Ethical issues in cluster randomized trials in health research

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Ethics and CRT design

- Cluster randomized trials pose difficult ethical issues because of features of their design

1. CRTs involve groups rather than individuals
2. The units of randomization, intervention, and outcome assessment differ within any given trial
3. Clusters may be randomized before cluster members can be approached for informed consent
4. Intervention may be directed at the level of the individual or the level of the cluster.

Ethics and CRT design

1. **CRTs involve groups rather than individuals**

- Individual RCTs involve individuals, commonly patients
- Ethics of RCTs is well understood and aims to protect the liberty and welfare interests of individuals
- CRTs involve social groups as well as individuals
- Moral status of social groups is not well understood (e.g., who may give permission on behalf of the group?)
- Group interests may conflict with individual interests and this complicates benefit-harm assessments.

Ethics and CRT design

2. **The units of randomization, intervention, and outcome assessment differ within any given trial**

- In an individual RCT the units of randomization, intervention, and outcome assessment are the same: e.g., the patient
- CRTs are complex and have multiple levels: e.g., hospitals are randomized, health care workers are intervened upon, and patient outcomes are assessed
- Complicates the identification of research participants
- From whom is informed consent required?

Ethics and CRT design

3. **Clusters may be randomized before cluster members can be approached for informed consent**

- In an individual RCT, patients are identified and approached for consent prior to study randomization
- In a CRT, clusters may be randomized prior to the identification of individual cluster members and informed consent
- Is consent to randomization required? If so from whom ought it be sought?
- May gatekeepers provide consent to randomization?

Ethics and CRT design

4. **Intervention may be directed at the level of the individual or the level of the cluster.**

- In individual RCTs, the study intervention is directed at the patient
- In a CRT, the study intervention may be directed at the individual or the cluster (or both)
- Cluster level interventions (e.g., public educational messages) may be difficult for individual cluster members to avoid
- In such cases, refusal of study participation may be meaningless.

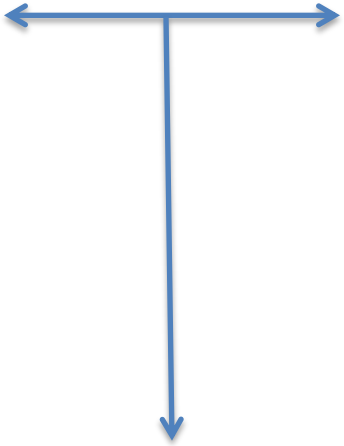
Moral sources

- Ethical principles as articulated in the *Belmont Report* and other sources
- Standard concepts in the research ethics literature (e.g., waiver of consent)
- We sought to accommodate the ethical challenges of CRTs within a standard ethical framework through rigorous analysis and minimal concept modification
- “The consensus statement should be interpreted in light of the laws and regulations of the host country or countries, as well as other applicable international standards”.

Ethical and policy issues in CRTs

Empirical study
- Systematic review
- Interviews with researchers
- Survey of researchers
- Survey of REC chairs

Ethical analysis
- Research participant
- Informed consent
- Clinical equipoise
- Benefit-harm analysis
- Gatekeepers
- Vulnerable participants



Consensus process
- Expert Panel
- Public meeting
- Closed meeting
- Consensus guideles

Who is the research participant in CRTs in health research?

A prerequisite for ethics protections

- Identification of research participants in CRTs is complicated
- The units of randomization, intervention, and outcome assessment differ within any given trial
- Identification of research participants is logically prior to the application of protections
- Two errors:
  - Over-inclusive definition runs the risk of unduly burdening research
  - Under-inclusive definition with fail to provide protections to those who have a right to them

Definition and criteria

- Definition: an individual whose interests may be affected as a result of study interventions or data collection procedures
- A research participant 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.

Implications for CRTs

- In public health studies in which an entire community is intervened upon, all community members may be research participants
- In knowledge translation studies, health professional who are intervened upon are research participants
- Patients of those health professionals are not research participants unless they are otherwise intervened upon, interacted with, or their private health information is collected.

Who is the research participant?

COMMIT Trial (cluster-cluster)

- Residents of intervention and control communities (2+3)

Tobacco treatment in primary care (professional-cluster)

- Physicians (1)
- Patients (4)

ObaapaVitA trial (individual-cluster)

- Women of reproductive age (1, 4)

When is informed consent required in CRTs in health research?

Challenges to informed consent

- Cluster level interventions
  - It may be difficult to avoid the intervention, making refusal of informed consent meaningless
  - With very large clusters, requiring informed consent may make the study infeasible
- Clusters may be randomised before cluster members can be approached for informed consent.

Waiver of informed consent

- When people are not research participants, their informed consent is not required
- Waiving the consent requirement can only be justified when it is necessary to do so, and when the risk involved is minimal
- Waiver of consent may be appropriate study participation poses minimal risk and
  - The cluster level intervention is difficult or impossible to avoid, or
  - Due to cluster size or other factors, requiring informed consent makes the study infeasible.

Post-randomized consent

- Often in CRTs, clusters are randomized before cluster members can be identified or approached for consent
- Seeking informed consent as soon as possible and before any study interventions or data collection procedures satisfies the moral purpose of informed consent
- Research participants have the opportunity to decline study participation before they are exposed to risks of study interventions or data collection procedures
- Consent to randomization in these circumstances is not required.

When is informed consent required?

COMMIT trial (cluster-cluster)

- Waiver of informed consent
- Consent to randomization not required

Tobacco treatment in primary care (professional-cluster)

- Physicians: waiver of informed consent
- Patients: waiver of informed consent
- Consent to randomization not required

ObaapaVitA trial (individual-cluster)

- Informed consent from women
- Clusters randomized before cluster members could be identified; consent sought prior to study interventions.

What is the role and authority of gatekeepers in CRTS in health research?

Gatekeepers

- "[A]n individual, body, or mechanism that can represent the interests of the cluster"
- Gatekeeper permission is widely sought in CRTs due to challenges in informed consent
- Our work mitigates concerns regarding informed consent by careful identification of research participants and application of waiver of consent
- Gatekeepers do not have the authority to provide proxy consent on behalf of cluster members, and CRTs should not proceed on the basis of such "consent".

Protecting group interests

- When a CRT may substantially affect cluster or organizational interests, gatekeepers may play and important role in protecting group interests
- Permission is appropriately sought when a gatekeeper has the legitimate political authority to provide it
  - A school principal may provide such permission after considering availability of staff, financial implications of participation, and the likelihood that teachers or students would be willing to participate
- Consultation with cluster members may protect group interests by subjecting the study to examination and discussion by those whose interests may be affected.

What is the role of gatekeepers?

COMMIT trial (cluster-cluster)

- Community consultation and consent

Tobacco treatment in primary care (professional-cluster)

- Permission of practice managers

ObaapaVitA trial (individual-cluster)

- Permission of department of health (fieldworkers).

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Guidelines and Guidance

The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials

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Introduction

Cluster randomized trials (CRTs), also known as group randomized, place-based, or community intervention trials, are increasingly important for the evaluation of interventions in health research [1–7]. In CRTs, groups, or "clusters", of individuals—rather than the constituent individuals themselves—are randomly allocated to study arms, and outcomes are then measured on the individual cluster members. Examples of clusters include medical practices, hospital wards, schools, and communities. CRTs often systematically explored. As a result, researchers and research ethics committees (RECs) currently lack specific guidelines to help them design, conduct, and review CRTs according to internationally accepted ethical standards. Predictably, the lack of comprehensive guidance has resulted in uncertainty and markedly different interpretations as to permissible ethical practices in CRTs, both within and across countries.

The aim of this consensus statement is to provide guidance on the ethical design and conduct of CRTs in health research. This guidance is primarily intended for researchers and RECs. It will

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