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