
  - In examples of CRTs
Conceptual challenges in applying regulations

- Need for case-based judgments
  - Depends on circumstances of particular case
  - Hard to make binary classification when multiple considerations
  - As more cases are determined, areas of clarity may emerge
Conceptual challenges in applying regulations

- In decentralized IRB system, what variation is appropriate?
  - Problem in multi-site research
  - Decisions might be too strict or too lenient
  - Can boundaries of acceptable variation in CRTs be clarified?
Practical challenges

- **Identifying IRBs in multi-site trials**
  - Many community hospitals, outpatient practices have no IRB
  - Collaborative arrangements administratively complex
  - Take advantage of existing IRB collaborations
Practical challenges

- IRB expertise regarding CRTs
  - May need ad hoc experts
Communicating guidance effectively
Suggestions:

1. Anticipate PI concerns

- Barriers to socially valuable projects
  - If same activities in marketing, not regulated as research
- Showing that you heard PI concerns may make them more receptive
Suggestions:
2. Anticipate misunderstandings

- Elicit and address foreseeable misunderstandings
  - Intention to publish signifies research
  - Randomization per se requires consent
Suggestions:
3. Make guidance more useful to audiences

• Value of case analyses
  • Active learning
  • Build areas of agreement through accumulation of cases
    • What risks should be considered?
    • Waiver of consent

• Reduce uncertainty
  • Safe harbors
  • Red flags, danger zones
Suggestions:
3. Make guidance more useful to audiences

- Hotline not linked to enforcement
- Outreach to elicit concerns
  - CIRM experience
- Guidance a process, living document
  - FAQs based on cases presented
Suggestions:
4. Address ethical as well as regulatory issues

- Ethical concerns may persist even if IRB review, consent not required
  - Minimization of risk
  - Respect for participants
    - Vulnerable participants for whom risks may be increased
Suggestions:
4. Address ethical as well as regulatory issues

- Ethical best practices
  - Community advisory boards can point out overlooked concerns, risks
    - Not gatekeeper or proxy consent
  - Respectful to inform participants even if informed consent not required
Suggestions:
2. Address ethical as well as regulatory issues

- Ethical best practices
  - Some review process even if no IRB review
    - Combined scientific and ethical review through CTSA
      - Methodological weakness of CRTs
Take home message

- Need for effective guidance on this complex topic
- Value of case studies and FAQs for active learning and clarifying points of agreement