



Scientific aspects of Cluster Randomized Trials

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Objectives

- Overview of Cluster Randomized Trials
 - What are they?
 - What issues do they raise?
 - Why do we use them?
- Introduce three case examples
- Describe the CIHR-funded project that led to publication of the Ottawa Statement

What is a Cluster Randomized Trial?

- Cluster randomization trials (CRTs) are experiments in which clusters of individuals – rather than independent individuals – are randomly allocated to interventions
- Commonly used clusters in health research:
 - Families
 - Classrooms, schools
 - Medical practices, nursing homes, hospitals
 - Housing units, neighbourhoods, villages
 - Sports teams, social clubs

What makes a CRT different?

- Standard randomized controlled trial (RCT):
 - Unit of randomization = Unit of intervention = Unit of observation
- Cluster randomized trial:
 - Unit of randomization = Cluster
 - Unit of intervention = Cluster, professional, individual
 - Unit of observation = Individual (\pm professional)
- This has implications for how we understand research ethics guidelines

Types of CRTs

- Convenient to distinguish between different CRTs based on the level at which the intervention is delivered
 - “Cluster-cluster trial”
 - Cluster-level intervention; not divisible at the individual level; impossible to avoid
 - “Professional-cluster trial”
 - Intervention administered to health or other professional associated with each cluster; consequences for individuals
 - “Individual-cluster trial”
 - Intervention administered directly to individuals within the clusters; possible to avoid

Examples

- **Cluster-cluster:**
 - Mass-media anti-smoking campaign, fluoridation of municipal water supplies, videos in hospital waiting rooms, introduction of specialist nurses at medical practices
- **Professional-cluster:**
 - Training of physicians to reduce prescriptions of antibiotics; training of school teachers to recognize symptoms of depression; training of shift supervisors to reduce job-related injuries
- **Individual-cluster:**
 - Vitamin supplementation, insecticide-treated bed nets, patient decision-aids

Case 1: *COMMIT - Community Intervention Trial for Smoking Cessation* (cluster-cluster)

- **Objective:** To evaluate the effect of a multi-modal, community-level smoking cessation intervention
- **Unit of randomisation:** 22 Communities in US & Canada
- **Intervention:** Media and billboard campaign; targeted messaging towards smokers from health professionals
- **Data collection:** Change in prevalence of smoking through telephone interviews with cross-sectional random samples of ~3000 households per community; Quit rates through 5-year prospective telephone follow-up of cohorts of ~1000 smokers per community
- **Result:** No significant impact on smoking prevalence; improved quit rate for mild to moderate smokers, no effect on the quit rate of heavy smokers

Am J Public Health 1995, 85(2):193-200; 1995, 85(2):183-192

Case 2: *Tobacco treatment in primary care* (professional-cluster)

- **Objective:** To evaluate enhancements to electronic health records to improve tobacco treatment & counseling in primary care
- **Unit of randomisation:** 26 primary care practices (521 clinicians) in Massachusetts
- **Intervention:** Smoking status icons, tobacco treatment reminders, facilitated ordering of medication and counseling referrals
- **Data collection:** Data on 315,962 patient visits from electronic records
- **Outcomes:** Proportion of smokers who made contact with a smoking cessation counselor; documentation of smoking status; prescription of cessation medications
- **Results:** Increased contact with a cessation counselor; increased documentation of smoking status; no effect on prescriptions

Linder e.a., Arch Intern Med. 2009;169(8):781-787

Case 3: *The ObaapaVita trial* (individual-cluster)

- **Objective:** To evaluate effect of weekly, low-dose Vitamin A supplementation on pregnancy-related and all-cause female mortality in Ghana
- **Unit of randomisation:** 1086 small clusters of compounds
- **Rationale:** Use of cluster randomization considerably simplified trial organization and fieldwork and minimized errors
- **Intervention:** Vitamin A or placebo capsules
- **Data collection:** Fieldworkers visited all compounds over a 1-2 month period to recruit women for the trial; ~200,000 women of reproductive age were enrolled; capsules distributed during monthly home visits
- **Outcomes:** Data on pregnancies, births, deaths
- **Results:** No significant effect on mortality

Kirkwood e.a., Lancet 2010;375(9726):1640-1649

Methodological challenges

- Disadvantage of CRTs over standard RCTs:
 - Multiple observations from the same cluster are correlated
 - This leads to a reduction in “effective sample size”
 - Standard statistical approaches are invalid
 - Standard sample size formulas will lead to underpowered study
 - Standard analysis methods will lead to spurious statistical significance
 - Other issues: higher risk of selection biases, baseline imbalances

Why adopt a CRT?

- Usually prefer individual randomization, unless there are cogent reasons for using cluster randomization:
 - Intervention is naturally applied at the cluster level
 - To avoid treatment group contamination
 - To enhance subject compliance
 - Administrative convenience
 - To obtain cooperation of investigators
 - Political considerations
 - Financial reasons
 - To study indirect effects of an intervention (herd immunity)

Need to justify choice of CRT

- It is well-recognized that there should be a clear rationale for the choice of cluster randomization
 - **CONSORT statement (2010):**
 - “Because a CRT increases the complexity of the research and usually requires more participants than in an individually randomized trial (to ensure equivalent statistical power) it is particularly important that the rationale for adopting a cluster design is outlined in the introduction.”
 - **Ottawa Statement (2012):**
 - “Recommendation 1: Researchers should provide a clear rationale for the use of the CRT design and adopt statistical methods appropriate for this design.”

The Ethics in CRTs Project

- Collaboration between the OHRI and Rotman Institute of Philosophy
- Funded by the Canadian Institutes of Health Research (2007, 2008)
- Study objectives:
 - To identify ethical issues arising in the design, review, and conduct of CRTs;
 - To analyse ethical issues in CRTs systematically;
 - To develop guidelines for the ethical conduct and review of CRTs through an international consensus process.

Study protocol

Open Access

Ethical and policy issues in cluster randomized trials: rationale and design of a mixed methods research study

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This article is available from: <http://www.trialsjournal.com/content/10/1/61>

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Empirical Studies

- Interviewed key informants (n=20)
- Reviewed random sample of 300 CRTs, published 2000-2008
- Surveyed corresponding authors of the sample of CRTs (n=182 respondents)
- Surveyed research ethics chairs in Canada, USA, & UK (n=194 respondents)

Empirical Studies

Clinical Trials 2013; 10: 257–268

CLINICAL TRIALS ETHICS

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BMJ

BMJ

Challenges in the research ethics review of cluster randomized trials: International survey of investigators

Shazia H Chaudhry^a, Jamie C Brehaut^{a,b}, Jeremy M Grimshaw^{b,c,d}, Charles Weijer^{d,e,f}, Robert Boruch^{g,h}, Allan Donner^{d,i}, Martin P Eccles^j, Andrew D McRae^{d,k}, Raphael Saginur^{c,l}, Zoë C Sked^{m,n}, Merrick Zwarenstein^o and Monica Taljaard^{a,b,d}

Background Cluster randomized trials (CRTs) complicate the interpretation of standard research ethics guidelines for several reasons. For one, the units of allocation, intervention, and observation often may differ within a single trial. In the absence of tailored and internationally accepted ethics guidelines for CRTs, researchers and research ethics committees have no common standard by which to judge ethically appropriate practices in CRTs. Moreover, lack of familiarity with and consideration of the unique features of the CRT design by research ethics committees may cause difficulties in the research ethics review process, and amplify problems such as variability in the requirements and decisions reached by different research ethics committees.

Purpose We aimed to characterize research ethics review of CRTs, examine investigator experiences with the ethics review process, and assess the need for ethics guidelines for CRTs.

Methods An electronic search strategy implemented in MEDLINE was used to identify and randomly sample 300 CRTs published in English language journals from 2000 to 2008. A web-based survey with closed- and open-ended questions was administered to corresponding authors in a series of six contacts.

Results The survey response rate was 64%. Among 182 of 285 eligible respondents, 91% indicated that they had sought research ethics approval for the identified CRT, although only 70% respondents reported research ethics approval in the published article. Nearly one-third (31%) indicated that they have had to meet with ethics committees to explain aspects of their trials, nearly half (46%) experienced variability in the ethics review process in multijurisdictional trials, and 38% experienced negative impacts of the ethics review process on their trials, including delays

Taljaard
http://

McRae et al. *Trial*
http://www.trials

RESEARCH

Research
cluster

Andrew D McRae,
Shazia Chaudhry
and Monica Taljaard

Abstract

Background study describes ethics review
Methods: D researchers.

Results: Info informed co ought to be regarding ris research eth informants. 1 that variability hampered th be helpful to

Conclusions: subjects, see for in-depth

Keywords: (translation, Quality improvement, Implementation research

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Survey Results

Perceived need for ethics guidelines	Agree or strongly agree	
	Trialists	Ethics Chairs
There is a need to develop ethics guidelines for CRTs	133 (74%)	148 (85%)
Ethics committees could be better informed about distinct ethical issues surrounding CRTs	126 (70%)	162 (93%)
Experienced significant variability in review of CRTs	47 (46%)	-
Experienced negative impact of research ethics review process on the CRT	65 (38%)	-

Survey Results

Consent practices	Intervention	Control
Cluster level participant consent? (n=147)		
Yes	121 (82%)	115 (78%)
No	26 (18%)	32 (22%)
Timing of consent		
Before randomization	86 (71%)	85 (74%)
After randomization	35 (29%)	30 (26%)
Individual level participant consent? (n=182)		
Yes	144 (79%)	142 (78%)
No	38 (21%)	40 (22%)
Timing of consent		
Before randomization	36 (25%)	36 (25%)
After randomization	108 (75%)	106 (75%)

Ethical Analysis

- Based on empirical studies and experience of research team members, six key questions were identified:
 - Who are the research subjects in CRTs?
 - From whom, how, and when must informed consent be obtained?
 - Does clinical equipoise apply to CRTs?
 - How do we determine if the benefits outweigh the risks of CRTs?
 - Who are gatekeepers and what are their responsibilities?
 - How ought vulnerable groups be protected in CRTs?
- In-depth ethical analysis of each, published as a series of articles in *Trials*



Ethical Analysis

Binik et al. *Trials* 2011, <http://www.trialsjournal.com/content/13/1/116>

Gallo et al. *Trials* 2012, **13**:116
<http://www.trialsjournal.com/content/13/1/116>

McRae et al. *Trials* 2011, <http://www.trialsjournal.com/content/13/1/116>

McRae et al. *Trials* 2011, <http://www.trialsjournal.com/content/13/1/116>

Weijer et al. *Trials* 2011, <http://www.trialsjournal.com/content/13/1/116>

RESEARCH

Ethical Analysis in Health Research

Charles Weijer, Allan Donner, Merrick Zwarenstein

Abstract

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RESEARCH

Who is t randomi

Andrew D McRae¹, Jamie C Brehaut^{5,8}, Monica Taljaard^{5,8}

Abstract

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RESEAR

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Andrew D McRae¹, Jamie C Brehaut^{5,8}

Abstract

This article is research. In t cluster trial i namely, from principle of i research sub size, present CRTs: How c What inform consent a v subjects in C We set out : provisions to a research ef consent to r randomizati with a detail detailed info serve a variety of practical ends, it may have a moral obligation to p consent to study participation.

RESEARCH

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Ariella Binik¹, Char Allan Donner^{3,9}, M

Abstract

This article is par research. In the i addressed if the questions posed, beneficence is th subjects. Two rel receive only usu: intervention in a In individually ra equipoise, that is disagreement in physician-researc that clinical equi and, as a result, (receiving only us interventions is s the course of a (the results are lik clinical equipoise important part o

RESEARCH

What is the role and authority of gatekeepers in cluster randomized trials in health research?

Antonio Gallo^{1,2}, Charles Weijer^{1,3,4*}, Angela White¹, Jeremy M. Grimshaw^{1,5,6}, Robert Boruch⁷, Jamie C. Brehaut^{5,8}, Allan Donner^{1,4,9}, Martin P. Eccles¹⁰, Andrew D. McRae^{1,4,11}, Raphael Saginur¹², Merrick Zwarenstein¹³ and Monica Taljaard^{1,5,8}

Abstract

This article is part of a series of papers examining ethical issues in cluster randomized trials (CRTs) in health research. In the introductory paper in this series, we set out six areas of inquiry that must be addressed if the CRT is to be set on a firm ethical foundation. This paper addresses the sixth of the questions posed, namely, what is the role and authority of gatekeepers in CRTs in health research? 'Gatekeepers' are individuals or bodies that represent the interests of cluster members, clusters, or organizations. The need for gatekeepers arose in response to the difficulties in obtaining informed consent because of cluster randomization, cluster-level interventions, and cluster size. In this paper, we call for a more restrictive understanding of the role and authority of gatekeepers. Previous papers in this series have provided solutions to the challenges posed by informed consent in CRTs without the need to invoke gatekeepers. We considered that consent to randomization is not required when cluster members are approached for consent at the earliest opportunity and before any study interventions or data-collection procedures have started. Further, when cluster-level interventions or cluster size means that obtaining informed consent is not possible, a waiver of consent may be appropriate. In this paper, we suggest that the role of gatekeepers in protecting individual interests in CRTs should be limited. Generally, gatekeepers do not have the authority to provide proxy consent for cluster members. When a municipality or other community has a legitimate political authority that is empowered to make such decisions, cluster permission may be appropriate; however, gatekeepers may usefully protect cluster interests in other ways. Cluster consultation may ensure that the CRT addresses local health needs, and is conducted in accord with local values and customs. Gatekeepers may also play an important role in protecting the interests of organizations, such as hospitals, nursing homes, general practices, and schools. In these settings, permission to access the organization relies on resource implications and adherence to institutional policies.

Background

This article is part of a series of papers examining ethical issues in cluster randomized trials (CRTs) in health research. CRTs are increasingly used in knowledge-translation research, quality-improvement research, community-based

adequately. In the introductory paper in this series, we set out six areas of inquiry that must be addressed if the CRT is to be set on a firm ethical foundation [1]. These include identifying research subjects, obtaining informed consent, applying clinical equipoise, performing risk-

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Consultation Process

<http://crtethics.wikispaces.com/>

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Discussion (1)

History

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 **PROTECTED**

Welcome to the Ethical Issues in Cluster Randomized Trials Discussion Pages!

Over the past four years, our international research group has been working on a Canadian Institutes of Health Research funded project (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725043/>) to study the ethical challenges in cluster randomised trials. The ultimate goal of our research project is to produce international consensus guidelines for the ethical conduct and ethics review of cluster randomized trials. We have been conducting an in-depth ethical analysis around six areas of inquiry. The results of our analysis are being published as a series of papers in the open-access journal *Trials*. We have created this Wiki webpage to facilitate an open discussion about the ideas expressed in this series of papers. (Two of the papers are currently in press and may be accessed below, and the remainder are in preparation.)

As the next phase of our research project, we are convening an Expert Panel of 20 members to develop consensus guidelines. The consensus conference is scheduled to take place in Ottawa, Ontario from 28-30 November, 2011. Discussion points raised by this wiki page will be provided to the Expert Panel in preparation for the consensus conference. We therefore welcome your thoughts and viewpoints on any of the points raised in these papers.

You may post your comments on any of these papers, by clicking on the relevant titles below. This will bring up the Wiki discussion page containing the published article, as well as the discussion tab for posting your message.

1. Introduction to the Series:

[Ethical Issues posed by cluster randomized trials in health research](#)

2. Second paper in the series:

[Who is the research subject in cluster randomized trials in health research?](#) (Coming soon)

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3. Informed consent in CRTs
4. Does clinical equipoise apply to CRTs?
5. Benefits and harms in CRTs
6. Gatekeepers in CRTs
7. CRTs in vulnerable populations

Consensus Process

- July 2011: appointed multidisciplinary Expert Panel (6 research team members +13 external)
 - ethicists (2)
 - trialists (6)
 - statisticians (2)
 - research ethics chairs (3: Canada, UK, USA)
 - funding agencies (2)
 - regulator (1)
 - consumer advocates (2)
 - journal editors (3)
 - low-middle income country perspective (2)
- Provided with discussion papers (results of our ethical analysis)

Consensus Process

- November 2011: Consensus conference (with simultaneous webcast) in Ottawa, Ontario
 - Day 1 (open session): attended by expert panel, 3 expert discussants, ~100 invited delegates
 - Day 2-3 (closed sessions): expert panel met to develop guidelines
- February 2012: Draft consensus statement posted to our Wikipage
 - Conference participants, key informants, trialists, and research ethics chairs invited to comment
- June 2012: Submitted “The Ottawa Statement” for publication

The Ottawa Statement on the ethical design and conduct of cluster randomised trials: précis for researchers and research ethics committees

Charles Weijer¹,
 Jamie C. Brakenbury²,
 Group[†]

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Introduction

Cluster randomised, parallel, controlled trials are increasingly important in research [1–7]. They are often used rather than the standard randomised controlled trial because of the difficulty of allocating individuals to different treatment groups. Individual cluster-level characteristics, such as hospital practices, hospital culture, and staff, may influence the evaluation of complex interventions. This article describes the development of the Ottawa Statement and outlines key implications for researchers and research ethics committees.

CRTs pose difficulties for researchers and research ethics committees. The units of randomisation and the units of analysis may differ. A new hand-washing intervention may be evaluated on hospital ward intervention measures.

RESEARCH METHODS & REPORTING

The Ottawa Statement on the ethical design and conduct of cluster randomised trials: précis for researchers and research ethics committees

Cluster randomised trials have unique features that complicate the application of standard ethics guidelines for research. The Ottawa Statement on the ethical design and conduct of cluster randomised trials was developed to provide detailed guidance to researchers, research ethics committees, regulators, and sponsors as they seek to fulfil their respective roles. This article describes the development of the Ottawa Statement and outlines key implications for researchers and research ethics committees.

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