Ethical Issues in Cluster Randomized Trials

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Holly Fernandez Lynch, J.D., M.Bioethics
Executive Director, Petrie-Flom Center, Harvard Law School
Faculty Member, Center for Bioethics, Harvard Medical School
Regulatory Foundations, Ethics, and Law Program, Harvard Catalyst
Disclaimers

- Salary support from Harvard Catalyst (NIH), PCORI, and NFLPA
- SACHRP has considered some of these issues – I am speaking only for myself
Key Resources

- **Ottawa Statement** – consensus statement on ethical design and conduct of CRTs for researchers, IRBs, regulators, and sponsors

- **SACHRP Recommendations on Regulatory Considerations in Cluster Randomized Trials** – October 2016
How are CRTs ethically unique?

- Traditional research ethics assumes **individual** consent, randomization, intervention, data collection – in that order
  - Typical course: Ask an individual to participate → then randomize her to a study arm → then intervene with that individual → then collect data about her

- In a CRT, the unit of **allocation** may differ from the unit of **intervention** which may differ from the unit of **outcome measurement** – all of which may involve **groups** rather than individuals, and **order** may be switched
  - Ex. CRT examining new hand-washing technique to avoid infection – randomize hospitals, intervene with health care professionals, measure infection rates in patients – consent when and from whom?
How are CRTs ethically unique?

- Traditional studies: Know exactly who needs to consent, for what, and when

- CRTs: Lack of clarity on each score
  - Does the health care professional need to consent?
  - If data were only collected from the health care professionals, would patients have to consent?
  - Is consent needed for data collection, intervention, both?
  - What about for randomization itself?

- Who needs ethical protection?

- Who has ethical responsibilities?
How are CRTs ethically unique?

- Cluster-level intervention affects everyone associated with the cluster (not targeted further) – and may be impossible to avoid
  - E.g., smoking cessation mass media campaign in a given geographic area

- Clusters may be randomized before it would be possible to identify individuals within the cluster

- Implications for right to refuse/withdraw
How are CRTs ethically unique?

- May intervene with one group to affect another, bifurcating aspects of the definition of a research subject
- Clusters may be huge, raising practicality questions for traditional research ethics standards
  - Consent
  - Post-trial access
- Involvement (or existence) of “gatekeepers” for different clusters – and interaction with individual consent
- New spin on old question: are standard of care groups research, especially if it’s not even possible to consent to randomization?
Justifying CRT Design

- Default, ethically, should be traditional, individual RCT

- Why? CRTs are:
  - More complex to design, conduct, and statistically analyze
  - Raise added, challenging ethical and regulatory issues

- So...need a good reason to take this approach
Justifying CRT Design

• BUT good reasons exist:
  • Intervention only possible to administer at cluster level – e.g., media campaign, environmental intervention
  • Interested in evaluating group effects of intervention – e.g., community smoking levels, disease transmission rates
  • Avoidance of experimental “contamination” – e.g., intervention is training delivered at provider level, so they can’t be “untrained” for controls
  • Improved compliance (for same reason CRTs raise issues about ability to refuse) – may avoid sharing/swapping
  • Reduced costs – e.g., less equipment/staff needed at all sites
  • Securing cooperation of gatekeepers/health professionals – e.g., if they want all their patients to have access

*Bad justification: avoiding individual informed consent*
Who Counts as a Subject?

- [First, make sure it is “research” or “clinical investigation” – or IRB need not get involved]

- Regulatory definitions may leave important gaps – who is intervened with and who has data collected about them may not coincide
  - [Preview - covered in more detail in regulatory presentation!]
  - Common Rule and FDA have different approaches
  - Should anyone who is intervened with for research count as a subject, even if no data or IPI is collected about them?
  - Should anyone affected by an intervention count as a subject, even if not intervened with directly?
  - What should count as research intervention? (ex. SOC arm)
Who Counts as a Subject?

• Ottawa Statement: Count as a subject any cluster member who is the recipient or direct target of a study intervention (including control condition), with whom researchers interact for study purposes or about whom IPI is collected
  • Could exclude patients of health professionals, if HPs are target of intervention and no patient IPI collected
  • But would count HPs even if no data collected about them

• SACHRP recommends a different approach
  • Count all cluster members as subjects, even if no data or IPI collected
  • “But for” test on environmental manipulation

• Serious implications – who consents?
Handling Informed Consent

- Challenges:
  - Defining subjects can be difficult – who to get consent from
  - When interventions are administered at cluster level, refusing/withdrawing consent doesn’t allow avoidance of intervention (but perhaps avoidance of data collection)
  - There may be pressure to consent (e.g., from employer)
  - Clusters can be massive – practicability issues
  - Clusters may be randomized before individual participants have been identified – timing issues and possible selection bias if allowed to decline post-randomization

- Have to consider regulatory standards for waiver or alteration of consent (and whether waiver is even permitted at all)
  - Cluster-by-cluster analysis, or whole study analysis?
  - [Hang tight for regulatory presentation]
Involvement of Gatekeepers

- When individuals are not the unit of randomization or intervention, need to think about community leaders representing clusters and their interests.
- Gatekeepers may control access – could decline participation on group’s behalf.
- BUT gatekeepers cannot ethically provide proxy consent, only permission – just an added safeguard when waiver/alteration conditions are satisfied.
- Can also help facilitate communication with group members.
Assessing Risks and Benefits

- CRTs affect both individuals and groups – consider risks and benefits at both levels
- Need equipoise between study arms, just as in individual randomized trials
- Similar standard of care issues for control cluster – when should it be augmented to reflect basic minimums?
  - When control arm is improved over usual standard of care, that also has implications for who must consent, i.e., whether that arm counts as research
  - Even when control arm is not augmented at all, consider implications if standard of care changes during the trial – will control arm remain status quo or change too?
- What counts as a research intervention/risk?
  - What if all clusters get interventions that fall w/i SOC?
  - Focus on but for test and manipulation of environment
Analogous and Overlapping Issues

- Emergency research
  - Community engagement
  - Difficulties with timing of consent
  - Implications for ability to refuse/withdraw

- Standard of care research
  - What’s a research intervention
  - Who needs to consent

- Learning health systems
  - Data collection about entire system/group
  - What’s a research intervention
  - Who needs to consent

- Involvement of children (or other vulnerable populations) in clusters – further complications
## Ottawa Statement: Summary of recommendations.

<table>
<thead>
<tr>
<th>Ethical Issue</th>
<th>Recommendation Number</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Justifying the cluster randomized design</td>
<td>1</td>
<td>Researchers should provide a clear rationale for the use of the cluster randomized design and adopt statistical methods appropriate for this design.</td>
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<td>REC review</td>
<td>2</td>
<td>Researchers must submit a CRT involving human research participants for approval by a REC before commencing.</td>
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<td>Identifying research participants</td>
<td>3</td>
<td>Researchers should clearly identify the research participants in CRTs. A research participant can be identified as an individual whose interests may be affected as a result of study interventions or data collection procedures, that is, an individual (1) who is the intended recipient of an experimental (or control) intervention; or (2) who is the direct target of an experimental (or control) manipulation of his/her environment; or (3) with whom an investigator interacts for the purpose of collecting data about that individual; or (4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual. Unless one or more of these criteria is met, an individual is not a research participant.</td>
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<td>Obtaining informed consent</td>
<td>4</td>
<td>Researchers must obtain informed consent from human research participants in a CRT, unless a waiver of consent is granted by a REC under specific circumstances.</td>
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<td>5</td>
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<td>When participants’ informed consent is required, but recruitment of participants is not possible before randomization of clusters, researchers must seek participants’ consent for trial enrollment as soon as possible after cluster randomization—this is, as soon as the potential participant has been identified, but before the participant has undergone any study interventions or data collection procedures.</td>
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<td>A REC may approve a waiver or alteration of consent requirements when (1) the research is not feasible without a waiver or alteration of consent, and (2) the study interventions and data collection procedures pose no more than minimal risk.</td>
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<td>7</td>
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<td>Researchers must obtain informed consent from professionals or other service providers who are research participants unless conditions for a waiver or alteration of consent are met.</td>
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<td>Gatekeepers</td>
<td>8</td>
<td>Gatekeepers should not provide proxy consent on behalf of individuals in their cluster.</td>
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<td>9</td>
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<td>When a CRT may substantially affect cluster or organizational interests, and a gatekeeper possesses the legitimate authority to make decisions on the cluster or organization’s behalf, the researcher should obtain the gatekeeper’s permission to enroll the cluster or organization in the trial. Such permission does not replace the need for the informed consent of research participants.</td>
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<tr>
<td>10</td>
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<td>When CRT interventions may substantially affect cluster interests, researchers should seek to protect cluster interests through cluster consultation to inform study design, conduct, and reporting. Where relevant, gatekeepers can offer facilitate such a consultation.</td>
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<td>Assessing benefits and harms</td>
<td>11</td>
<td>The researcher must ensure that the study intervention is adequately justified. The benefits and harms of the study intervention must be consistent with competent practice in the field of study relevant to the CRT.</td>
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<tr>
<td>12</td>
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<td>Researchers must adequately justify the choice of the control condition. When the control arm is usual practice or no treatment, individuals in the control arm must not be deprived of effective care or programs to which they would have access, were there no trial.</td>
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<tr>
<td>13</td>
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<td>Researchers must ensure that data collection procedures are adequately justified. The risks of data collection procedures must (1) be minimized consistent with sound design and (2) stand in reasonable relation to the knowledge to be gained.</td>
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<td>Protecting vulnerable</td>
<td>14</td>
<td>Clusters may contain vulnerable participants. In these circumstances, researchers and RECs must consider whether additional protections are needed.</td>
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<td>participants</td>
<td></td>
<td>When individual informed consent is required and there are individuals who may be less able to choose participation freely because of their position in a cluster or organizational hierarchy, RECs should pay special attention to recruitment, privacy, and consent procedures for those participants.</td>
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http://journals.plos.org/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1001346
Additional Resources

- Characteristics of cluster randomized trials and examples of ethical issues they raise:
  - [http://www.bmj.com/content/bmj/suppl/2013/05/09/bmj.f2838.DC1/talm010195.ww1_default.pdf](http://www.bmj.com/content/bmj/suppl/2013/05/09/bmj.f2838.DC1/talm010195.ww1_default.pdf) (from BMJ 2013; 346:f2838)

QUESTIONS?