CHALLENGES IN THE ETHICAL CONDUCT AND ETHICS REVIEW OF CLUSTER RANDOMIZED TRIALS: A SURVEY OF CLUSTER RANDOMIZATION TRIALISTS

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfilment of the requirements for the MSc degree in Epidemiology

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ABSTRACT

Unique characteristics of cluster randomized trials (CRTs) complicate the interpretation of standard research ethics guidelines. Variable interpretation by research ethics committees may further complicate review and conduct. An international web-based survey was administered to corresponding authors of 300 randomly sampled CRT publications. We investigated ethics review and consent practices, investigator experiences with ethics review, and the perceived need for CRT-specific ethics guidelines. The response rate was 64%. Ethics review and consent were under-reported in publications. Ethics approval was obtained in 91%, and consent from individual and cluster level participants in 79% and 82% of trials. Consent varied by level of experimental intervention, data collection, and cluster size. Respondents cited variability among ethics committees (46%), and negative impacts of ethics review on their studies (38%). The majority perceived a need for ethics guidelines (73%), and guidance for ethics committees (70%). CRT-specific ethics guidelines are required to ensure practices meet ethical standards.

ACKNOWLEDGEMENTS

I wish to express sincere thanks and appreciation to those who have helped me with this research study.

I am grateful to my Thesis supervisors, Drs. Monica Taljaard, Jamie Brehaut, and Jeremy Grimshaw, for their mentorship, and providing invaluable support in ideas and perspectives throughout my thesis project. I especially would like to thank Dr. Taljaard, to whom I am truly indebted, for her unwavering encouragement and support.

I wish to thank all members of the ethics grant research team for contributing their expertise and insight to the development of this study: Charles Weijer, Martin Eccles, Andrew McRae, Raphael Saginur, Robert Boruch, Merrick Zwarenstein, Allan Donner, Judith Belle Brown, Angela White, Ariella Binik, and Antonio Gallo. I would also like to thank Dong Vo, manager at the Methods Centre, for his technical expertise in launching our survey.

I remain grateful for the mentorship of my past professors and supervisors, including Dr. Jennifer Watson, who has encouraged and supported me from my early days as an undergraduate student, Drs. May Griffith and Baldwin Toye, who provided important research opportunities during my undergraduate studies, and Dr. Rama Nair, who helped me direct my research interests in Epidemiology.

Funding for this study was provided by the Canadian Institutes of Health Research (CIHR). Grant title: *Ethical and Policy Issues in Cluster Randomized Trials.*

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INTRODUCTION AND FRAMEWORK OF THE RESEARCH

In this chapter, we introduce the cluster randomized trial (CRT) design, identify various reasons that necessitate its use, and describe different contexts for its use in health research. Unique methodological and ethical challenges raised by the design are identified, with a focus on ethical challenges. The objectives and rationale of this thesis are presented within the context of ethical issues raised, and a larger research study on ethical and policy issues in cluster randomized trials.

1.1 THE CLUSTER RANDOMIZED TRIAL DESIGN

The cluster randomized trial (CRT) is a type of randomized controlled trial in which intact social units or clusters of individuals - rather than individuals themselves - are randomized to different intervention or control arms.[1] The term "cluster randomized trial" may be used synonymously with "group randomized trial" or "place randomized trial". The latter term reflects the intent of targeting entire *places* to 'enhance the well-being of people in those places or to decrease the risks that confront them.'[2] Diverse units of randomization have been observed in CRTs, including medical practices, cluster level professionals or administrators, hospitals, schools, and even entire neighbourhoods or communities.[1]

Both scientific and practical reasons underlie the use of cluster randomization. Scientific reasons for adopting randomization at the cluster level are as follows:

i) The intervention can only be implemented at the cluster level;

Interventions such as mass media health promotion campaigns or water fluoridation treatments are cluster-wide and therefore delivered to groups of individuals. Similarly, interventions that target professionals or administrators are intended to affect clusters of individuals under their care or instruction.[3,4] For example, an intervention targeting health

professionals to promote the use of evidence-based guidelines would necessitate randomization at the health professional or higher level.

ii) The intervention acts at the cluster level;

The cluster action of an intervention means that it acts at both the individual and community level, such that full effects of the intervention cannot be evaluated from individuals alone.[3] A common example is in the case of vaccine trials where outcomes in a participating individual may be affected directly by their own vaccination status, as well as indirectly through the vaccination status of individuals around them (i.e., herd immunity).[5]

iii) Intervention contamination is to be minimized;

Intervention effects may become diluted and, therefore, less detectable when participants from intervention and control arms are able to interact and exchange information.[6] For this reason, it may be beneficial to randomize clusters instead of individuals. In intervention studies aiming to change social behaviour or educate participants (e.g., intervention to promote weight loss), separating participants by clusters of space or time may prevent the sharing of knowledge and ideas by intervention arm participants, with participants in a control or alternative intervention arm.[3,4]

iv) Participant compliance with the intervention is to be enhanced.

An important component of the intervention may be to enhance subject compliance with the intervention through formal and informal discussions, and interactions between participants. In such cases, randomizing individuals grouped by their social or organizational unit would be desirable.[3]

Practical reasons for adopting randomization at the cluster level are as follows:

i) Administrative convenience or logistical constraints;

When special equipment or personnel are required to administer an intervention, cluster

randomization would allow personnel or equipment to be concentrated in fewer locations, which may be more efficient both administratively and financially.[3,4]

ii) Political constraints.

Under certain circumstances, it may be problematic or considered inappropriate to randomize individuals within the same organizational or social units to different intervention and control conditions. Economically developing nation settings present a particular challenge and researchers may find cluster randomization as necessary to promote cooperation and acceptance of a trial. Community leaders and stakeholders, for example may find it inacceptable if only some members of their community receive an intervention.[7] Citing their experiences with conducting public health trials in parts of Asia and Africa, Osrin *et al.*[8] explain that testing the delivery of an intervention to an individual might raise concerns if others are not included. To mitigate such concerns they have delivered interventions to groups, areas, institutions, or systems—collectively, rather than individually.

1.2 CLUSTER RANDOMIZED TRIALS IN HEALTH RESEARCH

Increasing use of the CRT design has been driven in part by efforts to generate dependable evidence on the effects of policies, programs and practices, most notably in the areas of health care, education, crime and justice, and social services.[2] In this thesis, we will focus exclusively on CRTs in two broad areas of health research: public health and health promotion, and primary and hospital care. Two examples of CRTs, the COMMIT[9,10] and IMPLEMENT[11] studies will be used to illustrate the diversity of CRTs in these areas of health research.

Community-based health intervention research is an encompassing term that includes studies in public health, health education, and health promotion.[12] In the arena of education,

trials evaluating prevention and health promotion programs in American schools have been conducted routinely since the 1980s.[13] Programs are delivered to intact units, which are usually classrooms or schools, to address health-compromising and high risk behaviours.[13] Community-based studies are also common in disease control, (with interventions aimed at lifestyle behaviour modification, screening, and early detection and management of risk factors), injury prevention, and genetic testing for disease susceptibility (with interventions targeting prevention and surveillance strategies).[12]

The COMMIT study is an example of a CRT conducted in public health. The Community Intervention Trial for Smoking Cessation (COMMIT) that was implemented from January 1989 to December 1992 in the USA and Canada, was the largest community-wide behavioural risk factor reduction study conducted at its time.[14] COMMIT was designed to test whether a multi-modal public health intervention would result in higher quit rates among heavy smokers. The community was selected as the unit of randomization because the intervention was community-wide. Telephone surveys using modified random digit dialling were conducted to estimate baseline and post-intervention smoking prevalence in each community, and to further identify cohorts of approximately 550 heavy smokers and 550 light-to-moderate smokers who would be prospectively followed over four years.[9,10] Eleven communities were pair-matched for geographic location, population size, and general socio-demographic factors; one community within each pair was randomly assigned to the intervention and the other served as the comparison. Communities received a fixed monetary allowance to support community task forces (consisting of community volunteers, local staff, or agencies), who implemented 58 mandated activities specified in the protocol. The intervention involved four main channels of delivery: public education through media and community-wide events, health care providers, work-sites, and other organizations.[9]

In primary and hospital care, cluster randomization may be used for the study of medical and healthcare delivery innovations, as well as for evaluations of their uptake and promotion.[1,15] The CRT design is considered optimal for evaluating health care professional and organizational behaviour change in promoting best practices.[16] Known as implementation research, it is the scientific study of methods to promote the systematic uptake of clinical research findings into routine clinical practice, by testing approaches to change organizational and professional behaviour.[15,17]

The IMPLEMENT study is an example of a CRT conducted in primary care, to promote the uptake of best practices by health professionals. The study was designed to test the effectiveness of strategies to encourage general practitioners (GPs) to implement a clinical practice guideline for acute low back pain. One of the key messages from the guideline was that diagnostic x-rays are rarely necessary in the management of acute low back pain. IMPLEMENT was conducted in general practices in the Australian province of Victoria from June to September 2007. Practices with their respective GPs were randomized in order to minimize contamination that would arise if GPs were to manage both intervention and control patients, and to minimize potential contamination that may occur if GPs within the same practice were randomly allocated to different intervention arms. Ninety-two invited practices with at least one GP consenting to participate were allocated to the intervention or control arm. The intervention consisted of facilitated face-to-face small group workshops, which included a combination of behaviour change techniques that were considered the best approach to address barriers and enablers to guideline implementation. The control group received the existing guideline dissemination strategy. Up to 25 patients per practice were recruited after the intervention period. Primary outcomes measured within a specified period of enrolment were whether or not the GP referred the patient for a plain X-ray, which was

assessed from medical records, and patient low back pain-specific disability, which was measured via telephone interviews.[11]

1.3 METHODOLOGICAL CHALLENGES POSED BY CLUSTER RANDOMIZED TRIALS

The design and analysis of CRTs requires particular methodological considerations. Increasing use of the CRT design has, however, driven the development of a well-accepted methodological foundation for its design and analysis.[1] Firstly, CRTs have special statistical requirements arising from the fact that observations within clusters cannot be assumed to be independent. Secondly, CRTs may be prone to post-randomization selection bias of participants within clusters.[4,5,18]

Members from the same cluster may behave similarly in important ways and their responses can therefore not be assumed to be independent. Using physicians and their clusters of patients as an example, patient care outcomes may be more similar among patients cared for by the same physician, compared to patients who are under the care of different physicians—due to factors such as practice location (i.e., the patient pool), and physician approaches to diagnoses and treatments. This degree of similarity is measured by the intra-cluster correlation (ICC) coefficient. A positive ICC indicates that variation in observations *between* clusters is greater than variation in observations *within* clusters. Not accounting for the ICC when conducting individual-level analyses can lead to an increase in the type 1 error rate due to over-estimation of intervention effects.[1] Appropriate statistical procedures that account for clustering in the analyses have been elucidated and are widely supported by common statistical software packages. The difference in variation observed between and within clusters also leads to a reduction in the effective sample size and as a result, CRTs have reduced statistical efficiency relative to randomized controlled trials

randomizing the same number of individuals.[1] Sample size calculation formulas are now widely available to adjust for clustering.

Biased allocation at the cluster level can be addressed by careful and independent allocation of clusters. After clusters are allocated, however, participants may also need to be identified and recruited.[4,5] Identification bias may occur if persons identifying participants have knowledge of individual characteristics and are aware of their allocation status.[5,18] Recruitment bias may occur if persons identifying or recruiting participants have knowledge of individual characteristics and are aware of their allocation status, or if different information is given to intervention and control arms.[5,19] Methodologists recommend identifying and recruiting individuals before cluster allocation. If this is not possible, 'independent' persons, especially those external to clusters and blind to allocation status, should identify and recruit participants.[5,18]

1.4 Ethical Challenges Posed by Cluster Randomized Trials

All forms of controlled trials involving human subjects require assurance that the proposed study meets commonly-accepted ethical standards, particularly the requirement of informed consent from research participants. Ethics guidelines with international reach, such as the Nuremburg Code[20] and World Medical Association Declaration of Helsinki,[21] have primarily been written to protect the liberty and welfare interests of individual research subjects as the unit of randomization. Similarly, various national ethics guidelines, such as the second (2010) edition of the Canadian Tri-council Policy Statement,[22] do not have provisions to deal with CRTs. One exception is the UK Medical Research Council (MRC) guideline published in 2002 on ethical and methodological considerations for CRTs.[4] Although the MRC-UK guideline, which was developed primarily by methodologists,

introduced some guidance on methodological and ethical issues in CRTs, the document does not address the broad scope of ethical issues raised by CRTs and the generalizability of the guidance beyond the UK context is also uncertain.[23] The standard views of research ethics are therefore largely based on individually randomized trials and CRTs, 'only partly fit within the current paradigm of research ethics.'[24]

The application of existing ethical standards to CRTs is particularly complex for two reasons: Firstly, the manner in which participants are involved in a CRT can vary depending upon the unit of randomization, the level(s) at which experimental interventions are targeted, and how study outcomes are observed.[3,24] It may not always be clear how to fulfill the ethical requirement of voluntary informed consent from research participants when there are, for example, participants who are only indirectly affected by cluster level interventions, or participants who have simply provided data.[24] Secondly, CRTs involve intact groups or socially cohesive units whose moral status is not completely understood. It is unclear, for instance, *who* may speak on behalf of a group of research participants and on what authority.[24] Given the relative absence of comprehensive guidelines for the ethical conduct of CRTs, these uncertainties may additionally lead to challenges with research ethics review and approval processes.

In contrast to methodological challenges, which are relatively well understood, ethical challenges posed by CRTs have been raised but have not yet received the same amount of attention—the traditional ways we think about ethics do not work for this design and the ethical implications of randomizing clusters as opposed to individuals have not yet been thoroughly explored.[25] It is these ethical considerations in the conduct and ethics review of CRTs that are the focus of this thesis.

1.4.1 Participant consent in CRTs

Informed consent is based on the bioethical principle of respect for persons, which entails a fundamental ethical consideration of respect for individual autonomy.[26,27] In the context of research, informed consent is therefore, 'an individual's *autonomous authorization*' of participation in research or an intervention.[28] The Nuremberg Code standard one of ten establishes informed consent as the first of ten standards to which physicians must conform when carrying out experiments on human subjects:

> "The voluntary consent of the human subject is absolutely essential. …before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. …"[20]

The World Medical association, in the Declaration of Helsinki[21] outlines similar principles for obtaining informed consent in medical research, and recommends that subjects' consent be confirmed in writing, or be appropriately documented if consent is obtained in a non-written form.[21(p4-5)] The International Ethical Guidelines for Epidemiological Studies, produced by the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), recognize that consent may also be expressed orally (i.e., with documentation), or a subject may imply consent through their voluntary actions.[27]

The COMMIT[9,10] and IMPLEMENT[11] studies cited previously illustrate a number of participant consent issues that can arise from the CRT design. In the IMPLEMENT[11] study, participating physicians served as the experimental unit by participating in face-to-face workshops for the implementation of a clinical practice guideline. Patients in both trial arms were indirectly targeted by the intervention (i.e., active versus passive guideline

dissemination strategies), but only a subset of eligible patients were thereafter recruited to participate in the study. Patient consent entailed medical record review, and participation in telephone interviews. In the COMMIT[9,10] study, all community members in the intervention communities were targeted by a mass media campaign, and cross-sectional samples of community members in both study arms were recruited and consented to participate in telephone interviews. Considering these studies, a number of questions arise regarding participant consent:

i) From whom should consent be sought?

In the IMPLEMENT study, should consent have been sought from physicians, patients, or both? In the COMMIT study, should consent have been sought from all community members, including those in the control arm who were not targeted by an experimental intervention?

ii) For what aspects of the study should consent be sought?

In both studies, participant consent was sought for the collection of data. In the IMPLEMENT study, should consent also have been sought from patients for interventions targeting their physicians? Similarly, in the COMMIT study, should consent have been sought from all community members affected by an experimental intervention?

iii) Can participant consent be sought post-randomization?

In both studies, individuals were approached for consent, albeit for data collection purposes only, *after* the randomization of clusters. Is it permissible to seek participant consent post-randomization? In addition, what information should be conveyed to cluster members when randomization has already taken place?

The level(s) at which interventions are applied, observations are measured, and participants are randomized, all have implications for participant consent.[3]

In an exploratory paper on ethical challenges in CRTs, Hutton[3] infers that unique design features are the reason CRTs, 'raise new issues on the nature and practice of informed consent…'[3] In their discussion of participant consent in CRTs, Edwards *et al.*[29] first distinguished between *cluster-cluster* trials in which an intervention is targeted towards an entire cluster, and *individual-cluster* trials in which an intervention is targeted primarily towards individuals within clusters. They explain that in *cluster-cluster* trials, the intervention itself is a cluster one (e.g., mass media health promotion), or it cannot easily be targeted towards individuals (e.g., piping fluoride-treated water to individual households). Edwards *et al.* posit that, although the distinction is not always clear, 'the more readily a treatment can be targeted at individuals, the easier it is for someone to avoid it.'[29] They argue, therefore, that in *individual-cluster* trials, individuals should provide consent by virtue of being able to decline or accept an intervention, whereas this is not the case in *cluster-cluster* trials, because individuals cannot act independently of others in the cluster.[29] The MRC-UK report on ethical considerations for CRTs[4] distinguishes between two types of interventions rather than trials, but follows similar lines of reasoning that interventions received by the whole cluster together do not allow for individual choice and even if consent is sought, a refusing individual may still receive the intervention chosen for the cluster.

In a review examining informed consent practices in primary care CRTs, Eldridge *et al.*[30] test the above hypothesis that the likelihood of patient consent (i.e., if reported as sought) varies according to interventions in the trial. They develop a more detailed typology of CRT interventions, which includes *professional-cluster* interventions that fall in-between *cluster-cluster* and *individual-cluster* interventions in the extent to which interventions are targeted towards individuals.[30] *Professional-cluster* interventions involve cluster level professionals or administrators (e.g., health professionals, school teachers) on whom

experimental interventions are applied, or who are intended to administer study interventions to individuals within clusters. Eldridge and colleagues[30] found that consent appeared to be more difficult to obtain in some types of intervention typologies: consent was more likely to be sought in CRTs without any *cluster-cluster* or *professional-cluster* interventions, and was least likely to be sought in CRTs that involved *cluster-cluster* interventions.

The units of observation in a CRT may include individual level participants, cluster level administrators, or both, with data collected directly from participants or from secondary sources, such as administrative databases. Other than participants, inferences may be made at the level of the cluster organization (i.e., using site level, aggregate data).[3] In some CRTs, the recipients of the study interventions may not be the same as the individuals providing data, further complicating informed consent practices.[3] *Professional-cluster* interventions, for example, may only indirectly affect individuals under the care or instruction of cluster level professionals or administrators. Study outcomes may be measured on those who directly receive an experimental intervention (e.g., health professionals), or on those who are intended to benefit indirectly from an experimental intervention (e.g., patients).[3]

Randomizing clusters—as opposed to individuals—can also affect the feasibility of fully informed consent.[3] Firstly, it may be too time consuming or impractical to approach all members of a large cluster for consent to cluster enrolment and intervention assignment.[30] Secondly, at the time of randomization, individuals forming a cluster may have yet to be identified (e.g., patients who will be recruited upon being diagnosed with a particular condition).[30] In such cases, obtaining informed consent from participants *before* the randomization of clusters may not be possible. In conventional biomedical research, it is well-accepted that fully informed consent ought to be obtained from individuals before any intervention is administered, although it has been argued as not ethically essential if doing so

would be logically impossible.[3] Hutton[3] argues that where practicable, consent should be sought from participants for intervention assignment *after* clusters are randomized. Further research is needed, however, to address what information will be provided to participants regarding intervention assignment in participants' own and alternate trial arms.[3]

Thus, to summarize: Whereas in conventional randomized controlled trials there is one type of trial participant from whom fully informed consent is sought, CRTs raise a number of questions which challenge conventional notions of informed consent, such as *from whom* consent should be sought (i.e., cluster professionals or administrators receiving or administering an intervention—henceforth referred to as cluster level participants, individuals within clusters—henceforth referred to as individual level participants), for *which aspects* of the study consent can and should be sought (e.g., the offer or administration of an experimental intervention while there may be little or no choice to opt-out of intervention effects), and *when* informed consent should be sought.

1.4.2 Cluster representation in CRTs

Approaching cluster members and seeking permission, authorization, or consent for a cluster's participation in a CRT may lead study investigators to persons at the head of or in charge of one or more clusters.[29] Of note, clusters may be formed of existing social units or groups (e.g., students, village residents), or they may consist of individuals who have yet to be identified (e.g., patients who will be diagnosed with a specific condition). Considering the COMMIT study[14] as an example, the research institutions conducting the trial had to demonstrate to the granting agency, the support of a number of persons from each pair-matched community:

> "Most research institutions used mailed information and telephone interviews to obtain general letters of support from community leaders:

> mayors, chambers of commerce, public health department directors, voluntary health agencies, medical societies, and the like."[14 (p 27)]

In the IMPLEMENT study,[11] general practices would only be considered eligible for the trial if the practice principal had agreed to the practice being involved in the CRT. Practices with at least one consenting GP and no objections from GP partners were thereafter randomized to intervention or control conditions.

The types of cluster representatives, their selection processes, and suggested roles have been discussed in the research literature. Edwards and colleagues[29] refer to agents who have the power to *deliver* a cluster, as 'guardians.' They propose that in *cluster-cluster* type trials, guardians ought to consent to both trial entry and the intervention in a single package. In *individual-cluster* trials, however, individual participants may accept or decline an intervention, but the decision of trial entry may take place without individual consent. Hutton[3] reasons that 'gatekeepers,' by virtue of their political or administrative positions, may be one or a series of representatives (e.g., local authorities, head teachers) who are able to consent for the randomization of those within clusters. Alternatively, the MRC guidelines for the conduct of CRTs suggest a cluster representation mechanism (CRM), which constitutes, "an individual, body, or mechanism that can represent the interests of the cluster."[4] The CIOMS ethics guidelines[27] also recognize the need to address the representation of cluster interests:

> "In a cluster-randomized trial, the investigator should identify an appropriate person or body (e.g., a community leader, headmaster, or local health council) that has authority to give permission for the cluster to participate in the study and to be assigned on a random basis to one arm or another of the study."[27 (p 25-26)]

The CIOMS ethics guidelines further recommend that a cluster decision-maker ought to consult the wider range of community representatives and advisors prior to making the

decision to permit the study. Consultation would, 'ensure that the risks of participation in the study and the randomization are commensurate with the benefits for the cluster or for society.'[27]

Practical recommendations regarding the duties of cluster representatives have been put forth, suggesting that they should: act in the best interests of the cluster represented,[29] inform the investigators about relevant local conditions, inform cluster members about the trial,[3] consider the trial to be in the best interests of the cluster as a whole,[4] and be independent of the research team or declare conflicts of interest if unavoidable.[4] It has been suggested that the roles of guardians of individual interests, as well as gatekeepers of access to individuals, are even more important in CRTs given that participants may not have the opportunity to provide informed consent.[4]

1.4.3 Ethics review and approval of CRTs

Participation in research can entail some risk or burden on the part of research participants. It is for this reason that various national and international guidelines oblige ethics review of research to 'ensure that such risks are managed by researchers and to protect research participants from exploitation by researchers.'[31] The Declaration of Helsinki, for example, recognizes that there may be situations that render consent impossible, impractical, or where obtaining fully informed consent would pose a threat to the validity of the research. In situations such as these, the declaration warrants that the research may be done only after the consideration and approval of a research ethics committee.[21] Ethics review committees operate at various levels, including institutional, local, regional, national, and international. Local regulations often mandate ethics committees operating under various jurisdictions, and so committees may differ in their views and approaches. Committees also set criteria that

exempt certain types of research from ethics review and approval. Common exemptions from ethics review include, for example, the use of publicly-available or anonymous data.[27]

The relative absence of comprehensive, international ethics guidelines for the conduct and ethics review of CRTs has led to documented inconsistencies in the ethics review process. For example, a series of health services implementation research studies involving primary care centres in the USA[32] found that a combined total of more than 100 ethics review applications, amendments, and renewals had to be submitted at 17 research sites; 35% of the sites considered the research as exempt from review, and 41% and 18% required expedited and full review, respectively. Moreover, among the seventeen sites, approximately half of the review boards had ethical concerns which necessitated changes to consent documents, and the time from application submission to approval ranged from 3 to 82 days.[32]

1.5 Overview of the Study

Despite the growing use of cluster randomization, the development of a well-accepted ethical foundation for this design is lacking.[25] In light of the ethical considerations raised, both researchers and research ethics committees require guidance to direct the ethically sound design and conduct of CRTs. This thesis is part of a larger, CIHR-funded grant entitled *Ethical and Policy Issues in Cluster Randomized Trials*,[23] which has the ultimate goal of developing internationally accepted, well-grounded guidelines for the ethical conduct and ethics review process of CRTs. As outlined in Figure 1, the three main components of the grant are the groundwork of empirical exploration into ethical issues to document current practices, an extensive ethical analysis to comprehensively analyze the ethical issues raised, and the organization of a consensus process to produce a guiding document for the ethical conduct of CRTs. The empirical component consists of a review of

a random sample of CRT publications, a survey of the corresponding authors of the selected CRT publications, which is the focus of this thesis, a survey of research ethics board chairs, and focus groups and in-depth interviews with trial participants and cluster gatekeepers.

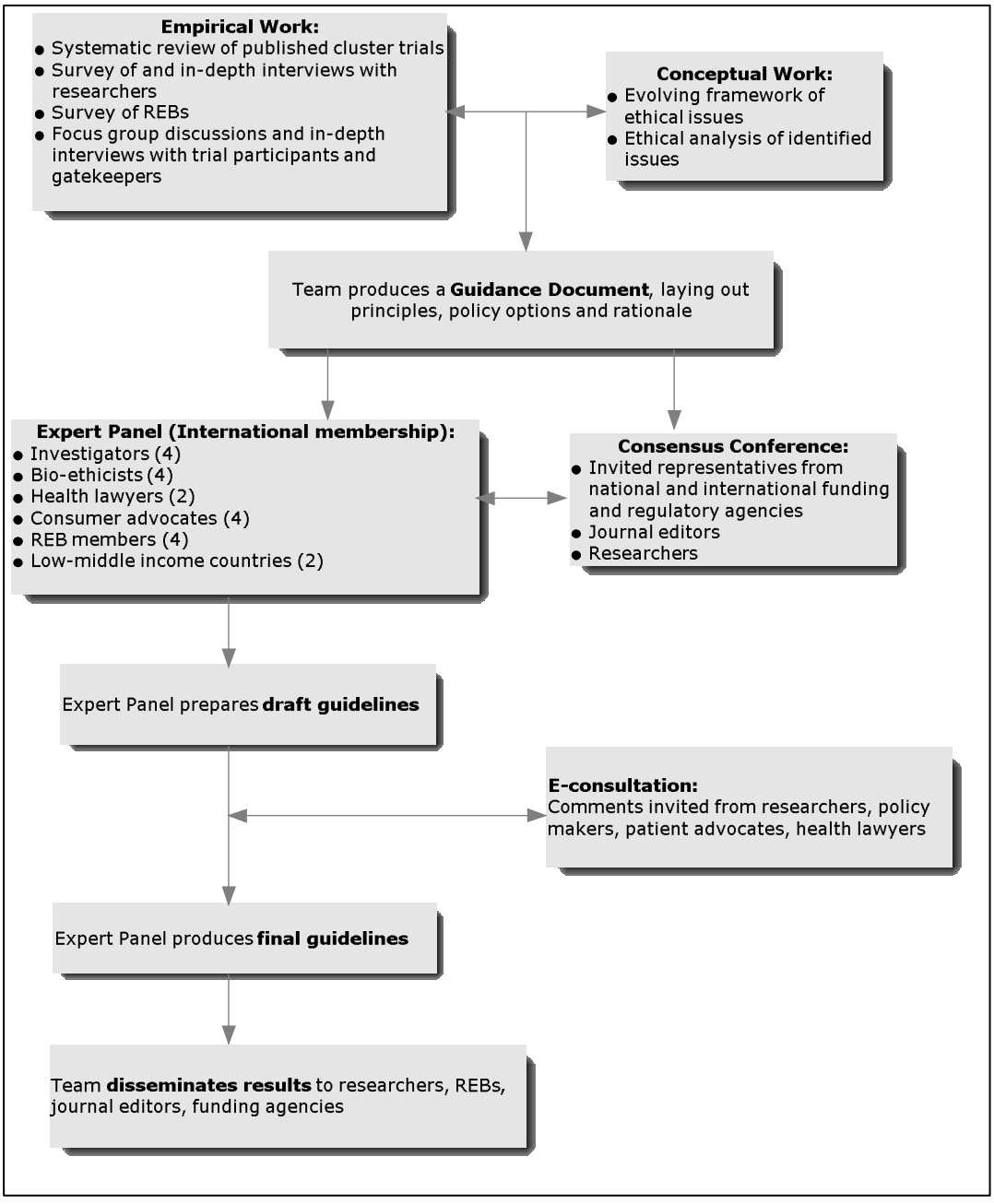

Figure 1: Outline of the larger research study of ethical and policy issues in CRTs

Reproduced from: Taljaard M, Weijer C, Grimshaw J, et al. (2009) Ethical and policy issues in cluster randomized trials: rationale and design of a mixed methods research study. Trials 10: 61.
Original Publisher: BioMed Central

As part of preliminary work conducted in preparation for the larger project, key informants (including experienced cluster trialists) were interviewed to generate an initial framework of ethical issues in CRTs.[33] In addition to describing challenges related to informed consent and the role of gatekeepers in CRTs, many participants expressed having experienced variability in the ethics review process of CRTs among different research ethics boards, especially for CRTs operating under more than one jurisdiction.[33] This problem may stem from review boards being unfamiliar with the CRT design and not having specific ethics guidance on the review of CRTs.[33] An equal number of participants perceived either positive or negative effects from the ethics review of CRTs. On the negative side, they described effects that included threats to the CRTs' internal validity and low subject enrolment due to requirements for consent. On the positive side, participants noted improved subject protections and 'greater methodological rigour and thoughtfulness in study design.'[33]

To identify ethical and methodological challenges with CRTs as reported in published trials, a random sample of published CRTs was selected and reviewed. This thesis focuses specifically on the selected set of CRTs. These trials were a random sample of CRTs, indexed in Medline between 2000 and 2008. The objectives of the publication review were to document consent practices, and identify ethical challenges arising in CRTs, as reported in published trials. The review found that the reporting of research ethics protections in cluster randomised trials is inadequate.[34] For example, 26% of trials failed to report ethics review and 32% failed to report what consent procedures (including waivers of consent) were used.

To better understand ethical issues, such as details of the ethics review process and informed consent procedures in CRTs, the next step was to conduct a survey of the authors of the reports to elicit additional information about procedures in the particular trial. A further goal of the survey was to gather information about the trialists' experiences, in

general, with other cluster randomized trials they may have conducted.

1.6 THESIS OBJECTIVES AND RATIONALE FOR THE STUDY

The **primary objectives** of this thesis were to conduct a survey of the corresponding authors of a random sample of published cluster randomized trials, to:

1) determine the perceived need for ethics guidelines for cluster randomized trials;
2) describe the ethics review process from the experience of researchers seeking ethics approval and identify factors associated with seeking research ethics review;
3) describe gatekeeper (i.e., cluster representative) permission and approval processes and identify the types of gatekeepers associated with various clusters;
4) describe consent processes from individual and cluster level participants and identify factors associated with obtaining consent; and
5) assess the adequacy of reporting ethics approval, gatekeeper permission, and consent practices in published CRTs by comparing published results with results of the survey.

There are new and original theoretical insights to be gained from this quantitative study for understanding the ethics review process and ethical conduct of CRTs. By helping to identify characteristics of and challenges in the ethical conduct and review of CRTs that are not reported in the literature, and eliciting the perspectives of researchers seeking ethics approval and conducting such trials in practice, this study will make major contributions to the objectives of the larger grant, which are to improve the process of ethics review of CRTs, generate guidelines for the ethical conduct of CRTs, and make recommendations for reporting necessary ethical details in the literature. Most importantly, the results of this study will contribute to the framework of ethical issues in CRTs, by contributing perspectives from cluster randomization trialists who are engaged in research and are not necessarily experts who would be involved in the formation of ethics guidelines.[35]

CHAPTER 2

STUDY DESIGN AND METHODOLOGY

In Chapter 2, we describe the methodology employed in the survey of cluster randomization trialists. This includes a description of the sampling strategy, choice of survey mode, questionnaire development, and questionnaire pre-testing procedures. The final questionnaire and survey implementation procedures are also described, followed by planned analyses of the survey results.

2.1 SAMPLING STRATEGY

2.1.1 Sample selection

Figure 2 outlines how the survey sample was selected. The target population of the survey was defined as researchers conducting CRTs in health research. The survey population was primary authors (i.e., first or corresponding authors) of CRT publications in health research that were published between the years 2000 and 2008. As mentioned previously, the survey sample was an existing sample of 300 published CRTs included in an earlier review of CRT publications, conducted as part of the parent study.

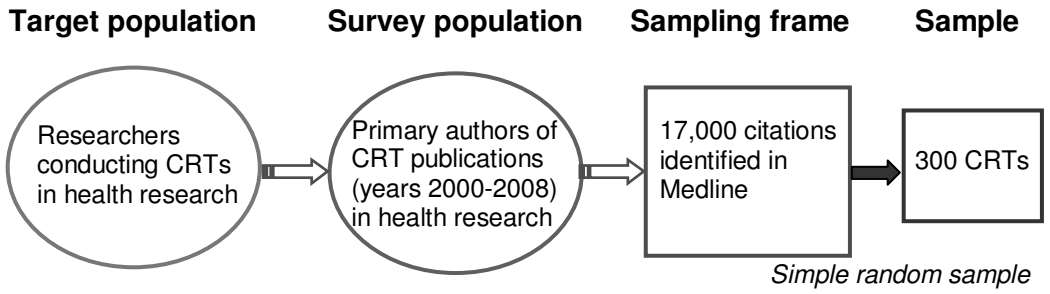

Figure 2: Outline of survey sampling strategy targeting cluster randomization trialists in health research

The procedure used to generate the sampling frame, and select the simple random sample of 300 trials has been described elsewhere.[34] Briefly: A published electronic search strategy[36] was implemented in Medline to identify a population of CRTs (or possible CRTs) in health research, published in English language journals between the years 2000 and 2008. The search strategy had a sensitivity of 90.1% for a gold standard set of 162 CRTs identified by hand search, and a positive predictive value of 18.4%.[36] The resulting sampling frame contained approximately 17,000 citations, to which computer-generated random numbers were assigned to sort by random number. Two reviewers independently screened a training sample of 300 records from the sampling frame based on the inclusion and exclusion criteria presented in Table 2.1. This was done until the k statistic assessing agreement in the identification of CRTs reached at least 0.85, which occurred after three rounds of screening. Thereafter the two reviewers separately screened records from the sampling frame until the target sample size of 300 CRTs was reached.[34]

Table 2.1: Inclusion and exclusion criteria for trials included in the review of CRT publications

Inclusion criteria:	
(i)	Random allocation by cluster;
(ii)	English language;
(iii)	Year of publication 2000 or later;
(iv)	Outcomes of interest pertain to individual or population health;
(v)	At least some outcomes observed on individuals within clusters.
Exclusion criteria:	
(i)	Quasi-randomized design;
(ii)	Further random or non-random allocation of individuals within clusters;
(iii)	Use of standardized patients only;
(iv)	Pilot or feasibility studies;
(v)	Trial protocols or methods papers;
(vi)	Obviously secondary analyses of trials with main results published elsewhere;
(vii)	Short communications, conference proceedings, letters to editor;
(viii)	Studies randomizing households, or dyads of different individuals (e.g., patient-caregiver, parent-child).

As only the primary author indicated for correspondence in each sampled publication was surveyed, sample members' contact details were compiled from the publications to include the name of the primary author, their affiliation, email address, postal address, and telephone number. Google™ *Web* and *Scholar* searches were conducted to retrieve the primary author's email address if not provided in the CRT publication. If a primary author's email address was not retrievable through internet searches, a co-author on a recent publication was contacted to obtain the sample member's current email address.

2.1.2 Sample Size

A sample size of 300 was deemed sufficient for the descriptive analyses of the survey as a two-sided 95% confidence interval for a proportion using the large sample normal approximation extends 0.041, 0.062 and 0.068 from the observed proportions of 0.1 (or 0.9), 0.3 (or 0.7), and 0.5, respectively, when factoring-in a response rate of 70%.[37]

The following formula was used for the sample size calculation:

$$E = Z_{(1-\alpha/2)}[p(1-p)/ n]^{1/2}$$

where E = margin of error

$Z_{(1-\alpha/2)} = 1.96$, where desired level of confidence is 95%

p = population proportion

n= 300

$n_{70\% \text{ response rate}} = 210$

For example, assuming a proportion of 10% yields the following margin of error:

$$E = Z_{(1-\alpha/2)}[p(1-p)/ n_{70\% \text{ response rate}}]^{1/2}$$
$$= 1.96[(0.1)(0.9)/210]^{1/2}$$
$$= 0.041$$

2.2 CHOICE OF SURVEY MODE

Commonly used survey modes include interviewer-administered methods such as face-to-face interviewing and telephone interviewing, and-self administered methods. Self-administered methods include mail surveys in which sample members are requested to complete a paper questionnaire, and web surveys in which sample members are requested to complete a questionnaire hosted on an internet website.[38] When selecting an appropriate survey mode, it is important to consider the survey objectives and resources available for a study.[38,39]

Given the dispersed (i.e., international) locations of the sample members in this study, it was possible to conduct the survey through either interviewer-administered telephone interviewing, or a self-administered mail or web questionnaire. A self-administered survey was the preferred choice as it would offer respondents greater convenience compared to an interviewer-administered survey, by allowing them to respond at their own pace and time. Self-administration would also offer the advantage of greater administrative efficiency in contacting the sample members and collecting their responses. Selecting the self-administered web survey mode was possible given that the target population of researchers was most likely to have internet access.

The selection of a web or mail survey requires consideration of the advantages each mode offers. With respect to study resources, the two survey modes can differ according to fixed and variable costs in development and administration. Fixed costs are those incurred regardless of the sample size, whereas variable costs are those that are incurred when contacting sample members (i.e., in materials and time required).[38] Web surveys may have proportionally greater fixed costs incurred in the development and programming of a

questionnaire, compared to variable costs from contacting members (e.g., by email). Mail surveys on the other hand often have proportionally greater variable costs incurred from printing and mailing questionnaires and reminders. In terms of administration, the advantages of web compared to mailed completion of a survey include faster delivery, numerous design options, quick response time, real-time error checking, and streamlined data collection and entry.[39]

Compared to web surveys, mail surveys tend to produce higher response rates.[40] Shih and Fan (2008)[41] confirmed this in a meta-analysis of thirty-nine studies that directly compared web and mail survey modes. They controlled for random versus non-random assignment of a web versus mail survey mode, type of population sampled, use of a survey incentive, follow-up reminder, and year the survey was conducted. The type of survey population was a factor that contributed statistically significantly (at α=0.01) to the variation of response rate differences—college students were found to be more responsive to web surveys than professionals, employees, and the general population.

We chose a self-administered web survey as the data collection mode for the trialist survey. For the purposes of this study, an electronic survey would be more efficient by allowing for stream-lined data entry of a large number of open-ended responses, which were anticipated from the respondents. Although the review by Shih and Fan[41] found that professionals are among the type of survey populations that are less responsive to web surveys, we focused on the use of incentives, personalized requests, and reminders to promote response to the web survey.[40]

2.3 USE OF SURVEY INCENTIVES

In increasing perceived benefits to participation and encouraging most of the sample to respond, incentives have been found to be effective in improving survey response rates and reducing the potential for non-response bias.[39,42] Dillman *et al.*[39] recommend providing a small token cash incentive, in the range of $25 to $100 for physicians in particular, to all sample members. Pre-paid cash incentives have been shown to have the largest effect on survey response rates.[39] When this is not feasible, Dillman *et al.*[39] recommend a carefully selected material incentive, which can also be beneficial. A Cochrane systematic review (2009)[42] of randomized controlled trials to increase response to paper or electronic (i.e., web-based) questionnaires found that the odds of response were increased by more than a half using non-monetary incentives. The odds of response also increased, but only by a third, using a lottery with immediate notification of results.

Given the likelihood that our sample members would be busy professionals and that some may also be physicians, an incentive provided to each participant was thought to be the most effective in promoting response to the survey. The monetary gift, however, would need to be substantial in what has been shown to work for physicians.[39] Considering the resources available for the study, we decided that a substantial non-monetary gift would be more suitable for participants, as increased effects of non-monetary incentives on survey response have been observed in web surveys.[42] Our sample members were therefore offered a more substantial and relevant gift—a book entitled, *Design and Analysis of Cluster Randomization Trials in Health Research*, by A. Donner and N. Klar, valued at $90.00 CAD. However, because some respondents may already have had a copy the book, or may not wish to receive the gift, we thought it useful to also offer the option of a charity donation made on behalf of

the respondent. Respondents would thereby have the choice of receiving the book, or having a $40.00 CAD donation made on their behalf to Doctors Without Borders/ Médecins Sans Frontières (MSF).

In order to determine whether the addition of a choice to donate to charity would have any detectable effect on survey response, sample members were randomized to *one* of the two gift versions. The smaller methodological study embedded within this project had the objective of comparing survey responses to two different types of incentives offered to professionals in a survey: namely, the offer of a gift only, or the offer of a choice: a gift or donation to charity. Stratified randomization in blocks of size 2 was performed in SAS ® version 9.1. Stratification factors selected were: year of CRT publication (2000-2004 versus 2005-2008), whether or not the trial was clearly identified as a CRT from the title or abstract (to balance trials based on adherence to reporting standards in the CONSORT-extention to CRTs[43]), and the country of the corresponding author (Canada-USA, versus other developed country, versus economically developing country). The findings of this sub-study will be explored in a manuscript external to this thesis.

2.4 SURVEY QUESTIONNAIRE DEVELOPMENT

2.4.1 Content of the questionnaire

The survey questionnaire was developed jointly by the candidate (SC) and supervisor (MT). First, item generation for the content of the questionnaire was performed independently by SC and MT, based on three main sources: a literature review of ethical issues and challenges in the conduct of CRTs, preliminary results from a qualitative analysis of in-depth interviews conducted with experienced cluster trialists,[33] and preliminary results from the review of published CRTs.[34] A preliminary draft of the questionnaire was

developed, and its clarity and relevance were assessed by completing the questionnaire in the context of a very diverse group of CRTs —these were specially selected studies with different types of intervention typologies in a variety of settings, including primary care practices, schools, nursing homes, and communities.

2.4.2 Pre-testing the questionnaire

Expert reviews

Once a well-elucidated draft of the questionnaire was formed, it was circulated amongst members of the research team who had expertise in one or more of the following areas: the design and conduct of CRTs, epidemiology, biostatistics, bioethics, and survey methodology. Throughout the questionnaire development period, feedback from the research team was important in assessing the face validity of the questionnaire, which is whether the questionnaire appeared to measure what it intended to measure, based on the study objectives.[44] Feedback was also important for assessing the clarity of the questions posed, appropriateness of question structures and response categories, potential question-order effects, and whether additional questions ought to be asked, helping to determine the content validity of the questionnaire.[39,44] In addition to expert reviews of the questionnaire, pre-testing was also conducted in the form of cognitive interviews.

Cognitive interviewing

Groves *et al.*[38] state that the standard for survey questions is such that they are, 'understood in the same way by all respondents, and this understanding should match the one the authors of the question intended.'[38] An important method of pre-testing a newly-developed questionnaire is cognitive interviewing. Cognitive interviews, also referred to as 'think-aloud' sessions are a means of determining whether sample members will comprehend

questions as intended by the surveyor, and whether questions can be answered accurately.[39] The interview entails completion of the questionnaire by participants who represent the target population of the survey. In a concurrent think-aloud session, participants are asked to verbalize their thought processes from the moment they are presented with the survey questionnaire, and as they proceed to answer each of the questions. Researchers may use probes and other procedures to discover how the participants have understood the questions, and how they arrive at their final answers.[45,46] Testing questionnaires in such a manner is important for: (a) establishing the face validity of a questionnaire, and (b) assessing the clarity of the questions posed, appropriateness of question structures and response categories, and potential question-order effects.[44]

The goal of the think-aloud pre-test in this study was to enable the detection of problems with the questionnaire, including potentially confusing question wording, incorrect interpretation, and feasibility of responses. Participants were selected on the basis of recommendations made by cluster trialists on the research team, as well as through internet searches of CRT publications. A representation of primary authors was sought among different countries, types of CRT interventions, and units of randomization (i.e., study settings). The individuals contacted were asked to participate in a 45 minute to one hour session to complete a questionnaire about their experiences with conducting CRTs; particularly with regard to a CRT they had conducted. Twelve individuals were invited to participate in a think aloud session over the phone and three were invited to participate in-person, if possible. Those agreeing were scheduled for a think-aloud session and informed that just prior to the session, they would be emailed the survey cover letter and a Microsoft Word® -fillable version of the questionnaire. Participants were asked not to view the documents until the start of the session.

Eight individuals agreed to and participated in the think-aloud session over the phone, and one agreed to and participated in the think-aloud session in-person. Two others completed and returned the MS Word-fillable form of the questionnaire, without participating in the think-aloud session. The session was conducted by SC under the supervision of MT. Participants were asked for permission to audio-record the session, and were then introduced to the study using a standard script (see **Appendix A**). As they completed the personalized (see section 2.4.3) questionnaire, participants were asked to verbalize everything they were doing and thinking, from reading the questions aloud, to telling us their thoughts, and giving their final answers. This included mentioning anything they liked or disliked about the questionnaire, in addition to a review and reflection on the questionnaire and implementation procedures.

Following each think-aloud session with a participant, the survey questionnaire was modified iteratively to reflect the new understandings that had arisen. Comments from earlier think-aloud sessions that the questionnaire is, for example, "complicated to work-through and read" contrasted with comments from later think-aloud sessions that the questionnaire is, for example, "nicely laid-out, easy to go through." Conducting pre-tests in the form of cognitive interviewing was therefore central to ensuring that the questionnaire was clear and understandable for its intended audience.

2.4.3 Personalization of the questionnaire

CRTs are often complex, involving multiple kinds of participants who may be approached for consent, namely those at the individual level and those at the cluster level. Additionally, it may not always clear exactly who the participants are: interventions may involve cluster and individual level participants directly or indirectly, and the degree to

which cluster members can opt-out of study intervention varies among CRTs. The diversity of CRT settings represented in the sample, and the varying levels of participant involvement presented challenges in designing a questionnaire that would be clear and interpretable to all sample members.

In earlier drafts of the questionnaire, terminology unique to CRTs was used to pose questions about consent from 'individual level' and 'cluster level' (if applicable) participants, and permission from a 'gatekeeper' or 'cluster representation mechanism,' among others. Our sample members, however, may not have encountered these terms and consequently, would need to identify *to whom* reference was being made in the context of their CRTs. For this reason, a short glossary of definitions was made to precede the questionnaire. For example, a cluster level participant was defined in the following manner: "Subjects at the **cluster level** may be health professionals, teachers, employers, or program staff who are targeted by the intervention and are intended to affect outcomes on individuals within clusters," and the concept of a gatekeeper was introduced as follows: "The decision to enroll a cluster in a trial may be taken by one or more cluster **gatekeepers** or **guardians**, who are authorities with oversight responsibilities who act on behalf of the study subjects and represent their interests." Terminology referring to a research ethics board (REB) also varies among countries. As a result, the term 'research ethics board (REB),' which is widely used in Canada, was described as being synonymous with, for example, institutional review board (IRB) and research ethics committee (REC).

Thus, on the one hand, the trialists surveyed would need to understand potentially new terminology that they may not have encountered before, and then to answer the questions, they would need to apply these terms in the context of their own studies. This not only could lead to misunderstanding, but the research team concluded that it might also mean

that we as the researchers were imposing our understanding of various terminologies on the trialists we were surveying.

To address this issue, the mail merge feature in MS Word was used to experiment with the personalization of the questionnaire and to generate terms unique to the study of each sample member. Mail merge is a function that creates personalized documents by bringing values for variables from a source database, into a template. The preexisting survey questionnaire in MS Word served as the template and was modified to include unique variables that were to be populated from a source Microsoft Excel ® database. The columns in the excel database served as variables and each entry within a row served as the unique value for a selected CRT. SC and MT tested the questionnaire for ease of completion using a diverse set of CRTs from the survey sample of CRT publications. We confirmed that the difficulties respondents may have encountered with understanding the questionnaire could now be resolved by generating a questionnaire that was unique for each sample member.

Questionnaire personalization was performed as follows: The candidate (SC) read through each sampled CRT publication, deriving and inputting into an Excel database, information pertaining to eight general categories that would be used to personalize the survey (Table 2.2, column 1). The study title, and journal and year of the CRT publication were collected to direct sample members to the specific study the questionnaire pertained to. Also documented was whether ethics approval was reported as sought, so that the question stem about ethics approval of the selected CRT could be personalized. We wished to make sample members aware of the fact that we had acquainted ourselves with their trial: '*Our review of your paper indicates that research ethics approval was sought to conduct the study. Is this correct?*' Terminology referring to ethics review was also collected because as mentioned, this can vary from country to country. In order to personalize questions about

gatekeeper permission or consent, the unit of randomization as well as examples of persons who could provide permission for the enrolment of the cluster were recorded—the latter taking the cluster setting into account. For example, in the IMPLEMENT[11] study that randomized general practices, practice managers and administrators would be mentioned as examples of persons functioning as gatekeepers. Of particular importance was collecting information about individual and cluster level participants in the study, so that questions about consent could be framed more specifically. For example, instead of asking whether consent was sought from *cluster level participants*, we would ask regarding the IMPLEMENT[11] study: 'Was consent sought from *physicians*…?' It was also noted whether the CRT involved one or more pre- or post-study qualitative components embedded within the larger trial, which often select a subset of participants. If a qualitative component was identified, respondents were requested to answer with regard to the main study only.

As shown in Table 2.2, values for 16 variables were subsequently derived from the information extracted from the CRT publications. Some variables were used only once in the questionnaire whereas others were used in multiple locations. The exact placement of the personalized fields within the questionnaire is presented in **Appendix B**.

Table 2.2: Variables in the personalized questionnaire

Information extracted from CRT publication	Variable	Examples of variable values [a]
Study title	(1) study title	1) Community Intervention Trial for Smoking Cessation (COMMIT): I. cohort results from a four-year community intervention.
Journal and year	(2) journal and year	2) American Journal of Public Health 1995
Was ethics approval sought?	(3) question 1 stem about ethics approval [b]	3) Did you seek research ethics approval to conduct the study? / Our review of your paper indicates that research ethics approval was sought to conduct the study. Is this correct?
Ethics review terminology	(4) ethics review terminology and acronym	4) institutional review boards (IRBs) / research ethics committees (RECs) / research ethics boards (REBs)
	(5) singular acronym	5) IRB / REC / REB
	(6) plural acronym	6) IRBs /RECs /REBs
Persons from whom permission could be sought to conduct study	(7) head of cluster permission	7) municipal administrators, community medical leaders
	(8) other study permission	8) Ministry of Health, advisory board
Unit of randomization	(9) unit of randomization	9) communities / general practices /schools
Participants at the cluster and individual level	(10) cluster and individual level participants	10) primary care providers (PCPs) and patients / school nurses and students / supervisors and employees
	(11) cluster level specification	11) primary care providers (PCPs) / school nurses / work supervisors
	(12) cluster level (shortened or acronym)	12) PCPs / nurses / supervisors
	(13) individual level specification	13) patients of PCPs / school students departmental employees
	(14) individual level (shortened or acronym)	14) patients / students / employees
Individual and cluster level clarifications for consent questions	(15) individual level clarification	15) (for the main study, not the qualitative component)
	(16) cluster level clarification	16) (for the main study, not the qualitative pre-study)

a- Multiple examples per variable are separated by a '/'

b- Variable 3 had two possible values only, which are shown in the third column of the Table

2.4.4 Web development of the questionnaire

The survey questionnaire incorporating features of personalization was designed into a web survey. Screen shots of the web-based questionnaire are shown in **Appendix C**. The web survey was designed by a senior programmer at the Methods Centre of the Ottawa Hospital Research Institute (OHRI). MS Visual Studio 2005 and MS SQL Server 2000 were the software programs used to develop the survey, which was then hosted on the OHRI web server. Due to questionnaire personalization, the survey was unique to every user, which made the format/GUI particularly complex to design.

The survey was password protected so that only users with a valid ID could log in. At each login attempt, registered users were time-stamped in the survey database. Users were able to review and change their responses using the 'previous' and 'save and continue' buttons featured at the bottom of each page. The selection of one response option was enforced in the programming of closed-ended questions containing mutually exclusive response categories. In some parts of the questionnaire, adaptive questioning was used to direct respondents past one or more questions that were inapplicable. Once a user submitted the questionnaire, their unique ID was de-activated and they would no longer be able to enter the survey. The survey was not programmed to check question completion and internal consistency among responses either during questionnaire completion, or at the time of submission. Our view was that prompting users to 'correct' or 'complete' their responses would impede full participation. Instead, open text boxes were placed throughout the questionnaire so that respondents could either clarify a selected response, or provide a written explanation without selecting a response.

Prior to implementation, the web survey was tested extensively. All tests of the

questionnaire were performed manually by the programmer, SC and MT. The web survey was also completed by five members of the research team, and a cluster trialist based at the OHRI. We ensured that the web-based questionnaire was tested on different browsers (MS Internet Explorer versions 6, 7 and 8, Mozilla Firefox, Google Chrome, and Safari), and on different platforms (Windows XP, Vista, Windows 7, and Macintosh). The application was also tested on various computers with different setups and configurations. Additionally, the programmer extracted the database multiple times during testing to validate users' inputs.

2.4.5 Description of the final web-based questionnaire

The final questionnaire consisted of 27 closed-ended questions in nine sections. There were 12 web pages in total; one for each section of the questionnaire, and an additional three pages that preceded the questionnaire: a login page, a page containing background information about the study, and a page containing details about the complimentary gift being offered to respondents. The first seven sections of the questionnaire contained questions specific to the identified CRT, the eighth section contained questions about trialists' experiences with conducting CRTs in general (focusing on the ethics review of CRTs), and the final section contained demographic questions and space for additional comments. The nine sections, including the pages that preceded them were as follows:

A- Login page
B- Background information
C- Gift confirmation
1- Permission to conduct the study and enrol clusters
2- Consent procedures for cluster level participants in the intervention arm
3- Consent procedures for cluster level participants in the control arm
4- Consent procedures for individual level participants in the intervention arm
5- Consent procedures for individual level participants in the control arm
6- Information provided to participants at the individual level
7- Information provided to participants at the cluster level
8- Ethics review of any CRTs you may have been involved with
9- Demographic information and additional comments

A- Login page

On the login page, sample members were welcomed to the survey and provided contact emails and phone numbers of the survey coordinator (SC) and study PI (Dr. Jeremy Grimshaw). A login box incorporating a semiautomatic login procedure allowed trialists to enter their unique password to begin the survey. Underneath the login box, users were advised that they could request an MS Word-fillable form (example shown in **Appendix B)** to complete their survey should they experience any technical difficulties with the web-based questionnaire.

B- Background information

The background information page was designed to provide sample members with helpful and important information about the study and survey questionnaire. The page included the title of the selected CRT publication, the estimated time to questionnaire completion of 15 to 20 minutes, the definition of a CRT, and additional information about the study. We also described the type of information we were interested in gathering from the questionnaire, including consent procedures for the specified participants in the selected CRT.

C- Gift confirmation

The gift confirmation page was programmed to display one of two incentive versions to which the sample member had been randomized. Respondents could enter their mailing address in the space provided if they were interested in receiving the complimentary book.

Section 1- Permission to conduct the study and enrol clusters

To describe ethics approval and gatekeeper permission in CRTs (thesis objectives 2 and 3), we asked whether ethics approval was sought to conduct the selected CRT (response options: yes/no-[explain in text box]), as well as whether gatekeeper permission and approval

processes were used (yes-[explain]/no). Ethics approval, and gatekeeper permission prevalence estimates were used to assess the adequacy of reporting ethics approval and gatekeeper permission in published CRTs (thesis objective 5), and to identify factors associated with ethics approval of a CRT (thesis objective 2).

Sections 2, 3, 4, and 5- Consent procedures for individual/cluster level participants in the intervention/control arm

To describe consent processes for individual and cluster level participants (thesis objective 4), we collected detailed information about consent from individual and cluster level participants, in both the intervention and control arms of the study. We asked whether participant consent was sought for any aspect of the CRT (yes/no-[explain]), as well as whether consent was sought from participants for receiving an intervention, and for data collection (NA/yes explicit/yes verbal/yes other consent procedure-[explain]/No: not notified/notified without opt-out opportunity/notified with opt-out opportunity/other notification procedure-[explain]). With regard to cluster level participants, we also asked whether consent was sought for delivering or administering a study intervention to individual level participants (response options as above). 'NA' as a response option was not presented when asking about individual level participant consent for data collection, because this was one of the criteria used to select CRT publications (Table 2.1). The web survey was programmed to skip questions about cluster level consent (sections 2 and 3) for those CRTs in which cluster level participants were not identified during the questionnaire personalization process. Consent prevalence estimates were used to describe consent practices and identify factors associated with participant consent (thesis objective 4), and to assess the adequacy of reporting consent practices in published CRTs (thesis objective 5).

Sections 6 and 7- Information provided to participants at the individual/cluster level

To further describe participant consent processes in CRTs (thesis objective 4), we asked whether participants in each of the intervention and control arms were informed about the use of different interventions in alternate study arms (yes/no-[explain]). Section seven about information provided to cluster level participants did not appear if cluster level participants were not identified from the CRT publication.

Section 8- Ethics review of any CRTs you may have been involved with

To describe the ethics review process from the experience of researchers seeking ethics approval (thesis objective 2), we asked sample members the following: whether they experienced variability in the ethics review of a CRT undergoing review by multiple ethics committee (NA/yes-[explain]/no), whether they have personally met formally with ethics committee members to explain a CRT (NA/yes-[explain]/no), and the impact the ethics review process had on one or more aspects of their CRTs (check all that apply). To determine the need for ethics guidelines for CRTs (thesis objective 1), we asked sample members to rate the extent of their agreement or disagreement with statements presented on: the need for ethics guidelines for CRTs, whether REB members need to be informed about distinct ethical challenges in CRTs, and whether REB application forms ought to be designed separately for investigators submitting a CRT for ethics approval (strongly disagree/disagree/agree/strongly agree/no opinion).

Section 9- Demographic information and additional comments

In this section we collected demographic information on the respondents' highest obtained degrees (check all that apply), and the countries where degrees were obtained. The section also contained an open text box allowing respondents to enter any other details about ethics

in CRTs that were not addressed by the survey. The bottom of the page displayed the questionnaire 'submit' button.

2.5 METHODS FOR IMPLEMENTATION

2.5.1 Survey implementation procedures

Conducting a quality survey requires optimal minimization of four types of errors: sampling, coverage, non-response, and measurement error.[38] Minimizing non-response error in particular requires the use of motivational features that will work together to encourage members of a sample to respond. This strategy is the basis for *Dillman's Tailored Design* method,[39] which is built on a scientific approach of reducing survey error, and on the social exchange theory of response, which aims to establish trust with the respondent and increase benefits while decreasing costs to participation.

We used *Dillman's Tailored Design*[39] method as a guide to develop survey implementation procedures intended to maximize response. The tailored method emphasizes a number of components as being important for maximizing response rates: Sending multiple contacts to potential survey respondents, such as a pre-notification and reminders, is a very effective way to increase response rates.[39,40] To legitimize the survey request, it is recommended that contacts be sent from a legitimate authority who may be known to the survey population.[38,39] A 'special' contact, which is different from the others has also been shown to improve overall response to mail surveys.[39]

All contact emails were sent by SC as a delegate on behalf of Dr. Jeremy Grimshaw. As a research scientist at the OHRI and specialist in CRTs in implementation research, Dr. Grimshaw served as a legitimate authority who would be recognizable to numerous trialists who have conducted similar types of studies in health research. As shown in Figure 3, a

series of up to six contacts based on Dillman's recommendations for the implementation of mail and internet surveys proceeded as follows: A pre-notification email was sent to the primary author, mentioning that they would be receiving a survey request regarding their published CRT. The email explained the purpose of the survey, and the importance of participation. A link to the published grant protocol was included to provide researchers with more information about our study on ethics in CRTs. The survey invitation email containing the cover letter text was emailed two to three days later. The cover letter contained the survey URL, a unique password, which was the unique identifier (UID) of the CRT publication in Medline, and details of the gift that trialists would receive upon completing the survey, which was personalized according to the incentive version the sample member had been randomized to. A thank you and reminder email was sent to all sample members one week after the first emailed request, explaining that a survey invitation had been sent, thanking those who had responded and encouraging those who had yet to do so. A reminder email was sent to non-respondents two weeks after the initial survey invitation email, indicating that a submitted questionnaire had not yet been received and urging the sample member to respond. Potential respondents were then mailed a reminder letter by postal mail. The letter thanked those who had recently responded, urged a response from those who had not within the next seven days, and also mentioned the personalized gift in detail once more. Because the survey was fielded during the summer months when some of the sample members were likely to be away on holiday, a final reminder email was sent in the fall to all non-respondents. The email mentioned that others had responded, contained the web survey link and password, and asked the non-respondents to complete the questionnaire by a specified deadline[42] which was 12 days away, after which the study would close. The survey implementation system therefore incorporated a number of features that would work to

encourage the sample to respond.[39] Samples of the email and postal letter contacts are presented in **Appendix D**.

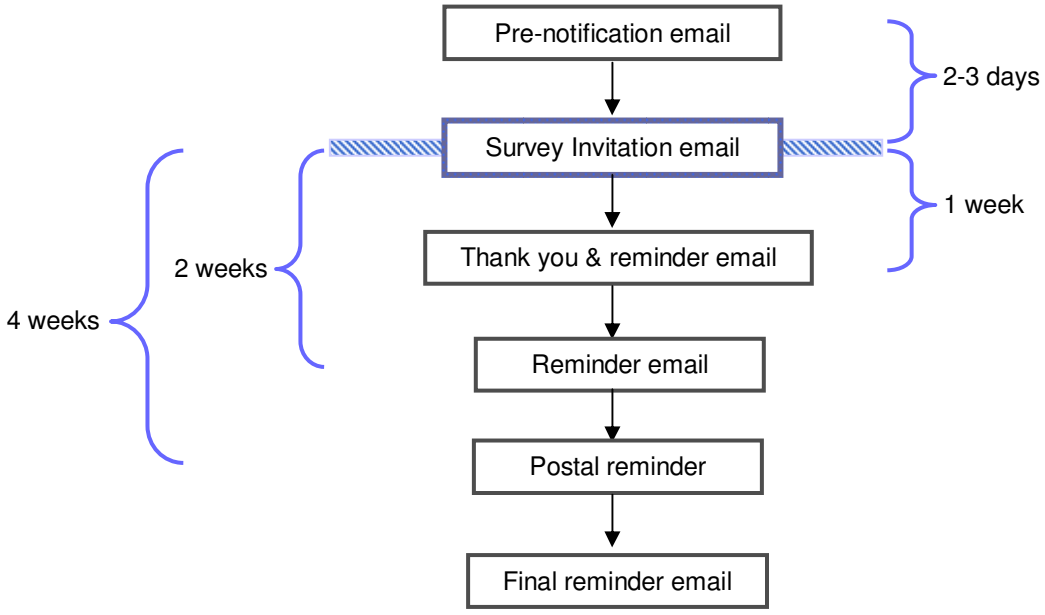

Figure 3: Outline of survey implementation procedures.

2.5.2 Survey pilot testing

Whatever the planned approaches for conducting a survey, a pilot test of the planned implementation procedures is important to determine whether the proposed questionnaire and procedures are adequate for implementation on the entire sample.[39] Dillman *et al.*[39] recommend selecting a random sample of sample members and inviting them to participate a few days or so ahead of the remaining sample. A more formal pilot study can also be conducted prior to the implementation of the survey on another sample from the sampling frame. This may be necessary if response distributions and other features of the survey need to be evaluated beforehand.[39]

The survey questionnaire and all implementation procedures were tested on 46 purposefully selected primary authors (16%) of CRTs in the survey sample. The pilot test would enable the detection of problems with the web-based questionnaire and operational issues in implementation procedures and data collection, with a goal of determining whether the proposed questionnaire and procedures were adequate for implementation on the entire sample.[39]

2.6 Calculation of Survey Response Rates

An important outcome by which surveys are judged is the response rate,[41] which can be defined as the number of complete interviews divided by the number of eligible units in the sample.[47] The American Association for Public Opinion Research (AAPOR) is an organization that seeks to standardize the computation of survey outcome rates so that comparisons can be made across studies. AAPOR has published a guideline that is updated periodically, titled, *Standard Definitions*,[47] which serves as a guide for four types of survey sampling modes: random digit dialling (RDD) telephone surveys, in-person household surveys, mail surveys of specifically-named persons, and internet surveys of specifically named persons. The guideline defines a numerical classification scheme for each sample member based on their final disposition. The categorization of sample members based on their final disposition codes is in turn used to define the calculation of survey outcome rates, namely the contact, cooperation, refusal, and response rates.

The AAPOR guideline for internet surveys of specifically named persons was used to assign final disposition codes to all sample members. Based on the assigned disposition codes, the survey contact rate, cooperation rate, refusal rate, and response rate were calculated. Response rates for the survey are presented in Chapter 3.

2.7 STATISTICAL METHODS

Statistical analyses were performed in SAS® version 9.2.

2.7.1 Dataset cleaning

Reponses from the web-based questionnaire were downloaded into an MS Excel workbook. The data file was structured for import and then imported into SAS ® version 9.2. The dataset was cleaned by running frequencies to responses, checking ranges of responses (i.e., the mean, median, min & max values), and cross-checking variable values. Where enough information was available, missing values were replaced with values that were deduced from textual explanations, responses to similar or related questions in the questionnaire, and the CRT publication. The cleaned survey dataset was merged with the cleaned dataset from the review of the sampled CRT publications (provided by MT), conducted as part of the larger study.

2.7.2 Analyses of survey results

Categorical variables were summarized using frequencies and percentages. Exact or asymptotic methods were used to calculate 95% confidence intervals of percentages. Continuous and ordinal variables were summarized using medians and inter-quartile ranges. Bi-variable statistical associations were tested using Pearson χ^2 or Fisher's exact tests for categorical variables, and Wilcoxon two-sample tests for continuous variables. The Cochran-Armitage test for trend was used to test the significance of changes in proportions over time. Textual responses were grouped into categories with similar underlying themes. Categorizations were assessed by MT for agreement.

Logistic regression analyses were conducted to identify factors associated with consent practices at the individual and cluster levels. A multivariable model was not fit to

identify factors associated with ethics review as there were an insufficient number of trials in which ethics approval was not sought. As a guide to sample size determination for a logistic regression model, the rule of thumb of 10 events per variable (EPV) has been oft-cited in the literature but simulations by Vittinghoff and McCulloch[48] suggest that this rule of thumb is not, 'a well-defined bright line.'[48] Their results indicate that problems of confidence interval coverage of less 93 percent, type I error rates greater than 7 percent, and relative bias greater than 15 percent are uncommon with 5-9 EPV and still observed with 10-16 EPV.[48] For the logistic regression analyses, it was estimated that among the 300 CRTs, approximately 50 percent, for example, would indicate informed consent to study participation at the individual level. Factoring-in a response rate of 70%, this translates to 105 events, which would allow for *at least* 6 independent variables in the binary logistic regression analysis.

In the logistic regression analyses, stepwise variable selection procedures were not employed because the goal of the analyses was not to construct the most parsimonious model predicting the outcome of interest, but rather to indentify important independent factors associated with individual and cluster level consent, by adjusting for all covariates of interest. Multicollinearity among the independent variables of interest was assessed using variance inflation factors (VIF). A VIF value above 2.5 raises the concern of multicollinearity in logistic regression.[49] Three regression diagnostic tools were employed to assess the fit of the model: The Hosmer-Lemeshow test, the area under the receiver operating curve (ROC) or 'c-statistic,' and the Nagelkerke adjusted pseudo R-squared value. The Hosmer-Lemeshow test works by forming 10 equally-sized groups of the ordered, estimated outcome probabilities and produces a goodness of fit statistic to assess the adequacy of the data. Concordance of the expected and observed frequencies in these groups is required for a

good fit.[50] The c-statistic provides an overall measure of classification accuracy, representing the overall proportion of outcomes correctly classified.[50] A pseudo R-squared value derived from a ratio of log-likelihoods indicates the degree to which the model parameters improve upon the prediction of the null model. The Nagelkerke pseudo R-squared adjusts for some measures to allow the R-squared value to reach 1.

CRT author, publication, and trial characteristics collected from the review of CRT publications were used in a number of analyses in this study. To investigate the possibility of survey non-response bias, these variables were used to compare survey respondents with non-respondents, and to compare survey respondents according to early, middle, or late questionnaire submission. The variables were also used in bi-variable and multivariable analyses to understand factors associated with participant consent and ethics approval (bi-variable analyses only). To examine the adequacy of reporting ethical practices in CRT publications, variables documenting the reporting of ethical practices (i.e., ethics approval, gatekeeper identification, and participant consent) in the CRT publications were used to make comparisons with the survey responses.

The following author and CRT publication characteristics were considered: Among author characteristics, we considered country of the primary author (categorized as Canada/USA / 'other' economically developed countries / economically developing countries). Among publication characteristics, we looked at whether the publication reported consent procedures from gatekeepers or individual/cluster level participants (yes-including waiver/no), and whether ethics review was reported (yes-including exemption/no). Similarly, we were interested in whether or not ethics approval and participant consent were reported as sought in the CRT publication (yes/waiver-exemption/no), and whether or not one or more

cluster gatekeepers were identified in the CRT (yes/no). There were two variables of interest pertaining to methodological quality of a CRT: whether the sample size calculation presented accounted for clustering (yes/no), and whether the analyses were appropriately conducted by accounting for the ICC (yes/no). Analyses were also considered to be appropriately conducted if inferences were being made towards the cluster using cluster level summary statistics. Because the risks of overstating statistical significance of study findings are more consequential than reduced statistical efficiency, we conducted a McNemar test for agreement between these two methodological indicators. Since the test was found to be statistically significant ($p<0.0001$), only the variable accounting for appropriate analyses conducted for the CRT design, was used in bi-variable and multivariable analyses. Publication year, and the journal impact factor of the CRT, which was collected elsewhere,[34] were also publication characteristics of interest.

Among trial characteristics, we considered the number of clusters randomized, and the average cluster size, which was computed by dividing the total number of subjects (i.e., individual level participants) providing data at baseline, with the total number of randomized clusters included in baseline data collection. If the number of randomized clusters included in baseline data collection was not apparent in the publication, the total number of clusters randomized was used to generate a plausible value for average cluster size. Also of interest were planned experimental and data collection interventions targeting individual and cluster level participants. A CRT was considered as having planned experimental interventions targeting individual level participants (yes/no) if the study involved individual health promotion or educational interventions, and direct individual level therapeutic interventions. Planned experimental interventions targeting cluster level participants (yes/no) were

considered if the CRT involved educational or quality improvement interventions targeting cluster level participants, and quality improvement interventions targeted at the cluster organization level. A third variable combined the targeted levels of planned study interventions in a CRT (individual level only/cluster level only/cluster and individual level). A CRT was considered as having planned data collection interventions targeting individual level participants (yes/no) if the study involved interviewer-administered individual level questionnaires, self-administered questionnaires, or physical examination or other intrusive data collection (e.g., blood sample) not required for normal care or procedures. Planned data collection interventions targeting cluster level participants (yes/no) were considered if the CRT involved a survey or interviews of cluster level participants. The use of routinely collected data, such as medical record review, was not considered as directly targeting participants for data collection. A third variable that was considered combined the targeted levels of planned data collection interventions in a CRT (routine data only/individual level only/cluster level only/cluster and individual level).

2.8. ETHICS CONSIDERATIONS IN THE STUDY

Participation in this study entailed completing a survey questionnaire, which presented no more than a minimal risk to sample members.[51] In the survey cover letter (**Appendix D**), sample members were informed that their participation is voluntary and that results are to be kept confidential, in accordance with the details on confidentiality. Submitting the survey questionnaire was therefore regarded as implied consent to participate in the study.

Upon obtaining approval for the survey of cluster randomization trialists from the Graduate Studies Council (GSC) of the department of Epidemiology and Community

Medicine at the University of Ottawa, an application for expedited review was submitted to the Ottawa Hospital Research Ethics Board (OHREB). The study was approved with minor clarifications (Protocol #2009693-01H). Ethics approval was sought and granted twice more for protocol amendments. Please refer to **Appendix E** for the letter confirming ethics approval for this study.

CHAPTER 3

SURVEY IMPLEMENTATION AND RESPONSE

In Chapter 3, we present descriptive results for the survey, including response rates and characteristics of the sample members and their studies. We evaluate the possibility of non-response bias by comparing characteristics of respondents and non-respondents to the survey; we also compare early, middle and late respondents to test the significance of changes in response over time.

3.1 SURVEY IMPLEMENTATION

Pilot testing of the survey was initiated in May of 2010. In June 2010, all remaining sample members were invited to participate in the survey. The data collection period of the study was closed in late September 2010, after a final email reminder had been sent to all remaining non-respondents in early September.

If during survey implementation it was found that the corresponding author was no longer available (i.e., retired, deceased), then the second author of the study was contacted as a proxy, to participate in the survey. If the primary author emailed back suggesting that another co-author on the CRT complete the survey, we asked the primary author to complete the last portion of the questionnaire themselves (as this contained questions related to their views and experiences with CRTs), but encouraged the respondent to involve other co-author(s) for completing the remainder of the survey related to the selected CRT publication. If an email invitation to a sample member was undeliverable, returned as an auto-reply that they had changed institutions (with or without new contact information), or if there was evidence that a sample member had been contacted at an outdated email address, then the sample member was re-contacted at a newer, updated email address (if obtainable).

3.2 SURVEY RESPONSE RATES

All 300 sample members were assigned final disposition codes according to the American Association for Public Opinion Research (AAPOR) guidelines.[47] Figure 4 shows the classification of sample members into six different categories based on their final disposition status. These categories form the basis of the response rate calculations. Table F-1 (**Appendix F**) outlines the detailed dispositions of sample members according to the guidelines. As shown in Figure 4, of the 300 trials that were included in the review of CRT publications conducted as part of the larger grant, thirteen researchers were the corresponding author for two trials while one researcher was the corresponding author for three trials in the sample. For these sample members, one of their CRTs was randomly selected for the survey using the random number generator function in MS Excel. This resulted in a final sample size of 285 CRTs whose corresponding authors were contacted via the survey implementation procedures.

3.2.1 Final dispositions of sample members

Category I: Returned questionnaire

Category '(I)' sample members consist of those who submitted a completed survey questionnaire and are therefore considered as respondents. The criterion for "questionnaire completion" was to have provided responses to questions in all sections of the questionnaire. A total of 182 sample members met this criterion and are therefore considered respondents. The AAPOR guidelines also include a category '(P)' for questionnaires that were partially completed or in which the respondent broke-off, but that resulted in sufficient information for inclusion in primary analyses. Amongst the five partially completed questionnaires, none provided responses past the midpoint of the questionnaire and therefore did not meet our

criterion of "questionnaire completion". These sample members were therefore categorized as non-respondents who implicitly refused to complete the survey (i.e., category R).

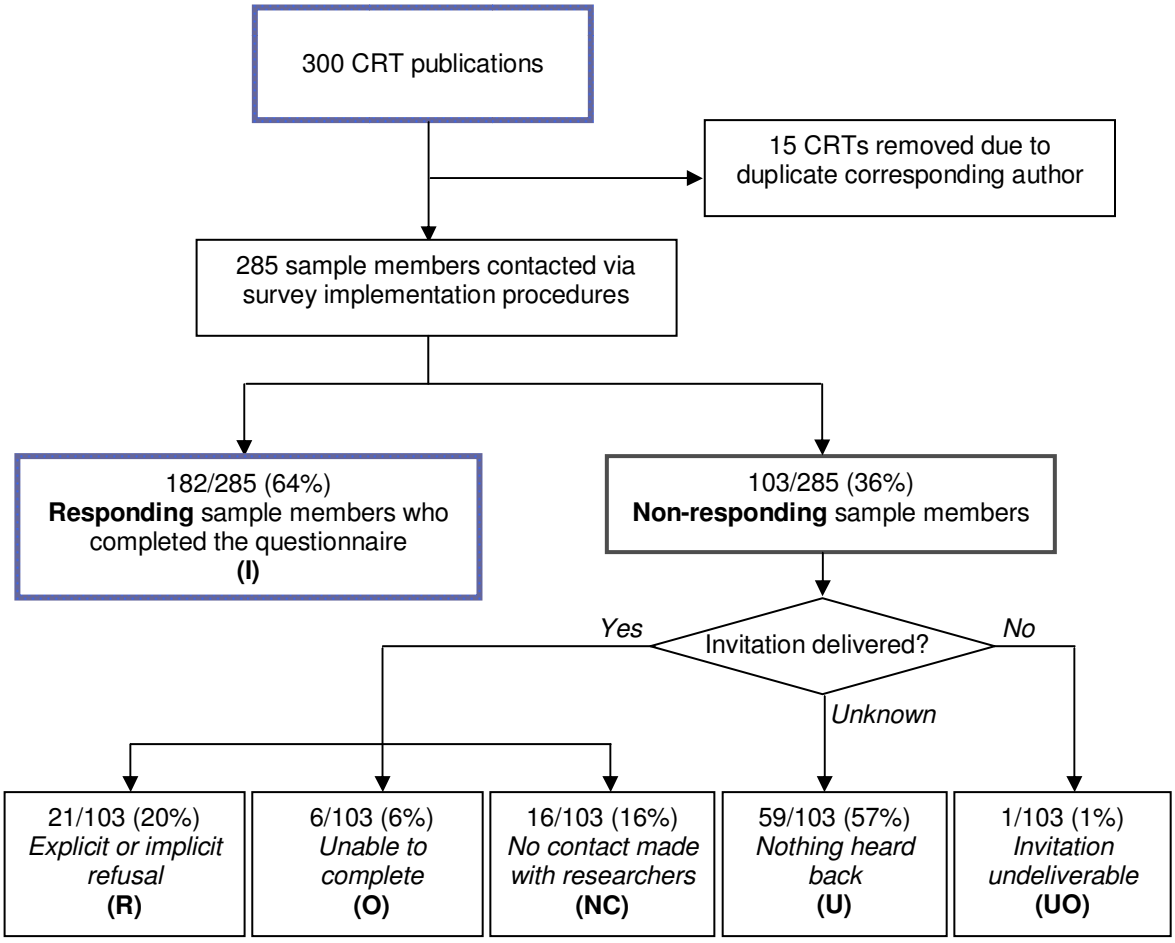

Figure 4: Flow chart illustrating response outcomes of sample members and corresponding disposition categories according to AAPOR guidelines.

Category R: Explicit or implicit refusal

Category '(R)' consists of non-responding sample members who explicitly or implicitly refused to participate in the study. A total of 21 sample members were classified in this category. Five sample members explicitly refused to participate in the survey. Reasons for refusal included the following: retirement, 'haven't been working in the field for some time,' no practical experience with CRTs—only involved with the data, confidentiality concerns, and experiencing technical difficulties with the web based questionnaire (one respondent).

Because the web server was programmed to time stamp sample members who logged into the survey, we found that eleven sample members logged into the survey at least once, but did not complete any questions. Another five sample members also logged into the survey and completed some questions but none were regarded as having provided sufficient information. These 16 sample members were therefore understood as having implicitly refused to complete the survey.

Category O: Unable to complete

Category '(O)' consists of non-responding sample members who contacted the survey administrator, and whilst not refusing, gave 'other' reasons for not yet having completed the questionnaire. Reasons included pre-occupation with existing work, and being away for an extended period of time. One sample member explained that the survey was hard to understand, which was understood as a possible language barrier given the sample member's location. A total of 5 sample members fit into this category.

Category NC: Non-contact -invitation delivered

Category '(NC)' consists of non-responding sample members who made no contact with the survey administrators, although their survey invitation was known to be delivered. These were 16 sample members from whom we received out of office auto-replies, providing evidence of a valid e-mail address and that the survey invitation was in fact delivered.

Category U: Non-contact -invitation delivery status unknown

Category '(U)' consists of 59 non-responding sample members who did not complete the survey questionnaire, and did not respond by any means (e.g., by website login, email, phone) to the survey invitations. The delivery status of their survey invitations remains unknown because nothing was heard from them.

Category UO: Invitation to sample member returned undelivered

Category '(UO)' consists of non-responding sample members whose survey invitations returned undelivered. This occurred for one sample member in the study.

3.2.2 Survey Response Rates

After categorizing invited sample members based on their response status, the survey response rates, including the contact, cooperation, and refusal rates, were calculated.

Contact rate

The survey contact rate is calculated as follows:

$$(I + P + R + O)/(I + P + R + O + NC + U + UO)$$

The calculation includes sample members who completed the survey completely or partially but with sufficient information (I + P), refused (explicitly or implicitly) to complete the survey (R), or gave reasons other than a refusal for not yet having completed the questionnaire at the time of contact (O), over all invited sample members (I, P, R, O, NC, U, UO). The proportion of sample members who made some form of contact with the research team was 74%.

Cooperation rate

The survey cooperation rate is calculated as follows:

$$(I + P)/(I + R + O)$$

The calculation includes sample members who completed the survey (I+P), over sample members who made contact with the researchers (i.e., sample members who completed the survey (I+P), refused (explicitly or implicitly) to complete the survey (R), or gave reasons

other than a refusal for not having completing the questionnaire to date (O)). The proportion of sample members who cooperated with the survey request, having made some form of contact with the research team was 87%.

Refusal rate

The survey refusal rate is calculated as follows:

$$(R)/(I+P+R+NC+O+U+UO)$$

The calculation includes sample members who explicitly refused to complete the survey, logged on to the survey but did not complete any items, or broke-off or partially completed the survey with insufficient information (R), over all invited sample members. The proportion of invited sample members who explicitly or implicitly refused to complete the survey was 7.4%.

Response rate

The survey response rate is calculated as follows:

$$(I+P)/(I+P+R+NC+O+U+UO)$$

The survey response rate was 64%. This minimal response rate calculation includes sample members who completed the survey (I), over all invited sample members, including all category (U) sample members for whom it is unknown whether the survey invitation reached them. These sample members are included in the denominator of the response rate because their contact details were confirmed and updated prior to survey implementation. It is estimated therefore that the majority of category (U) sample members received the survey invitation but chose not to respond.

3.3 CHARACTERISTICS OF SAMPLE MEMBERS AND SURVEY RESPONDENTS

Table 3.1 shows the characterization of the survey sample based on primary author, publication, and trial characteristics. Primary authors of the CRTs where characterized as follows: close to half were based in Canada or the USA, and less than 10% in various low and middle income countries. Among respondents, the median number of CRTs conducted was three; a quarter had conducted four or more CRTs—up to a maximum of 24. Doctoral and medical degrees were the most commonly held by respondents (69% and 41%, respectively).

Publication characteristics of the CRT included the following: Close to four-fifths of the studies were published after 2002. The median impact factor of journals the CRTs were published in was 2.8, with some in the sample as high as 50. Based on information abstracted from the published report, 33% of CRT publications did not report the study consent practices, including qualifying for waivers of consent. Similarly, 26% of the CRT publications did not report whether ethics approval was obtained, including exemptions from ethics review.

Table 3.1: Sample characterization by author, publication, and study characteristics

Characteristics	%, frequency (n=285[a])
Author characteristics	
Country of study author	
Canada or USA	47.4% (135)
Other economically developed	44.9% (128)
Developing	7.7% (22)
Number of CRTs conducted (n=168[1], of n=182 respondents)	
Median (inter-quartile range(IQR))	3 (2 – 4)
Range	1-24
Highest obtained degrees (n=168[1], of n=182 respondents)	
Any doctorate degree: yes	69.1% (116)
Any masters degree: yes	31.6% (53)
Any medical degree: yes	40.5% (68)
Any other higher degree: yes	14.3% (24)
Publication characteristics	
Publication year	
2000-2002	21.4% (61)
2003-2005	38.6% (110)
2006-2008	40.0% (114)
Journal impact factor	
Median (IQR)	2.84 (2.1- 5.1)
Range	0.45-50.0
Any participant consent reported	
Yes	67.4% (192)
No	32.6% (93)
Ethics approval reported	
Yes	73.7% (210)
No	26.3% (75)
Study characteristics	
Country of study recruitment	
Canada or USA	42.8% (122)
Other economically developed	42.5% (121)
Developing	14.7% (42)
Unit of randomization	
Health care organization or setting	
Primary care	28.4% (81)
Hospital care	8.8% (25)
Individual health professionals	13.7% (39)
Nursing homes	5.6% (16)
Non-health care organization or setting	
Schools or classrooms	20.7% (59)
Residential areas	13.3% (38)
Worksites	6.0% (17)
Sports teams, social clubs	3.5% (10)
Number of clusters randomized[2]	
Median (IQR)	21 (12 - 48)
Range	2 - 605
Average cluster size[2]	
Median (IQR)	33.9 (12.4- 88.5)
Range	1.1- 122855.0

Target of experimental interventions		
Cluster level only	33.3%	(95)
Individual level only	33.7%	(96)
Both cluster and individual level	33.0%	(94)
Target of data collection interventions		
Routine data only	15.1%	(43)
Cluster level only	8.1%	(23)
Individual level only	63.9%	(182)
Both cluster and individual level	13.0%	(37)
Sample size calculation accounting for ICC		
Yes	33.7%	(96)
No	66.3%	(189)
Analysis accounting for ICC		
Yes	69.8%	(199)
No	30.2%	(86)

a- Sample members defined as all eligible and contacted sample members
1- 14 observations missing
2- 19 observations missing

Study characteristics of the CRTs were as follows: close to 40% of the sampled studies were conducted in Canada or the USA, and 15% in various low and middle income countries. The unit of randomization included a diverse set of healthcare and non-healthcare organizations or settings, particularly hospitals and clinical practices, and schools and residential areas, respectively. The median number of clusters randomized was 21; with as few as 2 and as many as 605 clusters randomized in a single CRT. Clusters had a median average size of 34 individual level participants, and as many as 100,000 participants per cluster. About a third of the CRTs involved experimental interventions targeted towards both individual and cluster level participants, and also close to one-third targeted cluster level participants only, or individual level participants only. Data was collected from individual level participants in 64% of the CRTs, and from cluster level participants in 8% of the studies. In 15% of the CRTs, data collection was not directed towards study participants, but involved the use of routinely collected data only. As an indicator of methodological quality of the studies, 66% did not have a reported sample size that accounted for clustering, and about a third did not conduct analyses appropriate for the CRT design.

3.4 NON-RESPONSE ANALYSES

Table 3.2 shows that the respondents and their CRTs were similar to non-respondents and their studies on most selected characteristics. This includes the country of the study author, version of survey incentive offered, year of CRT publication, journal impact factor, type of CRT in health research, average cluster size, and the target of planned experimental and data collection interventions. Respondents' CRTs did differ statistically significantly from non-respondents' studies based on whether or not the study analyses were appropriate for the CRT design (p=0.0166). Survey respondents' studies were more likely to have analyses conducted appropriately for the CRT design (75%) compared to non-respondents' CRTs (61%).

Among respondents, we further investigated the distribution of selected author, publication, and trial characteristics according to the timing of the response, as early, mid, and late. This analysis was performed determine whether a specific trend, indicative of possible non-response bias, could be observed. Early, mid and late response was defined based on whether questionnaires were submitted before the thank you & reminder email, after the thank you & reminder email but before the mailing of the postal contact, and after the mailing of the postal letter, respectively[52]. As shown in Table 3.3, no statistically significant associations or trends were observed, which would suggest that characteristics such as primary author country, year of CRT publication, or version of survey incentive offer were associated with early, middle, or late survey response. The journal impact factor was found to be marginally statistically significantly associated with the timing of survey submission (p=0.0505), but as shown in Table 3.2, this trend did not materialize into a statistically significant difference between survey respondents and non-respondents

Table 3.2: Comparison of respondents and non-respondents

Variable	Respondents (n=182)	Non-respondents (n=103)	Overall (n=285)	p-value
Author characteristics				
Country of study author				
Canada or USA	46.7% (85)	48.5% (50)	47.4% (135)	0.3937
Other economically developed	43.9% (80)	46.6% (48)	44.9% (128)	
Developing	9.3% (17)	4.9% (5)	7.7% (22)	
Survey incentive offer				
Complimentary book	50.6% (92)	50.5% (52)	50.5% (144)	0.9917
Complimentary book or donation	49.4% (90)	49.5% (51)	49.5% (141)	
Publication characteristics				
Publication year				
2000-2002	19.2% (35)	25.2% (26)	21.4% (61)	0.3632
2003-2005	41.2% (75)	34.0% (35)	38.6% (110)	
2006-2008	39.6% (72)	40.8% (42)	40.0% (114)	
Journal impact factor				
Median (IQR)	2.9 (2.0 – 5.1)	2.8 (2.1 – 4.8)	2.84 (2.1 – 5.1)	0.8945 [a]
Any participant consent reported				
Yes	65.9% (120)	71.8% (72)	67.4% (192)	0.4924
No	34.1% (62)	28.2% (31)	32.6% (93)	
Ethics approval reported				
Yes	72.0% (131)	76.7% (79)	73.7% (210)	0.3846
No	28.0% (51)	23.3% (24)	26.3% (75)	
Study characteristics				
Unit of randomization				
Health care organization	59.3% (108)	55.3% (57)	57.9% (165)	0.5111
Other	40.7% (74)	44.7% (46)	42.1% (120)	
Average cluster size				
Median (IQR)	36.6 (12.4 – 95.1)	28.6 (12.5 – 66.0)	33.9 (12.4 – 88.5)	0.4698 [a]
Target of experimental interventions				
Cluster level only	36.8% (67)	27.2% (28)	33.3% (95)	0.1269
Individual level only	34.1% (62)	33.0% (34)	33.7% (96)	
Both cluster and individual level	29.1% (53)	39.8% (41)	33.0% (94)	
Target of data collection interventions				
Routine data only	13.2% (24)	18.5% (19)	15.1% (43)	0.0856
Cluster level only	11.0% (20)	2.9% (3)	8.1% (23)	
Individual level only	63.2% (115)	65.1% (67)	63.9% (182)	
Both cluster and individual level	12.6% (23)	13.6% (14)	13.0% (37)	
Analysis accounting for ICC				
Yes	74.7% (136)	61.2% (63)	69.8% (199)	0.0166*
No	25.3% (46)	38.8% (40)	30.2% (86)	

a- Wilcoxon rank sums test

(p=0.8945). Although a study analysis appropriately accounting for clustering was a statistically significant difference between survey respondents and non-respondents (Table 3.2), this association did not materialize into a trend in the timing of survey submission (p=0.6260).

Table 3.3: Investigation of trends in respondent characteristics by timing of questionnaire submission

Variable	Timing [a] of response			p-value [b]
	Early (n=74)	Middle (n=74)	Late (n=34)	
Author characteristics				
Country of study author				
Canada or USA	41.9% (31)	54.1% (40)	41.2% (14)	0.4371
Other economically developed	48.7% (36)	39.2% (29)	44.1% (15)	
developing	9.5% (7)	6.8% (5)	14.7% (5)	
Number of CRTs conducted (n=168)[1]				
Median (IQR)	3 (2 – 4)	2 (1– 4)	3 (2 – 4)	0.4691 [c]
Highest obtained degrees (n=168)[1]				
Any doctorate degree: yes	72.1% (49)	67.2% (45)	66.7% (22)	0.4691
Any masters degree: yes	25.0% (17)	41.8% (28)	24.2% (8)	0.5267
Any medical degree: yes	38.2% (26)	44.8% (30)	36.4% (12)	0.6499
Any other higher degree: yes	13.2% (9)	13.4% (9)	18.2% (6)	0.9720
Survey incentive offer				
Complimentary book	51.3% (38)	48.7% (36)	52.9% (18)	0.9648
Complimentary book or donation	48.7% (36)	51.4% (38)	47.1% (16)	
Publication characteristics				
Publication year				
2000-2002	17.6% (13)	17.6% (13)	26.5% (9)	0.0627
2003-2005	35.1% (26)	40.5% (30)	55.9% (19)	
2006-2008	47.3% (35)	41.9% (31)	17.7% (6)	
Journal impact factor				
Median (IQR)	2.8 (2.0 – 4.8)	3.3 (2.2 – 12.1)	2.4 (2.0 – 4.2)	0.0505 [c]
Study characteristics				
Analysis accounting for ICC				
Yes	75.7% (56)	75.7% (56)	70.6% (24)	0.6260
No	24.3% (18)	24.3% (18)	29.4% (10)	

a- Timing defined as submitting the survey as follows. Early: after survey invitation but before thank you/reminder email; Middle: after thank you/reminder email or reminder email but before postal notification; Late: After postal notification
b- Cochran-Armitage trend test
c- Wilcoxon rank sums test
1- 14 observations missing

By comparing the distribution of selected author and study characteristics available from the CRT publication (e.g., author country, publication year, type of cluster setting, reporting of participant consent) with the distributions of these characteristics in non-respondents, we assessed the possibility of unit non-response bias. Although we observed a proportionally higher methodological quality in respondents' studies, we do not suspect a serious issue of non-response bias that would arise from this difference. Statistically significant changes over time in questionnaire submission were not observed according to whether or not respondents had conducted analyses appropriate for the CRT design, or any of the other characteristics examined.

CHAPTER 4

INDIVIDUAL AND CLUSTER LEVEL CONSENT PRACTICES IN CRTS

In Chapter 4, we begin by presenting results on the prevalence of individual and cluster level consent procedures in the selected CRT publications. Next, respondents' reasons for adopting certain consent practices are described. Multivariable analyses of factors associated with individual and cluster level consent for experimental interventions and data collection are also presented. The Chapter ends with consent practices as reported in CRT publications, compared with the survey responses.

4.1 PREVALENCE OF PARTICIPANT CONSENT IN CRTS

In order to assess the prevalence of individual and cluster level consent, cluster trialists were asked whether or not they had sought consent from individual and cluster level participants for any aspect of their study. As described previously, the CRT design can present unique ethical challenges to trial consent processes. Often, questions arise regarding from whom, for what, and when consent should be sought. To ascertain the use of post-randomization consent in CRTs, trialists were requested to indicate the timing of consent relative to cluster randomization. Even though consent may have been sought from participants for any aspect of the CRT, we were interested in whether this extended to consent for the study intervention and data collection procedures, particularly if individual level participants, cluster level participants, or both were targeted by a study intervention or data collection procedures. In order to make comparisons between trial arms, and among individual and cluster level participants, questions regarding consent practices were posed separately for each trial arm (intervention and control), and type of study participant (individual and cluster level). Trialists were also asked whether participants in each study arm were informed about the presence of alternate study arms. Section 4.1.1 presents consent

prevalence in CRTs by trial arm (i.e., by intervention arm, control arm, and overall), separately for individual and cluster level participants. Section 4.1.2 presents overall consent prevalence, from both types of participants in the CRTs.

4.1.1 Prevalence of consent at the individual and cluster levels in CRTs

Results pertaining to individual level consent practices are presented in Table 4.1. We begin with the prevalence of any individual level consent sought in the selected CRTs. Overall (i.e., in either trial arm), 144 (79%, 95% confidence interval (CI) 73% to 85%) of the respondents indicated that consent was sought from individual level participants for any aspect of the study, whereas 38 (21%, 95% CI 14% to 30%) indicated that consent was not sought. The proportion of respondents who sought any individual level consent appeared to be similar across intervention and control arms. The timing of consent relative to cluster randomization also occurred in similar proportions across both trial arms. Of the respondents who sought individual level consent in the intervention arm, 25% (95% CI 18% to 33%) did so before the randomization of clusters, whereas 75% (95% CI 67% to 82%) sought consent post-randomization.

The results presented in Table 4.1 indicate that individual level consent from participants did not always extend to consent for receiving or being affected by a study intervention, or consent for data collection. Overall, consent was sought for receiving or being affected by a study intervention in 102 (56%, 95% CI 49% to 63%) of the CRTs. With regard to individual level consent for data collection procedures, Table 4.1 shows that overall, consent was sought in 137 (75%, 95% CI 68% to 81%) of the CRTs. Individual level consent for data collection was sought in similar proportions across both trial arms. Consent for receiving or being affected by a study intervention, however, was sought from a slightly

lower proportion of individual level participants in the control arm(s). Table 4.1 also shows that regardless of whether or not consent was sought, not all individual level participants were informed about interventions or treatment options in alternate arms: approximately 54% (95% CI 47% to 62%) in the intervention arm were informed about the use of the control arm, and vice versa.

Table 4.1: Prevalence of individual level consent in CRTs

	Value %, (frequency)					
	Intervention arm		Control arm		Overall	
					%, (frequency)	95% CI of %
Individual level consent sought for any aspect of the CRT? (n=182)						
Yes	79.1%	(144)	78.0%	(142)	79.1% (144)	72.5% to 84.8%
No	20.9%	(38)	22.0%	(40)	20.9% (38)	13.7% to 29.6%
If consent was sought:						
Timing of consent from participants?	**(n=144)**		**(n=142)**			
Before randomization	25.0%	(36)	25.4%	(36)	NA	18.2% to 32.9% [a]
After randomization	75.0%	(108)	74.7%	(106)	NA	67.1% to 81.8% [a]
Individual level consent sought for receiving an intervention? (n=182)						
Yes	56.0%	(102)	48.9%	(89)	56.0% (102)	48.5% to 63.4%
No	44.0%	(80)	51.1%	(93)	44.0% (80)	36.6% to 51.5%
Individual level consent sought for providing data? (n=182)						
Yes	75.3%	(137)	74.2%	(135)	75.3% (137)	68.4% to 81.4%
No	24.7%	(45)	25.8%	(47)	24.7% (45)	18.6% to 31.6%
Individual level participants informed about alternate arm(s)? (n=175) [1]						
Yes	54.3%	(95)	53.7%	(94)	NA	46.6% to 61.8% [a]
No	45.7%	(80)	46.3%	(81)	NA	38.2% to 53.4% [a]

a- Confidence interval presented for intervention arm
1- 7 observations missing

With regard to cluster level consent practices, we recall that in order to personalize the survey questionnaire, individual and cluster level participants were identified from each CRT publication included in the sample. Of the 285 CRTs in the final survey sample, 223

were identified as having cluster level participants who may have received or delivered an experimental intervention, or may have been involved in data collection procedures in the study. The cluster level participants identified (e.g., teachers, physicians, and employers) were those who had an existing relationship with individual level cluster members in the CRT. We posed questions about cluster level consent procedures only to sample members from whose CRT publications we had identified cluster level participants. Of the 149 respondents whose survey included questions about cluster level consent, two indicated that the cluster level participants we had identified neither received nor delivered any experimental interventions, and were not involved in data collection procedures. Therefore, 147 out of 182 of the respondents' CRTs involved cluster level members from whom consent could have been sought for some aspect of the study.

Results pertaining to cluster level consent practices are presented in Table 4.2. We begin with the prevalence of any cluster level consent sought in the selected CRTs. Overall, 121 (82%, 95% CI 75% to 88%) of the respondents indicated that consent was sought from cluster level participants for any aspect of the study, whereas 26 (18%, 95% CI 12% to 25%) indicated that they did not seek consent. The proportion of respondents who sought any cluster level consent appeared to be slightly lower in the control arm. The timing of consent relative to cluster randomization occurred in similar proportions across both trial arms. Of the respondents who sought cluster level consent in the intervention arm, 71% (95% CI 62% to 79%) did so before the randomization of clusters, whereas 29% (95% CI 21% to 38%) sought consent post-randomization.

Table 4.2: Prevalence of cluster level consent in CRTs

	Value %, (frequency)			
	Intervention	Control arm	Overall	
			%, (frequency)	95% CI of %
Cluster level consent sought for any aspect of the CRT? (n=147)				
Yes	82.3% (121)	78.2% (115)	82.3% (121)	75.2% to 88.1%
No	17.7% (26)	21.8% (32)	17.7% (26)	11.9% to 24.8%
If consent was sought:				
Timing of consent from participants?	**(n=121)**	**(n=115)**		
Before randomization	71.1% (86)	73.9% (85)	NA	62.1% to 79.0% [d]
After randomization	28.9% (35)	26.1% (30)	NA	21.0% to 37.9% [d]
Cluster level consent sought for receiving an intervention? (n=134 [a]) [1]				
Yes	61.9% (83)	52.2% (70)	61.9% (83)	53.2% to 70.2%
No	38.1% (51)	47.8% (64)	38.1% (51)	29.8% to 46.8%
Cluster level consent sought for delivering an intervention? (n=118 [b]) [2]				
Yes	62.4% (73)	57.6% (68)	66.1% (78)	56.8% to 74.6%
No	37.6% (44)	42.4% (50)	33.9% (40)	25.4% to 43.2%
Cluster level consent sought for providing data? (n=134 [c]) [3]				
Yes	76.1% (102)	70.1% (94)	74.6% (100)	66.4% to 81.7%
No	23.9% (32)	29.9% (40)	25.4% (34)	18.3% to 33.6%
Cluster level participants informed about alternate arm(s)? (n=147)				
Yes	91.8% (135)	85.7% (126)	NA	86.2% to 95.7% [d]
No	8.2% (12)	14.3% (21)	NA	4.3% to 13.8% [d]

a- Studies in which cluster level participants were specified as not receiving an intervention (i.e., respondent selecting 'N/A' to question 5) were excluded from the denominator
b- Studies in which cluster level participants were specified as not delivering or administering an intervention (i.e., respondent selecting 'N/A' to question 6) were excluded from the denominator
c- Studies in which cluster level participants were specified as not providing data (i.e., respondent selecting 'N/A' to question 7) were excluded from the denominator
d- Confidence interval presented for intervention arm
1- 2 observations missing
2- 1 observation missing: intervention arm (n=117)
3- 1 observation missing

The results presented in Table 4.2 further indicate that consent from cluster level participants did not always extend to consent for receiving or being targeted by a study

intervention, delivering a study intervention, or consent for providing data. Overall, cluster level consent was sought for receiving a study intervention in 83 (62%, 95% CI 53% to 70%) of the CRTs that involved cluster level participants receiving an intervention. Consent was sought from a slightly higher proportion of cluster level participants for delivering a study intervention to individual level participants—in 78 (66%, 95% CI 57% to 75%) of the CRTs that involved cluster level participants delivering or administering an intervention to individual level participants. With regard to cluster level consent for data collection procedures, Table 4.2 shows that overall, consent was sought in 100 (75%, 95% CI 66% to 82%) of the CRTs that involved data collection on, from, or by cluster level participants. Relative to the intervention arm(s), cluster level consent for receiving an intervention, delivering an intervention, and for providing data was sought from a slightly lower proportion of cluster level participants in the control arm(s). Table 4.2 also shows that regardless of whether or not consent was sought, not all cluster level participants were informed about interventions or treatment options in alternate arms: approximately 92% (95% CI 86% to 96%) in the intervention arm were informed about the use of the control arm, and 86% in the control arm were informed about the use of the intervention arm.

Consent practices for individual and cluster level participants were similar in some aspects, but differed in others. Approximately 70% of cluster level participants were approached for consent *before* the randomization of clusters, whereas this was the case for only 25% of the individual level participants. Consent for receiving an experimental intervention in the CRTs was sought at similar levels from both individual and cluster level participants, as was consent for data collection. More cluster level participants were informed about the use of alternate arms (close to 90%), compared to the proportion of

individual level participants who were informed about the use of alternate arms (close to 54%).

4.1.2 Overall prevalence of participant consent in CRTs

Results pertaining to participant consent (i.e., at the individual or cluster levels) for any aspect of the CRT are presented in Table 4.3. Consent for any aspect of the study was sought from participants at the individual level, cluster level, or both in 170 (93%, 95% CI 89% to 97%) of the CRTs. Since not all CRTs involved participants at both levels, participant consent for any aspect of the study is also presented according to CRTs with individual level participants only, and CRTs with both individual and cluster level participants. In CRTs with individual level participants only, consent for any aspect of the study was sought from participants at the individual level in 35 (100%, 95% CI 90% to 100%) of the CRTs. In studies with both individual and cluster level participants, consent for any aspect of the study was *not* sought at any level in 12 (8%, 95% CI 4% to 14%) of the CRTs.

Table 4.3: Consent from participants for any aspect of the CRT

	Value %, (frequency)	95% confidence interval of %
All Trials (n=182)		
Consent sought for any aspect of the study, in either trial arm?		
Yes, consent sought at any level	93.4% (170)	88.8% to 96.6%
No, consent not sought at any level	6.6% (12)	3.4% to 11.2%
Trials with no relevant cluster level participants (n=35 [a])		
Consent sought for any aspect of the study, in either trial arm?		
No consent at any level	0% (0)	0% to 11.8%
Consent at individual level only	100.0% (35)	90.0% to 100.0%
Trials with individual and cluster level participants (n=147 [b])		
Consent sought for any aspect of the study, in either trial arm?		
No consent at any level	8.2% (12)	4.3% to 13.8%
Consent at individual level only	9.5% (14)	5.3% to 15.5%
Consent at cluster level only	17.7% (26)	11.9% to 24.8%
Consent at both individual and cluster levels	64.6% (95)	56.3% to 72.3%

a- Denominator excludes CRTs without cluster level participants (i.e., in 35 of 182 CRTs, only individual level participants were involved in the study)

b- Denominator includes CRTs with cluster level participants (i.e., in 147 of 182 CRTs, both individual and cluster level were involved in the study)

Results pertaining to participant consent for a study intervention are presented in Table 4.4. Consent for a study intervention was sought from participants at the individual level, cluster level, or both in 127 (70%, 95% CI 63% to 76%) of the CRTs. Since not all CRTs included cluster level participants who were involved in the study intervention (i.e., who received or delivered a study intervention), participant consent for a study intervention is also presented according to CRTs with individual level participants only who received a study intervention, and CRTs with both individual participants who received a study intervention and cluster level participants who received or delivered a study intervention. In CRTs with individual level participants only, consent for receiving a study intervention was sought from participants at the individual level in 31 (84%, 95% CI 68% to 94%) of the CRTs. In studies where both individual and cluster level participants were involved in study

interventions, consent for a study intervention was *not* sought in 49 (34%, 95% CI 26% to 42%) of the CRTs.

Table 4.4: Consent from participants for a study intervention

	Value %, (frequency)	95% confidence interval of %
All Trials (n=182)		
Consent sought for a study intervention, in either trial arm?		
Yes, consent sought at any level	69.8% (127)	62.6% to 76.4%
No, consent not sought at any level	30.2% (55)	23.7% to 37.5%
Trials with no relevant cluster level participants (n=37 [a])		
Consent sought for a study intervention, in either trial arm?		
No consent at any level	16.2% (6)	6.2% to 32.0%
Consent at individual level only	83.8% (31)	68.0% to 93.8%
Trials with individual and cluster level participants (n=145 [b])		
Consent sought for a study intervention, in either trial arm?		
No consent at any level	33.8% (49)	26.2% to 42.1%
Consent at individual level only	22.8% (33)	16.2% to 30.5%
Consent at cluster level only	17.2% (25)	11.5% to 24.4%
Consent at both individual and cluster levels	26.2% (38)	19.3% to 34.2%

a- Denominator excludes CRTs without cluster level participants who received or delivered a study intervention (i.e., in 38 of 182 CRTs, individual level participants only, received an intervention)

b- Denominator includes CRTs with cluster level participants who received or delivered a study intervention (i.e., in 145 of 182 CRTs, individual level participants received an intervention and cluster level participants received or delivered a study intervention)

Results pertaining to participant consent for providing data are presented in Table 4.5. Consent for data collection was sought from participants at the individual level, cluster level, or both in 160 (88%, 95% CI 82% to 92%) of the CRTs. As not all CRTs included cluster level participants who were involved in data collection procedures (i.e., data were not collected on, from, or by them), participant consent for data collection is also presented according to CRTs with individual level participants only who provided data, and CRTs with both individual and cluster level participants who provided data. In CRTs with individual level participants only, consent for data collection was sought from participants at the

individual level in 42 (89%, 95% CI 77% to 97%) of the CRTs. In CRTs with both individual and cluster level participants, consent for data collection was *not* sought in 17 (13%, 95% CI 8% to 19%) of the CRTs.

Table 4.5: Consent from participants for data collection procedures

	Value %, (frequency)	95% confidence interval of %
All Trials (n=182)		
Consent sought for data collection, in either trial arm?		
Yes, consent sought at any level	87.9% (160)	82.3% to 92.3%
No, consent not sought at any level	12.1% (22)	7.7% to 17.7%
Trials with no relevant cluster level participants (n=47 [a])		
Consent sought for data collection, in either trial arm?		
No consent at any level	10.6% (5)	3.6% to 23.1%
Consent at individual level only	89.4% (42)	76.9% to 96.5%
Trials with individual and cluster level participants (n=135 [b])		
Consent sought for data collection, in either trial arm?		
No consent at any level	12.6% (17)	7.5% to 19.4%
Consent at individual level only	13.3% (18)	8.1% to 20.3%
Consent at cluster level only	17.0% (23)	11.1% to 24.5%
Consent at both individual and cluster levels	57.0% (77)	48.2% to 65.5%

a- Denominator excludes CRTs without cluster level participants who provided data (i.e., in 47 of 182 CRTs, individual level participants only, provided data)

b- Denominator includes CRTs with cluster level participants who provided data (i.e., in 135 of 182 CRTs, both individual and cluster level participants provided data)

4.2 RESPONDENT EXPLANATIONS FOR CONSENT PRACTICES

4.2.1 Reasons consent was not sought from participants

Individual level

Of the survey respondents who did not seek consent from individual level participants for any aspect of the study, most offered explanations as to why this was the case in their selected CRT. Table 4.6 lists the frequencies of the cited reasons.

Table 4.6: Reasons consent was not sought from individual level participants in a CRT

Reason	Number of respondents citing reason Frequency, (%) (n=33 [a]) [1]
Study procedures not directly targeting participants	17 (52%)
Usual procedures or standards of care	15 (45%)
Participants given the opportunity to opt-out of study procedures	4 (12%)
Minimal risk to participants	7 (21%)
Procedures meeting ethical requirements	4 (12%)
Minimal involvement (control arm)	1 (3%)

a- Respondents' CRTs in which individual level consent was not sought—in either study arm, or the control arm only

1- 7 respondents did not provide any explanation

Seventeen (52%) of the respondents who provided an explanation indicated that consent was not sought from individual level participants because there were no experimental or data collection interventions provided to participants at this level. Interventions were cited as being directed towards cluster level participants (e.g., providers) as in behavioural or educational interventions, or the system level (e.g., hospital) as in process quality improvement or service delivery initiatives:

> "This was a study of physician practice behavior. The intervention was with physicians, not patients. [*Research ethics committee*] agreed with us that although we studied patient outcomes, the consent was from physicians."

Respondents also explained that information was not directly obtained from individual level participants. In such cases data was retrieved from a central (e.g., administrative) database, and may also have been collected anonymously.

Fifteen (45%) of the respondents explained that consent was not sought because individual level participants in their study were under usual procedures or continued to receive best standards of care: "Patients received care from their physicians as before (i.e., per the physicians' discretion of best practice)." Additionally, four respondents (12%) cited

the ability of individual level participants to opt-out of study procedures, and 12% also cited the study procedures adequately meeting ethics requirements as reasons for not obtaining individual level consent.

Citing their study procedures, seven (21%) of the respondents indicated that the study was considered (i.e., by ethics committees, researchers, or the parties involved) as minimal risk, and therefore exempt from certain regulatory requirements for human research subject protections—particularly the requirement of consent from participants. In addition to minimal risk, one or more of the above and previously cited reasons may have contributed to a waiver of consent, as one respondent explained:

> "the study did not provide any intervention to the patients; all patient care was provided by the patients' usual care provider; it would not have been feasible to obtain consent from the thousands of individual patients in order to examine their records created in the course of their regular ongoing care and so requiring individual patient consent would have made it impossible to conduct a study of the quality improvement intervention; the study was minimal risk."

Cluster level

Of the survey respondents who did not seek consent from participants at the cluster level, most offered explanations as to why this was the case in their selected CRT. Table 4.7 lists frequencies of the cited reasons.

Table 4.7: Reasons consent was not sought from cluster level participants in a CRT

Reason	Number of respondents citing reason Frequency, (%) (n=24 [a]) [1]
Not considered research participants	6 (25%)
Participation required, or expected based on professional duty	11 (46%)
Participants given the opportunity to opt-out of study procedures	7 (29%)
Minimal involvement (control arm)	4 (17%)

a- Respondents' CRTs in which cluster level consent was not sought—in either study arm, or the control arm only

1- 8 respondents did not provide any explanation

Six (25%) of the respondents who provided an explanation indicated that consent was not sought from cluster level participants because they were not considered research participants. Respondents explained that the study interventions were not directed towards cluster level participants but rather towards individual level participants in the study:

> "We have consented physicians in these types of study if they are the object (target) of the intervention. In this case, we argued that the providers were simply being assisted to provide standard of care…"

Although study interventions may have targeted cluster level participants, 11 (46%) of the respondents explained that consent was not sought because participation was required or expected based on professional duty, as in the case of a new service introduced into a healthcare setting. Seven (29%) of the respondents also cited the ability to opt-out of intervention procedures as not necessitating cluster level consent: "The GPs could choose whether to use some or all of the interventions provided." Four (17%) of the respondents explained that where control arm participants were not consented, it was due to their minimal involvement in the study. These cluster level participants were not targeted by any study interventions and did not have any contact with the research team for the duration of the CRT.

4.2.2 Reasons participants were not informed about alternate study arms

Individual level

Of the survey respondents who indicated that individual level participants were not informed about the alternate study arm(s), most offered explanations as to why this was the case in their selected CRT. Table 4.8 lists frequencies of the cited reasons. Respondent explanations are reported together for intervention and control arms because most respondents identified identical reasons for the intervention and control arms.

Table 4.8: Reasons individual level participants were not informed about alternate study arms

Reason	Number of respondents citing reason Frequency, (%) (n=60 [a]) [1]
To maintain blinding	9 (15%)
To avoid contamination	2 (3%)
To avoid protest or competition	4 (7%)
Study procedures not directly targeting participants	16 (27%)
Intervention received by all study arms	9 (15%)
Timing or level of randomization	5 (8%)
Usual procedures or standards of care	8 (13%)
Participants not explicitly notified about all aspects of study	13 (22%)
Procedures met ethics requirements	3 (5%)
Minimal involvement (control arm)	1 (2%)

a- Respondents' CRTs in which individual level participants in the intervention arm, control arm, or both, were not informed about alternate study arms.

1- 22 respondents did not provide any explanation

Two reasons for not informing participants about alternate arms were unique to studies in which individual level consent was sought: Nine (15%) of the respondents cited efforts to maintain blinding of participants in order to preserve intervention effects and valid evaluation of outcomes. Two (3%) cited efforts to avoid contamination between the study arms.

Other reasons cited by the respondents were common to CRTs in which consent was either sought or not sought from individual level participants. Reasons included avoiding protest from participants or competition between participants in different clusters (7%), and that the study procedures did not intervene directly upon individual level participants (27%). Study procedures cited included experimental interventions that targeted cluster level participants, and interventions at the cluster organization level. Nine respondents (15%) explained that they did not inform individual level participants about the comparison study arms because some form of intervention was offered in all study arms. For example, control

arms that were wait-listed controls would receive the intervention after a period of time. Timing and level of consent were also mentioned (8%); respondents explained that individual level participants were not informed about the comparison arms because participants were approached for consent *after* the randomization of clusters, or because randomization did not occur at the individual level. Another reason cited by respondents was that all individuals were receiving the same quality and standards of care, and that the CRT added no bearing on their situation (13%). Additionally, a number of respondents (22%) indicated that individual level participants were not fully notified about the study and therefore not notified about alternate arms. A few (5%) also explained that the procedures used (i.e., with regard to not informing participants about alternate study arms) had met ethical requirements.

Cluster level

Of the survey respondents who indicated that cluster level participants were not informed about the alternate study arm(s), most offered explanations as to why this was the case in their selected CRT. Table 4.9 lists frequencies of the cited reasons. Respondent explanations are reported together for intervention and control arms (except where differentiated) because most of the respondents identified identical reasons for not informing cluster level participants in both study arms.

Table 4.9: Reasons cluster level participants were not informed about alternate study arms

Reason	Number of respondents citing reason Frequency, (%) (n=18 [a]) [1]
To maintain blinding	6 (33%)
To avoid contamination	2 (11%)
To avoid Hawthorne effects	1 (5.5%)
Intervention received by all study arms	2 (11%)
Participants not explicitly notified about all aspects of study	3 (17%)
Minimal involvement (control arm)	4 (22%)

a- Respondents' CRTs in which cluster level participants in both study arms or in the control arm only, were not informed about alternate study arms

1- 3 respondents did not provide any explanation

Two reasons for not informing participants about alternate arms were unique to studies in which cluster level consent was sought: Similar to what was found at the individual level, the reasons cited were efforts to maintain blinding of participants in order to preserve intervention effects and valid evaluation of outcomes (33%), and efforts to avoid contamination between the study arms (11%).

Other reasons cited by the respondents that were common to CRTs in which consent was either sought or not sought from cluster level participants were that study arm participants in both arms were involved in training procedures (11%), and that participants in the control arm specifically were not informed because of minimal involvement in the study (22%). Cluster level participants were cited as not having any contact with the researchers, not having received any intervention, or only participating in data collection: "They only answered questionnaires about [*medical condition*]."

In a CRT in which consent was not sought from cluster level participants, the respondent explained that cluster level participants were not informed about alternate arms in order to avoid Hawthorne effects; notification could affect behaviour, altering the impact of the intervention:

> "Since written guidance, training and/or support were the interventions - we felt that outlining what other [*cluster level participants*] were receiving might affect the impact of the intervention."

A few respondents (17%) also explained that participants were not notified about alternate arms because they were not fully notified about all aspects the study.

4.2.3 Participant consent and notification procedures for study interventions and data collection

When indicating whether or not participant consent had been sought for study interventions and data collection procedures, trialists were asked to specify the method of consent used (i.e., written, verbal, or other), and the method of notification if participant consent was not sought. In **Appendix G**, individual and cluster level consent and notification practices are presented in greater detail, by trial arm.

4.3 FACTORS ASSOCIATED WITH PARTICIPANT CONSENT

4.3.1 Variables of interest in bi-variable and logistic regression analyses of factors associated with individual and cluster level consent

Dependent Variables

The dependent variables considered in bi-variable and multivariable analyses of factors associated with individual and cluster level consent were the following:

i) Consent sought from individual level participants for receiving an experimental intervention;

ii) Consent sought from cluster level participants for receiving an experimental intervention;

iii) Consent sought from individual level participants for data collection; and

iv) Consent sought from cluster level participants for data collection.

The dependent variables were dichotomized 'yes' or 'no' as to whether consent was sought from participants, in either of the trial arms. Consent sought was the outcome of interest and no consent sought was the reference level. The fourth dependent variable, namely consent from cluster level participants for data collection, was not included in bi-variable and multivariable analyses of factors associated with participant consent. The survey inquired about consent from cluster level participants for data collected on, from, or by them, which was too over-encompassing to examine associations for consent.

Independent Variables

The independent variables considered in bi-variable and multivariable analyses of factors associated with individual and cluster level consent were the following:

Publication year of CRT

Publication year as a factor associated with consent was considered because there may have been changes in consent practices over time, influenced by emerging publications on ethical challenges in CRTs, and the publication of the MRC guidelines on ethical and methodological considerations for CRTs (published 2002). We hypothesize that consent from participants—for data collection or an experimental intervention, would be greater in the years 2005-2008, compared to 2000-2004, as awareness of consent issues in CRTs would have increased among the research community. The variable was dichotomized as years 2000 to 2004 and 2005 to 2008 to simplify interpretation of the logistic regression model and because empirical logit plots of publication year and each of the dichotomous outcomes revealed that the functional form of the association could not be described as linear.

Country of study conduct

It was hypothesized that consent procedures of CRTs conducted in Canada and the USA

would differ from other economically developed countries, because research regulations in these regions have developed relatively independently.[33] It was also hypothesized that due to differing social and economical conditions, consent procedures in CRTs conducted in economically developing countries would differ from those in other developed countries.

Unit of randomization

It was hypothesized that CRTs conducted in primary and hospital care would be less likely to obtain consent from participants. Some investigators conducting CRTs in healthcare settings (e.g., quality improvement initiative or implementation of best practices), may not consider the study as requiring human subjects' protections similar to protections in conventional biomedical research.

Cluster size at the individual level

It was hypothesized that in CRTs with large cluster sizes, individual level consent would be less likely to have been sought, given the impracticalities which may arise from having to obtain consent from a larger compared to smaller number of individuals. The variable was dichotomized with a split at the median to simplify interpretation of the model, and because fit statistics revealed that modeling average cluster size as a dichotomous variable improved upon model fit compared to modeling average cluster size as a continuous variable. Dichotomizing the variable allowed us to deduce missing values as either above or below the median: Nine studies had missing values for average cluster size, but plausible values for a cluster size that was less than or greater than the median average cluster size, could be deduced from the publication. To deduce plausible values, aspects of the CRT such as the type of cluster, and the number of individuals contributing data were taken into account.

Any participant level experimental intervention(s)

It was hypothesized that CRTs with planned experimental interventions intervening directly on participants or involving participant interaction with research team members would be more likely to seek consent from participants, especially for an experimental intervention.

Any participant level data collection intervention(s)

It was hypothesized that CRTs with planned data collection procedures intervening on participants or requiring participant interaction with researchers would be more likely to seek consent from participants, particularly for data collection.

Trial measurement design at individual level

It was hypothesized that trials with a nested cohort design or any cohort components where individual level participants are measured more than once or continuously for a period of time, would be more likely to seek consent for data collection from individual level participants.

Ethics approval of the CRT

It was hypothesized that trials not undergoing ethics approval may have been less likely to regard some subject protections (e.g., obtaining participant consent) as necessary, and would therefore be less likely to have sought consent from participants. This variable was not included in the multivariable analyses due to an insufficient number of trials not seeking ethics approval, which may lead to non-convergence of the model.

Study analyses accounting for the ICC

This variable was included to investigate whether there was any association between methodological quality of the trial and participant consent procedures.

4.3.2 Factors associated with participant consent for receiving an experimental intervention

Individual level

Bi-variable analyses of factors associated with individual level consent for an experimental intervention (Table 4.10) showed statistically significant associations with the following variables: publication year of the CRT (p=0.0242), unit of randomization (p=0.0014), average cluster size (p=0.0006), any experimental interventions targeting the individual level (p <0.0001), any data collection interventions targeting the individual level (p <0.0001), and ethics approval having been sought for the CRT (p<0.0001). Increased odds of seeking individual level consent were observed for CRTs published between the years 2005-2008 (compared to CRTs published between the years 2000-2004), CRTs directly targeting individual level participants with experimental interventions or data collection, and for CRTs in which ethics approval was sought. The unit of randomization including a healthcare organization (compared to CRTs randomizing non-healthcare organizations), and an average cluster size greater than the median, were associated with decreased odds of seeking individual level consent.

All variables of interest (except for ethics approval) were entered into the logistic regression model of factors associated with individual level consent for an experimental intervention, because variance inflation factor values were low. The highest value was 1.63, which indicated that multicollinearity among the independent predictors was not a cause for concern. The Hosmer-Lemeshow goodness of fit test produced a chi-squared value of 5.48, with a p-value of 0.7053. The null hypothesis that there is a goodness of fit cannot be rejected, which indicates goodness of fit of the model. Similarly, a c-statistic of 0.804 indicates good model discrimination. The adjusted R-squared value of 0.4019 also indicates

that the model parameters improve reasonably well upon the prediction of the null model.

Table 4.10: Bi-variable associations of factors predicting consent from individual level participants in a CRT, for receiving or being affected by an experimental intervention

	Individual level consent sought for an experimental intervention (n=182)					
Variable	**Yes**		**No**		**OR [95% CI]**	**p-value** [a]
Publication year						
2005-2008	63.6%	(63)	36.4%	(36)	1.97 [1.09, 3.58]	0.0242*
2000-2004‡	47.0%	(39)	53.0%	(44)		
Country of study conduct						
Canada or USA	56.4%	(44)	43.6%	(34)	1.16 [0.62, 2.20]	0.6378
Other economically developed‡	52.6%	(40)	47.4%	(36)		
Economically developing	64.3%	(18)	35.7%	(10)	1.62 [0.66, 3.96]	0.2885
Unit of randomization						
Health care organization	46.3%	(50)	53.7%	(58)	0.36 [0.20, 0.68]	0.0014*
Other‡	70.3%	(52)	29.7%	(22)		
Average cluster size						
Greater than median (36.6)	43.5%	(40)	56.5%	(52)	0.35 [0.19, 0.64]	0.0006*
Less than median (36.6) ‡	68.9%	(62)	31.1%	(28)		
Experimental interventions targeting individual level						
Yes	71.9%	(82)	28.1%	(32)	6.15 [3.17, 11.93]	<0.0001*
No‡	29.4%	(20)	70.6%	(48)		
Data collection interventions targeting individual level						
Yes	67.4%	(93)	32.6%	(45)	8.04 [3.56, 18.15]	<0.0001*
No‡	20.4%	(9)	79.6%	(35)		
Analysis accounting for ICC						
Yes	57.4%	(78)	42.7%	(58)	1.23 [0.63, 2.41]	0.5407
No‡	52.2%	(24)	47.8%	(22)		
Ethics approval sought						
Yes	60.8%	(101)	39.2%	(65)	23.3 [3.0, 180.7]	<0.0001*
No‡	6.3%	(1)	93.8%	(15)		

‡ - reference level

a- Pearson's χ^2 test

Adjusted associations for factors associated with individual level consent for an experimental intervention (Table 4.11) showed statistically significant adjusted associations with the following factors: Publication year of the CRT (p=0.0404), average cluster size (p=0.0002), any experimental interventions targeting the individual level (p=0.0031), and

any data collection interventions targeting the individual level (p =0.0047). The unit of randomization (p=0.3176) was no longer statistically significant. Specifically, an average cluster size greater than the median was associated with a 24% decrease (11% to 51%) in the odds of seeking consent. Similarly, CRTs published between the years 2005 to 2008 were associated with increased odds of individual level consent, as were CRTs targeting individual level participants with experimental or data collection interventions.

Table 4.11: Adjusted associations of factors predicting consent from individual level participants in a CRT, for receiving or being affected by an experimental intervention

Variable	OR [95% CI]	p-value [a]
Publication year		
2005-2008	2.14 [1.03, 4.45]	0.0404*
2000-2004‡		
Country of study conduct		
Canada or USA	0.93 [0.42, 2.06]	0.8662
Other developed‡		
Economically developing	2.24 [0.73, 6.88]	0.1577
Unit of randomization		
Health care organization	0.61 [0.27, 1.37]	0.2321
Other‡		
Average cluster size		
Greater than median (36.6)	0.24 [0.11, 0.51]	0.0002*
Less than median (36.6) ‡		
Experimental interventions targeting individual level		
Yes	3.74 [1.56, 8.97]	0.0031*
No‡		
Data collection interventions targeting individual level		
Yes	4.29 [1.56, 11.8]	0.0047*
No‡		
Analysis accounting for ICC		
Yes	2.27 [0.96, 5.3]	0.0618
No‡		

‡ - reference level
a- logistic regression analysis

Cluster level

Bi-variable analyses of factors associated with cluster level consent for receiving an intervention (Table 4.12) showed statistically significant associations for none of the

variables considered, namely publication year of the CRT (p=0.0547), country of study conduct (p=0.1171 and p=0.8742), unit of randomization (p=0.8185), any experimental interventions targeting cluster level participants (p=0.2879), any data collection interventions targeting cluster level participants (p=0.6027), study analysis conducted appropriately for the CRT design (p=0.7327), and ethics approval having been sought for the study (p=0.4003).

Table 4.12: Bi-variable associations of factors predicting consent from cluster level participants in a CRT, for receiving or being targeted by an experimental intervention

	Cluster level consent sought for an experimental intervention (n=136)					
Variable	**Yes**		**No**		**OR [95% CI]**	**p-value** [a]
Publication year						
2005-2008	68.5%	(50)	31.5%	(23)	1.97 [0.98, 3.97]	0.0547
2000-2004‡	52.4%	(33)	47.6%	(30)		
Country of study conduct						
Canada or USA	52.6%	(30)	47.4%	(27)	0.56 [0.26, 1.16]	0.1171
Other economically developed‡	66.7%	(42)	33.3%	(21)		
Economically developing	68.7%	(11)	31.3%	(5)	1.10 [0.34, 3.58]	0.8742
Unit of randomization						
Health care organization	46.2%	(61)	53.8%	(38)	1.09 [0.51, 2.37]	0.8185
Other‡	69.7%	(22)	30.3%	(15)		
Experimental interventions targeting cluster level						
Yes	59.1%	(68)	40.9%	(47)	0.58 [0.21, 1.60]	0.2879
No‡	71.4%	(15)	28.6%	(6)		
Data collection interventions targeting cluster level						
Yes	64.3%	(27)	35.7%	(15)	1.22 [0.57, 2.60]	0.6027
No‡	59.6%	(56)	40.4%	(38)		
Analysis accounting for ICC						
Yes	42.7%	(47)	57.3%	(63)	0.88 [0.41, 1.86]	0.7327
No‡	45.9%	(17)	54.1%	(20)		
Ethics approval sought						
Yes	44.7%	(59)	55.3%	(73)	1.62 [0.52, 5.0]	0.4003
No‡	33.3%	(5)	66.7%	(10)		

‡ - reference level

a- Pearson χ^2 test

All variables of interest were entered into the logistic regression model of factors associated with cluster level consent for an experimental intervention, because variance

inflation factor values were low. The highest value was 1.09, which indicated that multicollinearity among the independent predictors was not a cause for concern. The Hosmer-Lemeshow goodness of fit test produced a chi-squared value of 15.55, with a p-value of 0.0493. The null hypothesis that there is a goodness of fit can be rejected, which indicates lack of goodness of fit of the model. Although a c-statistic of 0.654 indicates acceptable model discrimination, the low adjusted R-squared value of 0.0811 indicates that the model parameters do not improve very well upon the prediction of the null model.

Table 4.13: Adjusted associations of factors predicting consent from cluster level participants in a CRT, for receiving or being targeted by an experimental intervention

Variable	OR [95% CI]	p-value [a]
Publication year		
2005-2008	2.21 [1.09, 4.48]	0.0278*
2000-2004‡		
Country of study conduct		
Canada or USA	0.51 [0.24, 1.07]	0.1382
Other developed‡		
Economically developing	0.82 [0.27, 2.50]	0.8034
Unit of randomization		
Health care organization	1.31 [0.60, 2.86]	0.4958
Other‡		
Experimental interventions targeting cluster level		
Yes	0.82 [0.40, 1.69]	0.5874
No‡		
Data collection interventions targeting cluster level		
Yes	1.57 [0.73, 3.37]	0.2503
No‡		
Analysis accounting for ICC	1.22 [0.55, 2.70]	0.6172
Yes		
No‡		

‡ - reference level
a- Logistic regression analyses

After adjusting for all factors, Table 4.13 shows a statistically significant association of cluster level consent for receiving a study intervention with one factor: publication year of the CRT (p=0.0278). As with the unadjusted associations, all other factors remained statistically insignificant. The CRT being published in the years 2005 to 2008, versus

publication in the years 2000 to 2004, was associated with an increase in the odds of seeking cluster level consent for receiving an intervention.

4.3.3 Factors associated with individual level consent for data collection

Bi-variable analyses of factors associated with individual level consent for data collection (Table 4.14) showed statistically significant associations with the following factors: unit of randomization ($p < 0.0001$), average cluster size ($p < 0.0001$), any experimental interventions targeting the individual level ($p < 0.0001$), any data collection interventions targeting the individual level ($p < 0.0001$), the trial measurement design ($p < 0.0001$), and ethics approval having been sought for the CRT ($p < 0.0001$). Decreased odds of seeking individual level consent were observed for the unit of randomization including a healthcare organization (compared to CRTs randomizing non-healthcare organizations), and an average cluster size greater than the median. Increased odds of seeking individual level consent were observed for CRTs targeting individual level participants with experimental interventions or data collection, CRTs with any cohort components in the trial measurement design (compared to CRTs with cross-sectional measurement components only), and for CRTs in which ethics approval was sought.

Table 4.14: Bi-variable associations of factors predicting consent from individual level participants in a CRT, for data collection

Variable	Individual level consent sought for data collection (n=182) Yes		No		OR [95% CI]	p-value [a]
Publication year						
2005-2008	80.8%	(80)	19.2%	(19)	1.92 [0.97, 3.80]	0.0588
2000-2004‡	68.7%	(57)	31.3%	(26)		
Country of study conduct						
Canada or USA	79.5%	(62)	20.5%	(16)	1.79 [0.86, 3.72]	0.1174
Other developed‡	68.4%	(52)	31.6%	(24)		
Economically developing	82.1%	(23)	17.9%	(5)	2.12 [0.72, 6.26]	0.1663
Unit of randomization						
Health care organization	64.8%	(70)	35.2%	(38)	0.19 [0.08, 0.46]	<0.0001*
Other‡	90.5%	(67)	9.5%	(7)		
Average cluster size						
Greater than median (36.6)	63.0%	(58)	37.0%	(34)	0.24 [0.11, 0.51]	<0.0001*
Less than median (36.6) ‡	87.8%	(79)	12.2%	(11)		
Experimental interventions targeting individual level						
Yes	88.6%	(101)	11.4%	(13)	6.91 [3.27, 14.60]	<0.0001*
No‡	52.9%	(36)	47.1%	(32)		
Data collection interventions targeting individual level						
Yes	88.4%	(122)	11.6%	(16)	14.7 [6.54, 33.22]	<0.0001*
No‡	34.1%	(15)	65.9%	(29)		
Trial measurement design						
Any cohort components	87.0%	(114)	13.0%	(17)	8.16 [3.85, 17.30]	<0.0001*
Cross-sectional only‡	45.1%	(23)	54.9%	(28)		
Analysis accounting for ICC						
Yes	75.7%	(103)	24.3%	(33)	1.10 [0.51, 2.37]	0.8044
No‡	73.9%	(34)	26.1%	(12)		
Ethics approval sought						
Yes	80.7%	(134)	19.3%	(32)	18.1 [4.88, 67.5]	<0.0001*b
No‡	18.8%	(3)	81.3%	(13)		

‡ - reference level
a- Pearson χ^2 test
b- Fisher's exact test

All variables of interest were entered into the logistic regression model of factors associated with cluster level consent for an experimental intervention, because variance inflation factor values were low. The highest value was 1.73, which indicated that multicollinearity among the independent predictors was not a cause for concern. The

Hosmer-Lemeshow goodness of fit test produced a chi-squared value of 12.86, with a p-value of 0.1167. The null hypothesis that there is a goodness of fit cannot be rejected, which indicates goodness of fit of the model. Similarly, a c-statistic of 0.898 indicates excellent model discrimination. The adjusted R-squared value of 0.5440 also indicates that the model parameters improve well upon the prediction of the null model.

Adjusted associations for factors associated with individual level consent for data collection (Table 4.15) showed statistically significant associations with the following predictor variables: the country of study conduct (p=0.0485), unit of randomization (p=0.0469), average cluster size (p=0.0004), and any data collection interventions targeting the individual level (p=0.0001). Any experimental interventions targeting the individual level (p=0.5864), and the trial measurement design (p=0.1305) were no longer statistically significant. The statistically significant association of CRTs conducted in economically developing countries (compared to other developed nations), with individual level consent for data collection should be interpreted cautiously. Although the p-value was significant (marginally), the confidence interval was wide due to a lower number of trials in the economically developing country category. Similarly, due to marginal statistical significance, the association of the unit of randomization including a healthcare organization, with consent for data collection should be interpreted cautiously. An average cluster size greater than the median was associated with a 15% decrease in the odds of seeking individual level consent for data collection. A highly statistically significant increase in the odds of individual level consent for data collection was observed in CRTs targeting individual level participants with data collection procedures.

Table 4.15: Adjusted associations of factors predicting consent from individual level participants in a CRT, for data collection

Variable	OR [95% CI]	p-value [a]
Publication year		
2005-2008	1.48 [0.57, 3.83]	0.4168
2000-2004‡		
Country of study conduct		
Canada or USA	1.82 [0.62, 5.28]	0.2733
Other developed‡		
Economically developing	4.39 [1.01, 19.1]	0.0485*
Unit of randomization		
Health care organization	0.30 [0.09, 0.98]	0.0469*
Other‡		
Average cluster size		
Greater than median (36.6)	0.15 [0.05, 0.43]	0.0004*
Less than median (36.6) ‡		
Experimental interventions targeting individual level		
Yes	1.38 [0.43, 4.46]	0.5864
No‡		
Data collection interventions targeting individual level		
Yes	9.06 [2.96, 27.7]	0.0001*
No‡		
Trial measurement design		
Any cohort components	2.25 [0.79, 6.43]	0.1305
Cross-sectional only‡		
Analysis accounting for ICC	2.32 [0.77, 7.05]	0.1365
Yes		
No‡		

‡ - reference level
a- logistic regression analysis

4.4 REPORTING PARTICIPANT CONSENT IN CRT PUBLICATIONS

Individual level

Table 4.16 shows that 111 of the 182 respondents' published CRTs reported whether or not individual level consent was sought. Where consent was reported as sought, survey respondents' responses were concordant (99% confirmed the fact). The survey response of one respondent, however, indicated that consent was not sought from individual level participants whereas the published report stated that consent was sought from the participants. The respondent later clarified that verbal consent was sought to participate in

the project, which would imply that consent was tacit rather than explicit. All but two survey responses were in concordance with the ten published reports which stated that the CRT was exempt from individual level consent. These two respondents later clarified that consent was sought from individual level participants for certain parts of the study, namely receiving the experimental intervention, or participating in data collection procedures.

Table 4.16: Consistency in reporting individual level consent in trial publication compared to survey response

	Publication review consent reported	
Survey response result	**Consent Sought (n=101)**	**Consent not Sought (waived) (n=10)**
Consent sought	99.0% (100)	20.0% (2)
Consent not sought	0.01% (1)	80.0% (8)

Considering 71 of the respondents' publications that did not state whether or not individual level consent was sought (Table 4.17), the majority (42 or 59%) stated that they did in fact seek individual consent for some aspect of the study, whereas 29 (41%) stated that they did not seek consent. Thus, the prevalence of under-reporting consent was found to be 59% overall, and according to the unit of randomization, 40% in primary and hospital care but 96% in public health CRTs. The under-reporting of consent differed statistically significantly among primary and hospital care, and public health and health promotion CRTs ($p<0.0001$). Specifically, the under reporting of consent was greater in public health and health promotion CRTs.

Table 4.17: Adequacy of reporting consent from individual level participants in either study arm, by type of CRT in health research

	Publication review consent not reported			
Survey response result	**Primary and hospital care (n=47)**	**Public health and health promotion (n=24)**	**Overall (n=71)**	**p-value**
Consent sought	40.4% (19)	95.8% (23)	59.2% (42)	<0.0001*
Consent not sought	59.6% (28)	4.2% (1)	40.8% (29)	

Cluster Level

Table 4.18 shows that 23 of the respondents' 147 published CRTs in which cluster level participants were identified, reported whether or not cluster level consent was sought. Where consent was reported as sought, survey respondents' responses were concordant (100% confirmed the fact). Similarly, survey responses were in concordance with the two published reports which stated that a waiver of consent from cluster level participants had been granted.

Table 4.18: Consistency in reporting cluster level consent in trial publication compared to survey response

	Publication review consent reported	
Survey response result	**Consent Sought (n=23)**	**Consent not Sought (waived) (n=2)**
Consent sought	100.0% (23)	0% (0)
Consent not sought	0% (0)	100.0% (2)

A total of 186 publications in which cluster level participants were identified, did not state whether or not cluster level consent was sought in the CRT. Considering the 122 publications among this group whose author responded to the survey (Table 4.19), the majority (98 or 80%) stated that they did in fact seek cluster level participant consent for some aspect of the study, whereas 24 (20%) stated that they did not seek consent. The

proportion of CRTs in which cluster level consent was sought (whilst not reported) did not differ statistically significantly among primary and hospital care, and public health and health promotion CRTs (p=0.8151).

Table 4.19: Adequacy of reporting consent from cluster level participants in either study arm, by type of CRT in health research

	Publication review consent not reported			
Survey response result	**Primary and hospital care (n=84)**	**Public health and health promotion (n=38)**	**Overall (n=122)**	**p-value**
Consent sought	79.8% (67)	81.6% (31)	80.3% (98)	0.8151
Consent not sought	20.2% (17)	18.4% (7)	19.7% (24)	

CHAPTER 5

INVESTIGATOR EXPERIENCES WITH THE RESEARCH ETHICS REVIEW AND APPROVAL PROCESSES OF CRTS

In Chapter 5 we present results pertaining to the research ethics review and gatekeeper approval processes of the selected CRTs. Also presented are the general experiences of trialists with regard to the research ethics review process of any CRTs they have conducted, and their views regarding the need for ethics guidelines for CRTs.

5.1 RESEARCH ETHICS REVIEW OF THE SELECTED CRT

Cluster trialists were asked whether or not they had sought ethics approval for their selected CRT. Table 5.1 shows that 166 (91%, 95% CI 86% to 95%) of the respondents sought research ethics approval to conduct their CRT, whereas 16 (9%, 95% CI 5% to 14%) indicated that ethics approval was not sought.

Table 5.1: Research ethics approval of the selected CRT

	Value	95% confidence interval of %
Research ethics approval sought? (n=182)		
Yes	91.2% (166)	86.1% to 94.9%
No	8.8% (16)	5.1% to 13.8%
Number of ethics committees approached for approval (n=163) [1]		
Median (IQR)	1 (1 – 2)	NA
Range (min, max)	90 (1, 91)	
Time delay (years) from ethics approval until CRT publication [a] **(n=166)**		
Median (IQR)	5 (3 – 7)	NA
Range (min, max)	16 (0, 16)	

a- Time delay calculated by subtracting the response to Question 1b from the CRT publication year
1- 3 observations missing

Of the respondents who sought ethics approval, the median number of ethics committees approached was 1, with an inter-quartile range of 1 to 2. At the maximum end of the range, as many as 91 ethics committees were approached for ethics approval of a CRT.

The median number of years from ethics approval to CRT publication was 5 years, with an inter-quartile range of 3 to 7 years. Moreover, the delay in time from ethics approval to CRT publication varied from 0 to16 years.

5.1.1 Factors related to seeking ethics approval

Respondent explanations for not seeking ethics approval

Of the 16 survey respondents who did not seek ethics approval, all offered explanations as to why this was the case for their selected CRT. Table 5.2 lists frequencies of the cited reasons.

Table 5.2: Reasons research ethics approval was not sought for a CRT

Reason	Number of respondents citing reason Frequency, (%) (n=16 [a])
Not required for the type of study conducted	11 (69%)
Lack of ethics guidance or framework for review	3 (19%)
Ethics considered by a research committee	2 (13%)

a- Respondents' CRTs in which ethics approval was not sought to conduct the study

Eleven of these trialists (69%) explained that research ethics review was not required for the type of study they had conducted. They stated, for example, that national ethics guidelines required review for certain types of research only, and their study did not fall into one of the categories of research that was recommended to undergo ethics review. Study characteristics they indentified included the following: that the intervention was educational, data collection was from administrative sources only or used non-identifiable data, the study was a process quality improvement or service evaluation initiative, or that the study was non-biomedical: "In our country we only need to have biomedical research with patient identification approved." Many of the respondents citing such reasons were based in The Netherlands, Denmark, or elsewhere in Western Europe

Another reason cited by three (19%) of the respondents for not seeking ethics approval was that a framework was not in place, which would provide mandatory guidance on obtaining ethics approval from a research ethics committee. For some respondents, an ethics committee or structure for ethics review to which research protocols could be submitted was not yet established.

Two (13%) of the respondents indicated that formal ethics review was not sought because ethical criteria were taken into consideration when a CRT protocol was reviewed by a research committee in a particular setting where the research would be conducted, such as a medical practice. In such cases the research committee verified that the proposal met human research subject protections requirements.

> "The study protocol was submitted to the School Districts Research and Evaluation Department for review. This office verifies that the research or evaluation meets student confidentially requirements as set out in [*provincial/state*] statute."

Bi-variable analysis of factors associated with seeking research ethics approval

Results of a bi-variable analysis investigating the association between seeking ethics approval with relevant CRT and author characteristics is shown in Table 5.3. Publication year and the unit of randomization were not associated with the propensity to seek ethics approval. Ethics approval for the CRT was, however, statistically significantly associated with the country of the study author, whether or not the analysis accounted for the ICC, the target of planned experimental interventions, and the types of data collection interventions employed in the study.

Lower proportions of ethics approval were observed in the CRTs of authors based high income countries other than Canada or the USA (p=0.0272). Ethics approval was also

less likely to be sought in CRTs that did not properly account for the intra-cluster correlation in the study analyses (p=0.0306), or when experimental interventions targeted cluster level participants only (such as health professionals) (p=0.0245). The strongest association was observed with the types of data collection interventions used in the study (p=0.0069). Lower proportions of ethics approval were observed in CRTs using data from administrative sources only (75%), compared to CRTs in which data collection procedures intervened on participants at the individual or cluster level (proportions of 85% and higher).

Table 5.3: Characteristics associated with obtaining research ethics approval in CRTs

	Ethics approval sought %, (Frequency)				
Characteristic	**Yes (n=166)**		**No (n=16)**		**p-value** [a]
Publication year					
2000-2002	94.4%	(33)	5.6%	(2)	0.2264
2003-2005	94.3%	(65)	5.7%	(10)	
2006-2008	86.7%	(68)	13.3%	(4)	
Country of study author					
Middle/low income countries	94.1%	(16)	5.9%	(1)	0.0272 *
Canada or USA	96.5%	(82)	3.5%	(3)	
Other high income countries	85.0%	(68)	15.0%	(12)	
Unit of randomization					
Health care organization	89.6%	(95)	10.3%	(11)	0.3722 [b]
Other	93.4%	(71)	6.6%	(5)	
Analysis accounting for ICC					
Yes	94.1%	(128)	5.9%	(8)	0.0306 *
No	82.6%	(38)	17.4%	(8)	
Target of planned interventions					
Individual level only	96.8%	(60)	3.2%	(2)	0.0245 *
Cluster level only	83.6%	(56)	16.4%	(11)	
Cluster and individual level	94.3%	(50)	5.7%	(3)	
Types of data collection interventions					
Routine data only	75.0%	(18)	25.0%	(6)	0.0069 *
Individual level only	95.7%	(110)	4.4%	(5)	
Cluster level only	85.0%	(17)	15.0%	(3)	
Cluster and individual level	91.3%	(21)	8.7%	(2)	

a- Fisher's exact test
b- Chi-square goodness of fit test

5.1.2 Reporting ethics approval in CRT publications

Table 5.4 shows that 131 of the 182 respondents' published CRTs reported whether or not ethics approval was sought. Where ethics approval was reported as sought, survey respondents' responses were concordant (100% confirmed the fact). Similarly, the survey responses were in concordance with the three published reports which stated that the CRT was exempt from research ethics approval.

Table 5.4: Consistency in reporting ethics approval in trial publication compared to survey response

	Publication review ethics approval reported	
Survey response result	**Approval Sought (n=128)**	**Approval not Sought (exempt) (n=3)**
Approval sought	100.0% (128)	0% (0)
Approval not sought	0% (0)	100.0% (3)

Of the 51 respondents whose CRTs publications that did not state whether or not research ethics approval was sought (Table 5.5), 38 (75%) reported that the study did in fact undergo ethics review, while 13 (25%) reported that the study did not undergo ethics review. The under-reporting of ethics approval (i.e., the proportion of CRTs in which ethics approval was sought, whilst not reported) did not differ statistically significantly among primary and hospital care, and public health and health promotion CRTs (p=0.2071).

Table 5.5: Adequacy of reporting ethics approval, by type of CRT in health research

	Publication review ethics approval not reported			
Survey response result	**Primary and hospital care (n=23)**	**Public health and health promotion (n=28)**	**Overall (n=51)**	**p-value**
Approval sought	65.2% (15)	82.1% (23)	74.5% (38)	0.2071[a]
Approval not sought	34.8% (8)	17.9% (5)	25.4% (13)	

a- Fisher's exact test

5.2 GATEKEEPER PERMISSION IN THE SELECTED CRT

Cluster trialists were asked whether or not they had sought permission from one or more persons at the head of or in-charge of clusters and any other approval to conduct their CRT. Table 5.6 shows that 172 of the respondents (95%, 95% CI 91% to 98%) sought gatekeeper permission for their study whereas 9 (5%, 95% CI 2% to 9%) indicated that agreement or consent was not sought.

Table 5.6: Gatekeeper permission for the selected CRT

	%, (Frequency)		95% confidence interval of %
Gatekeeper permission sought? (n=181) [1]			
Yes	95.0%	(172)	90.6% to 97.7%
No	5.0%	(9)	2.3% to 9.3%
Gatekeeper permission by cluster setting			
Primary care (n=60)	93.3%	(56)	NA
Hospital (n=18) [1]	94.4%	(17)	
Individual health professional (n= 22)	86.4%	(19)	
Nursing home (n=6)	100.0%	(6)	
Residential area (n=20)	100.0%	(20)	
School or classroom (n=41)	97.6%	(40)	
Worksite (n=9)	100.0%	(9)	
Sports team, social group (n=6)	83.3%	(5)	

1- 1 observation missing

As outlined in Table 5.6, gatekeeper permission was sought in high proportions across all types of cluster settings, with little or no exceptions in school or classroom (98%), nursing home (100%), residential area (100%), or worksite settings (100%). Where individual health professionals were randomized, gatekeeper permission occurred at a slightly lower proportion (86%) compared to primary and hospital care (93% and 94%, respectively), and nursing home (100%) settings.

5.2.1 Types of Gatekeepers in CRTs

Survey respondents who indicated that gatekeeper permission was sought to conduct their study were requested to specify who agreed or consented at the head of the cluster or

provided approval of any other sort to conduct the study. Table 5.7 lists the most commonly cited sources of gatekeeper permission, arranged by cluster setting.

Table 5.7: Sources of gatekeeper permission in CRTs, by cluster setting

Setting	Sources of permission
Primary care	**Practice or health center**: one or more practice partners, senior practice partner, head or chief practitioner, management (clinical, administrative) **Agency or organization**: healthcare delivery organization **Government**: local health department, provincial health department, federal ministry of health
Hospital	**Hospital/health center**: head of ward, head of division, management (clinical, administrative), research committee **Agency or organization**: healthcare delivery organization **Government**: local health department, provincial/state health department, federal ministry of health
Individual health professional	**Clinic or health center**: participating physician, head or chief physician, head of division, management (clinical, administrative), research committee **Agency or organization**: Professional association, health delivery agency **Government**: local health department, provincial/state health department, federal ministry of health
Nursing home	**Nursing home**: Ward head, management (clinical, administrative) **Agency or organization**: home corporate office
Residential area	**Residential**: Residential and housing management/authorities **Community**: community leaders (medical, other), community advisory board **Agency or organization**: Community hospital /health centre, national health program **Government**: local district authorities (municipal, health), provincial/state health department, federal ministry of health
School or classroom	**School**: head or principal, administration, head teacher, one or more teachers **Community**: community participatory group, community advisory board **District**: district school board (superintendent, research office) **Agency or organization**: council (cultural, religious), head organization **Government**: local department (health, education), provincial/state department (health, education), federal ministry (health, education)
Worksite	**Company**: administration, management (department, unit) **Agency or organization**: worker's (professional) association, union **Government**: local administration
Sports team, social group	**Club/team**: leader, coach **Agency or organization**: club association

Primary care

In the primary care setting, sources of gatekeeper permission at the practice level included a single GP agreeing on behalf of a practice, or all GPs involved agreeing prior to randomization. Respondents also cited permission from a senior practice partner, or head physician with clinical responsibility for patient care:

> "…We obtained consent first from the senior doctor or principal of the practice if there was one, and then approached each doctor within that practice to obtain consent. For some multi-doctor practices, not all doctors participated in the study."

Permission was also commonly sought from administrators or managers of a practice or health centre:

> "The medical director in each of the [*number*] offices agreed to have the clinic participate in the study. However, this agreement was NOT sufficient for patient consent as each patient provided their own written consent."

Some respondents cited approval from an agency or organization, such as a health delivery organization (e.g., clinical governance leads): "we executed contracts with each of the delivery organizations whose clinics participated in the study," a governing body of general practitioners, a university R&D panel, an advisory board consisting of research experts, and a funding agency: "The study was funded by [*organization*] so it was reviewed and approved by the study section and appropriate [*organization*] council."

Various levels of government were also involved as gatekeepers in primary care CRTs, including managers of health departments responsible for running the clinics, and regional directors of health services. Permission was also sought from federally-commissioned agencies, as well as provincial and federal ministries of health: "Met with Ministry representatives regularly to explain study and obtain

approval."

Hospital

In the hospital setting, sources of gatekeeper permission included ward managers, chiefs of a specialty, department heads, and a hospital research projects committee. Permission was also sought from the administrative or clinical management, such as the head of a hospital, hospital directors, senior administrators, and medical directors.

A few respondents cited approval from a health delivery organization, a government-funded health program, and agencies which, 'financially supported (and thus approved)' the CRT. As with gatekeeper permission in primary care CRTs, respondents cited approval from regional health authorities (municipal or provincial) and a federal ministry.

Individual health professionals

CRTs randomizing health professionals took place primarily in primary care and hospital settings. The types of gatekeepers cited by respondents were therefore similar to the gatekeepers cited in the latter settings. Permission was also provided by the participating physicians who were randomized and whose patients formed the cluster, as well as a head or chief physician: "We sought consent from each participating clinician and endorsement from each site leader." Another researcher explained that the clinic chief physician acted as the head of the cluster, "but each physician elected on their own whether to participate."

Nursing home

In the nursing home setting, gatekeepers at the management level included the home administrator or manager, and director of nursing. Permission from the home organization via a representative of the corporate office was also required in some cases. Additionally, approval was cited from the head of a nursing ward, and medical affiliates of the nursing

home, such as a central hospital, or a county primary care trust.

Residential area

CRTs set in residential areas were conducted with widely varying objectives, which is reflective of the different types of gatekeepers cited by the survey respondents. Permission at the residential level was sought from estate managers, apartment complex managers, and housing development authorities. At the community level, permission was sought from such persons as members of a community advisory board established by the study investigators, community medical leaders, and community leaders via discussions and input to study investigators. Some CRTs involved community hospitals and health centres and so permission was also sought from these institutions. Respondents conducting CRTs under an existing health program (national or otherwise) cited permission from a head of the program site, or the office of the program itself.

Many of the respondents sought permission from various levels of government. This included permission from municipal authorities, and the health and administrative district authorities:

> "leaders of each [*type of sector*] provided agreement/permission for our project to work in the sectors within their jurisdiction. Prior to this, we also received the permission/agreement of the local (i.e. district level) health authorities to conduct the study"

Permission from provincial and federal ministries was sought from persons such as a provincial medical director, or as a respondent described, by having representatives from the ministry of health on the study advisory board.

School or classroom

At the school level, gatekeeper permission was most commonly cited by respondents

as being given by the school principal (or head). Permission was also given by such persons as school directors, a local director of studies, chief administrator, or obtained through meetings with the school governing body (consisting of staff). Respondents also cited permission from head teachers, or permission from teachers on staff: '[we] required 85% approval from teachers in the elementary schools to include them in random assignment.' Another source of cluster representation cited was the use of a community participatory group at each school, which would inform the school community about the study's aims and methods.

Approval at the school district level included the superintendent, school district research office (i.e., staff/coordinators), or a research approval board as a respondent explained, "We applied for permission from the school district - they have a research approval board (not exactly an ethics committee, but they review and approve all the materials)." In a number of school or classroom based CRTs, respondents indicated that permission was sought at more than one level. A respondent explained how permission may have to be gained sequentially from higher to lower levels: "Superintendent agreed and school board agreed to allow us to approach schools...Principals agreed to allow us to approach teachers." Another approach described was to first ask the school to specify from whom approval would be required: "in the initial letter we asked what authorities were needed in their school to obtain authorized approval. We relied on that information."

Respondents cited approval from various agencies and organizations such as a faith-based education office, and tribal councils that participants were associated with. In CRTs conducted in a pre-school or child care centre settings, permission was most often obtained from the administrator or owner of the centre.

CRTs conducted in school or classroom settings involved approval from local, provincial/state, and federal government levels, in both the health and education departments. A respondent explained that approaching the ministry was, 'essential to ensure school participation': "Ministry of education in [*location*] was approached and agreed that the schools in their area would participate." Approval at the national level was often sought in conjunction with approval from the provincial level:

> "Ministry of Health at central, provincial and district/city level as well as the Department of Education at provincial and district/city level had to agree with the study before we could approach the schools."

Worksite

In worksite settings gatekeeper permission was most often sought at the company level, such as from the company director or executives, and usually in conjunction with permission from the head of departments or units. For some respondents the study could not have been carried out without the support of the programs and agencies involved, such as a worker's association or employee union.

Sports team, social group

In sports team or social group based CRTs, respondents cited permission by club leaders, the team head or coach, and the club association (e.g., chairman, president).

5.2.2 Reporting gatekeeper permission in CRT Publications

Table 5.8 shows that 40 of the 182 respondents' published CRTs identified one or more gatekeepers from whom permission was sought to conduct the study. Where a gatekeeper was identified, survey respondents' responses were concordant (95% confirmed the fact). In the case of two CRTs, the publication identified persons in a gatekeeper role, but

the authors when responding to the survey did not identify anyone fulfilling this role in their study. Of the 141 CRTs publications that did not identify a gatekeeper, the survey responses indicated that 95% did in fact seek gatekeeper permission to conduct their CRT.

Table 5.8: Gatekeeper identification in trial publication compared to survey response

Survey response result	Gatekeeper identified (n=40)	Gatekeeper not identified (n=141)
Gatekeeper identified	95.0% (38)	95.0% (134)
Gatekeeper not identified[1]	5.0% (2)	5.0% (7)

1- 1observation missing

5.3 INVESTIGATOR EXPERIENCES AND PERSPECTIVES ON ETHICS IN CRTS

5.3.1 Trialist experiences with the ethics review process of CRTs

The latter part of the cluster trialist survey questionnaire queried investigators about their experiences with the research ethics review process of any CRTs they had conducted.

Meeting with ethics committee(s) to explain a CRT

Table 5.9 shows that 53 (31%, 95% CI 24% to 39%) of the survey respondents who sought ethics approval for any CRT indicated that they have personally met formally with ethics committee members to explain a CRT. Close to two-fifths of these respondents, primarily from the USA and the UK explained that they are routinely required, or it is recommended for them to attend formal ethics committee meetings for the purpose of presenting their study, or answering questions and providing clarifications during the initial review or when the ethics committee is about to deliver its decision. Respondents also met ethics committee members to answer their queries related to the study design, trial protocol, and address methodological or ethical issues that had been raised. Ethical issues mentioned by respondents included cluster recruitment and consent, participant consent, and protections of vulnerable subjects.

Table 5.9: Trialist experiences with research ethics committees in the ethics review of a CRT

	%, (Frequency)	95% confidence interval of %
Personally having to meet formally with ethics committee members to explain a CRT (n=171[a]) [1]		
Yes	31.0% (53)	24.2% to 38.5%
No	69.0% (118)	61.5% to 75.8%
Experiencing variability in the ethics review of a CRT undergoing review by more than one REB (n=102[b]) [2]		
Yes	46.1% (47)	36.2% to 56.2%
No	53.9% (55)	43.8% to 63.8%
Impact of the ethics review process on various aspects of respondents' CRTs (n=171[a]) [1]		
Any negative impact of ethics review on a CRT	38.0.% (65)	30.7% to 45.7%
Timely initiation of the trial		
Negative	28.1% (48)	21.5% to 35.4%
Positive	1.8% (3)	0.4% to 5.0%
Financial cost of conducting the trial		
Negative	9.9% (17)	5.9% to 15.4%
Positive	1.2% (2)	0.1% to 4.2%
Feasibility of participant recruitment		
Negative	16.4% (28)	11.2% to 22.8%
Positive	4.1% (7)	1.7% to 8.3%
Methodological quality of the trial		
Negative	9.4% (16)	5.4% to 14.8%
Positive	5.3% (9)	2.4% to 9.8%
Other aspects of the CRT		
Negative	5.3% (9)	2.4% to 9.8%
Positive	1.8% (3)	0.4% to 5.0%

a- Trialists who indicated that ethics approval was not sought for any of their CRTs (i.e., respondent selecting 'N/A' to question 23) were excluded from the denominator

b- Trialists who indicated that ethics approval was not sought for any of their CRTs or whose ethics review of a CRT did not involve multiple ethics committees (i.e., respondent selecting 'N/A' or no response to question 23 and 'N/A' to question 25) were excluded from the denominator

1- 2 observations missing

2- 3 observations missing

Experiencing variability in the ethics review process

Of the respondents who sought ethics approval for a CRT undergoing review by more than one ethics committee, 47 (46%, 95% CI 36% to 56%) indicated that they experienced variability in the ethics review. Respondents perceived ethics committees as having different underlying views or agendas with regard to the ethics review process: "Different boards have different ideas regarding what constitutes research, how much information they require, and

their role in assessing the scientific validity of the study design." Some perceived ethics committee variability as stemming from cultural differences (e.g., economically developed versus developing settings), or from the types of institutions reviewing a study (e.g., medical versus non-medical). Others stated that they did not think the variability was due to the CRT design but rather from lack of clarity in the ethics committees' roles:

> "I've experienced very considerable variation across [*ethics committees*] in reviewing trial protocols. However, I don't have any sense that this variation is related to whether a trial has a CRT design, vs. patient-level randomization or some other design. Fundamentally, I think there is a need for much better clarity about [*ethics committees'*] scope of responsibility and authority - but that's a general matter, not specific to CRTs in my experience."

Trialists experienced variability in the type of review required, procedural review processes, and study requirements: "in one study…the initial review of the protocol by [*ethics committees*] ranged from "this study is exempt from [*ethics committee*] oversight" thru "you can do this study as an expedited protocol w/o written informed consent" to "requires written informed consent from clinicians."" Many respondents cited that the differences they experienced were sorted out over time. Some also explained that differences were minor and that "…it's about clarification rather than disagreement about fundamental procedures." Some differences such as in consent formats, however, were regarded as difficult to "homogenize."

Research ethics review impact on the study

Cluster trialists were also asked whether the ethics review process had an impact on various aspects of their CRTs, and if so, to explain whether the impact was positive or negative in nature. Table 5.9 shows that overall, 65 respondents (38%, 95% CI 31% to 46%) experienced negative impacts of the ethics review process on one or more aspects of their CRTs. Respondents experienced greatest negative impacts on the timely initiation of their

CRTs, at 28%, (95% CI 22% to 35%), followed by the feasibility of participant recruitment, at 16% (95% CI 11% to 23%). Negative impacts were also experienced by respondents, but to a lesser extent, on the financial cost of conducting their CRTs, at 10% (95% CI 6% to 15%), the methodological quality of their trials, at 9% (95% CI 5% to 15%) and other aspects of the trial, at 5% (95% CI 2% to 9%). Perceived positive impacts of the ethics review process were not experienced in as large numbers of respondents, but were the greatest for the methodological quality or scientific validity of the trial, for 5% of the respondents (95% CI 2% to 10%).

Ethics review impact: Timely initiation of a trial

With regard to timely initiation of their CRTs, perceived negative effects of the ethics approval process included a delay in ethics approval and subsequent delayed implementation of a trial. A few trialists cited delays over one year in trial initiation. Causes for delay in ethics approval were cited as due to having to approach multiple ethics committees, experiencing inter-ethics committee variability, undergoing multiple rounds of back-and forth review with ethics committees, infrequent ethics committee meetings and early submission deadlines, and lack of protocol agreement related to participant recruitment and consent procedures:

> "Difficult to obtain [*ethics committee*] approval from all sites, with significant inter-[*ethics committee*] variation. Responses in one study ranged from "this is not research" to major concerns."

Respondents also cited there being a lack of understanding of the CRT design by ethics committees: "The [*ethics committee*] involved in one of the trials did not seem to be familiar with cluster randomized trials and raised some issues (which were either irrelevant or not applicable), which delayed the initiation of the trial."

Respondents who reported a positive impact of the ethics review process on the timely initiation of their CRTs commented that the ethics committee was helpful in ensuring ethics review was timely and the initiation of their study was not delayed as a result.

Ethics review impact: Financial cost of conducting a trial

With regard to the financial cost of conducting the trial, perceived negative effects of the ethics approval process were in the form of higher costs incurred for the CRT. Respondents cited reasons for higher costs which included having to extend the trial period because of delays in ethics approval:

> "because implementation delayed, the total length of treatment was affected, requiring stretching out of intervention into time originally planned for data analysis and dissemination, leading to greater costs in long-term to successfully complete the study"

Costs were also incurred from ethics committee requirements that were not originally budgeted for, such as additional benefits to trial participants, and changes to recruitment or consent procedures: "[*ethics committees*] required us to deliver a sham survey to non-participants, which complicated field procedures considerably and resulted in some field errors that needed remediation."

Respondents who reported a positive impact of the ethics review process on the financial cost of conducting their CRTs were few in number and did not provide any further details about the impact.

Ethics review impact: Feasibility of participant recruitment

With regard to feasibility of participant recruitment, perceived negative effects of the ethics approval process included lower cluster and participant recruitment rates, biased recruitment, and unfeasible participant recruitment procedures. Perceived negative effects were mainly due to ethics committee requirements although delay in ethics approval was also

cited as a barrier to cluster recruitment when study procedures were closely tied to the calendar year. Respondents cited concerns about the use of formal participant consent procedures in community-based studies of social programs or CRTs involving healthcare providers. Formal consent form language or the use of explicit disclaimers in information sheets was also regarded as a barrier to recruitment:

> "Some [*ethics committee*] forms are now so complicated and detailed it scares people away from participating in answering surveys. Not all community trials, even RCTs are set up like double-blind placebo trials conducted by medical schools, but that is the [*ethics committee*] protocol and language many [*ethics committee*] use as the basis for doing this type of research"

Ethics committee preference for opt-in recruitment and active consent procedures, over opt-out procedures was also viewed by trialists as a cause for lower recruitment rates. Ethics committee concerns about confidentiality were also cited as problematic and leading to biased recruitment.

Respondents who reported a positive impact of the ethics review process on the feasibility of participant recruitment viewed ethics committee suggestions as helpful and constructive. From the point of view of participants, the backing of the study by the ethics committee was seen as positive reinforcement for the trial investigators: "participants knew we took the study seriously."

Ethics review impact: Scientific validity or methodological quality of the trial

With regard to the scientific validity or methodological quality of the trial, perceived negative effects cited by the respondents included decreased response rates or biased recruitment procedures stemming from mandated consent and recruitment procedures: "in the study that required consent of clinicians we can be less certain of the generalizability of the findings to other clinicians at the same sites who did not participate." Trialists also cited

decreased methodological quality for having to provide information about the intervention to control arm participants, thus 'diluting' the intended intervention effects. The requirement of a delayed control condition or a delayed control condition for a specified period of time only, was seen as having a negative impact for the decreased length of time investigators had to make comparisons for the study outcomes:

> "Since the control arm consisted of a waiting-list period, we were asked by the [*ethics committee*] not to place them longer than [*number*] months on this waiting-list for ethical reasons. This period was rather short to expect significant differences between the experimental and control groups regarding the health measures. One of the methodological weaknesses of our study."

Respondents who reported a positive impact of the ethics review process on the scientific validity or methodological quality of a trial valued ethics committee opinions to improve trial methodology and pick up any flaws in the trial:

> "…At the end of the day, however, whilst our ethics committee can be very demanding, they do keep us 'safe' and generally their requested revisions improve the quality of our studies."

Ethics review impact: Other impacts on the trial

Perceived negative effects of the ethics review process on other aspects of respondents' CRTs included added time and effort that investigators had to commit to obtain ethics approval for their studies:

> "The ethics review preparation and responses to their inquiries take most of my time. Administration of the CRTs leave little time or energy for the actual conduct of the study."

Higher workload to fulfill ethics committee requirements was also cited as discouraging by a respondent:

> "my experience with the consent process for this study was so negative, and the impact on my staff so negative, that I decided never to conduct another study that involves consent forms. I had to spend a huge proportion of my own time and my staff's time on work that did not contribute meaningfully to any

> human subjects' protection but was just paperwork to satisfy thoughtlessly applied [*ethics committee*] requirements. It detracted from the ability to conduct research and was a huge waste of time."

Perceived positive impacts of the ethics review process on other aspects of respondents' CRTs included pushing the research group to articulate various aspects of their studies. The ethics review and approval process was also perceived by respondents as important for the acceptance of their trial and intervention by local health authorities, funders, and participants alike.

5.3.2 Challenges arising from the CRT design in the ethics review process of CRTs

In citing their experiences with the ethics review process of CRTs (please refer to section 5.3.1), some respondents cited challenges related to the CRT design, which are listed with supporting quotes in Table 5.10. One of the issues cited was the necessity of informed consent from cluster members and whether or not they were to be regarded as research subjects:

> "In one instance we spoke by phone with the [*ethics committee*] leader and made the case that patients need not be consented as the intervention was at the level of the physician or care team. Patient care was not substantively altered. If we had been required to consent the patients the study would not have been feasible."

Another difficulty encountered was the use of gatekeeper agreement or consent for cluster protections: "…It was difficult for the [*research ethics committee*] to understand the RCT and how the communities consented to be involved--we provided clarity for them." Additional issues cited were ethics committees' understanding of quality improvement initiatives, and potential harms and benefits the CRT posed to participants. Respondents interpreted their interventions as posing little to no risks participants:

> "one major delay was caused by one [*ethics committee*] making a specific finding that clinicians are "vulnerable subjects". In addition to an [*number*]-

page consent form for clinicians to agree to receiving recommendations about what the guidelines are, this [*ethics committees*] required that we obtain a certificate of confidentiality from [*funding agency*] (presumably to protect the information that a clinician might not be completely following the guidelines). Another [*ethics committees*] did not accept the wording of the [*funding agency*] certificate because of a disagreement among lawyers about interpretation of the law. the process delayed the start of the intervention for more than a year."

Table 5.10: Ethical challenges experienced by trialists in dealings with ethics committees

Ethical challenge	Supporting quote
Participant consent	"Subsequent [*number*]-site cluster randomized trial was shut down by [*health organization office of research oversight*] (equivalent to [*funding agency office of research oversight*]) for 1 year. Patients were randomized by site to different [*intervention*]…We had made the argument that individual informed consent was not necessary, since randomization was at the site level. Both active [*ethics committees*] agreed and approved the study. [*Office of research oversight*] disagreed, saying that any randomization means the patient is engaged in research. As a result, we modified our approach to consent for that and all subsequent studies."
Cluster recruitment and consent	"[*Research ethics committee*] had a difficult time with Community Advisory Boards as being representatives of the community and providing "consent" to conduct a CRT."
Balance of harms and benefits to participants	"… the application of patient-safety procedures that make sense for patients to clinicians who were not receiving any medical intervention made no sense." "Whether the benefits outweigh the risks, if any."
Quality improvement/ Implementation research	"I met with our [*ethics committee*]…But I think the issue was more about "usual care' than the cluster design. First the [*ethics committee*] wondered why we needed the trial (improving [*medical condition*]) "Just tell the doctor and everything will be OK" "

5.3.3 Trialist perspectives on challenges in the conduct and ethics review process of CRTs

The final part of the survey questionnaire probed trialists about their views on ethics guidelines for CRTs and the ethics review process of CRTs. Trialists rated the extent of their agreement (or disagreement) with each of the statements presented. A number of trialists also elaborated upon their expressed views in the space provided for additional comments.

Table 5.11: Trialist views on ethics guidelines and the ethics review process of CRTs

	%, (Frequency)	95% confidence interval of %
There is a need to develop ethics guidelines for CRTs (N=181)[1]		
Disagree or strongly disagree	16.0% (29)	10.7% to 21.4%
Agree or strongly agree	73.5% (133)	67.1% to 79.9%
No opinion	10.5% (19)	6.0% to 15.0%
Ethics committees could be better informed about distinct ethical issues surrounding CRTs. (N=180) [2]		
Disagree or strongly disagree	12.2% (22)	7.4% to 17.0%
Agree or strongly agree	70.0% (126)	63.3% to 76.7%
No opinion	17.8% (32)	12.2% to 23.4%
Ethics committee application forms standardized for various study designs, are hard to use in the context of the CRT study design. (N=181) [1]		
Disagree or strongly disagree	29.8% (54)	23.2% to 36.5%
Agree or strongly agree	46.4% (84)	39.1% to 53.7%
No opinion	23.8% (43)	17.6% to 30.0%

1- 1 observation missing
2- 2 observations missing

Ethics guidelines for CRTs

Table 5.11 shows that 133 respondents (74%, 95% confidence interval 67% to 80%) agreed or strongly agreed that there is a need for ethics guidelines for CRTs. Respondents commented that they would like the ethics guidelines to address quality improvement (QI) interventions, which often use the CRT design because QI poses somewhat different issues, including health professional obligations to participate: “To me, one fundamental issue is whether the intervention should be considered 'quality improvement' (that is, something the employees are expected to participated in, regardless of consent) or a voluntary activity.” Additionally, clarity on consent procedures at various levels is sought:

> “Informed consent procedures of clusters, care providers, and patients need careful attention, and procedures designed for 'regular' RCTs rarely work. For patients, informed consent is more similar to (multiple) parallel cohort studies, while clusters / care providers need to provide consent to be randomised often along with their entire patient population. This needs careful thought...”

Although they agreed with the statement, some respondents think that ethical challenges

posed by CRTs can be incorporated under existing ethics guidelines for individually randomized trials, but they nonetheless welcome ethics guidelines for CRTs: "It is always good to have ethical guidelines, as long as they are appropriate and do not increase the compliance workload of researchers unnecessarily"

Twenty-nine respondents (16%, 95% CI 11% to 21%) disagreed or strongly disagreed that there is a need for ethics guidelines for CRTs and 19 (10.5%, 95% CI 6% to 15%) had no opinion. CRT issues are not perceived by some trialists as more ethically complex than other study designs, with the exception, however, of CRTs that do not intervene directly on individual level participants: "I think one should make a distinction between CRTs where individuals do or do not directly receive an intervention. In the first case, ethics guidance might be useful." Several respondents did not see the need for ethics guidelines because they have not experienced problems with the ethics review of their CRTs. For some it is not the clustered design that proved difficult but the context of their research. Usual rules are also regarded as reasonably applicable to the CRT design, but it is guideline *interpretation* by ethics committee members which is seen by some as the issue that needs to be addressed.

Ethics committees being better informed about distinct ethical issues surrounding CRTs

Table 5.11 shows that 126 respondents (70%, 95% CI 63% to 77%) agreed or strongly agreed that ethics committees could be better informed about distinct ethical issues surrounding CRTs. Respondents elaborated that they think it is important for ethics committees to have members with RCT experience in low resources communities, because otherwise they "…cannot often fairly or appropriately evaluate the ethical dimensions of those trials." Ethics committees are also seen as needing to understand the concept of system

level interventions:

> "In general I have found that traditional [*ethics committees*] struggle to understand research at a care delivery or system level. The concept that the intervention is on the system of care, rather than individual patients is sometimes difficult for the [*ethics committee*] to grasp..."

Twenty-two respondents (12%, 95% CI 7% to 17%) disagreed or strongly disagreed that ethics committees could be better informed about distinct ethical issues surrounding CRTs, and 32 (18%, 95% CI 12% to 23%) expressed no opinion. Among these respondents, some expressed that their ethics committees are capable of handling CRTs and associated issues.

Ethics committee forms standardized for various study designs

When presented with a statement about ethics committee application forms which are standardized for various study designs, Table 5.11 shows that 84 respondents (46%, 95% CI 39% to 54%) agreed or strongly agreed that such forms are hard to use in the context of the CRT study design. Respondents cited their institution's forms as being hard to use for their epidemiological studies because the forms are often optimized for specific types of studies, such as clinical drug trials. Another difficulty cited with the use of standardized forms is explaining the various levels of participant consent in a CRT:

> "The [*ethics committee*] forms are difficult to complete for cRCTs, in particular defining the different consent levels (participant/cluster) and defining what is meant by a "participant". We often have to use the terms "patient participants" and "health professional participants""

The standardization of ethics committee forms was seen by one respondent as a reflection of unfavourable ethics review practices: "Standardization of forms is always problematic, as ethical evaluation is not a rote process that can easily be categorized like a checklist (although many of our [*ethics committee*] procedures seem to be set up this way)"

Fifty-four respondents (30%, 95% CI 23% to 37%) disagreed or strongly disagreed

that standardized application forms are hard to use in the context of the CRT study design and 43 (24%, 95% CI 18% to 30%) had no opinion. Creating separate processes for different types of research is regarded by some as further complicating the ethics review process. Standardisation is viewed as useful and achievable to a certain extent.

CHAPTER 6

DISCUSSION OF SURVEY FINDINGS

Chapter 6 begins with a summary of the strengths and limitations of this study. We discuss the main survey findings relating to the need for ethics guidelines for CRTs, trialists' experiences with the ethics review process, the reporting of standard ethics procedures in CRT publications, CRT design characteristics associated with participant consent, and gatekeeper approval and consent practices.

6.1 STRENGTHS AND LIMITATIONS OF THE STUDY

A unique questionnaire was created specifically for this study to elicit challenges in the conduct and ethics review process of CRTs. We achieved an acceptable response rate of 64% for a 15 to 20 minute survey.[39] The survey supplemented findings of the review of CRT publications[34] by providing more complete information on current practices in research ethics review, gatekeeper approval processes, and consent procedures in CRTs. Additionally, the survey contributed insight into cluster trialists' experiences with the conduct and ethics review process of CRTs, and their perspectives on the need for ethics guidelines for CRTs.

Conducting a quality survey required optimal minimization of sampling, coverage, non-response, and measurement error.[38] A random sample of CRT publications was selected from the sampling frame using a predefined set of inclusion and exclusion criteria. The electronic search strategy had a sensitivity of approximately 90%, meaning 10% of eligible CRTs would be missing from the sampling frame. The methodological quality of these studies would likely be poorer than those identified by the search strategy in lieu of not having been recognized and therefore clearly identified as a CRT in the trial publication. However, this is unlikely to skew our results to a significant degree because such trials would represent the subgroup of studies in the sample that were of poorer methodological

quality. The use of a relevant incentive and sending encouraging reminders were motivational features that encouraged sample members to respond. These features worked to minimize the potential for non-response error arising from differences between respondents and non-respondents. Information retrieved from the CRT publications allowed us to investigate the possibility of non-response bias. We were limited, however, to the use of one author characteristic (i.e., author country) with which to compare respondents and non-respondents. We could not, therefore, rule out other factors affecting survey response, such as author age (i.e., experience), gender, and area of research. Extensive pre-testing in the form of expert reviews and cognitive interviewing was conducted to ensure that the survey questionnaire was as clear and comprehensible as possible. Personalization of the questionnaire had the benefit of reducing the misclassification of cluster gatekeepers and individual and cluster level participants in respondents' selected CRTs. Misclassification from personalization of the questionnaire may have occurred in a small amount of studies, but cluster trialists were also encouraged to provide explanations in the text boxes provided so that their responses could be understood and analyzed accurately. The survey questionnaire and collection procedures were therefore designed to produce an accurate understanding on current practices in the conduct and ethics review of CRTs, by minimizing potential sources of error.

6.2 STUDY FINDINGS

6.2.1 There is a need for ethics guidelines for CRTs

Researchers conducting CRTs seek direction regarding the ethically sound design and conduct of their trials: The majority of respondents (approximately 70%), agreed that ethics guidelines for CRTs are needed, and that ethics committees could be better informed about

distinct ethical issues arising from CRTs. Ethics committees may be unfamiliar with the CRT design and would likely benefit from specific guidelines on adequate protections for participants. Respondent agreement was less unanimous with regard to the need for separate application forms for the CRT design: Close to one third of the respondents disagreed that forms standardized for various study designs are hard to use in the context of the CRT design. This suggests that standard ethics application forms accommodating the different levels of intervention and participation in CRTs, may be more useful to cluster trialists than separate forms altogether.

6.2.2 Investigator experiences with the ethics review process of CRTs could be improved

Investigators conducting CRTs are experiencing challenges with the ethics review process, in part due to ethical issues underlying the CRT design. The challenges experienced by respondents appeared to be due to both ethics committee approaches to review, as well as challenges specific to CRTs. We cannot be certain how much the CRT design contributed to the challenges experienced, but our finding that the majority of respondents perceived a need for ethics guidelines and ethics committee education on ethical issues, confirms that CRT-specific issues are an important contributing factor to the challenges experienced. CRT-specific challenges that have been raised during the ethics review of trialists' studies include the appropriateness of community consent (i.e., gatekeeper functions), participant consent requirements, and interpreting the balance of harms and benefits to study participants. The ethical challenges investigators are experiencing during ethics review are the very ethical issues that have been identified in the research literature considering the complexities of the CRT design.[24]

The survey included investigators conducting CRTs in different areas of health research and with varying levels of experience, and found that many of them have experienced challenges with the ethics review process. In particular, the ethics review process impacted negatively more so than positively on the timely initiation of a trial, and feasibility of participant recruitment. In addition, variability in the ethics review process was experienced by close to half of the respondents whose CRTs underwent review by more than one ethics committee. Although several other studies have investigated variability among research ethics committees,[32,53-56] to the best of our knowledge, this is the first to focus on the CRT design, and the first to survey a representative sample of trialists to understand their collective experience as a group of researchers, as opposed to focusing on the research ethics review of a particular trial.

Variability experienced in the ethics review process may stem from differing standards held by ethics committees regarding the type of research that requires ethics approval. Some respondents indicated that their CRTs of educational and non-biomedical interventions were considered exempt from ethics review and approval. We also found that ethics approval was less likely to be obtained in CRTs with data collected primarily from administrative sources, and in CRTs that only directly targeted cluster level participants with experimental interventions. Regional differences in requirements may also play a role in varying standards. Lower proportions of ethics approval were observed in CRTs with primary authors based in high income countries other than Canada or the USA. Therefore, approaching more than one ethics committee for approval—which was common among survey respondents—where committees may demonstrate variable ethical standards, can have negative implications for cluster trialists.

We found that trials appropriately accounting for clustering in the analyses were more likely to have sought research ethics approval. This is similar to findings of a study on ethical reporting in CRT publications (conducted as part of the larger research study), which also found an association between reporting ethics review and this indicator of methodological quality.[34] This association may arise because ethics committees often include methodologists (e.g., statisticians) who may alert CRT investigators to the fact that adjustments for clustering (if not already accounted for) are needed. In the research leading up to this study, experienced cluster trialists expressed similar views about the positive contribution of ethics review to the methodological quality of their trials.[33] Therefore, although cluster trialists may be experiencing challenges with the research ethics review process, research ethics approval is contributing positively to the design and conduct of methodologically sound trials.

6.2.3 Ethical practices are under-reported in CRT publications

Findings from the survey indicate that all three measures of research participant protections, namely having obtained ethics approval, gatekeeper permission, and participant consent, have been under-reported in CRT publications. The prior review of the random sample of 300 published CRTs found that ethics review, gatekeeper permission, and participant consent were not reported in 26%, 77%, and 32% of trials, respectively.[34] The survey results indicated that of the respondents whose CRTs publication did not report on the ethical practices, 75%, 95%, 59%, and 80% had sought ethics approval, gatekeeper permission, individual level consent, and cluster level consent, respectively. Therefore, inadequate reporting of ethical practices in CRT publications reflects an under-reporting of ethical practices, and is not commensurate with an absence of these practices. Inadequate and

under-reporting of ethical practices in CRTs—participant consent in particular—also reflects the difficulties researchers may face in the absence of explicit guidance for the ethical conduct of CRTs. As there can be varying levels of experimental and data collection interventions targeting different levels of participants in CRTs,[24] investigators may be unclear as to the types of protections that are required for participants in their studies.

6.2.4 Unique characteristics of the CRT design are associated with consent from individual level participants

With regard to CRT characteristics associated with individual level consent, we found that obtaining consent for experimental interventions and data collection is associated with smaller cluster sizes of individual level participants. CRTs often randomize large clusters such as communities and hospitals, which can make obtaining consent from all participants infeasible, for logistical and financial reasons. We also found that obtaining consent from individual level participants for experimental interventions and data collection is associated with the use of experimental and data collection interventions targeting individual level participants. This is similar to the findings of Eldridge and colleagues,[30] who found that patient consent appeared to be more difficult to obtain in interventions delivered at the cluster organization and cluster professional levels. Participants who are directly targeted by an intervention—as opposed to indirectly affected—will more often have the ability to opt-out of study procedures. When given the ability to opt-out, consent from individual level participants directly targeted by an intervention would be more meaningful, compared to consent being sought from participants for less direct interventions, where participant refusal can be rendered less meaningful if there is limited ability to opt-out.

With regard to consent from individual and cluster level participants for receiving an intervention, we found that obtaining consent was associated with a more recent publication

year (i.e., after 2005). Experimental and data collection interventions directly targeting cluster level participants were not found to be associated with cluster level consent. As we learned from the survey respondents, cluster level participants may be expected to participate in study procedures as part of professional duties. Additionally, where there is more direct involvement of individual level participants in a study, cluster level participants may not be regarded as the subjects of a study. The emergence of publications on ethical challenges in CRTs is likely to have influenced increased awareness regarding individual and cluster level consent practices. The MRC guidelines published in 2002, for example, contain ethical considerations for CRTs and explicitly identify two types of participant—individual *and* cluster level—from whom consent should be sought.

6.2.5 Further ethical analyses are required to determine whether CRT practices meet the highest ethical standards

Gatekeeper approval practices

In the prior review of CRT publications, 33% identified a cluster gatekeeper or representation mechanism, whereas 95% of the survey respondents identified some form of gatekeeper permission for their study. Cluster representation cited by the respondents included government approval at the local, provincial and federal levels, agencies or organizations representing the interests of clusters or cluster members, and various authorities in cluster settings (e.g., principals of schools, directors of companies). The variability of CRT participants and groups involved poses a challenge for researchers trying to identify persons or bodies who will perform gatekeeper functions.[57] Based on the widespread use of cluster gatekeepers, as reported by the survey respondents, it is unclear whether they have necessarily or unnecessarily fulfilled their designated roles and whether or not they have had the authority to do so. Ethics guidelines based on ethical analyses[57] would

serve to clarify gatekeeper roles and the scope of their authority, and to simplify the types and number of gatekeepers sought for individual, cluster, and institutional protections in CRTs.

Participant consent practices

Results from the survey indicated that consent from individual and cluster level participants did not always include consent for an experimental intervention, and data collection procedures. When consent was sought, a greater proportion of cluster level participants were approached for consent *before* the randomization of clusters, compared to individual level participants. Additionally, participants were not always informed about study conditions in alternate arms. We also recall that consent from individual level participants for receiving an intervention or providing data was more likely to be sought if the experimental intervention and data collection procedures directly targeted individual level cluster members. Fully informed consent sought prior to randomization, as normally obtained in individually randomized controlled trials, is therefore not the customary practice in CRTs. An ethical analysis[58] based on moral foundations is needed to justify and validate the use of non-conventional informed consent procedures observed in CRTs.

6.3 CONCLUSION

Unique features of the cluster randomized trial design complicate the interpretation of standard research ethics protections, such as ethics approval and participant consent practices, leading to investigator challenges with the ethics approval process of their cluster randomized trial. The under-reporting of standard ethics procedures in trial publications is further reflective of the uncertainties surrounding the cluster randomized trial design. From the perspective of investigators conducting cluster randomized trials, there is a perceived

need for ethics guidelines, as well as education for ethics committees about ethical issues unique to this trial design.

The findings from this study were used to inform an in-depth ethical analysis about the ethical challenges in cluster randomized trials. An international consensus conference was held in November 2011 in Ottawa, Canada, with the aim to develop international consensus guidelines for cluster randomized trials. All survey sample members were invited to attend the conference and thereafter to comment on a draft guidance document that was produced by an independent expert panel appointed by the investigator team. The results of this survey contribute a rich set of trialist experiences and perspectives in the conduct and research ethics review of cluster randomized trials. These new understandings will help target planned educational activities for researchers and research ethics committees, in order to alleviate the uncertainties and challenges indentified by the survey participants.

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APPENDIX A: COGNITIVE INTERVIEWING SCRIPT

1) Welcome:
Thank you for taking your time to help us-out with a trial run of the survey. I'm going to begin by explaining the rationale for conducting this survey and will then explain how a think-aloud session works. After that, we'll have the think-aloud session of the questionnaire. This will be followed by a review and reflection with additional questions, and then we'll end the hour with a brief discussion.

2) Introduce the study:
This survey part of a larger study entitled Ethical and Policy Issues in Cluster Randomized Trials. As you know, all studies that involve human subjects require assurance that the proposed study meets commonly-accepted ethical standards but the vast majority of ethical guidelines have been written from the perspective of the individual as the unit of randomization. This makes the task of ethical assurance in the adherence to standards such as informed consent particularly complex. So the aims of the larger study, which is funded by the Canadian Institutes of Health Research, is to promote high ethical standards in, and uniformity in the ethics review process of CRTs, by developing explicit guidelines for the ethical conduct and ethics review of CRTs. We have selected a random sample of 300 cluster randomized trials from MEDLINE and plan to survey the corresponding author on each trial, about their study. This survey is an attempt to understand ethical issues in the conduct and review of CRTs from the perspective of trialists who conduct these types of studies. The survey will be web-based, with the web-link sent to the respondent by email. As you have kindly agreed, your role today is to help us pilot test the survey questionnaire.

3) Explain interview procedure:
As you complete and fill-in the questionnaire, we'd like you to verbalize everything you are doing and thinking … from reading the questions aloud, to telling us your thoughts and giving your final answers. This includes mentioning anything you like or dislike about the questionnaire. The reason we'd like you to think-aloud is because it will help us understand how you arrive at your answer and whether the questions can be answered accurately. Just act as if you are alone in a room and talking to yourself.

[*If interview conducted over the phone*]: This type of interview would normally be done in-person so since we're on the phone, you may be reminded you to keep talking if you are silent for any length of time.

APPENDIX B: PERSONALIZATION OF QUESTIONNAIRE

BACKGROUND INFORMATION

How you came to be selected for this survey:

Your study: "IMPLEmenting a clinical practice guideline for acute low back pain evidence-based manageMENT in general practice (IMPLEMENT)" published in Implementation Science 2008, is one of 300 cluster randomized trials randomly selected for a systematic review, as well as this survey, from among thousands of trials indexed in Medline.

What is a cluster randomized trial?

A cluster randomized trial (CRT) is a special type of randomized controlled trial, in which the units of randomization are not individuals themselves, but rather intact social units or groups of individuals such as clinics, schools, or communities.

What our research study is about:

The randomization of intact units or groups presents unique ethical and methodological challenges: for example, conventional informed consent procedures are complicated by the fact that informed consent may be possible at more than one level. In addition, the vast majority of ethics guidelines have been written from the perspective of the individual as the unit of randomization. Among the objectives of our research study are identifying ethical challenges arising in CRTs and learning how they are currently being addressed, understanding how ethics reviews of CRTs are carried out in countries around the world, and developing well-grounded guidelines for the conduct and ethics review of CRTs.

What type of information will be gathered in this questionnaire?

We are hoping that you will set aside 15-20 minutes of your time to help us gather information regarding the ethics review and approval process of your CRT, details of possible consent procedures for the practice physicians and patients in your study, and your perspectives on ethical challenges in CRTs you have been involved with.

What if your study was conducted long ago and you cannot remember all the details?

If you wish to consult study documents or other authors on the study, please do so, or simply indicate that you cannot remember and continue.

Where can you provide additional details about your responses?

As CRTs and possible consent procedures can be very diverse, we encourage you to elaborate or provide additional comments in the fields provided throughout the questionnaire.

Additional information about this study:

Our research protocol has been published and may be accessed here:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725043/

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As an appreciation for your help with this study, we would like to mail you a book or donate on your behalf to the charity below, upon receipt of your response. Please select **one** of the two gift options:

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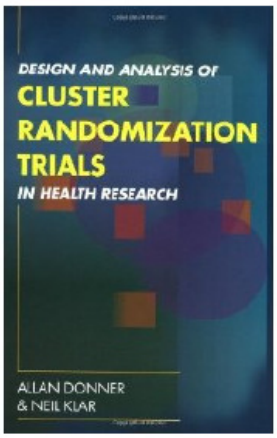

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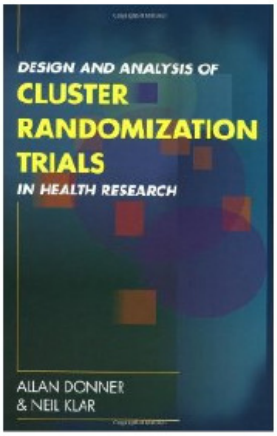

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PERMISSION TO CONDUCT THE STUDY AND ENROL CLUSTERS

In this section, we are interested in whom you may have sought permission from to conduct your study and/or to enrol particular clusters in the trial.

3

1) Did you seek research ethics approval to conduct the study?

☐ NO

└→ **If No, please specify the reason(s) ethics approval was not sought:**

4

☐ YES

└→ **If Yes, how many research ethics committees (RECs) did you approach for approval in total (excluding notification only) and in approximately which year was this process initiated?**

5

a) Number of RECs approached:

b) Year (*yyyy*):

9

2) Did one or more persons at the head of (or in charge of) each of the general practices (i.e. clusters), provide agreement or consent to their involvement in your study (e.g., permission from administrators, senior managers)?

☐ NO

☐ YES

7

└→ **If yes, please specify who agreed or consented on behalf of each cluster:**

3) Did you seek approval from anyone else to conduct the study (e.g., authority or body other than participants, such as Ministry of Health, advisory board)?

☐ NO

☐ YES

8

└→ **If yes, please specify from whom permission was sought:**

Please provide any additional comments or explanation here (optional):

CONSENT PROCEDURES FOR CLUSTER LEVEL PARTICIPANTS IN THE INTERVENTION ARM

In the following questions, we are interested in consent procedures for practice physicians in the study intervention arm.

In some CRTs, no consent is sought from any participants at the cluster level for administering an intervention to individuals within each cluster, or for data collection.

Note: If there was more than one intervention arm in your study, please choose the study arm with the most intensive intervention for these questions.

4) Was consent sought from physicians in the intervention arm for any aspect of the study?

☐ NO

└→ **If No, please specify why consent was not considered necessary:**

☐ YES

└→ ☐ Before the randomization of general practices

☐ After the randomization of general practices

Additional comments or explanation (optional):

5) Did physicians in the intervention arm consent to receiving a study intervention (i.e., a targeted change in practice)?

☐ N/A: the study did not involve physicians receiving an intervention

☐ YES, explicit written

☐ YES, explicit verbal

☐ YES, other consent procedure. Please specify in the text box under additional comments

☐ NO

└→ **If No, please specify whether physicians were:**

☐ a) Not notified about receiving an intervention

☐ b) Notified about receiving an intervention without the opportunity to opt-out

☐ c) Notified about receiving an intervention with the opportunity to opt-out

☐ d) Other, please explain:

Additional comments or explanation (optional):

6) Did physicians in the intervention arm consent to delivering or administering a study intervention to patients?

☐ N/A: the study did not involve physicians delivering or administering an intervention directly to patients

☐ YES, explicit written
☐ YES, explicit verbal
☐ YES, other consent procedure. Please specify in the text box under additional comments
☐ NO

└→**If No, please specify whether physicians were:**

☐ a) Not notified about delivering/administering an intervention
☐ b) Notified about delivering/administering an intervention without the opportunity to opt-out
☐ c) Notified about delivering/administering an intervention with the opportunity to opt-out
☐ d) Other, please explain:

Additional comments or explanation (optional):

7) Did physicians in the intervention arm consent to providing data (e.g. by questionnaire, access to records, direct observation)?

☐ N/A: No data collected on/from/by physicians

☐ YES, explicit written
☐ YES, explicit verbal
☐ YES, other consent procedure. Please specify in the text box under additional comments
☐ NO

└→**If No, please specify whether physicians were:**

☐ a) Not notified about data collection procedures
☐ b) Notified about data collection procedures without the opportunity to opt-out
☐ c) Notified about data collection procedures with the opportunity to opt-out
☐ d) Other, please explain:

Additional comments or explanation (optional):

CONSENT PROCEDURES FOR CLUSTER LEVEL PARTICIPANTS IN THE CONTROL ARM

11

*In the following questions, we are interested in consent procedures for the **practice physicians** in the study control arm.* 16

Note: If there was no control arm in your study, please choose the study arm with the least intensive or delayed intervention for these questions.

12

If consent procedures for physicians in the control arm were identical to those in the intervention arm, please click here ☐ and proceed to the next section (question 12).

12

8) Was consent sought from physicians in the control arm for any aspect of the study?

☐ NO

└→ **If No, please specify why consent was not considered necessary:**

☐ YES

└→

9

☐ Before the randomization of general practices

☐ After the randomization of general practices

9

Additional comments or explanation (optional):

12

9) Did physicians in the control arm consent to receiving a study intervention (i.e., a targeted change in practice)?

12

☐ N/A: the study did not involve physicians receiving an intervention

☐ YES, explicit written

☐ YES, explicit verbal

☐ YES, other consent procedure. Please specify in the text box under additional comments

☐ NO

12

└→ **If No, please specify whether physicians were:**

☐ a) Not notified about receiving an intervention

☐ b) Notified about receiving an intervention without the opportunity to opt-out

☐ c) Notified about receiving an intervention with the opportunity to opt-out

☐ d) Other, please explain:

Additional comments or explanation (optional):

10) Did physicians in the control arm consent to delivering or administering a study intervention to patients?

☐ N/A: the study did not involve physicians delivering or administering an intervention directly to patients

☐ YES, explicit written
☐ YES, explicit verbal
☐ YES, other consent procedure. Please specify in the text box under additional comments
☐ NO

└→**If No, please specify whether physicians were:**

☐ a) Not notified about delivering/administering an intervention
☐ b) Notified about delivering/administering an intervention without the opportunity to opt-out
☐ c) Notified about delivering/administering an intervention with the opportunity to opt-out
☐ d) Other, please explain:

Additional comments or explanation (optional):

11) Did physicians in the control arm consent to providing data (e.g. by questionnaire, access to records, direct observation)?

☐ N/A: No data collected on/from/by physicians

☐ YES, explicit written
☐ YES, explicit verbal
☐ YES, other consent procedure. Please specify in the text box under additional comments
☐ NO

└→**If No, please specify whether physicians were:**

☐ a) Not notified about data collection procedures
☐ b) Notified about data collection procedures without the opportunity to opt-out
☐ c) Notified about data collection procedures with the opportunity to opt-out
☐ d) Other, please explain:

Additional comments or explanation (optional):

CONSENT PROCEDURES FOR INDIVIDUAL LEVEL PARTICIPANTS IN THE INTERVENTION ARM

*In the following questions, we are interested in consent procedures for the **patients of participating physicians** in the study intervention arm.*
In some CRTs, no consent is sought from any participants at the individual level (for example, because individuals are not directly receiving an intervention); in other CRTs, consent may be sought from individuals for receiving an intervention or simply for data collection.

Note: If there was more than one intervention arm in your study, please choose the study arm with the most intensive intervention for these questions.

12) Was consent sought from patients in the intervention arm for any aspect of the study?

☐ NO
└→ **If No, please specify why consent was not considered necessary:**

☐ YES
└→ ☐ Before the randomization of general practices
☐ After the randomization of general practices

Additional comments or explanation (optional):

13) Did patients in the intervention arm consent to receiving (or being affected by) a study intervention?

☐ N/A: the study did not involve patients receiving an intervention

☐ YES, explicit written
☐ YES, explicit verbal
☐ YES, other consent procedure. Please specify in the text box under additional comments
☐ NO
└→ **If No, please specify whether patients were:**
☐ a) Not notified about receiving (or being affected by) an intervention
☐ b) Notified about receiving (or being affected by) an intervention without the opportunity to opt-out
☐ c) Notified about receiving (or being affected by) an intervention with the opportunity to opt-out
☐ d) Other, please explain:

Additional comments or explanation (optional):

14) Did patients in the intervention arm consent to providing data (e.g. by questionnaire, blood sample, review of records)?

- ☐ YES, explicit written
- ☐ YES, explicit verbal
- ☐ YES, other consent procedure. Please specify in the text box under additional comments
- ☐ NO

└→**If No, please specify whether patients were:**

- ☐ a) Not notified about data collection procedures
- ☐ b) Notified about data collection procedures without the opportunity to opt-out
- ☐ c) Notified about data collection procedures with the opportunity to opt-out
- ☐ d) Other, please explain:

Additional comments or explanation (optional):

CONSENT PROCEDURES FOR INDIVIDUAL LEVEL PARTICIPANTS IN THE CONTROL ARM

*In the following questions, we are interested in consent procedures for the **patients of participating physicians** in the study control arm.*

Note: If there was no control arm in your study, please choose the study arm with the least intensive or delayed intervention.

If consent procedures for patients in the control arm were identical to those in the intervention arm, please click here ☐ and proceed to the next section (question 18).

15) Was consent sought from patients in the control arm for any aspect of the study?

☐ NO

└→ **If No, please specify why consent was not considered necessary:**

☐ YES

└→

☐ Before the randomization of general practices

☐ After the randomization of general practices

Additional comments or explanation (optional):

16) Did patients in the control arm consent to receiving (or being affected by) a study intervention?

☐ N/A: the study did not involve patients receiving an intervention

☐ YES, explicit written

☐ YES, explicit verbal

☐ YES, other consent procedure. Please specify in the text box under additional comments

☐ NO

└→ **If No, please specify whether patients were:**

☐ a) Not notified about receiving (or being affected by) an intervention

☐ b) Notified about receiving (or being affected by) an intervention without the opportunity to opt-out

☐ c) Notified about receiving (or being affected by) an intervention with the opportunity to opt-out

☐ d) Other, please explain:

Additional comments or explanation (optional):

14

17) Did patients in the control arm consent to providing data (e.g. by questionnaire, blood sample, review of records)?

- ☐ YES, explicit written consent
- ☐ YES, explicit verbal consent
- ☐ YES, other consent procedure. Please specify in the text box under additional comments
- ☐ NO

14

└→ **If No, please specify whether patients were:**

- ☐ a) Not notified about data collection procedures
- ☐ b) Notified about data collection procedures without the opportunity to opt-out
- ☐ c) Notified about data collection procedures with the opportunity to opt-out
- ☐ d) Other, please explain:

Additional comments or explanation (optional):

INFORMATION PROVIDED TO PARTICIPANTS AT THE INDIVIDUAL-LEVEL

13

*In the following questions, we are interested in whether the **patients of participating physicians** were informed about the comparison arm(s). In some CRTs, participants in one or more arms are not informed about the comparison arm(s), for example, to avoid contamination, to maintain study blinding, or simply because there was no direct contact with members of the cluster.*

14

18) In the intervention arm, were patients informed about the use of the control arm?

☐ YES
☐ NO

└→ **If No, please specify why the comparison arm was not mentioned:**

14

19) In the control arm, were patients informed about the use of the intervention arm?

☐ YES
☐ NO

└→ **If No, please specify why the intervention arm was not mentioned:**

Please provide any additional comments or explanation here (optional):

INFORMATION PROVIDED TO PARTICIPANTS AT THE CLUSTER-LEVEL

11

*In the following questions, we are interested in whether the **participating physicians** were informed about the comparison arm(s).*

12

20) In the intervention arm, were physicians informed about the use of the control arm?

☐ YES
☐ NO

└→ **If No, please specify why the comparison arm was not mentioned:**

12

21) In the control arm, were physicians informed about the use of the intervention arm?

☐ YES
☐ NO

└→ **If No, please specify why the intervention arm was not mentioned:**

Please provide any additional comments or explanation here (optional):

ETHICS REVIEW OF ANY CRTS YOU MAY HAVE BEEN INVOLVED WITH

In the following questions, we would like to gather information about your general experiences in the ethics review of this trial, and/or any other CRTs you may have been involved with.

22) How many cluster randomized trials in total (including all current and past studies), have you conducted as a principal investigator or co-investigator, and/or been significantly involved with (e.g. as a grant-holder)?
[*This does not include roles such as trial management, consultation, or data analysis alone*]

Number of CRTs: ☐

6

23) In your dealings with RECs reviewing the CRTs, did you ever personally have to meet formally with any members of the REC(s) to explain your study?

5

☐ N/A: Did not seek ethics approval for any of the above cluster randomized trials.
→ *Proceed to Question 25*

☐ NO
☐ YES
└→ **If yes, please describe the purpose of your meeting(s):**

24) For any of the CRTs, did the ethics review process ever have an impact on any of the following aspects of the study?
[*Check all that apply and please explain whether the impact was positive or negative in the text box provided*]

☐ Timely initiation of the trial.	
☐ Financial cost of conducting the trial.	
☐ Feasibility of participant recruitment.	
☐ Scientific validity or methodological quality of the trial.	
☐ Other.	

25) Did you ever experience variability in the ethics review of a CRT undergoing review by more than one REC? [*This may include variability in the type of review, procedural review processes, REC requirements, and decision outcomes*]

☐ N/A: Ethics review of a CRT did not involve multiple RECs

☐ No

☐ Yes

└→**If yes, please explain what differences arose:**

26) Please rate your agreement or disagreement with each of the following statements:

	Strongly disagree	Disagree	Agree	Strongly agree	No opinion
a) There is a need to develop ethics guidelines for CRTs	☐	☐	☐	☐	☐
b) RECs could be better informed about distinct ethical issues surrounding CRTs	☐	☐	☐	☐	☐
c) REC application forms standardized for various study designs, are hard to use in the context of the CRT study design	☐	☐	☐	☐	☐

Please provide any additional comments or explanation here (optional):

DEMOGRAPHIC INFORMATION AND ADDITIONAL COMMENTS

27) What are your highest obtained degrees?

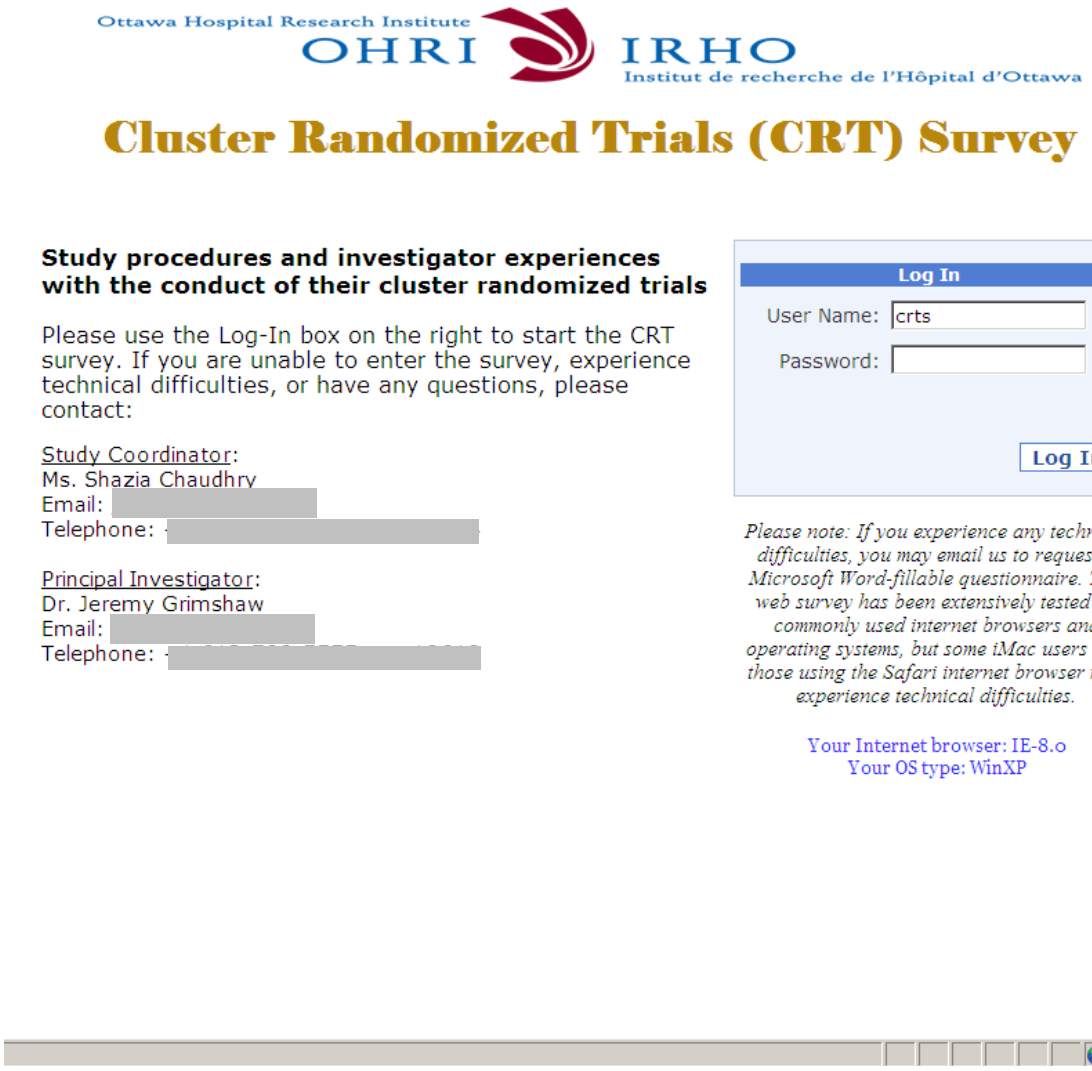
[*Check all that apply and indicate country in which degree was conferred*]

- ☐ Doctorate — Country: _____
- ☐ Masters degree — Country: _____
- ☐ Medical degree — Country: _____
- ☐ Other higher degree, please specify: _____ — Country: _____

Are there any additional details about the ethics review or conduct of CRTs that have not been addressed in this survey? If yes, please describe.

Thank you for taking the time to complete the survey. Your responses are greatly appreciated!

APPENDIX C: WEB-BASED QUESTIONNAIRE



Ottawa Hospital Research Institute
OHRI IRHO
Institut de recherche de l'Hôpital d'Ottawa

Cluster Randomized Trials (CRT) Survey

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BACKGROUND INFORMATION

How you came to be selected for this survey:

Your study:
A pragmatic cluster randomised trial of a Diabetes Recall And Management system: the DREAM trial

published in **Implementation Science 2007** is one of 300 cluster randomized trials randomly selected for a systematic review, as well as this survey, from among thousands of trials indexed in Medline. You may click here to view your study publication.

What is a cluster randomized trial?

A cluster randomized trial (CRT) is a special type of randomized controlled trial, in which the units of randomization are not individuals themselves, but rather intact social units or groups of individuals such as clinics, schools, or communities.

What our research study is about:

The randomization of intact units or groups presents unique ethical and methodological challenges: for example, conventional informed consent procedures are complicated by the fact that informed consent may be possible at more than one level. In addition, the vast majority of ethics guidelines have been written from the perspective of the individual as the unit of randomization. Among the objectives of our research study are identifying ethical challenges arising in CRTs and learning how they are currently being addressed, understanding how ethics reviews of CRTs are carried out in countries around the world, and developing well-grounded guidelines for the conduct and ethics review of CRTs.

What type of information will be gathered in this questionnaire?

We are hoping that you will set aside 15-20 minutes of your time to help us gather information regarding the ethics review and approval process of your CRT, details of possible consent procedures for the **clinicians and patients** in your study, and your perspectives on ethical challenges in CRTs you have been involved with. Depending on your study, you will be directed to answer up to 27 questions appearing on a maximum of 12 screens.

What if your study was conducted long ago and you cannot remember all the details?

If you wish to consult study documents or other authors on the study, please do so, or simply indicate that you cannot remember and continue.

Where can you provide additional details about your responses?

As CRTs and possible consent procedures can be very diverse, we encourage you to elaborate or provide additional comments in the fields provided throughout the questionnaire.

Additional information about this study:

Our research protocol has been published and may be accessed here:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725043/

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Cluster Randomized Trials (CRT) Survey

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Gift Confirmation

As an appreciation for your help with this study, we would like to mail you a book or donate on your behalf to the charity below, upon receipt of your response. Please select **one** of the two gift options:

☐ **Donation to Doctors without Borders/Médecins Sans Frontières (MSF)**

http://doctorswithoutborders.org/
An international medical humanitarian organization providing independent, impartial assistance to those most in need, in nearly 60 countries.
Amount of Donation: $40.00 CAD

☐ **Design and Analysis of Cluster Randomization Trials in Health Research. 2000**

by Allan Donner and Neil Klar
ISBN-13: 978-0340691533
Value: $90.00 CAD

Book cover

If you would like to receive the book, please enter your mailing address in the fields below. This information will be used for the sole purpose of addressing your mailed gift.

Mailing Address

Name	
Affiliation *(optional)*	
Address 1	
Address 2	
City	
State / Province	
Zip / Postal Code	
Country	
Phone Number *(optional)*	

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Cluster Randomized Trials (CRT) Survey

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GIFT CONFIRMATION

As an appreciation for your help with this study, we will be mailing the gift below upon receipt of your response:

Design and Analysis of Cluster Randomization Trials in Health Research. 2000

by Allan Donner and Neil Klar
ISBN-13: 978-0340691533

Value: $90.00 CAD

Book cover

In the fields below, please enter your mailing address. This information will be used for the sole purpose of addressing your mailed gift.

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Address 1	
Address 2	
City	
State / Province	
Zip / Postal Code	
Country	
Phone Number *(optional)*	

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PERMISSION TO CONDUCT THE STUDY AND TO ENROL CLUSTERS

*In this section, we are interested in whom you may have sought permission from **to conduct** your study and/or **to enrol** particular clusters in the trial.*

1) Our review of your paper indicates that research ethics approval was sought to conduct the study. Is this correct?

☐ **NO** ⟶ If No, please specify the reason(s) ethics approval was not sought:

☐ **YES** ⟶If Yes, how many research ethics committees (RECs) did you approach for approval in total (excluding notification only) and in approximately which year was this process initiated?

a) Number of RECs approached:

b) Year (yyyy):

2) Did one or more persons at the head of (or in charge of) each of the general practices (i.e., clusters), provide agreement or consent to their involvement in your study (e.g., permission from practice administrators, senior managers)?

☐ **NO**

☐ **YES** ⟶If Yes, please specify who agreed or consented on behalf of each cluster:

3) Did you seek approval from anyone else to conduct the study (e.g., authority or body other than participants, such as Ministry of Health, advisory board)?

☐ **NO**

☐ **YES** ⟶If Yes, please specify from whom permission was sought:

Please provide any additional comments or explanation here (optional):

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CONSENT PROCEDURES FOR CLUSTER LEVEL PARTICIPANTS IN THE INTERVENTION ARM

*In the following questions, we are interested in consent procedures for **primary care clinicians** in the study intervention arm . In some CRTs, no consent is sought from any participants at the cluster level for administering an intervention to individuals within each cluster, or for data collection.*

Note: If there was more than one intervention arm in your study, please choose the study arm with the most intensive intervention for these questions.

4) Was consent sought from clinicians in the intervention arm for any aspect of the study?

☐ **NO** → If No, please specify why consent was not considered necessary:

☐ **YES** → If Yes, select 1 option below

→ ○ Before the randomization of general practices

→ ○ After the randomization of general practices

Additional comments or explanation (optional):

5) Did clinicians in the intervention arm consent to receiving a study intervention (i.e., a targeted change in practice)?

☐ **N/A** →the study did not involve clinicians receiving an intervention

○ YES, explicit written

○ YES, explicit verbal

○ YES, other consent procedure. Please specify in the text box under additional comments

○ NO

→If **No**, please specify whether clinicians were:

○ a) Not notified about receiving an intervention

○ b) Notified about receiving an intervention without the opportunity to opt out

○ c) Notified about receiving an intervention with the opportunity to opt out

○ d) Other, please explain:

Additional comments or explanation (optional):

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CONSENT PROCEDURES FOR CLUSTER LEVEL PARTICIPANTS IN THE INTERVENTION ARM

6) Did clinicians in the intervention arm consent to delivering or administering a study intervention to patients?

☐ **N/A** →the study did not involve clinicians delivering or administering a study intervention to patients

- ○ YES, explicit written
- ○ YES, explicit verbal
- ○ YES, other consent procedure. Please specify in the text box under additional comments
- ○ NO

→If **No**, please specify whether clinicians were:

- ○ a) Not notified about delivering/administering an intervention
- ○ b) Notified about delivering/administering an intervention without the opportunity to opt out
- ○ c) Notified about delivering/administering an intervention with the opportunity to opt out
- ○ d) Other, please explain:

Additional comments or explanation (optional):

7) Did clinicians in the intervention arm consent to providing data (e.g. by questionnaire, access to records, direct observation)?

☐ **N/A** → No data collected on/from/by clinicians

- ○ YES, explicit written
- ○ YES, explicit verbal
- ○ YES, other consent procedure. Please specify in the text box under additional comments
- ○ NO

→If **No**, please specify whether clinicians were:

- ○ a) Not notified about data collection procedures
- ○ b) Notified about data collection procedures without the opportunity to opt out
- ○ c) Notified about data collection procedures with the opportunity to opt out
- ○ d) Other, please explain:

Additional comments or explanation (optional):

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CONSENT PROCEDURES FOR CLUSTER LEVEL PARTICIPANTS IN THE CONTROL ARM

*In the following questions, we are interested in consent procedures for the **primary care clinicians** in the study control arm .*

Note: If there was no control arm in your study, please choose the study arm with the least intensive or delayed intervention for these questions.

If consent procedures for clinicians in the control arm were identical to those in the intervention arm, please click here ☐ to proceed to the next section.

8) Was consent sought from clinicians in the control arm for any aspect of the study?

☐ **NO** → If No, please specify why consent was not considered necessary:

☐ **YES** → If Yes, select 1 option below

→ ○ **Before the randomization of general practices**

→ ○ **After the randomization of general practices**

Additional comments or explanation (optional):

9) Did clinicians in the control arm consent to receiving a study intervention (i.e., a targeted change in practice)?

☐ **N/A** →the study did not involve clinicians receiving an intervention

○ YES, explicit written

○ YES, explicit verbal

○ YES, other consent procedure. Please specify in the text box under additional comments

○ NO

→If **No**, please specify whether clinicians were:

○ a) Not notified about receiving an intervention

○ b) Notified about receiving an intervention without the opportunity to opt out

○ c) Notified about receiving an intervention with the opportunity to opt out

○ d) Other, please explain:

Additional comments or explanation (optional):

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CONSENT PROCEDURES FOR CLUSTER LEVEL PARTICIPANTS IN THE CONTROL ARM

10) Did clinicians in the control arm consent to delivering or administering a study intervention to patients?

☐ N/A → the study did not involve clinicians delivering or administering an intervention directly to patients.

- ○ YES, explicit written
- ○ YES, explicit verbal
- ○ YES, other consent procedure. Please specify in the text box under additional comments
- ○ NO

→If No, please specify whether clinicians were:

- ○ a) Not notified about delivering/administering an intervention
- ○ b) Notified about delivering/administering an intervention without the opportunity to opt out
- ○ c) Notified about delivering/administering an intervention with the opportunity to opt out
- ○ d) Other, please explain:

Additional comments or explanation (optional):

11) Did clinicians in the control arm consent to providing data (e.g. by questionnaire, access to records, direct observation)?

☐ N/A → No data collected on/from/by clinicians

- ○ YES, explicit written
- ○ YES, explicit verbal
- ○ YES, other consent procedure. Please specify in the text box under additional comments
- ○ NO

→If No, please specify whether clinicians were:

- ○ a) Not notified about data collection procedures
- ○ b) Notified about data collection procedures without the opportunity to opt out
- ○ c) Notified about data collection procedures with the opportunity to opt out
- ○ d) Other, please explain:

Additional comments or explanation (optional):

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CONSENT PROCEDURES FOR INDIVIDUAL LEVEL PARTICIPANTS IN THE INTERVENTION ARM

*In the following questions, we are interested in consent procedures for the **patients** in the study intervention arm . In some CRTs, no consent is sought from any participants at the individual level (for example, because individuals are not directly receiving an intervention); in other CRTs, consent may be sought from individuals for receiving an intervention or simply for data collection.*

Note: If there was more than one intervention arm in your study, please choose the study arm with the most intensive intervention for these questions.

12) Was consent sought from patients in the intervention arm for any aspect of the study?

☐ **NO** → If No, please specify why consent was not considered necessary:

☐ **YES** →If Yes, select 1 option below

→ ○ **Before the randomization of general practices**

→ ○ **After the randomization of general practices**

Additional comments or explanation (optional):

13) Did patients in the intervention arm consent to receiving (or being affected by) a study intervention?

☐ **N/A** → The study did not involve patients receiving an intervention

○ YES, explicit written
○ YES, explicit verbal
○ YES, other consent procedure. Please specify in the text box under additional comments
○ NO

→If No, please specify whether patients were:

○ a) Not notified about receiving (or being affected by) an intervention
○ b) Notified about receiving (or being affected by) an intervention without the opportunity to opt out
○ c) Notified about receiving (or being affected by) an intervention with the opportunity to opt out
○ d) Other, please explain:

Additional comments or explanation (optional):

14) Did patients in the intervention arm consent to providing data (e.g. by questionnaire, blood sample, review of records)?

- ○ YES, explicit written
- ○ YES, explicit verbal
- ○ YES, other consent procedure. Please specify in the text box under additional comments
- ○ NO

→If No, please specify whether patients were:

- ○ a) Not notified about data collection procedures
- ○ b) Notified about data collection procedures without the opportunity to opt out
- ○ c) Notified about data collection procedures with the opportunity to opt out
- ○ d) Other, please explain:

Additional comments or explanation (optional):

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CONSENT PROCEDURES FOR INDIVIDUAL LEVEL PARTICIPANTS IN THE CONTROL ARM

*In the following questions, we are interested in consent procedures for the **patients** in the study control arm .*

Note: If there was no control arm in your study, please choose the study arm with the least intensive or delayed intervention.

If consent procedures for patients in the control arm were identical to those in the intervention arm, please click here ☐ to proceed to the next section.

15) Was consent sought from patients in the control arm for any aspect of the study?

☐ **NO** → If No, please specify why consent was not considered necessary:

☐ **YES** → If Yes, select 1 option

→ ○ **Before the randomization of general practices**

→ ○ **After the randomization of general practices**

Additional comments or explanation (optional):

16) Did patients in the control arm consent to receiving (or being affected by) a study intervention?

☐ **N/A** →the study did not involve patients receiving an intervention

○ YES, explicit written
○ YES, explicit verbal
○ YES, other consent procedure. Please specify in the text box under additional comments
○ NO

→If **No**, please specify whether patients were:

○ a) Not notified about receiving (or being affected by) an intervention
○ b) Notified about receiving (or being affected by) an intervention without the opportunity to opt out
○ c) Notified about receiving (or being affected by) an intervention with the opportunity to opt out
○ d) Other, please explain:

Additional comments or explanation (optional):

17) Did patients in the control arm consent to providing data (e.g. by questionnaire, blood sample, review of records)?

- YES, explicit written
- YES, explicit verbal
- YES, other consent procedure. Please specify in the text box under additional comments
- NO

→If **No**, please specify whether patients were:

- a) Not notified about data collection procedures
- b) Notified about data collection procedures without the opportunity to opt out
- c) Notified about data collection procedures with the opportunity to opt out
- d) Other, please explain:

Additional comments or explanation (optional):

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INFORMATION PROVIDED TO PARTICIPANTS AT THE INDIVIDUAL LEVEL

*In the following questions, we are interested in whether the **patients** were informed about the comparison arm(s). In some CRTs, participants in one or more arms are not informed about the comparison arm(s), for example, to avoid contamination, to maintain study blinding, or simply because there was no direct contact with members of the cluster.*

18) In the intervention arm, were patients informed about the use of the control arm?

☐ **YES**

☐ **NO** →If No, please specify why the comparison arm was not mentioned:

19) In the control arm, were patients informed about the use of the intervention arm?

☐ **YES**

☐ **NO** →If No, please specify why the intervention arm was not mentioned:

Please provide any additional comments or explanation here (optional):

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INFORMATION PROVIDED TO PARTICIPANTS AT THE CLUSTER LEVEL

*In the following questions, we are interested in whether the **primary care clinicians** were informed about the comparison arm(s).*

20) In the intervention arm, were clinicians informed about the use of the control arm?

☐ **YES**

☐ **NO** →If No, please specify why the comparison arm was not mentioned:

21) In the control arm, were clinicians informed about the use of the intervention arm?

☐ **YES**

☐ **NO** →If No, please specify why the intervention arm was not mentioned:

Please provide any additional comments or explanation here (optional):

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ETHICS REVIEW OF ANY CRTS YOU MAY HAVE BEEN INVOLVED WITH

In the following questions, we would like to gather information about your general experiences in the ethics review of this trial, and/or any other CRTs you may have been involved with.

22) How many cluster randomized trials in total (including all current and past studies), have you conducted as a principal investigator or co-investigator, and/or been significantly involved with (e.g. as a grant-holder)?
[*This does not include roles such as trial management, consultation, or data analysis alone*]

Number of CRTs: [ ]

23) In your dealings with RECs reviewing the CRTs, did you ever personally have to meet formally with any members of the REC?

☐ **N/A** → Did not seek ethics approval for any of the above cluster randomized trials
→ **Proceed to Question 25**

☐ **NO**

☐ **YES** → If Yes, please describe the purpose of your meeting(s):

[ ]

24) For any of the CRTs, did the ethics review process ever have an impact on any of the following aspects of the study?
[*Check all boxes that apply and please explain whether the impact was positive or negative in the text box provided.*]

- ☐ Timely initiation of the trial.
- ☐ Financial cost of conducting the trial.
- ☐ Feasibility of participant recruitment.
- ☐ Scientific validity or methodological quality of the trial.
- ☐ Other.

Please provide any additional comments or explanation here (optional):

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ETHICS REVIEW OF ANY CRTS YOU MAY HAVE BEEN INVOLVED WITH

25) Did you ever experience variability in the ethics review of a CRT undergoing review by more than one REC? [*This may include variability in the type of review, procedural review processes,REC requirements, and decision outcomes.*]

☐ **N/A** ⟶ Ethics review of a CRT did not involve multiple RECs

☐ **NO**

☐ **YES** ⟶If Yes, please explain what differences arose:

26) Please rate your agreement or disagreement with each of the following statements:

a) There is a need to develop ethics guidelines for CRTs.

○ Strongly Disagree
○ Disagree
○ Agree
○ Strongly Agree
○ No Opinion

b) RECs could be better informed about distinct ethical issues surrounding CRTs.

○ Strongly Disagree
○ Disagree
○ Agree
○ Strongly Agree
○ No Opinion

c) REC application forms standardized for various study designs, are hard to use in the context of the CRT study design.

○ Strongly Disagree
○ Disagree
○ Agree
○ Strongly Agree
○ No Opinion

Please provide any additional comments or explanation here (optional):

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ADDITIONAL COMMENTS AND SUBMISSION

27) What are your highest obtained degrees?
[*Check all that apply and indicate country in which degree was conferred*]

☐ Doctorate
Country

☐ Master's Degree
Country

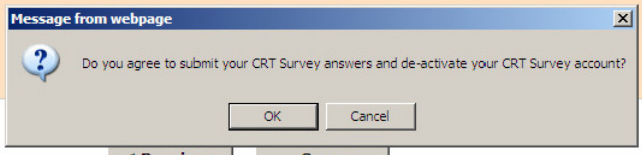
☐ Medical Degree
Country

☐ Other higher degree, please specify:

Country

Are there any additional details about the ethics review or conduct of CRTs that have not been addressed in this survey?

If Yes, please describe:



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When you have completed the questionnaire and are satisfied with your responses, please click on the 'Submit' button. Your questionnaire will be received once you have submitted the survey.

Submit

→ **Thank you for taking the time to complete the survey. Your responses are greatly appreciated!**

APPENDIX D: SURVEY INVITATION LETTERS

Pre-notification email

Subject: Cluster randomized trial survey: Invitation to participate

June 11, 2010

Dear Professor Smith,

I am writing to you on behalf of researchers at the Universities of Ottawa, Western Ontario, and Toronto (Canada), Newcastle upon Tyne (UK), and Pennsylvania (USA), who are conducting a study to develop guidelines for the ethics review and ethical conduct of cluster randomized trials (CRTs). Our research protocol may be accessed here: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725043/

In the next few days, you will receive a request to complete our survey about your experiences in conducting CRTs, particularly with regard to your trial: *Community Intervention Trial for Smoking Cessation (COMMIT): I. cohort results from a four-year community intervention*, published in Am J Public Health 1995. This trial was randomly selected from Medline for a systematic review and this survey, which will include questions about the ethics review process of your trial, as well as any consent procedures at the individual and cluster level.

Your feedback is very valuable to us. We hope you will take 15 to 20 minutes of your time to complete the survey. To thank you for your time, we will offer a gift as a token of appreciation for your participation.

Yours sincerely,

Dr. Jeremy Grimshaw

Senior Scientist, Clinical Epidemiology Program, Ottawa Hospital Research Institute
Director, Centre for Best Practices, Institute of Population Health, University of Ottawa
Full Professor, Department of Medicine, University of Ottawa
Director, Canadian Cochrane Network and Centre
Canada Research Chair in Health Knowledge Transfer and Uptake

Tel:
Fax:
E-mail:

Survey Invitation email- *Cover letter with incentive version 1*

Subject: Survey about your cluster randomized trial: Prenotification

June 15, 2010

Dear Professor Smith,

This research study we are asking you to participate in is designed to explore and understand investigator experiences and perspectives on the conduct and ethics review of cluster randomized trials (CRTs). You have been selected for this survey because you are the corresponding author of a cluster randomized trial which was randomly selected from among thousands of trials indexed in MEDLINE between 2000 and 2008; specifically: *Community Intervention Trial for Smoking Cessation (COMMIT): I. cohort results from a four-year community intervention*, published in Am J Public Health 1995.

We would be grateful if you could spare approximately 15-20 minutes to complete the web-based questionnaire. Please click on the link below to go to the survey website (or copy and paste the survey link into your Internet browser) and then enter the password to begin the survey.

Survey link: http://crtsurvey.ohri.ca

Password: 12345678

Your responses are voluntary and will be kept confidential. No information will be published or released that can identify you as a respondent or link your responses to the particular published trial. All study records will be coded and kept in a password-protected computer and locked cabinet at the Ottawa Hospital for 15 years after the termination of this study.

If you have any questions about this survey, please contact the study coordinator, Ms. Shazia Chaudhry at [redacted] or the co-Principal Investigator, Dr. Monica Taljaard at telephone [redacted] or [redacted]. This research study has been reviewed and approved by the Ottawa Hospital Research Ethics Board (OHREB). If you have any questions about your rights as a study participant, you may contact the Vice-Chair of the OHREB at [redacted]

As a token of our appreciation, you will, if you wish receive a complimentary book: *Design and analysis of cluster randomization trials in health research* (2000), by A. Donner & N. Klar, which will be mailed to you upon completion of your survey (details provided at the start of survey questionnaire).

Sincerely,

Dr. Jeremy Grimshaw

Senior Scientist, Clinical Epidemiology Program, Ottawa Hospital Research Institute
Director, Centre for Best Practices, Institute of Population Health, University of Ottawa
Full Professor, Department of Medicine, University of Ottawa
Director, Canadian Cochrane Network and Centre
Canada Research Chair in Health Knowledge Transfer and Uptake

Tel:
Fax:
E-mail:

On behalf of:

University of Ottawa
Dr. Monica Taljaard
Dr. Jamie Brehaut
Dr. Raphael Saginur

University of Western Ontario
Dr. Charles Weijer
Dr. Allan Donner

University of Toronto
Dr. Merrick Zwarenstein

University of Newcastle upon Tyne, U.K.
Dr. Martin Eccles

University of Pennsylvania, U.S.A
Dr. Robert Boruch

Survey Invitation email- *Cover letter with incentive version 2*

June 15, 2010

Dear Professor Smith,

This research study we are asking you to participate in is designed to explore and understand investigator experiences and perspectives on the conduct and ethics review of cluster randomized trials (CRTs). You have been selected for this survey because you are the corresponding author of a cluster randomized trial which was randomly selected from among thousands of trials indexed in MEDLINE between 2000 and 2008; specifically: *Community Intervention Trial for Smoking Cessation (COMMIT): I. cohort results from a four-year community intervention*, published in Am J Public Health 1995.

We would be grateful if you could spare approximately 15-20 minutes to complete the web-based questionnaire. Please click on the link below to go to the survey website (or copy and paste the survey link into your Internet browser) and then enter the password to begin the survey.

Survey link: http://crtsurvey.ohri.ca

Password: 12345678

Your responses are voluntary and will be kept confidential. No information will be published or released that can identify you as a respondent or link your responses to the particular published trial. All study records will be coded and kept in a password-protected computer and locked cabinet at the Ottawa Hospital for 15 years after the termination of this study.

If you have any questions about this survey, please contact the study coordinator, Ms. Shazia Chaudhry at [redacted] or the co-Principal Investigator, Dr. Monica Taljaard at telephone [redacted] or [redacted]. This research study has been reviewed and approved by the Ottawa Hospital Research Ethics Board (OHREB). If you have any questions about your rights as a study participant, you may contact the Vice-Chair of the OHREB at [redacted]

As a token of our appreciation, we will ask you whether you would prefer 1) a $40 donation on your behalf to Doctors without Borders /Médecins Sans Frontières (MSF), or 2) a complimentary book: *Design and analysis of cluster randomization trials in health research* (2000), by A. Donner & N. Klar, which will be mailed to you upon completion of your survey (details provided at the start of survey questionnaire).

Sincerely,

Dr. Jeremy Grimshaw

Senior Scientist, Clinical Epidemiology Program, Ottawa Hospital Research Institute
Director, Centre for Best Practices, Institute of Population Health, University of Ottawa
Full Professor, Department of Medicine, University of Ottawa
Director, Canadian Cochrane Network and Centre
Canada Research Chair in Health Knowledge Transfer and Uptake

Tel:
Fax:
E-mail:

On behalf of:

University of Ottawa
Dr. Monica Taljaard
Dr. Jamie Brehaut
Dr. Raphael Saginur

University of Western Ontario
Dr. Charles Weijer
Dr. Allan Donner

University of Toronto
Dr. Merrick Zwarenstein

University of Newcastle upon Tyne, U.K.
Dr. Martin Eccles

University of Pennsylvania, U.S.A
Dr. Robert Boruch

Thank you and Reminder Email

Subject: Cluster randomized trial survey: Thank you/ Reminder

June 23, 2010

Dear Professor Smith,

Last week a questionnaire was emailed to you because your trial was randomly selected as part of a research study about the ethics review and conduct of cluster randomized trials.

If you have already completed and submitted the questionnaire, please accept our sincere thanks. If not, we ask that you do so at your earliest convenience.

You may click on the link below to access the survey website (or copy and paste the survey link into your Internet browser) and then enter the password to begin the survey.

Survey link: http://crtsurvey.ohri.ca

Password: 12345678

If you have any questions about the survey, please do not hesitate to contact us.

Sincerely,

Dr. Jeremy Grimshaw

Senior Scientist, Clinical Epidemiology Program, Ottawa Hospital Research Institute
Director, Centre for Best Practices, Institute of Population Health, University of Ottawa
Full Professor, Department of Medicine, University of Ottawa
Director, Canadian Cochrane Network and Centre
Canada Research Chair in Health Knowledge Transfer and Uptake

Tel:
Fax:
E-mail:

Reminder Email

Subject: Cluster randomized trial survey: Reminder

July 1, 2010

Dear Professor Smith,

We understand how valuable your time is and are hoping you may be able to give about 15-20 minutes to help us collect important information on the ethics review and conduct of your trial.

If you have already submitted the survey, we really appreciate your participation. If you have not yet responded, we would like to urge you to complete the survey questionnaire. We plan to end the study soon, so we wanted to email everyone who has not responded to make sure you have had a chance to participate and provide us with your valuable perspective.

As a reminder you can click on the link below to go to the survey website (or copy and paste the survey link into your Internet browser) and then enter the password to begin the survey.

Survey link: http://crtsurvey.ohri.ca

Password: 12345678

Thank you in advance for completing the survey. Your responses are important! Cluster randomization trialists are the best source of information to understand the ethics review and conduct of cluster randomized trials. As a token of appreciation for your participation, please also select to receive our offer of a free gift, details for which are provided at the start of the questionnaire.

Sincerely,

Dr. Jeremy Grimshaw, on behalf of the research team

Senior Scientist, Clinical Epidemiology Program, Ottawa Hospital Research Institute
Director, Centre for Best Practices, Institute of Population Health, University of Ottawa
Full Professor, Department of Medicine, University of Ottawa
Director, Canadian Cochrane Network and Centre
Canada Research Chair in Health Knowledge Transfer and Uptake

Tel:
Fax:
E-mail:

***Postal Follow-up**: Letter with incentive version 1*

Ottawa Hospital Research Institute
OHRI IRHO
Institut de recherche de l'Hôpital d'Ottawa

RE: Last chance; CRT study is closing July 7, 2010

Professor J. Smith
University of Ottawa
[redacted]

Dear Professor Smith,

A few weeks ago we sent an email inviting you to complete a questionnaire about the ethics review and conduct of your cluster randomized trial. If you have recently submitted your responses, we thank you; if you have not, we ask that you consider completing your survey within the next 7 days. The data collection phase of our survey is now closing so we are writing again because it is only by hearing from as many people in the sample as possible that we can be sure that the results represent the trials and perspectives of cluster randomization trialists as yourself.

The questions should only take about 15-20 minutes to complete. Your responses are voluntary and will be kept confidential. The questionnaire can be completed using the web-based format: just enter this web page address in your internet browser, and then type in your password to begin the survey.

http://crtsurvey.ohri.ca

Password: 12345678

If you have any questions about the survey, Ms. Shazia Chaudhry, the study coordinator will be happy to help and can be reached by telephone [redacted] or by email at [redacted] You may also email me at [redacted]

As a token of our appreciation, we are offering a complimentary book: *Design and Analysis of Cluster Randomization Trials in Health Research* (2000), by A. Donner & N. Klar, which will be mailed to you upon completion of your survey.

Thank you for your consideration.

Sincerely,

Dr. Jeremy Grimshaw, *on behalf of the research team*

Dr. Jeremy Grimshaw

Senior Scientist
Ottawa Hospital Research Institute;
Clinical Epidemiology Program

[redacted]

Civic Campus
Campus Civic

[redacted]

WWW.OHRI.CA

***Postal Follow-up**: Letter with incentive version 2*

Ottawa Hospital Research Institute
OHRI IRHO
Institut de recherche de l'Hôpital d'Ottawa

RE: Last chance; CRT study is closing July 7, 2010

Professor J. Smith
University of Ottawa
[redacted]

Dear Professor Smith,

A few weeks ago we sent an email inviting you to complete a questionnaire about the ethics review and conduct of your cluster randomized trial. If you have recently submitted your responses, we thank you; if you have not, we ask that you consider completing your survey within the next 7 days. The data collection phase of our survey is now closing so we are writing again because it is only by hearing from as many people in the sample as possible that we can be sure that the results represent the trials and perspectives of cluster randomization trialists as yourself.

The questions should only take about 15-20 minutes to complete. Your responses are voluntary and will be kept confidential. The questionnaire can be completed using the web-based format: just enter this web page address in your internet browser, and then type in your password to begin the survey.

http://crtsurvey.ohri.ca

Password: 12345678

If you have any questions about the survey, Ms. Shazia Chaudhry, the study coordinator will be happy to help and can be reached by telephone [redacted] or by email at [redacted] You may also email me at [redacted].

As a token of our appreciation, we are offering the choice of 1) a donation of $40 CAD on your behalf to Doctors without Borders /Médecins Sans Frontières (MSF), or 2) a complimentary book: *Design and Analysis of Cluster Randomization Trials in Health Research* (2000), by A. Donner & N. Klar, which will be mailed to you upon completion of your survey.

Thank you for your consideration.

Sincerely,

Dr. Jeremy Grimshaw, *on behalf of the research team*

Dr. Jeremy Grimshaw

Senior Scientist
Ottawa Hospital Research Institute;
Clinical Epidemiology Program

[redacted]

Civic Campus
Campus Civic

[redacted]

WWW.OHRI.CA

Final reminder Email

Subject: "Questions about your study"

September 1, 2010

Dear Professor Smith,

Our survey about the conduct and ethics review of cluster randomized trials has been completed by many researchers across the world. We noticed that you have not yet submitted your survey and we would like to give you a final opportunity to do so.

We plan to include only responses submitted before or by **September 13th, 2010**, and we would like to urge you to submit your response before then. You can click on the link below to go to the survey website (or copy and paste the survey link into your Internet browser) and then enter the password to begin the survey.

Survey link: http://crtsurvey.ohri.ca

Password: 12345678

Obtaining responses from a representative sample of trialists is important, because it will help us obtain an accurate picture of how cluster trialists around the world conduct their studies. We hope to use this information to produce a set of ethics guidelines for the conduct and review of CRTs.

If you have any questions, please do not hesitate to contact us.

Sincerely,

Dr. Jeremy Grimshaw, on behalf of the research team

Senior Scientist, Clinical Epidemiology Program, Ottawa Hospital Research Institute
Director, Centre for Best Practices, Institute of Population Health, University of Ottawa
Full Professor, Department of Medicine, University of Ottawa
Director, Canadian Cochrane Network and Centre
Canada Research Chair in Health Knowledge Transfer and Uptake

Tel:
Fax:
E-mail:

APPENDIX E: LETTER OF ETHICS APPROVAL


Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

http://www.ohri.ca/ohreb

Thursday, November 05, 2009

Dr. Monica Taljaard
Ottawa Hospital - Civic Campus
Clinical Epidemiology Program

Dear Dr. Taljaard:

Re: Protocol # 2009693-01H	**Challenges in the Ethical Conduct and Ethics Review of Cluster Randomized Trials: A Survey and In-Depth Interviews of Cluster Randomized Trialists**
Protocol approval valid until -	**Thursday, November 04, 2010**

Thank you for the e-mail from Ms. Chaudhry received today. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol or the consent form without the OHREB's review and approval.

Approval is for the following documentation:
- Protocol dated July 2009
- English Initial e-mail to participants received October 22, 2009
- English First Phone-Call received October 22, 2009
- English Interview Guide (verbal confirmation of consent over the phone) received October 22, 2009
- English Pre-notification letter for survey received October 22, 2009
- English Letter for interview received October 22, 2009
- English Questionnaire for Pilot Test, version 1 (Cluster and Individual level) received October 22, 2009
- English Questionnaire for Pilot Test, version 2 (Individual level only) received October 22, 2009

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

Vice-Chairman
Ottawa Hospital Research Ethics Board

/cb

APPENDIX F: FINAL DISPOSITION CODES OF THE SURVEY SAMPLE

Table F-1: Sample disposition codes according to AAPOR guidelines for internet surveys of specifically named persons

Category	Disposition code	Number of sample members (n=300)
1. Returned questionnaire	**1.0**	**182**
Complete interview (I)	1.1	182
Partial interview or break-off with sufficient information (P)	1.2	0
2. Eligible, 'Non-Interview'	**2.0**	**43**
Refusal (R)	2.11	0
Explicit Refusal	2.111	5
Implicit Refusal	2.112	0
Logged on to survey, did not complete any items	2.1121	11
Read receipt confirmation, refusal	2.1122	0
Break-off or partial with insufficient information (R)	2.12	5
Non-contact (NC)	2.20	14
Respondent was unavailable during field period	2.26	2
Completed questionnaire, but not returned during field period	2.27	0
	2.30	5
Other, non refusal (O)	2.33	1
Language barrier		
3. Unknown Eligibility, 'Non-interview'	**3.0**	**60**
Nothing known about respondent or address (U)	3.10	0
No invitation sent	3.11	0
Nothing ever returned	3.19	59
Invitation returned undelivered (UO)	3.30	1
Invitation returned with forwarding information	3.40	0
Other (UO)	3.90	0
Returned from an un-sampled email address	3.91	0
4. Not Eligible, Returned	**4.0**	**15**
Selected respondent screened out of sample	4.10	0
Quota filled	4.80	0
Duplicate listing	4.81	15
Other	4.90	0

APPENDIX G: DETAILS OF PARTICIPANT CONSENT AND NOTIFICATION PROCEDURES

Individual level

Table G-1: Individual level consent for receiving an intervention

	Value %, (Frequency)	95% confidence interval of %
Intervention Arm		
Consent sought for receiving an intervention? [a] (n=182)		
Yes	56.0% (102)	48.5% to 63.4%
No	44.0% (80)	36.6% to 51.5%
If yes, method of consent: (n=102)		
Explicit written	85.3% (87)	
Explicit verbal	14.7% (15)	NA
Other consent procedure	0% (0)	
If no, method of notification: (n=77) [1]		
Not notified	55.8% (43)	
Notified without opt-out opportunity	7.8% (6)	NA
Notified with opt-out opportunity	22.1% (17)	
Other	14.3% (11)	
Control Arm		
Consent sought for receiving an intervention? [b] (n=182)		
Yes	48.9% (89)	41.4% to 56.4%
No	51.1% (93)	43.6% to 58.6%
If yes, method of consent: (n=89)		
Explicit written consent	86.5% (77)	
Explicit verbal consent	13.5% (12)	NA
Other consent procedure	0% (0)	
If no, method of notification: (n=88) [2]		
Not notified	56.8% (50)	
Notified without opt-opt opportunity	8.0% (7)	NA
Notified with opt-opt opportunity	19.3% (17)	
Other	15.9% (14)	

a- Question 13: Did <<individual level participants>> in the intervention arm consent to **receiving (or being affected by)** a study intervention?

b- Question 16: Did <<individual level participants>> in the control arm consent to **receiving (or being affected by)** a study intervention?

1- 3 observations missing

2- 5 observations missing

Table G-2: Individual level consent for providing data

	Value %, (Frequency)	95% confidence interval of %
Intervention Arm		
Consent sought for data collection? [a] (n=182)		
Yes	75.3% (137)	68.4% to 81.4%
No	24.7% (45)	18.6% to 31.6%
If yes, method of consent: (n=137)		
Explicit written	80.3% (110)	
Explicit verbal	13.1% (18)	NA
Other consent procedure	6.6% (9)	
If no, method of notification: (n=41) [1]		
Not notified	53.7% (22)	
Notified without opt-opt opportunity	4.9% (2)	NA
Notified with opt-opt opportunity	29.3% (15)	
Other	12.2% (5)	
Control Arm		
Consent sought for data collection? [b] (n=182)		
Yes	74.2% (135)	67.2% to 80.4%
No	25.8% (47)	19.6% to 32.8%
If yes, method of consent: (n=135)		
Explicit written consent	80.0% (108)	
Explicit verbal consent	13.3% (18)	NA
Other consent procedure	6.7% (9)	
If no, method of notification: (n=43) [2]		
Not notified	58.1% (21)	
Notified without opt-opt opportunity	4.7% (7)	NA
Notified with opt-opt opportunity	27.9% (17)	
Other	9.3% (14)	

a- Question 14: Did <<individual level participants>> in the intervention arm consent to **providing data** (e.g., by questionnaire, blood sample, review of records)?

b- Question 17: Did <<individual level participants>> in the control arm consent to **providing data** (e.g., by questionnaire, blood sample, review of records)?

1- 4 observations missing

2- 4 observations missing

Cluster level

Table G-3: Cluster level consent for receiving an intervention

	Value %, (Frequency)	95% confidence interval of %
Intervention Arm		
Consent sought for receiving an intervention? [a] (n=134 [b]) [1]		
Yes	61.9% (83)	53.2% to 70.2%
No	38.1% (51)	29.8% to 46.8%
If yes, method of consent: (n=83)		
Explicit written	51.8% (43)	
Explicit verbal	45.8% (38)	NA
Other consent procedure	2.4% (2)	
If no, method of notification: (n=50) [2]		
Not notified	22.0% (11)	
Notified without opt-out opportunity	30.0% (15)	NA
Notified with opt-out opportunity	30.0% (15)	
Other	18.0% (9)	
Control Arm		
Consent sought for receiving an intervention? [c] (n=134 [b]) [1]		
Yes	52.2% (70)	43.4% to 60.9%
No	47.8% (64)	39.1% to 56.6%
If yes, method of consent: (n=70)		
Explicit written consent	58.6% (41)	
Explicit verbal consent	38.6% (27)	NA
Other consent procedure	2.9% (2)	
If no, method of notification: (n=39) [3]		
Not notified	45.9% (28)	
Notified without opt-out opportunity	18.0% (11)	NA
Notified with opt-out opportunity	16.4% (10)	
Other	19.7% (12)	

a- Question 5: Did <<cluster level participants>> in the intervention arm consent to **receiving** a study intervention (i.e., a targeted change in practice)?

b- Studies in which cluster level participants were specified as not receiving an intervention (i.e., respondent selecting 'N/A' to question 5) were excluded from the denominator

c- Question 9: Did <<cluster level participants>> in the control arm consent to **receiving** a study intervention (i.e., a targeted change in practice)?

1- 2 observations missing

2- 1 observation missing

3- 3 observations missing

Table G-4: Cluster level consent for delivering or administering a study intervention

	Value %, (Frequency)	95% confidence interval of %
Intervention Arm		
Consent sought for delivering an intervention? [a] **(n=117** [b]**)** [1]		
Yes	62.4% (73)	53.0% to 71.2%
No	37.6% (44)	28.8% to 47.0%
If yes, method of consent: (n=73)		
Explicit written	46.6% (34)	
Explicit verbal	53.4% (39)	NA
Other consent procedure	0% (0)	
If no, method of notification: (n=41) [2]		
Not notified	9.8% (4)	
Notified without opt-opt opportunity	26.8% (11)	NA
Notified with opt-opt opportunity	36.6% (15)	
Other	26.8% (11)	
Control Arm		
Consent sought for delivering an intervention? [c] **(n=118** [b]**)**		
Yes	57.6% (68)	48.2% to 66.7%
No	42.4% (50)	33.8% to 51.4%
If yes, method of consent: (n=68)		
Explicit written consent	44.1% (30)	
Explicit verbal consent	50.0% (34)	NA
Other consent procedure	5.9% (4)	
If no, method of notification: (n=37) [2]		
Not notified	38.3% (18)	
Notified without opt-opt opportunity	21.3% (10)	NA
Notified with opt-opt opportunity	19.2% (9)	
Other	21.3% (10)	

a- Question 6: Did <<cluster level participants>> in the intervention arm consent to **delivering or administering** a study intervention to <<individual level participants>>?

b- Studies in which cluster level participants were specified as not delivering or administering an intervention (i.e., respondent selecting 'N/A' to question 6) were excluded from the denominator

c- Question 10: Did <<cluster level participants>> in the control arm consent to **delivering or administering** a study intervention to <<individual level participants>>?

1- 1 observation missing

2- 3 observations missing

Table G-5: Cluster level consent for providing data

	Value %, (Frequency)	95% confidence interval of %
Intervention Arm		
Consent sought for providing data? [a] (n=134 [b]) [1]		
Yes	76.1% (102)	68.0% to 83.1%
No	23.9% (32)	16.9% to 32.0%
If yes, method of consent: (n=102)		
Explicit written	59.8% (61)	
Explicit verbal	36.3% (37)	NA
Other consent procedure	3.9% (4)	
If no, method of notification: (n=31) [1]		
Not notified	12.9% (4)	
Notified without opt-opt opportunity	38.7% (12)	NA
Notified with opt-opt opportunity	35.5% (11)	
Other	12.9% (4)	
Control Arm		
Consent sought for providing data? [c] (n=134 [b]) [1]		
Yes	70.1% (94)	61.6% to 77.7%
No	29.9% (40)	22.3% to 38.4%
If yes, method of consent: (n=94)		
Explicit written consent	61.7% (58)	
Explicit verbal consent	35.1% (33)	NA
Other consent procedure	3.2% (3)	
If no, method of notification: (n=31) [2]		
Not notified	32.4% (12)	
Notified without opt-opt opportunity	29.7% (11)	NA
Notified with opt-opt opportunity	27.0% (10)	
Other	10.8% (4)	

a- Question 7: Did <<cluster level participants>> in the intervention arm consent to **providing data** (e.g., by questionnaire, access to records, direct observation)?

b- Studies in which cluster level participants were specified as not providing data (i.e., respondent selecting 'N/A' to question 7) were excluded from the denominator

c- Question 11: Did <<cluster level participants>> in the control arm consent to **providing data** (e.g., by questionnaire, access to records, direct observation)?

1- 1 observation missing

2- 3 observations missing