1-31-2011 12:00 AM

Ethical Challenges in Cluster Randomized Trials

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

ETHICAL CHALLENGES IN CLUSTER RANDOMIZED TRIALS

(Spine title: Ethical Challenges in Cluster Randomized Trials)

(Thesis format: Integrated-Article)

by

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A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

The School of Graduate and Postdoctoral Studies
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THE UNIVERSITY OF WESTERN ONTARIO
SCHOOL OF GRADUATE AND POSTDOCTORAL STUDIES

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entitled:

Ethical Challenges in Cluster Randomized Trials

is accepted in partial fulfillment of the
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Doctor of Philosophy

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Abstract:

Background: Cluster randomized trials (CRTs) are a widely used research design in healthcare, health services, public health and education research. CRTs randomly assign groups of individuals to different experimental arms. Because CRTs randomize groups rather than individual subjects, they pose ethical challenges that do not arise in individually-randomized clinical trials.

Research Questions: This dissertation sought to examine how ethical challenges in CRTs, particularly challenges relating to obtaining informed consent, are addressed in practice. This dissertation also sought to provide principled guidance as to who must be considered a research subject in a CRT, and when consent must be sought from research subjects in CRTs.

Methods: The association between consent practices in healthcare CRTs and particular trial features were examined using a multivariable logistic regression model. Information on ethical challenges encountered by CRT researchers in practice was obtained using descriptive qualitative analysis of semi-structured interviews with experienced CRT investigators. Two normative questions, "Who is the research subject in CRTs?" and "When is consent required in CRTs?" were addressed by appealing to a conceptual framework derived from the basic principles of research ethics.

Results: Consent in CRTs is associated with publication after 2004, publication in higher-impact journals, smaller cluster sizes, and the use of individual-level experimental and data collection interventions. CRT researchers are most concerned with issues around informed consent, and less concerned with issues related to the analysis of harms and benefits in CRTs.

Research subjects are individuals who are intervened upon by investigators, either directly or via manipulation of their environment; who interact with investigators; or who contribute identifiable private information. Consent must be sought for CRT participation from research subjects. Seeking consent after randomization of clusters is permissible if methodologically necessary. Some CRTs may meet criteria for a waiver of informed consent. Consent is not required from cluster members who are not research subjects.

Conclusions: This dissertation describes the state of the art of ethics practices in CRTs, and presents guidance around consent issues in CRTs that will inform the development of international ethics guidelines for CRTs.

Keywords:
Research ethics; Cluster randomized trials; Informed consent; Public health research; Health services research.

Co-Authorship Statement

Chapter 3:

Andrew McRae, Monica Taljaard, Allan Donner, Charles Weijer, Carol Bennett, Zoe Skea, Jeremy Grimshaw, Martin Eccles

Andrew McRae contributed to the revision of the data abstraction instrument, abstracted data from selected studies, designed and performed the data analysis, and drafted and edited the manuscript. Monica Taljaard conceived the study, drafted the data abstraction instrument, conducted the literature search, jointly selected published studies for review, abstracted data from the selected studies, provided input in the data analysis, and contributed to revisions of the manuscript. Carol Bennett jointly selected published studies for review and abstracted data from the selected studies. Zoe Skea abstracted data from the selected studies. Allan Donner provided supervisory support, provided substantive input into the design and conduct of the data analysis, and contributed to revisions of the manuscript. Charles Weijer provided supervisory support, contributed to the design of the data analysis and contributed to revisions of the manuscript. Jeremy Grimshaw and Martin Eccles contributed to revisions of the manuscript.

Chapter 4:

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Andrew McRae contributed to revisions of the interview guide, jointly conducted the interviews, jointly performed the data analysis, and drafted and edited the manuscript. Monica Taljaard conceived the study, drafted the initial interview guide, and contributed to revisions of the manuscript. Judith Belle Brown contributed to the revision of the interview guide, to the data analysis and to revisions of the manuscript. Carol Bennett jointly performed the interviews and data analysis. Charles Weijer provided supervisory support, contributed to revisions of the interview guide and contributed to revisions of the manuscript. Allan Donner provided supervisory support and contributed to revisions of the manuscript. Jeremy Grimshaw, Jamie Brehaut, Martin Eccles, Ariella Binik and Shazia Chaudhry contributed to revisions of the manuscript.

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Dedication

For my parents and brother, and for Michelle.

Acknowledments

The work in this dissertation would not have been possible without the assistance and support of friends, colleagues, and supervisors.

Thank you to Zoe Skea, and Julia Taleban for your assistance in abstracting data from published CRT reports that were used in the regression analysis in chapter three.

Thank you to Carol Bennett for your assistance with the data abstraction, for shouldering an equal portion of the work in conducting interviews with CRT investigators and for sharing the work of the data analysis.

I am indebted to Jamie Brehaut, Bob Boruch, Shazia Chaudhry, Martin Eccles, Ray Saginur, Merrick Zwarenstein, my collaborators on the CIHR-funded CRT project, who provided valuable feedback on drafts of the manuscripts in chapters three to six.

I am profoundly grateful to Ariella Binik, Chad Heilig, Spencer Hey, Carolyn McLeod, Angela White, my colleagues at the Rotman Institute of Philosophy who provided critical feedback during the drafting of chapters five and six.

Thank you to Anthony Belardo for your editorial assistance with chapters five and six.

Thank you to Neil Klar, Carolyn McLeod and Amardeep Thind for valuable constructive feedback during and after the defense of my dissertation proposal.

I am grateful for the input of Judith Belle Brown, an advisory committee member who was invaluable to the design, conduct, analysis and reporting of the qualitative research presented in chapter four.

I am particularly thankful for Jeremy Grimshaw’s enthusiasm for this project, and for his counsel and mentorship.

I am immensely grateful to Monica Taljaard. She has been the driving force behind the CIHR-funded CRT project, and a valuable advisory committee member, who provided vital guidance at all stages of the dissertation, from study design to writing.

My deepest thanks to my co-Supervisor, Allan Donner. His knowledge, experience, and high standards were essential to the empirical work, and his wisdom and enthusiasm was vital to the completing the conceptual work in chapters five and six.

I will always be thankful for my friendship and working relationship with Charles Weijer. He has been my co-Supervisor, friend and mentor for the better part of a decade. His enthusiasm, high expectations and faith in my ability to rise to the challenge of this work were essential to the completion of this dissertation.

Finally, the greatest thanks of all go to Michelle Jackman, my wife, partner, and best friend. Without her unconditional love and support, none of this would have been possible. Words cannot express the depth of my love and gratitude. Thank you.

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Appendices

Chapter 1

Introduction

This dissertation will address ethical challenges associated with cluster randomized trials (CRTs). It asks two related questions: 1) what is currently being done in CRTs to address some of the unique ethical challenges that stem from the CRT design? 2) How ought two key ethical challenges—the identification of research subjects in CRTs and adherence to proper informed consent practices—be addressed?

The cluster randomized trial is an experimental design that has become increasingly commonplace in health services research, quality improvement, education, public health and a variety of other fields[1-4]. It differs from individually-randomized controlled trials (RCTs) in fundamental ways[1]. In an RCT, subjects are recruited individually and then randomly assigned to different intervention arms. Subjects are subjected to different experimental interventions in each study arm. Outcome data is collected from the individual subjects and analyzed. Based on the data collected, inferences are then made about the comparative effectiveness of the experimental interventions.

In a CRT, groups of individuals are randomly assigned to different intervention arms. Depending on the kind of interventions under study, the experimental interventions may be applied either to the entire group, or to the members individually. Data may be collected from all group members, from a sample of group members, or from other sources that may reflect the group members' response to the intervention such as hospital administrative data. After the data analysis, inferences may be made about the effects of the experimental interventions on the group-level outcomes, on individual-level outcomes or both.

Thus, in typical RCTs, the individual research subject is the unit of randomization, intervention, and analysis. In CRTs, the cluster is the unit of randomization. The unit of intervention may be the cluster, individual cluster members, or another entity closely associated with the cluster (such as a health professional) such that the intervention on that entity produces a cluster-level effect. The unit of analysis may be the cluster, the individual, or both[1,5].

The randomization of groups leads to a host of ethical challenges that are unique to the CRT design. It is not always obvious who is the research subject in CRTs[4,6-8]. This is especially true in CRTs with interventions that are administered broadly at the cluster level, such as in large scale CRTs of public health interventions. Are all residents of a community participating in a CRT research subjects? What if they are not affected by the study intervention? Identifying the research subject is also complicated in CRTs in such fields as healthcare or education, in which the study interventions are administered to an individual such as a health professional or teacher, and the effect evaluated by collecting data on group members such as patients or students[4,6-8]. Are the research subjects the cluster members, individuals who receive interventions in order to produce cluster-level effects (such as health professionals or teachers), or both?

In some large CRTs, it may not be feasible to obtain informed consent from all cluster members[2,4,9]. It may also not be possible for some cluster members to avoid experimental interventions that are designed to affect the entire cluster[2,4,9]. There are also concerns that obtaining informed consent from subjects in some CRTs may threaten the validity of trial findings[2,4,9]. Because of these challenges, investigators' obligations with respect to obtaining informed consent in CRTs are not well-established.

It is not clear whether the typical criteria that are used to evaluate the harms and benefits of interventions performed on individual subjects in traditional RCTs can be easily applied to CRTs of group-level interventions[5,6].

The moral status of groups is unclear. Some clusters may be groups of individuals with legitimate structure and representation, such as communities[10]. Other kinds of clusters are less well defined with no clear leadership, such as customers in a shopping mall that is participating in a CRT[11]. There is little principled guidance as to who has the authority to decide on behalf of clusters whether or not to participate in a trial[12], nor is there any normative work outlining the scope of authority of these "gatekeepers". Furthermore, there is no normative work addressing the question whether groups of individuals may have collective interests that are in need of protection as that group participates in a CRT. Communities may have collective interests that require regulatory protection[10], but the status of groups that are not communities (e.g. sports teams, schools, medical practices) is not clear.

Recent research ethics guidelines recognize some of the difficult ethical challenges that arise in CRTs. The United Kingdom Medical Research Council included recommendations for ethical CRT conduct within its methodological guidelines for CRTs[12]. The Council of International Organizations of Medical Science's 2009 ethical guidelines for epidemiological research also take note of the logistical challenges in obtaining informed consent in some CRTs[13]. However a systematic examination of the ethical challenges related to CRTs has yet to be undertaken. As a result, there is no authoritative, comprehensive guidance on the ethical conduct of CRTs to aid investigators in performing research with high ethical standards.

Similarly, research ethics committees have no standard to guide their review of CRT protocols[6,14]. The lack of comprehensive, authoritative guidance on the ethical conduct of CRTs has lead to substantial variability in the findings of research ethics committees who have evaluated CRT protocols[14]. This variability in research ethics review has become an impediment to the conduct of multicenter CRTs[6,14]. One group of authors highlighted this problem, writing that "…the moral hazard of this uncertainty is that few formal patient safety studies may be undertaken, resulting in a slowdown in progress…"[15].

This dissertation is undertaken in the context of a larger project, funded by the Canadian Institutes of Health Research[16]. This project, which includes both empirical methods and philosophical reflection by a group of experienced CRT investigators and ethicists, is designed to comprehensively evaluate the key ethical challenges related to CRTs, and to spearhead the development of international consensus guidelines for the ethical conduct of CRTs[16]. The conclusions of each of the papers that comprise this dissertation will contribute to the body of scholarly work that addresses the ethical challenges of CRTs. This work will be invaluable in informing the guideline development process, and will also provide useful guidance to investigators and research ethics boards who deal with the ethical challenges of CRTs on a daily basis.

In order to address the two questions posed at the beginning of this chapter, the dissertation will proceed as follows:

Chapter two will review the basic methodological features of CRTs and the ethical challenges that stem from this design. Chapter two will also outline the basic principles of research ethics that form the conceptual basis for research ethics guidelines and

regulations. The basic principles of research ethics will be used as the framework for evaluating the empirical findings in chapters three and four, and as the basis for normative work in chapters five and six.

Chapter three provides a quantitative description of current informed consent practices in healthcare CRTs. It examines consent practices in a sample of 161 CRTs in primary and hospital care settings. The chapter includes descriptive statistics on the proportion of CRTs that obtained informed consent from patients. The chapter also describes a logistic regression analysis that identifies methodological features of CRTs that are independently associated with the practice of obtaining informed consent from patients in healthcare CRTs.

Chapter four describes an empirical study in which 20 CRT investigators were interviewed about the ethical challenges associated with CRTs and their experiences in addressing these challenges. Qualitative analysis methods were used to provide a rich descriptive summary of researchers' experiences addressing the ethical challenges that are unique to CRT design and conduct.

Chapter five addresses a key ethical question: "Who is a research subject in healthcare CRTs?" In this chapter I argue for a principled, comprehensive definition of "research subject" and I apply it to the CRT context. This work allows the formulation of guidelines that adequately protect subjects in CRTs while avoiding excessive regulatory burdens on CRT investigators, and enables research ethics boards to consider protections for research subjects on a more pragmatic level.

Chapter six reviews the challenges associated with obtaining informed consent in CRTs, including the feasibility of seeking informed consent in large-scale CRTs, the potential for bias introduced by the consent process, and the timing and content of consent discussions. This chapter then draws on one moral theory that underpins the requirement for informed consent for research participation to argue when, and from whom, informed consent is required in CRTs, and what information must be disclosed to potential subjects during consent discussions.

Chapter seven summarizes the preceding chapters, and reflects on the findings of the empirical work in the light of the conclusions of the two normative chapters. This chapter includes a reflection on the relationship between empirical work and normative work in the scholarly enterprise of research ethics. It considers the implications of the findings in this dissertation for the development of ethical guidelines for CRTs. It also considers the implications of this work for other study designs that are used in the quality improvement, health services and public health fields. Finally, chapter seven lays out plans for future work that stems from both the content and the methodology used in this dissertation.

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Chapter 2

Literature Review and Glossary of Terms

This chapter introduces the CRT design and the ethical questions that arise from its methodological features. First, the features of the CRT design will be explained. Basic statistical issues, the uses of the CRT design, and CRT typology will be reviewed. Second, a conceptual framework for the evaluation of ethics challenges in human subjects research will be described. Third, this conceptual framework will be used to guide a comprehensive review of the literature outlining the ethical problems relating to CRTs

Introduction: Cluster Randomized Trials

What is a Cluster Randomized Trial?

A cluster randomized trial (CRT) is an experiment in which groups of individuals (clusters) are randomly assigned to different intervention arms, so that the same intervention is delivered to the entire cluster[1]. The efficacy of the experimental intervention may be evaluated using data from several sources. Data may be obtained from all cluster members or from a sample of the cluster membership. Cluster-level data may also be obtained from other sources, such as administrative databases.

CRTs are becoming an increasingly important methodological tool in a variety of fields, including public health, education, health services research, and for the evaluation of quality improvement and knowledge translation interventions in healthcare.

What are the methodological differences between CRTs and RCTs?

Randomization of Groups Instead of Individuals

In an individual randomized, controlled trial (RCT), individual subjects are randomly assigned to one trial arm or another. The hallmark feature of the CRT is that, rather than randomly assigning individual research subjects to study arms, groups of individuals are randomly assigned to different study arms.

It is important at this point to distinguish between the cluster—the actual group of individuals under study --andthe unit of randomization—the entity that is actually randomly assigned. In many CRTs, the cluster and the unit of randomization are the same. This happens most often when the cluster is an intact social unit, such as a community, family or sports team. Alternatively, the unit of randomization can be an entity that is distinct from the cluster, but whose association with the cluster results in randomization of the entire cluster. For example, in a primary care CRT, a clinic may be the the unit of randomization, creating clusters comprised of that clinic's patients.

Correlation of outcomes between cluster members

Cluster members' responses to the experimental intervention are often correlated with one another. In other words, the effect of the intervention may vary between clusters for reasons unrelated to the efficacy of the intervention, but related instead to common characteristics of cluster members. Depending on the type of cluster and the type of intervention under study, responses between cluster members may be correlated for several reasons:

- Cluster members may share similar environments, such as in CRTs of public health interventions in which all members of the same community receive a cluster-level intervention;
- Cluster members may have genetic similarities, such as when families or isolated communities are used as clusters in a CRT.
- Individuals with particular traits that are relevant to treatment response may self-select cluster membership because of a particular cluster characteristic. For example, older patients may choose a physician with a reputation for being skilled in geriatric medicine.
- Personal interactions between cluster members that result in sharing of information about experimental interventions may create a clustering effect. Similarly, personal interactions between cluster members may lead to rapid spread of communicable diseases[1].

Increased sample size, decreased precision

The correlation in responses between cluster members violates an assumption of standard statistical tests that observations on different subjects are independent. Accordingly, sample size calculations and hypothesis tests must be adjusted to account for the correlation between cluster members. The degree of within-cluster correlation may be quantified using the intra-cluster correlation coefficient (ICC, ρ). One interpretation of the ICC is simply the pairwise Pearson correlation between any two members of the same group or cluster[1]. An ICC of 0 indicates that there is no within-cluster correlation of subjects' responses to an experimental intervention, while an ICC of 1 indicates perfect

correlation. In practice, the ICC may be estimated based on existing literature, or measured empirically in a pilot sample.

Formulae for sample size and hypothesis tests must be adjusted to account for the within-cluster correlation. To account for clustering effects, the estimate of the required number of individuals in each trial arm should be multiplied by a variance inflation factor, $[1+(m-1)\rho]$, where m is the number of individuals in each cluster, and ρ is the ICC. This gives a sample size that accounts for within-cluster correlation[1]. Because of these adjustments, CRTs generally require larger sample sizes than do individually-randomized trials to achieve the same degree of precision.

Hypothesis testing involving procedures such as the t-test or chi-squared test, as well as formulae for confidence interval estimation, must be similarly adjusted. These adjustments result in larger p-values for hypothesis tests, and wider confidence intervals around the estimated effect sizes[1]. A common approach to adjusting for within-cluster correlation in the analysis of CRT data is to add a random effect term to a multivariable regression model so that standard errors are adjusted for within-cluster variation. It is also possible to conduct analyses of summary measures of outcomes at the cluster-level, thereby avoiding the need to adjust for within-cluster correlation.

As a result of the need for larger sample sizes, CRTs often impose greater administrative and financial burdens on study investigators and sponsors. For this reason, the selection of the CRT design for a study must have a very good rationale.

Why is a CRT used?

Given the statistical and logistical disadvantages of the CRT design, the use of the CRT must be justified by some other methodological advantage. There are several reasons for choosing the CRT design. For some studies, there may be multiple reasons for choosing the CRT design.

The CRT Evaluates Group-level Interventions

CRTs are often used to evaluate interventions that are designed to affect the entire group. For example the COMMIT study compared the efficacy of different public education and media strategies aimed at increasing smoking cessation in participating communities[2]. These interventions are administered to the entire community, and therefore the community was used as the unit of randomization.

This same justification for cluster randomization may apply to some CRTs in healthcare, particularly to CRTs evaluating knowledge translation (KT) or health service interventions. KT CRTs evaluate training or educational interventions for health professionals that are intended to improve patient care. Outcomes of interest may include health professional behaviours as well as patient-level outcomes. For example, one CRT evaluated the efficacy of different educational strategies for physicians designed to improve evidence-based prescribing for patients with diabetes and cardiovascular disease[3]. The outcomes evaluated included physicians' perceptions of the efficacy of the intervention, as well as objective changes in prescribing practices as ascertained from patients' prescription data accessed from a national pharmacy database. CRTs are used to evaluate changes in health service provision or changes to healthcare systems, as these

interventions are conducted only at the cluster level. For example, a CRT evaluating a modification to patients' electronic medical record to issue prescribing reminders for patients with diabetes[4] is most easily implemented at the practice level. For this reason, a CRT design was chosen with the medical practice being the unit of randomization.

Avoidance of Treatment Contamination and Maximizing Adherence

The CRT design may be chosen in order to avoid treatment contamination. Treatment contamination refers to a phenomenon observed in individually randomized trials in which subjects assigned to one arm may share elements of their intervention with subjects in another trial arm who are in close proximity[1]. For example, contamination might be observed if individuals in the same family are participating in a trial of a dietary intervention, and are randomly assigned to different arms. It is possible that subjects would share elements of the different interventions with each other. Treatment contamination tends to bias the outcome of a trial toward a null result. CRTs are therefore used to evaluate individual-level interventions that are easily shared by individuals who may be participating in the same trial[1].

CRTs are also used to evaluate interventions directed at healthcare professionals or organizations in which it would be difficult to apply the intervention to some patients and not to others[1]. One example of such a trial evaluated the efficacy of early breastfeeding in reducing the frequency of postpartum hemorrhage[5]. The unit of randomization for this trial was the birth attendant rather than the individual patients, as the birth attendants may have found it difficult to only advise early breastfeeding to half of their patients.

Random assignment in clusters may also improve intervention adherence within the cluster. A CRT evaluating the effect of treated nasal tissues on incidence of respiratory illness randomized families rather than individuals[6]. Investigators believed that adherence to use of the assigned tissue type would be enhanced if entire families were the unit of randomization rather than individuals within families.

Evaluation of Individual- and Group-level outcomes

The CRT design permits the evaluation of both individual-level outcomes and group-level outcomes within the same study[1]. This is particularly advantageous in CRTs evaluating vaccine efficacy[7]. A CRT randomly assigning communities to two different vaccine programs allows for comparison between the relative efficacy of vaccine programs for vaccinated persons (an individual-level outcome) as well relative vaccine efficacy at the community level (a group-level outcome that includes both vaccinated and unvaccinated individuals)[7].

Political, Logistical and Administrative Reasons

The CRT design has sometimes been employed for political reasons, often in developing countries in which communities were the unit of randomization. Investigators have encountered situations in which community leaders have refused to allow random assignment of individuals within communities, and have insisted that all community members be offered the same intervention. One example is a CRT evaluating the effect of vitamin A supplementation on child mortality. 450 villages in Indonesia were randomly assigned to either participate in mass vitamin A supplementation or to serve as control

communities. Investigators reported that it was “not politically feasible” to randomly assign individuals within communities to either intervention or control arms[8].

The statistical inefficiency of the CRT design may be outweighed by administrative or logistical factors[9]. Randomization in clusters may decrease the number of research personnel required to collect data, and decrease the logistical challenges required for data collection such as time and travel requirements[9]. Some subjects, such as patients, may only be accessible through health professionals or health care organizations, so the use of these professionals or health care organizations as the unit of randomization may be necessary[9]. It may also be easier to access administrative data or private health information in some circumstances if a health professional or health care organization is used as the unit of randomization[9].

In some CRTs, medical practices were randomized rather than individual patients in order to assuage the fears of health professionals who were uncomfortable having their patients randomly assigned to either the intervention or control arms[1].

Typologies of CRTs

Two typologies have emerged to describe the variety of interventions that may be evaluated in the multiple fields that employ the CRT design. The aim of developing a typology is to be able to easily refer to CRTs or to CRT interventions that share common features. These two typologies group CRTs and CRT interventions based on the ability of individual cluster members to either consent or opt out of study interventions.

Edwards and colleagues created a dichotomous typology to describe CRTs[10]. Cluster-cluster CRTs are trialsin which experimental interventionsare administered at the cluster

level and designed to affect all individuals in the cluster. Examples include public health interventions such as mass media campaigns or water treatments, curricular innovations in education, or healthcare quality improvement innovations that are implemented at the level of a hospital or health system. Individual-cluster interventions are CRTs in which experimental interventions are administered to individual cluster members, primarilyto avoid experimental contamination, with the intent of producing an individual-level effect. Examples include individual health interventions evaluated in CRTs that randomize medical practices in order to avoid contamination.

Eldridge and colleagues expanded Edwards' classification to four categories: cluster-cluster, individual-cluster, professional-cluster and external-cluster[11]. Importantly, Eldridge et al recognize that a CRT may include both interventions administered at the cluster level as well as interventions administered to individual cluster members. Therefore, the Eldridge typology classifies CRT *interventions*, rather than classifying CRTs as a whole.

Cluster-cluster interventions have a similar meaning for Eldridge et al. as for Edwards et al. The key feature of a cluster-cluster intervention is that the intervention is applied at the cluster level, and affects all cluster members. Cluster members cannot avoid or opt out of a cluster-cluster intervention.

Individual-cluster interventions are also similarly classified in the Eldridge and Edwards typologies. These interventions are applied to individuals, who have the opportunity to choose whether or not to participate in the CRT. The CRT is chosen to avoid experimental contamination in the administration of the experimental intervention.

Professional-cluster interventions are used in CRTs in which the cluster is defined by its relationship to a professional, such as a teacher or healthcare professional. These are

typically educational or quality improvement interventions directed at professionals, and are designed to influence how those professionals serve those for whom they are responsible. An example is the use of automated reminders of optimal prescribing practices of antiplatelet medications for diabetic patients in primary care[4]. Patients do not have the opportunity to avoid the effects that the experimental intervention may have on their care, although there may be an opportunity for patients to decline to have their data used[11].

External-cluster interventions are primarily used in healthcare CRTs, and refer to interventions that re-organize health systems by using additional or different healthcare providers[11]. Randomization of clusters is done to avoid contamination, or for logistical or financial reasons. An example of an external-cluster intervention is the use of a nurse specialist to administer asthma care instead of or in addition to a primary care physician[12]. Patients can opt out of studies using external-cluster interventions simply by refusing to utilize the additional staff[11].

These categories may be useful in categorizing interventions that have different ethical implications, particularly respect to subjects' ability to choose whether or not to undergo a particular type of intervention. However, this typology hasa number of problems that limit its widespread use without further clarification and validation.

First, these categories only refer to the experimental interventions under study in a CRT. Trials also include interventions used solely to collect data[13]. In CRTs, these may be interactions with, or interventions on individual subjects; they may consist of collection of subjects' identifiable private information; or they may use administrative data that allows the evaluation of group-level outcomes. The categories in the Eldridge typology do not take account of data-collection procedures.

Second, while it makes sense to categorize the experimental interventions in a CRT, rather than categorizing the trials themselves (which may contain different kinds of interventions), it is easy for users to conflate a typology describing the interventionsas describing the trials themselves. Therefore, it is important to be clear on the distinction between a subject's ability to avoid or opt out of an *intervention*, and a subject's ability to avoid or opt out of a *trial*.Subjects can only opt out of a trial if they are able to avoid or opt out of all experimental and data-collection interventions.

Third, Eldridge concedes that users may disagree on the categorization of a particular intervention, and that there may be overlap between categories[11].

Fourth, the typology does not capture all of the interventions in CRTs in which the cluster is defined by its relationship to a professional such as a healthcare professional or teacher. These CRTs may have interventions that are directed at those professionals, and are designed to produce a specific effect on those professionals, such as in increase in knowledge. These interventions do not necessarily have a measurable cluster-level effect, and so describing them using the professional-cluster typology seems inappropriate.

Finally, the four-category Eldridge typology for CRT interventions may be reducible to two categories that resemble Edwards' classification. Professional-cluster interventions closely resemble cluster-cluster interventions, in that they are administered at the cluster level that cannot be avoided by individual cluster members. The fact that a cluster member may opt out of data collection is a feature of the trial, not of the intervention in question, so professional-cluster interventions are probably best thought of as a subspecies of cluster-cluster interventions. External-cluster interventions resemble individual-cluster interventions, in that individual cluster members can choose not to participate in the trial or

see the additional staff members. For CRTs of external-cluster interventions, cluster randomization is undertaken for practical reasons, not because of the nature of the interventions. It may be reasonable to think of external-cluster interventions as a subspecies of individual-cluster interventions.

In this dissertation, the preferred terminology will refer to cluster-level interventions and individual-level interventions. Cluster-level interventions are those that are directed at the entire cluster, and intended to produce an effect on all cluster members, independent of their ability to avoid the intervention. These include Eldridge's cluster-cluster and professional-cluster interventions. Individual-level interventions are those that are directed at individual subjects and are intended to produce an effect on that particular subject. These include Eldridge's individual-cluster and external-cluster interventions. Interventions directed at professionals that are designed to produce an effect on those professionals, without necessarily producing a cluster-level effect, will be considered separately.

A Conceptual Framework for Addressing Ethics Questions in CRTs

There is a small but growing literature that discusses the ethical issues of the CRT design. Specifically, commentators have been concerned with the logistical feasibility of obtaining consent from subjects in large trials[9-11,14-16], the potential biasing effect of the consent negotiations in CRTs of behavioural interventions[9,10,15,17], the lack of benefit to subjects in control groups[14,15], and questions about who has the authority to speak on behalf of a cluster [9,10,18].

CRTs share many of the characteristics of individually-randomized clinical trials. It therefore makes sense to appeal to the robust literature on the ethics of clinical trials as a starting point for a discussion of the ethical questions of CRTs. In some instances, however, there will be a lack of fit between research ethics guidelines for individually-randomized clinical trials and CRTs that randomize groups of individuals. Current research ethics guidelines and regulations were developed to address ethical challenges in which subjects are recruited individually, as in a typical RCT. The ethics of CRTs in which a cluster is the unit of randomization and/or the unit of intervention are less clear.

In instances in which widely-accepted solutions for ethical challenges in individually randomized trials do not address problems in CRTs, it is helpful to turn to a broadly-accepted framework for the discussion of ethical issues in human subjects research. This conceptual framework has been developed over more than forty years of scholarly work. By using this approach, solutions to ethical problems posed by CRTs can be defended by appealing to widely accepted ethical principles, and to the moral theories on which these principles are based.

The Ethics and Regulation of Human Subjects Research

The study of the ethics of research involving human subjects evolved largely in the second half of the twentieth century[19,20]. Scholarly work in research ethics occurred in parallel with the development of regulations governing human research that have been promulgated by various international bodies and federal governments. Both normative reflections on human subjects research and regulatory documents generally refer to research in which subjects are identified and recruited individually, prior to the application

of research interventions. With a few notable exceptions, CRTs are not specifically mentioned in most scholarly work and regulatory documents, meaning that the application of research ethics principles and guidance to CRTs is left to the interpretation of ethicists, researchers and research ethics boards. Below, we review first the evolution of scholarly work that lays out the basic principles of the ethics of human subjects research, then review in detail the key regulatory documents that researchers and research ethics boards may draw upon while reflecting on the ethical questions posed by CRTs.

Basic Ethical Principles for Human Subjects Research

The most broadly accepted articulation of the basic ethical principles for human subjects research comes from the Belmont Report, the 1979 Report of the US National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (referred to hereafter as the "National Commission")[21]. The Belmont Report outlines three basic ethical principles that guide the conduct of human subjects research: respect for persons, beneficence, and justice. The Belmont report also specifies moral rules that stem from each of these principles[21].

The principle of *respect for persons* is derived from a philosophical heritage that emphasizes the unconditional worth of all autonomous individuals[21-23]. Therefore, the principle of respect for persons requires that the choices of autonomous individuals be respected, and that individuals with diminished autonomy be protected. The Belmont Report states that to respect an autonomous individual is to respect that individual's wishes with regard to research participation, and to maintain the confidentiality of private information. Thus, the principle of respect for persons entails moral rules requiring the

informed consent for research participation from research subjects, as well as requirements for safeguarding subjects' private information. The Belmont Report also recognizes that individuals with diminished autonomy are vulnerable to exploitation. To respect these individuals requires extending additional protections. These include requirements for consent from an authorized substitute decision-maker, the requirement for the potential subjects' assent for research participation, and limits on the kinds of risks to which an individual with diminished autonomy may be exposed as a result of research participation[21].

The principle of *beneficence* encompasses two moral obligations: to refrain from doing harm, and to maximize possible benefits while minimizing harms. The principle of beneficence entails moral rules with respect to the analysis of harms and benefits that particular studies pose to their subjects. Investigators and ethics committees are responsible for ensuring that the risks and benefits to research subjects stand in reasonable relation[21].

The principle of beneficence also applies more broadly to societal benefits that accrue from scientific research. It is an issue of beneficence as to whether the knowledge benefits of a scientific research program justify the risks that research poses both to individual subjects and to our social fabric[21].

The principle of *justice* refers to the fair distribution of the burdens and benefits of research, and entails moral rules about selection of study populations and subjects. *Justice* requires that no individuals or groups of individuals be systematically excluded from research, thus depriving them of the benefits of research participation, unless that exclusion can be justified on scientific grounds. This requirement is particularly relevant to groups such as women and children, who might stand to benefit from research participation, but

who have historically been unjustifiably excluded from research studies. Justice also requires that a group not be unfairly burdened with the risks of research participation. This means that a group should not be used as a population of convenience, as has occurred in the past with hospitalized individuals, visible minorities, underprivileged persons, and prisoners[21].

More recently, a fourth principle, *respect for communities,* has been proposed and is gaining increasing acceptance[24]. This principle recognizes the value of communities as a source of personal values and self-understanding, and their importance for the well-being of community members. Some types of communities legitimately exercise power to make decisions that are binding on their members. The principle of respect for communities demands that investigators respect communal values and social structures, and abide by decisions of legitimate community authorities[24].

These basic principles are intended to entail *prima facie* obligationsthat must be fulfilled[25]. Ethical challenges arise when obligations stemming from one principle conflict with obligations stemming from another. There is no implicit hierarchy of principles:

> "Although we begin our discussion of principles of biomedical ethics with respect for autonomy, our order of presentation does not imply that this principle has priority over all other principles. A misguided criticism of our account is that the principle of respect for autonomy overrides all other moral considerations. This we firmly deny.[25]".

It is the task of the research ethics committee to resolve ethical dilemmas resulting from a conflict between principles. This can be done by a weighing of the competing moral demands[20,22,26], which requires a thoughtful appeal to the moral theories that underpin each

of the basic principles[22]. In subsequent chapters, we will apply this approach to a critical examination of the ethical questions posed by CRTs.

Ethical Guidelines for Human Subjects Research

Guidelines for the ethical conduct of research involving human subjects were promulgated prior to the systematic articulation of basic ethical principles in the Belmont Report [27,28]. Although early guidelines are not obviously based on the Belmont Report principles, these guidelines and the Belmont Principles reflect common moral norms[25].

The promulgation of the Nuremberg Code marks the effective start of international efforts to regulate the conduct of human subjects research. The Code comprises a set of recommendations for the conduct of ethical research that emerged from the trial of Nazi physicians who conducted medical experiments on non-consenting prisoners during the Second World War. The experiments in question often caused terrible suffering to subjects, and frequently had little scientific importance or methodological validity. These experiments took place in spite of research regulations in German and Russian law that required the informed consent of research subjects[29]. The Nuremberg Code's first requirement isabsolute: researchers must obtain informed consent from subjects. The Nuremberg Code also requires that the research be scientifically valid, that unnecessary suffering should be avoided, that risks be justified by the humanitarian importance of the research, and that research be stopped if there is risk of death or injury to the subject[29].

The Nuremberg Code does not specifically address the broad range of areas of inquiry and variety of research methodologies in human subjects research. It does not contemplate such challenges as research on individuals with limited decision-making

capacity such as children or incapable adults, nor does it recognize that some human research necessarily involves interventions that may pose serious risks to research subjects. Taken literally, the Nuremberg requirements would curtail the biomedical research enterprise.

The World Medical Association has promulgated its own ethical guidelines, which have become known as the Declaration of Helsinki. Initially published in 1964, and revised on eight occasions, most recently in 2008, the Declaration of Helsinki has become the most widely utilized international guideline for the conduct of human subjects research. The Declaration of Helsinki differs from the Nuremberg Code in that it explicitly allows for research on subjects with diminished autonomy, even though it pays more attention to the use of vulnerable or disadvantaged populations in research.

Revisions of the Declaration of Helsinki[27], Guidelines from the Council of International Organizations of Medical Science[30,31], and guidelines from the Canadian Institutes of Health Research, National Science and Engineering Research Council and Social Sciences and Humanities Research Council[32], along with the Australian National Health and Medical Research Council[33] include their own statements of basic principles. Although each agency's guidelines articulate basic principles differently, all are clearly indebted to the authors of the Belmont Report[27,30-33]. Numerous research ethics guidelines therefore outline specific moral rules that stem from the basic principles of respect for persons, beneficence and justice outlined in the Belmont Report.

In 1981, US Department of Health and Human Services issued new human subjects research regulations in 1981 based on the recommendations of the National Commission. A subpart of these regulations that includes informed consent requirements and rules for

Institutional Review Board review are known as the Common Rule because, as of 1991, they apply to all human subjects research conducted or funded by US Federal departments[34]. The Common Rule offers specific guidance as to the procedural requirements for research ethics review. It also outlines, in great detail, requirements for informed consent, including a provision for a waiver of consent for certain kinds of research[34]. Human subjects research in Canada is governed by the guidelines adopted by the country's three major research funding agencies, namely the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans[32]. The Tri-Council Policy lays out eight basic ethical principles that are largely reducible to the three Belmont Principles. This framework of ethical principles gives rise to detailed guidance for consent processes, the assessment of the harms and benefits of research, and the just recruitment and treatment of research subjects[32].

Guidelines for CRTs

Two guidelines address specific ethical problems in CRTs, but neither comprehensively addresses the breadth of ethical questions that have been encountered in CRTs.

The 2009 revision of the Council of International Organization of Medical Science (CIOMS) International Ethical Guidelines for Epidemiological Studies[30] clearly derives from three Belmont Report principles of respect for persons, beneficence, and justice. CRTs are one of five types of studies for which the CIOMS guidelines state that a waiver of consent may be permissible: If a CRT is evaluating cluster-level interventions that are difficult to avoid, then a waiver of consent may be permissible.

The CIOMS guidelines suggest that even if consent is not possible, that community residents should still be notified that a CRT is being conducted[30]. If consent from individual cluster members is not possible, the CIOMS guidelines require that investigators identify an entity that has the authority to give permission for the cluster to be enrolled in the CRT. According to CIOMS, the decision-maker should have the authority to make decisions to undertake interventions similar to those being evaluated by the CRT. The decision-maker may also choose to consult the community more broadly prior to agreeing to CRT participation. The CIOMS guidelines give research ethics committees the latitude to require that investigators consult with community members prior to commencing a study, in order to seek the community's input into the study protocol. The CIOMS guidelines also contain sections pertaining to research performed on underprivileged populations that may be applicable to CRTs conducted in developing countries[30].

The 2002 UK Medical Research Council's statement *Cluster Randomized Trials: Methodological and Ethical Concerns*[18] contains guidance with respect to consent procedures and the role of cluster decision makers. The MRC guidelines require investigators to seek consent from individual cluster members whenever possible (i.e. for CRTs involving individual-level experimental interventions or interventions on individual cluster members for the purpose of data collection)[18]. The MRC guidelines also set out detailed guidelines for the function of individuals who make decisions on behalf of clusters, referred to in the guidelines as Cluster Representation Mechanisms (CRMs)[18]. CRMs must act in the interests of both the cluster and the individual cluster members, which may be difficult if these interests conflict. The CRM has rights similar to those of an

individual subject in an individually randomized trial, including the right to withdraw the cluster from the CRT.

Neither set of guidelines clearly identifies when seeking informed consent is necessary and when using a waiver of consent is acceptable. They only specify circumstances in which consent may not be required. Nor do these guidelines detail the essential elements of disclosure in consent negotiations. Neither the CIOMS nor MRC guidelines lay out clear rules for the analysis of harms and benefits in CRTs.

Using a conceptual framework for research ethics to address ethics questions in CRTs

This dissertation will employ a conceptual framework rooted in the basic ethical principles of respect for persons, beneficence, and justice. Ethical questions arising from the CRT design will be framed in terms of conflicts between obligations that stem from conflicting principles. Ethical challenges in CRTs will then be addressed by evaluating the competing moral demands of each conflicting principle. By appealing to the moral theories on which each principle is founded, and to associated moral concepts articulated in the research ethics literature, one can hope to identify a justifiable solution to the ethical problems associated with the CRT design. This work will, in turn, inform the development of comprehensive research ethics guidance that adequately addresses the breadth of ethical questions arising in CRTs[35].

Ethical Questions in CRTs

Many of the ethical problems relating to CRT conduct have been identified in the literature by CRT investigators who have encountered these challenges in practice. This dissertation contributes to the activities of a working group of experienced CRT investigators and ethicists, funded by the Canadian Institutes of Health Research. This working group systematically reviewed the literature on the ethics of CRTs and identified key ethical questions raised in the literature. Using the conceptual framework outlined above, the working group identified important ethical issues that had not surfaced in the CRT literature[35,36] as well as questions arising from the conceptual framework for research ethics. It identified six broad questions that, once addressed, will provide comprehensive guidance to investigators and research ethics committees:

1) Who is the research subject in CRTs?
2) When, from whom, and how must consent be obtained?
3) Does clinical equipoise apply to CRTs?
4) How should the risks and potential benefits of CRTs be evaluated?
5) How ought vulnerable groups be protected in CRTs?
6) Who are cluster gatekeepers, and what are their responsibilities?

Each of these questions will now be briefly considered.

1) Who is the research subject in CRTs?

A key ethical problem in CRTs is the identification of research subjects[36]. In typical RCTs it is generally obvious who the research subjectis. The subject is any individual who

is recruited, enrolled, and intervened upon. In CRTs it may be unclear who the research subjectsare. CRTs often target groups of individuals, but it is not obvious that all group members who may be affected by CRT interventions are, in fact, research subjects. For example, a CRT may randomly assign communities to different mass media campaigns aimed at increasing residents' participation in physical activity[37]. Although there are no direct interventions on the community residents, they may still be research subjects. What if a resident is not exposed to the campaign? What about individuals who may be visiting that community? What about residents of control communities that do not receive any intervention?

Some CRTs may intervene upon professionals (e.g., physicians or teachers) and evaluate the effect of the intervention using data from the individuals that the professionals serve (e.g. patients or students). It is unclear whether the research subjects arethe professionals who are intervened upon, the individuals that they serve, or both[9,38-40]. In one example, a trial randomized primary care clinics to different continuing education strategies, and evaluated the effect of the education strategies on prescription patterns by abstracting data from patients' prescriptions[41]. Are the patients research subjects? How about the health professionals who are the recipients of the study interventions?

There are two important reasons to examine the question of who the research subject is in CRTs. First, failure to correctly identify who is and who is not a research subject in CRTs may result in the failure to adequately protect some research subjects or may, conversely, lead to overzealous protection of individuals who are not research subjects, leading to the hindrance of important research. Second, research subjects in CRTs must be identified before other ethical challenges, such as consent issues or the analysis of harms

and benefits, may be considered either as a normative question or as a pragmatic issue for investigators and research ethics boards.

Both the MRC ethics guidelines for CRTs[18] and the CIOMS guidelines for epidemiologicresearch [30] assume that cluster members will necessarily be subjects, without providing any justification. The issue of whether or not professionals who are the recipients of educational or quality improvement interventions in CRTs are research subjects has been addressed in two papers in the research ethics literature; both concluded that health professionals are research subjects[39,40]. Several other papers offer diverging views on whether consent is required from health professionals, without explicitly considering whether or not the professional is, in fact, a research subject. Some authors argue that consent should be sought from health professionals[9,38], while others argue that consent requirements should be waived[42].

Only one paper has explicitly considered whether the patients of health professionals participating in a CRT need to be considered research subjects[39]. The paper concluded that patients of a health care provider whose care may be indirectly affected as a result of interventions on the provider are research subjects. However, no argument is offered in support of this conclusion[39]. Further normative work is required to examine arguments that may support or refute these conclusions. The question of who is a research subject will be addressed in detail in Chapter Five of this dissertation.

2) *When must consent be obtained in CRTs?*

The bulk of the literature on the ethical challenges of CRTs focuses on issues around obtaining informed consent from research subjects[1,9-11,14-16,42]. Ethical problems relating to

informed consent in CRTs can be grouped into four broad categories. Each of the issues described below will be addressed in more detail in Chapter Six of this dissertation.

2.1) Feasibility of obtaining informed consent in CRTs

CRTs have become the gold standard methodological technique for evaluating the efficacy of public health interventions applied to groups such as neighborhoods, communities or larger social-political entities. Assuming that citizens of communities participating in public health CRTs are research subjects (something that is not a foregone conclusion), the logistical effort and expense that would be required to obtain consent for research participation from all subjects would make many large community-based CRTs unfeasible[1,9,10,14,15,18,39,40]. Some research ethics guidelines include rules for waiving the requirement for obtaining informed consent if this is not feasible[18,27,30,32,34]. However, there has been no principled examination of the moral justification for the use of a waiver of consent. Identifying a justification for the use of a waiver of consent will be helpful in developing clear guidelines that specify when the use of a waiver of consent is permissible for CRTs.

2.2) Threats to internal validity due to consent requirements

CRTs are often used to evaluate interventions designed to modify the behaviour of the research subjects. Several commentators have suggested when information is disclosed to subjects during consent negotiations about the study's purpose and interventions, this may be sufficient to prompt a behavioural change among subjects[10,15,17,42]. This unintended behavioural change effect may be sufficient to threaten the validity of effect estimates.

Some have argued that the potential for bias in CRTs of behavioural interventions is sufficient to justify either a waiver of consent for some CRTs, or an alteration of the information that is disclosed to potential subjects during consent negotiations[10,15]. A principled moral justification for waiving consent requirements because of potential threats to validity from disclosure in consent negotiations has yet to be articulated in the CRT literature.

One strategy for minimizing bias and for increasing sample sizes has been to use a passive consent, or "opt-out" model for subject enrollment. This has been used frequently in education[43] and health services research[44-46]. Subjects are assumed to be agreeable to CRT participation unless they (or their substitute decision-maker) explicitly opt out. Although national and international ethics guidelines allow for waivers or alterations of consent requirements in specific circumstances, none discuss the use of an opt-out consent model[18,27,30-34]. Furthermore, there has been no substantive normative work that examines whether or not an opt-out consent model is sufficiently respectful of subjects' autonomy so as to be a reasonable substitute for seeking informed consent.

2.3) Timing and Meaning of informed consent in CRTs

In typical RCTs, subjects give consent for trial participation at the time of enrolment. This consent includes consent to random assignment, to receive the study intervention, and to undergo any interventions necessary to gather data. In many CRTs, investigators may not be able to seek subjects' consent for random assignment or for the experimental interventions[11,42]. Whether obtaining consent for CRT participation is possible prior to randomization depends, in large part, on the type of cluster and unit of randomization[47]. It

may be possible to enroll a cluster and obtain consent prior to randomization if the cluster is small and all members are easily accessible, such as in a family. If clusters are large, or if cluster members are not identifiable at the outset of a trial, obtaining consent after randomization is the only option[47].

If random assignment of clusters is done before subjects are enrolled, then consent for random assignment is not possible. It is also unclear what information must be disclosed to subjects who are enrolled in a CRT after random assignment of clusters. Some commentators have expressed concern that obtaining consent after randomization of clusters violates subjects' autonomy rights[14,15,42].

The experimental intervention may be a cluster-level intervention that individual subjects may not be able to avoid. In these cases, refusal would be meaningless[11,42]. Some cluster-level interventions which are unavoidable may be eligible for a waiver of consent, but consent for some data-collection interventions may still be required. Some of the conceptual work in this dissertation will examine whether the pragmatic challenges relating to obtaining informed consent in CRTs can be reconciled with investigators' obligations to respect subjects' autonomy.

2.4) Can professional obligations mandate CRT participation?

Many professionals must engage in continuing education in order to maintain their licensure. Similarly, organizations such as hospitals or school boards may undertake quality improvement initiatives. Continuing education and quality improvement programs may be evaluated using CRTs. Can a professional obligation to partake in continuing education entail an obligation to participate in a CRT evaluating a continuing education

program? Can organizations that choose to participate in a quality improvement CRT mandate participation by their employees? Commentators[42] have offered several arguments as to why professional obligations should necessarily entail CRT participation by professionals. These arguments will be examined in Chapter Six.

3) Does clinical equipoise apply to CRTs?

In individually-randomized medical clinical trials, the random assignment of patient-subjects to trial arms is justified by the concept of clinical equipoise. Clincal equipoise refers to a state of honest professional disagreement in a community of experts as to the preferred treatment. If such a state exists, then subjects are not disadvantaged by random assignment to one arm or another. The RCT must be designed to disturb this state of clinical equipoise, and thus change practice[48].

Although equipoise is pointed to in the CRT literature as a moral requirement[14], it is not obvious whether the traditional conception of clinical equipoise is easily applied to CRTs[49]. Clinical equipoise in typical RCTs is grounded in the fiduciary duties that physicians owe their patients; a physician is only justified in recommending enrolment in an RCT to her patient if clinical equipoise exists[48,49]. In many CRTs, the researcher-subject relationship is not analogous to the physician-patient relationship. So, it is not obvious whether clinical equipoise may be used as a moral justification for random cluster assignment[49].

4) How should the risks and potential benefits of CRTs be evaluated?

Neither the literature nor ethics guidelines offer substantive advice on how investigators and REBs should consider the harms and benefits in a CRT. REBs may be able to consider the harms and benefits of interventions in a CRT that are directly applied to individual subjects using the same criteria as those used in individually-randomized clinical trials[13]. The principle of beneficence requires that investigators maximize benefits to research subjects, while minimizing harms. Investigators and ethics committees are thus charged with ensuring that the risks posed to subjects in CRTs are reasonable in relation to the potential benefits.

A widely accepted approach, called component analysis, provides a systematic framework for the assessment of harms and benefits in human subjects research[13]. Component analysis first divides study interventions into two categories. Therapeutic interventions are typically the interventions being evaluated in a clinical research study. They offer the prospect of direct benefit to subjects. In a clinical trial, therapeutic procedures must satisfy the conditions of clinical equipoise, must be consistent with competent care, and may only pose risks that are justified by the expected therapeutic benefit. Non-therapeutic interventions are those that are used to collect data, and thus solely serve a scientific purpose. The risks of non-therapeutic interventions must be minimized, consistent with sound scientific design, and must stand in reasonable relation to the knowledge that is expected to be gained from these interventions[13].

Component analysis may be applied to CRTs in which the study interventions are directed at individual subjects. It is not obvious whether component analysis can be applied as easily to CRTs that evaluate cluster-level interventions[36]. It remains an open question

whether public health interventions administered at the cluster level can be considered in the same way as therapeutic interventions that are administered to individual subjects. It is also unclear how to evaluate the harms and potential benefits of complex interventions that are designed to modify professional behaviour such as in healthcare knowledge translation or quality improvement studies[36].

5) How ought vulnerable groups be protected in CRTs?

The principle of justice entails moral rules for subject selection, requiring that no individuals or groups be inappropriately excluded from research while also ensuring that vulnerable groups or individuals are not exploited as a population of convenience[21]. CRTs using vulnerable groups such as individuals in developing countries or populations with low socioeconomic status face similar justice issues to typical RCTs. CRTs must be responsive to the health needs of the population under study. In other words, the population under study must be selected because the use of that population is necessary to the scientific question of the trial, and the study itself must address the needs of that population[27]. Other questions of justice that have proven to be challenging for RCTs also apply to CRTs[36]. What ethical standards for subject protections ought to apply: local standards, or the standards of the study sponsor's country? Should subjects in the control arm be offered the best proven control intervention, or thebest intervention that is locally available? What obligations do investigators and study sponsors have to subjects and host communities after a CRT is completed?

6) Who is a gatekeeper, and what are their responsibilities?

There may be ethical, logistical or political reasons for seeking permission to enroll a group in a CRT. This permission is typically sought from an entity that has been described in various publications as a decision-maker[30], guardian[10], gatekeeper[15,18], or cluster representation mechanism[18]. Requirements to seek permission from a cluster decision-maker leads to several important questions. Who is empowered to speak on behalf of a community or group of individuals with respect to CRT enrolment? What is the source of their authority? What is the scope of their authorization for CRT participation: does it supplement or obviate the need for consent from individual cluster members? What out to be done if no legitimate cluster decision-maker can be identified? What criteria ought cluster decision-makers use to guide their decisions whether or not to enroll a cluster in a CRT?

Many communities, whether geographic, cultural, religious or otherwise, have legitimate political representatives who are empowered to protect the collective interests of that community[24]. Examples of such individuals may include a mayor or tribal leader. The status of other groups that may be recruited as clusters in CRTs, including hospitals, schools, sports teams, workplaces, and many others, is less clear. Some of these groups may even have clear leaders, such as a hospital CEO or the coach of a sports team. The diversity of groups that may be involved in CRTs leads to difficulties defining the scope of a gatekeeper's authority, and the criteria they ought to use when deciding whether or not the cluster they lead should participate in a CRT.

Summary

Current research ethics guidance does not comprehensively address the numerous ethical challenges that arise from the CRT design. A systematic enumeration of these ethical questions and a plan to address each key ethical problem is necessary in order to provide investigators and research ethics committees with guidance as to how to conduct important research while simultaneously safeguarding the interests of research subjects.

This dissertation will contribute to the systematic evaluation of ethics challenges in CRTs. This literature review enabled an enumeration of the key ethical questions stemming from the CRT design. This review also provided a summary of a robust conceptual framework for the ethics of human subjects research. This framework will be used to critically reflect on the findings of the empirical evaluation of ethics practices in CRTs described in the following two chapters. This framework will also form the basis of normative analysis of the questions “Who is a research subject?” and “When is consent required in CRTs?” in chapters five and six.

Glossary of terms

Bias: The distortion of a measure of association between an exposure or intervention and an outcome due to some sort of systematic error. Subtypes include (but are not limited to) information bias, such as measurement error, or selection bias, which is a systematic problem with subject recruitment that influences study findings[50].

Clinical Equipoise: The ethical justification for random assignment in a clinical trial. Clinical equipoise exists if there is "state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment.[48]" If clinical equipoise exists, then subjects are not disadvantaged by random assignment to one trial arm or another.

Cluster: In a CRT, a cluster is a group of individuals with common features. The cluster may be the unit of randomization, unit of intervention, unit of analysis, unit of inference, or any combination of the above.

Contamination: A source of bias that results from subjects in one trial arm having access to the interventions delivered in another trial arm.

Knowledge Translation: Activities or processes that facilitate the transfer of high-quality evidence from research into effective changes in health policy and clinical practice[51]. May include such activities as practitioner education or processes of care such as electronic reminders of best practices.

Quality Improvement: Interventions that arelinked to assessment and that have thegoal of improving the process, outcome,and efficiency of complex systemsof health care[52]. These most often are intended to result in local improvements in quality of healthcare delivery, and are not necessarily generalizable to other settings.

Randomization/Random Assignment: The random assignment of individual subjects (in an RCT) or clusters into different arms of a clinical trial. This ensures that the features of subjects that may influence the study's findings are similarly distributed in each trial arm.

Research: A systematic investigation designed to develop or contribute to generalizable knowledge[34].

Risk: The probability and magnitude of harm posed to a research subject by a research intervention

Unit of Randomization: The entity that undergoes randomization to create trial arms. In a CRT, this may be the cluster itself (e.g. a community), or it may be an individual with an affiliation with a cluster that enables randomization of the cluster (e.g. a physician whose practice defines the cluster).

Unit of Intervention: The entity that undergoes the experimental intervention. In a CRT, this may be the cluster itself (e.g. a community), or individuals within the cluster.

Unit of Analysis: The entity to which statistical inferences are imposed. Depending on the scientific question of a CRT, this may be the individual cluster member, the cluster as a group, or both.

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Chapter 3

Factors Associated with Reporting of Patient Consent in Healthcare Cluster Randomized Trials

Introduction

Cluster Randomized Trials (CRTs) have become an important research tool in evaluating the effectiveness of interventions designed to improve the quality or efficiency of health care services. CRTs may evaluate several kinds of healthcare interventions. They may evaluate the effect of a therapeutic intervention that is directed at individual subjects, and randomly assign subjects to trial arms in groups in order to avoid experimental contamination within groups[1]. Alternatively, some CRTs randomly assign healthcare professionals or organizations to trial arms in order to evaluate the effect of an intervention on the professional or healthcare organization. These trials may evaluate patient outcomes as well as professional or organization-level outcomes.

The CRT design poses several unique challenges with respect to obtaining informed consent from study subjects. In studies with large clusters, such as communities, it may be logistically very difficult to obtain consent from all cluster members[1,2]. Some studies may include several types of subjects who receive different interventions in the same study. For example, in CRTs of educational interventions administered to health professionals, the professionals themselves are subjects and, in certain circumstances, their patients may be subjects as well[3-5]. In some studies, subject recruitment occurs after clusters have been randomly assigned to trial arms. Therefore, it is only possible to obtain consent for trial participation post-randomization. Some commentators have expressed concern that this may infringe on subjects' autonomy rights[1,2]. Some methodologists have also expressed

concern that the information disclosed during the consent process may bias the findings of CRTs of behavioural interventions[6,7].

It has been postulated[1-3] and observed empirically[8] that consent practices in healthcare CRTs may vary depending on the kinds of interventions under study. Consent requirements for CRTs have been noted to vary between jurisdictions and ethics committees[9,10], and over time[10]. Uncertainty over whether some CRTs constitute research or quality improvement (QI)[11,12] may have also led to variability in consent practices in CRTs that evaluate healthcare QI interventions.

This study has two objectives. 1) To estimate the frequency of reporting of informed consent from patients in healthcare CRTs; 2) To determine whether reporting of informed consent from patients in healthcare CRTs is associated with particular methodological features of a CRT or with secular features such as country of study conduct or the quality of journal in which a trial is published. Multivariable regression modelling was used to test for the presence of independent association between reporting of informed consent and these features of healthcare CRTs.

Methods

This study was conducted in the context of a larger project, funded by the Canadian Institutes of Health Research. This larger project is using multiple methods to examine ethical challenges posed by CRTs, with the ultimate goal of developing consensus-based international ethics guidelines for the conduct of

CRTs. One of the components of this project was to examine reporting of various ethical issues in published CRTs in health research. The search strategy described below was used to identify a sample of 300 published CRTs in health research. However, this thesis focuses solely on the reporting of obtaining informed consent from patients in CRTs that randomize health care providers or organizations.

Sample

A highly sensitive electronic search strategy (sensitivity 90.1%, precision 18.4%)[13] was implemented in Medline to identify reports of CRTs published between 2000 and 2008. This search strategy identified 27149 study reports that may have been cluster randomized trials. These were sorted in random order, and screened serially until a sample of 300 CRTs was reached. The following inclusion and exclusion criteria were applied to define the population of candidate CRTs for the larger study:

Inclusion criteria

(i) Random allocation by cluster;

(ii) English language;

(iii) Year of publication 2000 to 2008;

(iv) Outcomes of interest pertain to individual or population health;

(v) At least some outcomes observed on (or aggregated from) 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) Obvious 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);

The sample for this thesis is a subset of the sample of 300 CRT reports conducted in primary care and hospital settings. Therefore, an additional inclusion criterion was applied to identify this sub-sample:

(i) CRTs in which the unit of randomization or unit of intervention was a healthcare provider, teams of healthcare providers or healthcare organization (e.g., primary care practice or group of practices, hospital or hospital wards, nursing home), or CRTs which were conducted in a healthcare organization. Two authors (MT and CB) determined whether

or not studies met this criterion. Disagreements were resolved with input from a third author (AM).

It was estimated *a priori* that studies in primary and hospital care would comprise approximately half of the sample of 300 CRTs identified for the larger CIHR-funded study. A previous review of primary care CRTs published from 1997-2000 demonstrated a frequency of patient consent reporting of 39%[8]. CRT investigators perceive that consent requirements have become more stringent in recent years[10]. Therefore, for the purposes of sample size calculations, we will postulate a frequency of consent reporting of 50% in our sample of CRTs. A sample size of 150 trials is sufficient to give a 95% two-sided confidence interval extending ± 8% from an observed proportion of 50%. If, as Eldridge observed[8], the frequency of consent reporting is less than 50%, this conservative sample size estimate will provide greater precision around a smaller proportion. 150 trials with a postulated prevalence of 50% for the reporting of patient consent will also be sufficient to allow a multivariable logistic regression model to include approximately seven predictor variables, according to a widely used rule of thumb[14].

Data Abstraction

The 65-item abstraction form (Appendix A) includes items on the characteristics of the study design, study interventions, outcomes collected, consent procedures at the patient, health professional and cluster levels, and details of the ethics review process. Questions regarding the methodological features of the CRTs

were drafted and revised based on input from members of the study team with methodological expertise. Questions regarding ethical issues were drafted and revised based on input from study team members with research ethics expertise. The abstraction form was then pilot tested on a sample of 25 healthcare CRTs. This sample of 25 studies was also used for calibration of data abstraction by 4 reviewers. Afterward, data was abstracted from each study report by a pair of reviewers, working independently. Disagreements were resolved by consensus.

Statistical Analysis

All analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC). Bivariable associations between the dependent and independent variable were evaluated using Pearson's χ^2, with Fisher's exact test used if the expected frequency of events was small. Multivariable logistic regression modeling was used to generate adjusted odds ratios for the relationships between the dependent variable and each independent variable.

Specification of Variables

Dependent Variable

Reporting of informed consent from individual patients.

Whether or not investigators reported obtaining informed consent from patients was coded as a binary variable. The reference level, "no", was recorded if the study explicitly stated that consent from individuals was not obtained, if the

study reported that a waiver of informed consent was used, or if the study did not report obtaining informed consent from individual patients. The variable was coded "yes" if articles explicitly state that consent was obtained from individual patients. The purpose of this dichotomization was to model actual consent practice. It was assumed that if informed consent from patients was not reported that it was not sought.

Independent variables

Twelve candidate independent variables relating to trial methodology were specified *a priori* by co-investigators on the CIHR project. Four authors (AM, AD, CW, MT) discussed the candidate independent variables, and came to a consensus that date of publication, country of study conduct, journal impact factor, unit of randomization, reporting of a study as quality improvement, type of experimental interventions, type of data collection interventions, and average cluster size would be included in the regression model.

Five candidate variables which were initially put forward were not entered as candidate predictors: total sample size, trial type (individual- vs. cluster-level interventions), unit of randomization, unit of inference, and type of outcome observed.

The trial sample size was considered less likely to be predictive of consent practices than average cluster size. Large individually-randomized RCTs obtain informed consent from all participants. However, obtaining informed consent may

be logistically more challenging in CRTs that randomize large clusters, such as communities[15].

The trial type (either cluster-cluster or individual-cluster, according to the typology proposed by Edwards et al.[6] was considered likely to be correlated with the type of experimental intervention and type of data collection intervention variables.

The unit of randomization was difficult to dichotomize into a conceptually meaningful binary variable with an easily interpretable odds ratio because of the heterogeneity of units of randomization (health care providers, institutions, communities, blocks of time).

The unit of inference (patient-level vs. cluster-level) was considered likely to be correlated with the unit of randomization and the two variables describing trial interventions.

The type of outcome observed (patient-level health outcomes vs. professional-level outcomes, process measures or economic outcomes) was considered likely to be correlated with the data collection intervention variable.

The seven variables chosen for the bivariable and multivariable regression analyses are specified as follows:

Date of Publication

Date of publication was recorded as a binary variable comparing the periods of 2000-2004 and 2005-2008. This dichotomization point is approximately two years following the November 2002 publication of the UK Medical Research Council's guidelines for the conduct of CRTs[16], which also addresses the issue of informed consent. Studies whose consent practices may have been influenced by the promulgation of these guidelines would likely have been published in 2005 or later. We hypothesize that, because of the influence of the MRC guidelines and because of trends toward more restrictive research ethics review of CRTs observed by CRT researchers[10], studies published in 2005 or later will be more likely to obtain informed consent from individual cluster members.

Country of Study Conduct

The variable country of study conduct grouped CRTs conducted in the United States and Canada as the alternate level, and CRTs conducted elsewhere as the reference level. We chose to dichotomize this variable in this way because research regulations in the US and Canada share many similarities, and evolved historically at different times and under different influences than ethics guidelines elsewhere. The practices of research ethics committees in the US and Canada are similar, but may differ from those elsewhere in the world.

Journal Impact Factor

We hypothesized that studies published in lower quality journals would be less likely to report obtaining patient consent. An empirical logit plot identified the

appearance of a discontinuity in the relationship between reporting of patient consent and journal impact factor occurring around the first quartile. It appeared that journals in the lower one quarter of impact factor were less likely to report obtaining patient consent, with journals in the upper three quartiles having a higher but roughly similar probability of reporting consent. Therefore, journal impact factor was dichotomized into a binary variable at the second quartile (2.219). The alternate value for the variable includes studies published in a journal with an impact factor less than 2.219. The reference value includes studies published in journals with an impact factor greater than or equal to 2.219. There were a small number of studies that had missing data for journal impact factor. The decision to dichotomize this variable allowed us to estimate a plausible value for impact factor either above or below the second quartile, thus avoiding their exclusion from the multivariable logistic regression analyses.

Quality Improvement

This variable will identify CRTs that are self-described as a trial of a healthcare quality improvement (QI) intervention. The reference level included CRTs that are not identified as QI, while the alternative level of the variable included reports of CRTs that specifically describe the study as an evaluation of a QI intervention. Informed consent from patients for healthcare QI activities is generally not required[11,17]. We hypothesized that studies that are identified as QI evaluations will be less likely to report informed consent from individual patients.

Type of Experimental Intervention

Interventions targeted at individual patients, such as medical treatments, typically require informed consent and are distinct from interventions directed at the cluster-level which may have indirect effects on individual patients, such as educational interventions for health professionals or health system QI initiatives[3]. The reference level for this variable included studies which have only cluster-level experimental interventions and no patient-level experimental interventions. The alternate level included studies that have any patient-level experimental interventions. We hypothesized that studies that include patient-level experimental interventions will be more likely to report obtaining informed consent from patients.

Type of Data Collection interventions

The reference level for this variable included studies that do not employ any intervention upon or interaction with patients for data collection purposes, and use only routinely available data such as administrative or medical records. The alternate level included studies that do use direct interventions on patients, such as additional examinations or medical tests, or interactions such as surveys or interviews, for data collection purposes. The use of administrative data or private health information does not routinely require the use of informed consent[18,19], although some jurisdictions and ethics committees have required consent for use of private health information[20]. We hypothesized that studies in which investigators

interact with or intervene upon patients for data collection purposes will be more likely to report obtaining informed consent from patients.

Average Cluster Size

It has been noted that obtaining informed consent from individual cluster members is logistically difficult in CRTs with large cluster sizes[10,15]. We therefore hypothesized that CRTs with larger cluster sizes would be less likely to report obtaining informed consent from patients. The average cluster size was calculated by dividing the number of individual patients included in each CRT at the time of baseline data collection by the number of clusters in the CRT at the time of baseline data collection. In cases in which the number of clusters at baseline was not reported, the number of clusters randomized was used. Empirical logit plots with average cluster size divided into deciles confirmed that the odds of reporting consent tended to decrease as average cluster size increased. Since there remained a small number of trials for which cluster size could not be determined, a decision was made to dichotomize mean cluster size into a binary variable, split at the median. This decision allowed us to estimate a plausible value for mean cluster size either above or below the median value for most studies, thus avoiding their exclusion from the multivariable logistic regression analyses. The reference level includes studies with an average cluster size less than 29.5, while the alternate level includes studies with an average cluster size of 29.5 or greater.

Bivariable Analyses

Bivariable associations between the dependent variable and each independent variable were examined with contingency tables. Relationships were tested for statistical significance using Pearson's χ^2 or Fisher's exact test in the case of small expected frequencies. Odds ratios with 95% confidence intervals were generated for the unadjusted associations between the dependent variable and each of the independent variables.

Logistic Regression Analysis

The adjusted association between the dependent variable (reporting of individual informed consent) and the independent variables was examined using a multivariable logistic regression model. The aim of this analysis was to estimate the association between the dependent variable and all candidate independent variables, rather than to develop the most parsimonious model. We planned to estimate effect measures for each independent variable, which we hypothesized *a priori* based on conceptual and empirical work to be associated with consent practices. For this reason, all independent variables with no linear dependencies as revealed by multicollinearity diagnostics were entered into the model with no stepwise variable selection procedure. Multicollinearity was evaluated using the VIF and TOL options in SAS PROC REG.

Handling of Missing Data

Missing data were observed for the variables Impact Factor and Average Cluster Size. Both of these variables were coded as binary variables, split at the median value. Values for missing data were estimated as follows. For studies with missing impact factor data (n=7), a value, either above or below the median value for this variable (3.052), was estimated. For studies with missing data on average cluster size (n=23), the full text of the article was examined for references to the number of subjects as well as for text that would allow estimation of the number of clusters. An estimate of the number of subjects and number of clusters was substituted so that a plausible value of average cluster size either below or above the median value for this variable (29.5) could be included in the dataset. We could estimate with reasonable certainty whether the average cluster size for most CRTs with missing data was either greater or lesser than the median value for this variable. Studies were excluded if no plausible value for number of subjects or number of clusters could be estimated (n=7), meaning that 16 studies had estimated data for the mean cluster size variable. Given that there were only seven remaining studies with missing data, the additional complexity of multiple imputation was not considered justified. A sensitivity analysis, to evaluate how estimation of missing data influenced the results of the analysis, was planned. A regression model was fitted using all independent variables, but eliminating studies with estimated data. Odds ratio estimates were compared to those generated by the model fit in the primary analysis that employed the dataset with estimated values.

Regression Model Diagnostics

The calibration of the model was evaluated using the Hosmer-Lemeshow test using ten strata. Calibration refers to the ability of a model to match predicted and observed event rates across the spread of data.

The discriminative power of the model was evaluated using the c-statistic, also known as the area under the ROC curve, which measures concordance between predicted and actual outcomes[21-23]. The c-statistic denotes the frequency with which the model can successfully discriminate between pairs of CRT reports, with one CRT reporting patient consent and one CRT that does not. A value of 0.5 indicates a discriminative value no better than chance, while a value of 1.0 indicates perfect discriminative power[21-23].

For logistic regression, there is no widely accepted analog to the coefficient of determination (R^2), which is used in linear regression to quantify the proportion of variation explained by the regression model[24-27]. Several R^2 analogs have been proposed in the literature. Two in particular make most conceptual and mathematical sense, and are used here. The first, R^2_O, is the squared Pearson correlation between the observed and predicted values of the dependent variable[24,25]. This approach is appealing because it is mathematically equivalent to the R^2 used in linear regression. However, it is not a true measure of the proportion of variation explained, because R^2 in linear regression and R^2_O in logistic regression are based on minimizing two different quantities[24]. The second, called R^2_L, is the proportional reduction in the value of the -2 log likelihood test between the null and

complete models. Although this is mathematically different from R^2 and R^2_O, it has a more useful interpretation than R^2_O as the proportional reduction in prediction error between the null and complete models[24].

Secondary Analyses

A prespecified secondary analysis was performed after dichotomizing country of study conduct as either a developing country or as developed country (identified by the International Monetary Fund as an Emerging or Developing Economy[28]). The relationship between reporting of consent from individual subject and country of study conduct (developing vs. developed) was examined in a bivariable analysis, and using a logistic regression model including the other independent variables described above.

Results

The final sample of primary care and hospital-based CRTs, selected from a sample of 300 CRTs published 2000-2008, included 168 studies. Seven studies were excluded because of missing data for which plausible values could not be estimated. The analyses described below are based on a sample of 161 studies (Figure 1).

Of the 161 studies included in the final sample, 86 (53.4%, 95% CI 45.7-61.1%) reported obtaining informed consent from individual patients. 11 studies (6.8%) reported using a waiver of informed consent. 64 studies (39.8%) did not report obtaining informed consent from patients.

Bivariable Analyses (Table 1).

No significant associations were observed between reporting of informed consent from patients and the country of study conduct. A significant bivariable association was observed between the reporting of informed consent from patients and the journal impact factor, the year of study publication, reporting of the study as QI, the use of patient-level experimental interventions, the use of patient-level data collection interventions, and average cluster size.

Studies published in journals in the lower quartile of impact factor were less likely to report obtaining informed consent from patients. Studies published 2005-2008 reported obtaining informed consent from individual cluster members more frequently than did studies published 2000-2004. CRTs reported as evaluating a QI intervention report obtaining informed consent from individual cluster members less frequently than non-QI CRTs. Studies evaluating patient-level experimental interventions reported obtaining informed consent from individual cluster members more frequently than did studies with only cluster-level experimental interventions. CRTs employing patient-level data collection interventions reported obtaining informed consent from individual cluster members more frequently than did studies that only used examination of medical or administrative data to evaluate outcomes. Studies with an average cluster size below the median value for this variable (29.5) reported obtaining informed consent from individual cluster members more frequently than did studies with a larger average cluster size.

Multivariable Analyses

There was no statistical evidence of multicollinearity between the independent variables. Therefore, all candidate independent variables were included in the logistic regression analysis. Significant adjusted associations were observed between the dependent variable and journal impact factor, the year of publication, average cluster size, type of experimental interventions and type of data collection interventions (Table 2). These independent variables may be considered independent predictors of reporting of informed consent in healthcare CRTs.

The country of study conduct (North America vs. others), and whether or not the study evaluated a QI intervention were not associated with reporting of informed consent from individual subjects after accounting for the other variables in the model.

Regression Model Diagnostics

The Hosmer-Lemeshow test indicates adequate goodness of fit for the multivariable model (C2 6.01, DF=8, p=0.645). Thus, the number of CRT reports that describe obtaining informed consent from individual cluster members is not significantly different than the number that would be predicted by the model.

The model's discriminative power is very good, indicated by a c-statistic value of 0.863.

The pairwise correlation between the observed and predicted reporting of informed consent from individual cluster members is 0.616. R^2_O, the square of the

correlation, is 0.379. R^2_L, the relative reduction in predictive error between the null and complete model is 0.320.

Effect of Missing Data (Table 3)

Seven studies required estimation of data for the journal impact factor, while 16 had required estimation of data for the average cluster size (2 studies had estimated data for both variables). A logistic regression model was fitted with all independent variables after excluding all studies with estimated data (n excluded= 21, n included=140). The adjusted odds ratios were similar to the multivariable analysis that included all studies, although the adjusted odds ratio for journal impact factor was no longer statistically significant in this analysis.

Secondary Analyses (Table 4)

12 CRTs in the sample were performed in developing countries. Because of the relatively small number of studies performed in developing countries, Fisher's Exact Test was used for the bivariable analysis, rather than Pearson's χ^2. A significant association between reporting of informed consent from individual cluster members and country of study conduct (developing vs. developed) was identified in a bivariable analysis. CRTs performed in developing countries reported obtaining informed consent from cluster members less frequently than in studies performed in developed countries (Unadjusted OR 0.21, 95% CI 0.06-0.79, p=0.012).

After adjusting for the other independent variables, the association between study conduct in developing vs. developed countries and reporting of individual informed consent remained statistically significant (Adjusted OR 0.20, 95% CI 0.04-0.86, p=0.030). In this adjusted analysis, odds ratios for the other independent variable did not qualitatively change. However, the odds ratio for the Quality Improvement variable became statistically significant (Table 4), while the adjusted odds ratio for journal impact factor only approached statistical significance.

Discussion

Just over 60% of the CRT reports in this sample described the patient consent procedures used: 86 (53.4%) studies reported seeking patient consent, while 11 (6.8%) reported using a waiver of consent. It is a source of concern that nearly 40% of studies did not report describe consent procedures. For these studies, it is unknown whether consent was sought, whether a waiver was used as provided in research ethics guidelines[16,19,29-31], or whether consent was not sought for some other reason. CRT reporting guidelines[32] do not explicitly require reporting of consent procedures, but this has been suggested in the CRT literature[1], and is required in general research reporting guidelines[33]. Researchers' omission of reporting of consent procedures is a source of concern, as no indication is given in these CRT reports whether subjects' interests were adequately protected.

This study has identified independent associations between reporting of informed consent from patients in healthcare CRTs and the journal impact factor,

the year of publication, average cluster size and the use of both patient-level experimental interventions and patient-level data collection interventions. These features have been previously noted in the CRT and bioethics literature as being likely to influence consent practices. This study provides empirical evidence to support these intuitions.

All of the demonstrated associations between the reporting of informed consent and the independent variables fit our hypotheses. Investigators were more likely to report obtaining informed consent from patients if the CRT used patient-level experimental interventions, if the study used patient-level data collection interventions, and if the study was published in 2005 or later. Investigators were less likely to report obtaining informed consent from patients if the average cluster size was large, if the CRT was described as evaluating a QI intervention, or if the study was published in a lower-quality journal. There is also evidence to suggest that patient consent is less likely to be reported in CRTs conducted in developing countries.

The increased likelihood of reporting of informed consent in later years may be related to a number of factors. The UK Medical Research Council's methodological guidelines for CRTs includes ethical guidelines that emphasize that individual informed consent should be obtained when possible[16]. These guidelines were published in 2002 and may have influenced investigators' practices and ethics committees' determinations in more recent years, both in the UK and in other countries. An ever-growing number of publications on the ethical challenges of

CRTs may have had similar influence. The association between reporting of patient consent and date of publication fits with researchers' anecdotal observations that consent requirements have become more stringent in recent years[10]. Increasing awareness of reporting requirements for informed consent[33] may have also contributed to increased reporting of patient consent in recent years.

Studies with large cluster sizes were less likely to report obtaining informed consent from patients. In many cases, this is likely related to the logistical difficulty in obtaining consent from members of large clusters, such as all patients in a hospital system. The logistical effort required to obtain consent from all patients in some large CRTs would make some studies infeasible[2,15]. Current research ethics guidelines permit a waiver of consent for research posing only minimal risk that would otherwise not be feasible without the waiver[19,29,30]. Many healthcare CRTs meet these criteria and would be eligible for a waiver of informed consent[3]. This may account for the finding that studies with large cluster sizes were less likely to report patient consent.

It has previously been observed that reporting of informed consent from patients was more likely in CRTs that include patient-level experimental interventions[8]. This study confirms that the use of patient-level experimental interventions is independently associated with the reporting of informed consent from individual patients.

Eldridge et al. conducted a review of 199 CRTs conducted in primary care settings. They developed a four-level typology of the kinds of experimental interventions used in these CRTs.

- Individual-cluster interventions include such things as experimental treatments, information provided to patients, or the use of information on individual patients by health professionals to customize care. These interventions are targeted primarily at individual patients, and patients will ordinarily be able to choose whether or not to participate in the trial. The CRT design was typically chosen to avoid experimental contamination

- External-cluster interventions refer to the use of additional staff in patient treatment that would not be available in routine care. These changes in cluster organization are intended to directly affect patient care, and patients will ordinarily be able to choose whether or not to participate in the trial. The CRT design is most often chosen in trials of external-cluster interventions for logistical reasons, in that it is easier to assign additional staff to a cluster such as a medical practice than it is to randomly assign patients from the same practice to either have or not have access to the additional staff.

- Professional-cluster interventions are interventions that are directed at the health professionals, such as continuing professional development activities. They may have an indirect effect on the care

of individual patients, and patients are not able to avoid or opt out of the intervention. The CRT design is chosen to avoid contamination, as it is difficult for professionals to selectively apply new knowledge to different patients.

- Cluster-Cluster interventions are targeted at the health professional, cluster organization or cluster population. The CRT design is chosen as the nature of the intervention is such that it can only be applied at the cluster level. Individual patients are not able to avoid or opt out of the intervention[8].

Eldridge et al. observed that 31% of trials that included cluster-cluster interventions (and possibly other interventions) reported obtaining patient consent. 49% of trials with professional-cluster interventions but no cluster-cluster interventions reported obtaining patient consent. 80% of trials that contained no cluster-cluster or professional-cluster interventions (meaning that they had only external-cluster or individual-cluster interventions) reported obtaining patient consent[8].

Although our analytic approach was different from Eldridge et al., our findings are similar. Our definition of patient-level interventions included those that Eldridge et al. described as individual-cluster interventions (with the exception of the provision of individualized patient information to healthcare providers) and external-cluster interventions. Individual-cluster interventions are interventions directed at patients. External-cluster interventions represent innovative modes of

service delivery with unproven efficacy that can be likened to interventions directed at individual subjects[3]. We observed that studies that included patient-level interventions were more likely to report obtaining patient consent. Studies that included patient-level interventions may have also included cluster-level interventions. However, our analysis focused on whether or not a study included any patient-level interventions[3,8,16,34].

We also identified an independent association between reporting patient consent and the use of patient-level interventions to collect data. We defined patient-level data collection interventions as any procedure administered to patients specifically to collect data, any interaction between researchers and patients to collect data, such as surveys or interviews, or the use of identifiable private information[3,35]. The use of de-identified or aggregate group data is not sufficient to make a patient a research subject[3], and so is not included in our definition of patient-level data collection intervention. We observed a strong positive association between the use of patient-level data collection interventions and the reporting of informed consent.

Quality improvement interventions are generally targeted at healthcare systems and practitioners, and rarely employ patient-level experimental interventions. Generally, informed consent from patients is not required for healthcare quality improvement activities[11,17,36]. This study demonstrates that this notion is reflected in current practice as the reporting of a CRT as QI is inversely associated with reporting of obtaining informed consent from individual patients,

when examined in a bivariable analysis. After adjusting for the other independent variables, the confidence interval crosses the null value, indicating a borderline association.

Limitations

The primary limitation of this study is that the dependent variable, reporting of informed consent from individual patients, may not reflect actual consent practices. It is conceivable that informed consent from patients was obtained, but not reported, for some studies. However, given that guidelines from the International Committee of Medical Journal Editors require reporting of informed consent procedures[33], we believe that the reporting of informed consent is a reasonable surrogate for the actual practice of obtaining consent from patients.

This review examines a sample of studies published between 2000 and 2008, and is likely representative of all published CRTs within that timeframe. However, quality improvement studies are frequently unreported in the literature[11]. Only 24 of the 161 studies in this sample of published CRTs are explicitly identified as being studies of quality improvement interventions, and therefore quality improvement studies may be under-represented in this sample and in the population from which they were drawn. One possibility for future work would be to repeat the analysis after including a sample of CRTs taken from the Cochrane Effective Practice and Organisation of Care Register of Studies[37]. However, studies in this database may not conform to standard clinical trial reporting guidelines[32,33] and may be missing data with respect to other variables of interest.

The number of studies in this sample that were performed in developing countries was relatively small. For this reason, the confidence interval around the adjusted odds ratio for whether or not informed consent was reported in trials conducted in developing vs. developed countries is wide. In spite of the lack of precision of this estimate, the finding that CRTs performed in developing countries are less than 20% as likely to report obtaining informed consent compared to CRTs performed in developed countries is noteworthy.

Some data were missing for the independent variables describing journal impact factor and mean cluster sizes. Given the dichotomous nature of the variables, plausible values for each missing data point were easily estimated. To evaluate the possible effect of this estimation method on the validity of our conclusions, a multivariable regression model was fitted using only data from studies with complete data. Excluding seven studies with estimated data for impact factor resulted in a loss of sufficient power to identify a statistically significant relationship between consent reporting and impact factor. However, no qualitative difference was observed for the estimated odds ratios for the other independent variables in the sensitivity analysis, indicating that are findings are largely robust in spite of the use of estimated data for two variables.

Conclusions

The methodological features that are independently associated with consent practices for individual patients in healthcare CRTs in this sample generally reflect the study features that have been identified in the cluster trial and bioethics

literature as likely having an influence on consent practices. Researchers' perceptions of temporal trends toward increased requirement for patient consent in CRTs have been noted[10], and are demonstrated empirically here. The notion that obtaining consent from individual cluster members may not be feasible in studies with large clusters[2,15] appears to be reflected in current practice, according to this multivariable analysis. The importance of the type of interventions for consent practices has been discussed in the literature[2,6,7,15] and observed empirically in a descriptive analysis[8]. The types of interventions evaluated in CRTs are here shown empirically to be independently associated with reporting of consent practices.

This paper represents an empirical description of current practices with regard to obtaining informed consent from patients in healthcare CRTs. Whether or not current practices are satisfactory in respecting the interests of individual patients depends on the findings of further normative reflection. Conceptual work is required to determine under what circumstances patients in healthcare CRTs need be considered to be research subjects[3,38], and then under what circumstances consent for CRT participation is required[34,38]. Only then can we reflect on the empirical findings to determine whether the current practices of researchers and ethics committees are acceptable. Consideration of these findings, informed by additional conceptual work that articulates a principled justification for consent requirements in CRTs, is essential for reinforcing good practices in trial conduct and ethics review, for remediation of errors in consent practices and ethics review, and for the development of regulatory guidance for CRTs.

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Figure 1

Selection of studies for systematic review data abstraction

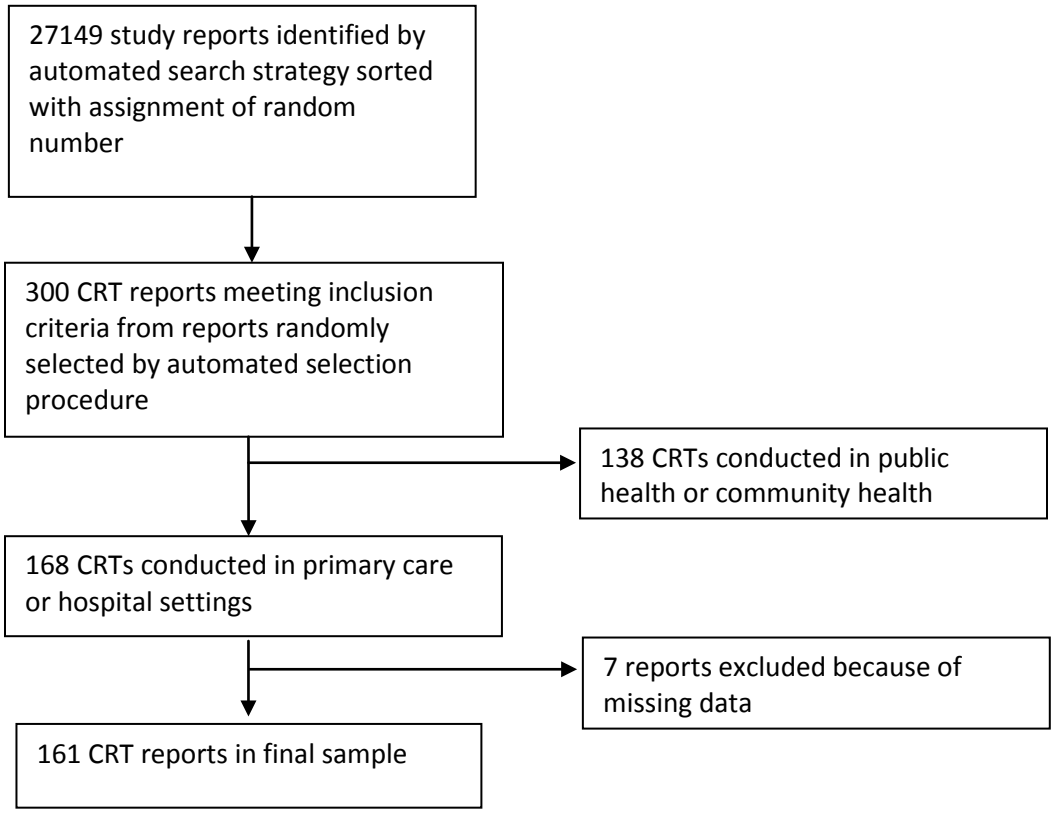

Table 1. Bivariable associations between reporting of informed consent from cluster members and independent variables. N=161

Independent Variable	**Reporting of Informed consent from cluster members**		**Odds ratio (95% CI)**	**p**
	Yes	**No**		
Journal Impact Factor (binary)				
2.2.19+*	73 (59.8%)	49(40.2%)	0.34 (0.16, 0.72)	0.004
<2.219	13 (33.3 %)	26 (66.7%)		
Country of Study Conduct				
North America	35 (53.0%)	31(47.0%)	0.97 (0.52, 1.83)	0.935
Other*	51 (53.7%)	44 (46.3%)		
Year of Publication				
2005-2008	57 (67.9%)	27 (32.1%)	3.49 (1.82, 6.69)	<0.001
2000-2004*	29 (37.78%)	48 (62.3%)		
Quality Improvement				
Yes	7 (29.2%)	17 (70.8%)	0.30 (0.12, 0.78)	0.010
No*	79 (57.7%)	58 (42.3%)		
Patient-level data collection interventions				
Yes	75 (68.2%)	35(31.8%)	7.79 (3.58, 16.97)	<0.001
No*	11 (21.6%)	40 (78.4%)		
Patient-level experimental interventions				
Yes	54 (72.0%)	21 (28.0%)	4.34 (2.23, 8.46)	<0.001
No*	32 (37.2%)	54 (62.8%)		
Average cluster size				
29.5+	28 (35.9%)	51 (64.1%)	0.23 (0.12, 0.44)	<0.001
<29.5*	58 (69.9%)	24 (30.1%)		

* indicates reference level of binary variable

Table 2. Adjusted odds ratios between obtaining informed consent from cluster members and independent variables. N=161.

Independent Variable	Adjusted Odds Ratio (95% CI)	p
Journal Impact Factor (2.219+* vs.<2.219)	0.35 (0.13, 0.95)	0.040
Country of Study Conduct (North America vs.Other*)	0.85 (0.36, 2.04)	0.715
Year of Publication (2005-2008 vs.2000-2004*)	3.95 (1.74, 8.98)	0.001
Quality Improvement (Yes vs.No*)	0.33 (0.10, 1.05)	0.060
Patient-level Data Collection Interventions (Yes vs.No*)	4.95 (1.89, 12.97)	<0.001
Patient-level Experimental Interventions (Yes vs.No*)	2.63 (1.12, 6.18)	0.027
Mean Cluster Size (29.5+ vs.<29.5*)	0.25 (0.11, 0.55)	0.001

* indicates reference level of binary variable

Table 3. Adjusted odds ratios for obtaining informed consent from cluster members and independent variables, using only non-estimated data. N=140.

Independent Variable	Adjusted Odds Ratio (95% CI)	p
Journal Impact Factor (2.219+* vs.<2.219)	0.40 (0.12, 1.38)	0.147
Country of Study Conduct (North America vs.Other*)	0.75 (0.27, 2.05)	0.573
Year of Publication (2005-2008 vs.2000-2004*)	5.19 (2.00, 13.42)	<0.001
Quality Improvement (Yes vs.No*)	0.41 (0.12,1.43)	0.161
Patient-level Data Collection Interventions (Yes vs.No*)	6.13 (2.11, 17.79)	<0.001
Patient-level Experimental Interventions (Yes vs.No*)	3.11 (1.18, 8.23)	0.022
Mean Cluster Size (29.5+ vs. <29.5*)	0.24 (0.10, 0.59)	0.002

* indicates reference level of binary variable

Table 4. Adjusted odds ratios between obtaining informed consent from cluster members and independent variables, with country of study conduct comparing developed countries to developing countries. N=161.

Independent Variable	Adjusted Odds Ratio (95% CI)	p
Journal Impact Factor (2.219+* vs.<2.219)	0.40 (0.15, 1.04)	0.059
Country of Study Conduct (Developing vs. developed*)	0.22 (0.05, 0.96)	0.043
Year of Publication (2005-2008 vs.2000-2004*)	3.98 (1.73, 9.12)	0.001
Quality Improvement (Yes vs.No*)	0.28 (0.09, 0.88)	0.030
Patient-level Data Collection Interventions (Yes vs.No*)	4.92(1.86, 13.03)	0.001
Patient-level Experimental Interventions (Yes vs.No*)	2.63 (1.10, 6.26)	0.029
Mean Cluster Size (29.5+ vs.<29.5*)	0.26 (0.12, 0.59)	0.001

* indicates reference level of binary variable

Chapter 4

Researchers' Perceptions of Ethical Challenges of Cluster Randomized Trials: A Qualitative Analysis

Introduction

Cluster randomization is a research design commonly used in public health, educational, social science and health services implementation research[1]. Cluster randomized trials (CRTs) are different from conventional randomized controlled clinical trials (RCTs). RCTs randomly assign individual research participants to different intervention arms and evaluate the comparative effectiveness of the study interventions using data collected from each participant. CRTs randomly assign groups of individuals to different intervention arms. The comparative effectiveness of the interventions in each arm is evaluated using data collected from individual cluster members, or from other sources such as administrative databases[1].

CRTs pose unique ethical challenges that stem from their methodological differences compared to conventional randomized trials. It can be difficult to identify precisely who is the research subject in a CRT, particularly in large community-based public health CRTs and in CRTs evaluating educational interventions aimed at health professionals[2-4]. It is unclear under which circumstances, and from whom, informed consent is required in large community-based CRTs[1,5,6]. Some CRTs have employed “gatekeepers”, individuals who have made decisions regarding CRT participation on behalf of randomized clusters. There is little clear information as to how and when these individuals ought to be identified, and what is the scope of their authority[7]. There is no authoritative guidance as to how the risks and potential benefits in CRTs ought to be evaluated by research ethics committees[5,7,8].

The objective of this study was to examine how CRT investigators, in practice, have addressed the ethical challenges in the CRTs they have conducted. A series of interviews was conducted with experienced CRT investigators. A qualitative analysis was then performed: 1) To describe how experienced Cluster Randomized Trial (CRT) researchers have addressed ethical challenges arising from the CRT design. 2) To describe CRT researchers' views on the ethics review process. 3) To document CRT researchers' views on the need for comprehensive ethics guidelines for CRTs.

Methods

A qualitative approach was employed to capture rich data on informants' experiences and insights[9,10]. A descriptive analysis approach was chosen[11], with the goal of detailing the experiences and ideas of the informants. This descriptive approach is used to provide a comprehensive depiction of everyday events[11]. This is in contrast to the grounded theory type of analysis, which uses informants' responses to develop theories that explain social phenomena, and phenomenology, which seeks to describe individuals' lived experiences and perceptions in reaction to social phenomena [9,11].

Sample Recruitment

Based on the suggestions of the members of a multidisciplinary team assembled to study the ethical challenges associated with CRTs[12], a purposive sample of potential informants was identified. To be considered eligible, potential

informants must have been the primary investigator on two or more cluster-randomized trials or have published papers addressing the ethics of cluster-randomized trials.

Initial contact with potential informants was made via e-mail by senior members of the study team (RB, AD, ME, JG, MZ). The email introduced the study design and purpose, and inquired about the potential informant's willingness to participate. If the potential informant was willing to participate, the interviewer (AM, CB) arranged a time for the telephone interview A letter of information and a copy of the interview template was sent by email. At the time of the interview, informants were notified that the interview would be recorded and transcribed, but that no identifiable features would be reported. Verbal consent for participation was obtained, and the interview was conducted.

The target sample size in qualitative research is achieved when data saturation occurs, that is when no new themes are identified with respect to a particular question of interest in successive interviews. This typically occurs after 12-20 interviews. After analyzing 20 transcribed interviews, data saturation with respect to responses around the issue of informed consent in CRTs had been achieved.

Final Sample

Twenty-five potential informants were approached to participate in the study. Four individuals declined to participate. The interview from one informant was discarded as the recording was of insufficient quality for transcription and analysis.

The final sample included 20 experienced cluster trial researchers. There were ten European informants, six American informants, and four Canadian informants. All participants had been co-investigators on between two and twenty CRTs.

Data Collection

A semi-structured telephone interview guide was developed (Appendix A) and pilot tested on colleagues. The interview guide included questions about informants' experience with CRTs, ethical issues in CRTs, ethical challenges encountered with particular CRTs and the ethics review process, and questions seeking input on ethics guidelines for cluster-randomized trials. Two trained interviewers conducted the interviews. The interview guide was modified in real-time by the interviewers to allow them to seek clarification from the informants or to probe important issues raised by the informants. The interview guide was also updated in an iterative fashion to explore issues that were raised by informants in previous interviews. All of the interviews were audiotaped, then transcribed verbatim. Transcripts were reviewed for accuracy by the interviewers.

Data Analysis

Each interview transcript was imported into qualitative data analysis software (NVivo 8, QSR Inc.). A directed content analysis approach was used, in that predetermined text analysis categories were used [13]. The initial coding template for response categorization was developed by consensus of the investigators. Each transcript was reviewed independently by two of the researchers (AM and CB), and

responses assigned to the appropriate thematic coding categories. New categories were added in an iterative fashion by each researcher to his or her coding template in order to accommodate response themes that did not correspond to predetermined coding themes.

After the initial coding, the researchers met and resolved disagreements in the emerging coding assignments by consensus. The coding template was then revised to include additional categories created in the first round of independent analysis, and to delete unused categories. This template revision also ensured fidelity in a second round of thematic coding, since both researchers were working from the same revised template. A second round of thematic coding was performed by the two researchers, using the new master coding template (Appendix B). Following this, the researchers met again to resolve discrepancies by consensus.

Ethics Approval

This study was approved by the Ottawa Hospital Research Ethics Board (File 2007191-01H) and the University of Western Ontario Health Sciences Research Ethics Board (File 13755E).

Results

Informants were asked questions based on the main pre-identified themes of (1) ethical issues in the CRTs, (2) experiences with the ethics review process for CRTs, and (3) the need for, and input on, possible ethics guidelines for CRTs.

Ethical Issues in CRTs

1. Informed consent

Informants' comments on the question of when informed consent is required from individual research participants varied widely. For many informants, whether or not informed consent was required in a particular CRT depended on the kind of intervention being evaluated.

"The type of intervention that is being trialed is...of crucial importance. So, for example, whether...you are changing the way the entire service is delivered, or whether you are intervening at an individual level and you are just randomizing at a higher level for convenience. So it is about which level...is the intervention being targeted at..." (Informant 11, Primary Care Researcher)

The type of data collection procedures used in a CRT could also determine the need for consent from cluster members. Researchers almost universally obtained consent from cluster members if they interacted with these cluster members or intervened upon them to collect data.

"If we interact with the participant we get consent first. If we are making observations in a public setting, we are not required to get consent...Those activities don't require consent." (Informant 3, Public Health Researcher)

Many informants related concerns over the effect of obtaining informed consent on the validity of a CRT's findings. In particular, informants worried that disclosure of the nature of the interventions under study in CRTs of behavioural interventions may lead to bias if research participants modify their behaviour as a result of information disclosed during consent negotiations rather than as a result of the study interventions.

"One of the things I am concerned about is bias. If you get really informed consent from people in trials it results in either bias or contamination." (Informant 5, Statistician)

Informants also shared a related concern with respect to studies of health services or quality improvement interventions in which the only intervention on individual patients is using health information for data collection. Informants expressed concern that requiring informed consent may make such CRTs logistically unfeasible. Several informants felt that these methodological challenges were sufficient to justify a waiver of informed consent for cluster members.

"Wherever people propose that (requiring individual patient consent), it is the death of those kinds of studies. It is the death of health services research. You can quote me on that. If you require consent to use the data...to look at the performance of a system, it will be a complete disaster." (Informant 1, Hospital Care/QI Researcher)

With respect to healthcare implementation research, informants had different perspectives on when, if ever, consent or permission from healthcare professionals is required. Investigators often asked permission, either from individual healthcare professionals or from a group practice, to enrol these professionals in their study.

"Normally [permission would be obtained] at a general practice level. That would have been done at a partner level, so there would be a discussion within the practice and then agreement at a practice level. There would have been consensual agreement between the partners, between the individual general practitioners that their practice would take part." (Informant 11, Primary Care Researcher)

Other informants proceeded with practice-based CRTs without securing the agreement of all healthcare professionals in the practice who might be affected by the intervention.

"For the ones targeted at practitioners, we had to install software in their electronic medical records systems and computers in their offices so that it would have been GPs in the practice who gave consent. Within a practice, they didn't all have to agree." (Informant 2, Primary Care Researcher)

Some informants argued that healthcare professionals have a professional obligation to participate in CRTs involving a knowledge translation or quality improvement intervention, which therefore overrides any requirement to obtain consent.

"I would argue that [there is a] professional responsibility to practitioners to take part in research that involves clinical knowledge." (Informant 9, Primary Care Researcher)

2. Role of the cluster gatekeeper or decision-maker

Informants identified several ethical challenges related to the role of the gatekeeper, the individual who makes a decision with respect to CRT participation on behalf of a cluster. Informants noted challenges identifying the appropriate gatekeeper for certain kinds of groups, particularly municipalities. Opinions varied on whether municipal leaders had the appropriate authority to allow their community to participate in a CRT.

"In some instances there really is no party to go to for permission when we are doing a community study for example and we are randomly assigning counties or cities. There really isn't anybody that gives permission for that kind of thing. Even in a city where there is a mayor, the mayor can't give permission for a city to participate in something. At least that has always been my view." (Informant 3, Public Health Researcher)

Informants also recognized that some clusters, such as schools and hospitals, may have multiple gatekeepers because of the organizational structure of these institutions.

"First off you have to have the district agree that you can even work in this district. Then you have to get the principal to agree that they want to

participate in the project. And then we had... the president of the local parent leadership group." (Informant 16, Public Health Researcher)

In situations in which researchers had difficulty identifying the appropriate gatekeeper for community-based research, they typically sought the approval of some local advisory committee.

"Our approach in virtually every instance was to organize a local community advisory board made up of community residents in the city if we were working with cities or in the county if we were working with counties. We would get their input on a variety of things though the basic design was set." (Informant 3, Public Health Researcher)

Another ethical challenge concerning gatekeepers related to the scope of the gatekeeper's decision-making authority. Responses varied on whether the gatekeeper possessed sufficient authority to provide consent on behalf of all cluster members, or whether the gatekeeper was simply permitting access to individual cluster members who would subsequently provide consent for CRT participation.

"I think the main issues for me still stem around the issue of consent. Who [gives] consent? Whether consent needs to be achieved at every level of cluster or whether almost guardian consent is acceptable and that has been where the most discussion has happened really about in the ethical issues of cluster trials for me." (Informant 11, Primary Care Researcher)

Some informants seemed comfortable accepting a gatekeeper's consent on behalf of an entire cluster for studies that were evaluating cluster-level interventions, such as educational or quality improvement interventions targeted at health care systems or practitioners.

"I would say most of them have been looking towards a cluster guardian...consent because most of the interventions I have been involved have been mainly around management interventions where the real intervention is at the level of either the practitioner, the health professional or the health care organization and this specific intervention hasn't really been targeted at the lower level of the cluster, the patient level." (Informant 11, Primary Care Researcher)

Other informants expressed a different opinion. They felt it was important to obtain consent from individual patients in healthcare CRTs, regardless of whether consent for cluster enrolment was obtained from a gatekeeper.

"So there is a consent for the patient and a consent for in our case, the practice so there are 2 levels of consent if you like. If there wasn't patient consent involved, then obviously there would be very significant ethical issues but I have come to the view that if patients are given information and they consent, then that is fine." (Informant 9, Primary Care Researcher)

3. Risks and potential benefits

Our interview guide included items addressing the risks posed by CRT participation. Informants had few concerns regarding the risks posed to cluster members by CRTs. “Risks were none. I think we came up with some for the ethics committee.” (Informant 14, Primary Care Researcher)

The interventions under evaluation in CRTs were perceived as standard care with little or no incremental risk to cluster members. “None of the interventions that we have evaluated have put anyone at any kind of risk... there is certainly little risk involved” (Informant 3, Public Health Researcher)

For healthcare CRTs that evaluated the effect of interventions on health professionals using patients’ health information, informants identified threats to privacy as the sole risk. “I think the core risk is loss of privacy. That really is the only issue because we weren’t studying...a therapeutic intervention.” (Informant 8, Hospital Care/QI Researcher)

Some informants voiced concern that members of clusters assigned to control groups may not benefit from an experimental intervention. “The dilemma and the tension again was this trial that is basically about the QI where the controlled practices got nothing. They didn’t get anything but normal care.” (Informant 14, Primary Care Researcher)

One commonly employed solution to address this dilemma was to offer the experimental intervention to the control clusters after the CRT had been

completed. “Sometimes we are so concerned about the control arm feeling that they don’t get anything that it might affect recruitment. We offer them the intervention once the trial is over.” (Informant 14, Primary Care Researcher)

An additional risk identified by one informant was that CRT enrolment may entail an increased clinical or administrative workload for participating medical practices. “The only risk I feel in doing a lot of research here is practices become overburdened by having to do research. (Informant 5, Statistician)

Experiences with the ethics review process

Many of the informants noted wide variability among research ethics committees, and across jurisdictions, in both the ethics review process and in ethics boards’ decisions. Informants noted that this variability has made it more difficult to do multicenter CRTs. “cluster...trials of hospitals randomise independent institutions, each of which has an [ethics committee]. Each [ethics committee], with its slightly different application procedures, forms and timelines has been a separate and trying process.” (Informant 7, Primary Care Researcher)

Several informants commented that the ethics review process was easier in the past, and has become more cumbersome in recent years. “...generally it hasn’t been too bad up until the last 5 years. Beforehand we were quite comfortably able to get ethics approval ... but it is different now” (Informant 13, Primary Care Researcher)

However, other informants commented that as ethics boards become familiar with the CRT design, the review process has gone more smoothly. “...Now CRTs are

widely accepted research methods, particularly in primary care studies, primary care settings. Ethics committees are now actually quite comfortable with them. ” (Informant 14, Primary Care Researcher)

Informants’ opinions varied on the effect of the ethics review process and regulatory requirements on the validity of a CRT. Half of the informants reported a positive impact of the ethics review process on the quality of their studies, while the other half reported negative effects. Perceived negative effects included threats to validity from consent processes, and diminished enrolment because of consent requirements.

“As the participation rates drop...then the results are less generalizable and less helpful. There is no question that the higher hurdles for consent in school studies and certainly in clinic based studies have made it more difficult to do the work and to get high participation rates.” (Informant 3, Public Health Researcher)

Perceived positive effects included requirements for greater methodological rigor and thoughtfulness in study design, and improved protections for research participants.

“I am a great believer that ethics committee do ask...searching questions...Just the process of thinking about the ethical implications of your design is something that we might not do if we didn’t have to go to ethics

committees...I think I would say for all my research, it is improved the quality of what we do." (Informant 14, Public Health Researcher)

Developing ethics guidelines for CRTs

Informants were supportive of efforts to develop ethics guidelines for the conduct and review of CRTs. "I think there does still need to be a discussion document...on when is individual level consent an absolute requirement." (Informant 11, Primary Care Researcher)

The most common suggestion for the content of ethics guidelines was to include education for research ethics committees on the ethical and methodological aspects of CRTs that make CRTs distinct from individually randomized trials.

"I think that there are issues which make cluster trials different to the sort of trials that review boards normally see and that it would give me confidence as an investigator if I knew that they fully understood the difference." (Informant 20, Hospital Care/QI Researcher)

Discussion

This study was designed to elicit the views of experienced CRT researchers on the key ethical issues involved in the conduct of CRTs, and to describe their experiences with the ethics review process for CRTs.

Informants' opinions on whether or not informed consent should be obtained from cluster members appeared to depend on the scientific question and experimental

interventions in particular CRT. Informants asserted that individual informed consent was necessary for CRTs in which cluster members were directly intervened upon. Informants in this sample frequently used waivers of informed consent for individual cluster members in large community-based CRTs, or in CRTs evaluating quality improvement or implementation strategies in healthcare or education.

One reason often cited for avoiding obtaining informed consent from individual cluster members was a concern over consent practices possibly inducing some sort of bias that would threaten the validity of the CRT. This concern has been noted in the literature[6,14]. Further conceptual work appears necessary to clarify when, if ever, it may be permissible to waive requirements for informed consent from cluster members, and to identify the moral underpinning for such a waiver. Ethics guidelines, built on a robust conceptual foundation, should clearly lay out under what circumstances obtaining informed consent from individual cluster members is required, and under what circumstances the requirement for informed consent may be waived.

Informants reported frequent challenges in identifying an appropriate gatekeeper who has legitimate authority to grant permission for a cluster such as a municipality or social group to be enrolled in a CRT. The gatekeeper for a professional group, such as a medical practice, hospital or school, may be more obvious. However it is unclear whether the agreement of all professionals (i.e. doctors, teachers) is required prior to the participation of a professional group in a CRT. Informants expressed concern over the scope of authority of the gatekeeper,

particularly with respect to whether permission from the gatekeeper was ever sufficient to obviate the need for informed consent from individual cluster members. Future conceptual work and guidelines for the ethical conduct of CRTs, should provide clear guidance on these issues.

Many informants identified the problem of variability in ethics review between jurisdictions. They also described increasingly onerous oversight requirements imposed by ethics boards in recent years. This variability may be attributable to the fact that most jurisdictions do not have authoritative guidelines for the review of CRTs. Ethics boards are therefore required to use their own judgment in applying guidelines that do not address the unique ethical challenges posed by the CRT design, potentially resulting in idiosyncratic decisions. This indicates the need for comprehensive ethical guidelines that can direct the review of multi-jurisdictional CRTs.

Several issues identified in the literature, and included in our interview guide, were not mentioned by informants. With respect to the assessment of harms and benefits of CRT participation, informants identified threats to privacy and risks of suboptimal treatment in control arms, as well as burdens to medical practices that participate in CRTs. Informants did not express concern about risks to individual research participants, especially in studies in which individual cluster members were not directly intervened upon. We suspect that this is because the interventions being evaluated in CRTs are often low-risk interventions designed to improve medical care or educational processes, and posed little ethical concern to investigators. However,

the view expressed by informants that CRT interventions pose no risk is misguided, as no experimental intervention in a trial can be considered to be free of risk[15,16]. Guidance on the ethical conduct of CRTs should educate investigators and research ethics committees on the identification of all important harms and benefits of CRT enrolment. Ethics guidance should also address how the analysis of risks and potential benefits for CRTs should be performed[7,17].

Limitations

Our sample included experienced CRT researchers and individuals who have contributed to the literature on the ethics of CRTs. Their experiences may not necessarily be transferable to all CRT researchers. However, we are reassured that experienced researchers from a variety of locations, and in a variety of fields, voiced similar opinions on key ethical issues. Furthermore, the experience of the informants interviewed in this study lends weight to their views, and to our conclusions.

Our informants worked mostly in developed countries, although some did perform CRTs in marginalized or underprivileged populations. This may be the reason that no informants voiced concerns about issues of distributive justice, such as fair participant selection, the reasonable distribution of burdens of CRT participation, and other issues encountered when conducting CRTs in developing countries.

Conclusions

Informants described challenges CRT investigators percieve with the ethics review process, expressed concern over when informed consent is required from

cluster members, and over the authority of cluster gatekeepers. Other important ethical challenges, such as the relationship between harms and benefits and issues of distributive justice appeared to be either less concerning to CRT researchers, or were under-appreciated. These views, offered by experienced CRT researchers, point to the need for further conceptual work on the ethics of CRTs, as well as the need for clear authoritative guidelines that address the unique ethical and methodological challenges of CRTs.

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Chapter 5

Who is the Research Subject in Cluster Randomized Trials?

Introduction

The CRT design is used in a diverse range of fields, including education, criminology, public health and health services research. Who ought to be considered a research subject in a CRT for the purposes of the regulation of research may be unclear. Are individual cluster members always research subjects? Does it matter whether cluster members directly receive an experimental intervention? Does it matter whether individual cluster members' identifiable private information is used to generate outcome data? In some CRTs, individuals such as health professionals will be the ones randomly assigned to receive an experimental intervention. Are the health care professionals research subjects? Does it matter whether or not outcome data are collected from the professionals? Are patients necessarily research subjects if the intervention administered to the healthcare professional indirectly affects their care?

The question of who constitutes a research subject in a CRT is important for two related reasons. First, the consequences of misidentifying research subjects in CRTs are significant for both subjects and investigators. If we fail to identify individuals who ought to be recognized as research subjects in a CRT, then we will fail to adequately protect their interests. If we are overly inclusive in identifying individuals as research subjects in a CRT, then investigators will be unnecessarily subjected to regulatory burdens that may hamper important research. Second, as a pragmatic concern for research ethics committees, research subjects must be appropriately identified before such issues as informed consent, assessment of benefits and harms, and the appropriateness of subject selection procedures may be considered.

This paper aims to develop a principled definition of "research subject" that investigators and research ethics committees can use in all types of human subjects research. This definition will be particularly helpful to CRT investigators and research ethics committees who review CRTs. We contend that the answer to the question "Who is a subject in a CRT?" may vary, depending on the specific study design, the population, and the interventions being evaluated.

Examples: Challenges in identifying the research subject in CRTs

CRTs are heterogeneous with respect to design, population, and interventions. The following four examples (a) illustrate the complexity of the question "Who is a research subject in CRTs?", and (b) highlight the need for a principled definition of research subject that can be employed across the spectrum of CRTs.

Example 1: The COMMIT Trial

The COMMIT trial[1,2] evaluated a multimodal community-level intervention aimed at reducing cigarette consumption, including a media and billboard campaign as well as targeted messaging toward smokers. Communities were randomly assigned to either the intervention or control arm. The effect of this complex intervention was evaluated using interviews with a random sample of smokers in each community, and also by comparing the amounts of tobacco purchased by people living in the intervention and control

communities. The study found that the intervention led to an improved quit rate for mild to moderate smokers, with no effect on the quit rate of heavy smokers.

Who were the research subjects in this study? The survey respondents? Only residents of the communities who smoke? Every resident of participating municipalities?

Example 2: A CRT of bed net distribution to reduce malaria prevalence

A CRT that evaluated malaria prevention interventions[3] randomly assigned Cambodian communities either to an intervention group in which bed nets were distributed to all residents in the intervention communities, or to a control group in which no bed nets were distributed. To evaluate local malaria prevalence, the population size was obtained from local census data and the number exposed to malaria was obtained from blood tests performed on a random sample of village residents. No identifying information on sampled individuals was retained. The study identified non-significant trends toward decreased malaria incidence and prevalence in the intervention communities.

Who were the research subjects in this study? Only citizens of intervention communities who received bed nets? Citizens of control communities who provided blood samples? All citizens in intervention and control communities?

Example 3: A CRT comparing interventions to improve primary care prescribing

Naughton et al.[4] compared the efficacy of two quality improvement interventions aimed at increasing prescribing by family physicians' of antiplatelet and lipid lowering medications for patients with cardiovascular disease (CVD) or diabetes mellitus (DM).

Family physicians were randomly assigned to receive either a personalized summary of their prescribing practices for patients with CVD or DM via an academic detailing visit, or to receive a postal bulletin about optimal prescribing practices. The effect of the intervention on prescribing practices was evaluated by surveying physicians' perception of the perceived effects of the intervention, as well as using objective data on prescribing practices from the national pharmacy insurance program database. The data on the patients and their prescriptions included the prescription type, age, gender, and a numeric identifier, but no name or address. Both interventions led to similar improvements in prescribing practices.

In this study, there was no direct intervention on patients or any use of identifiable private information. Who were the research subjects in this study? All of the DM or CVD patients in participating practices? All patients in participating practices? The physicians receiving the interventions?[5,6]

Example 4: A CRT comparing modes of educating patients prior to breast cancer surgery

Goel et al.[7] describe a CRT comparing the efficacy of two methods of informing breast cancer patients of their surgical treatment options. The intervention under study was directed at the patients, but administered by their surgeons. Surgeons were randomly assigned either to discuss treatment options with patients using a specially developed decision tool, or to use standard practice with the addition of extra printed information. The study compared the effect of the decision tool on patient anxiety and knowledge regarding

their options. No difference was observed in the study's primary outcome between intervention and control groups.

Who were the research subjects in this study? The patients? The surgeons?

Methods

The aim of this paper is to offer a principled definition of a research subject, and to apply this definition to CRTs, in order to assist investigators and research ethics committees. Currently available regulatory definitions of "research subject" are based on lists of procedures, i.e., an individual may only be classified as a research subject if he or she undergoes a procedure listed in regulations[8-12]. List-based criteria are not exhaustive, and may not be helpful in identifying subjects in novel research designs such as CRTs. Moreover, a principled definition of research subject may be used reflexively, to determine the adequacy of current and future research ethics regulations.

Our analysis proceeds as follows. First, we review research ethics regulations and guiding documents for criteria that identify research subjects. Second, we search for a common theme on which we can build a definition of "research subject". Third, we posit that a research subject is an individual whose interests are put at risk in the context of a research study. Fourth, we apply our definition of a research subject to CRTs and examine whether the effects of group-level environmental interventions are, by themselves, sufficient to make cluster members research subjects, and we consider the impact of random assignment on an individual's status as a research subject. Fifth, we discuss how

our definition of research subject may be applied in a variety of CRT designs and contexts to identify research subjects who are entitled to regulatory protections.

Who is a Research Subject?

1. Regulatory definitions of "research subject"

The definition of a research subject is a foundational problem in the ethics of human subjects research. However, there is very little regulatory guidance that helps to address this problem. Most international and national research ethics guidelines, including those of Canada and the UK,[10,13-15] omit a definition of research subject. These documents were promulgated to guide the ethical conduct of research in which subjects are recruited individually, in which case it is usually clear from the outset who is the research subject. In addition, The UK Medical Research Council's ethical guidelines for CRTs[16] and CIOMS *International Ethical Guidelines for Epidemiologic Studies*[17] fail to define a research subject. Perhaps more problematically, they appear to assume that cluster community members will necessarily be subjects, although they offer no meaningful rationale for this assumption[16,17].

One of the few national regulations to contain a definition of research subject is the United States Federal research regulations 45 CFR 46[8]. These regulations, known as the Common Rule, govern all human subjects research conducted or funded by departments of the US federal government. The Common Rule is accompanied by a wealth of background

documents and commentary, and has been influential in other countries' development of their own research ethics guidelines.

The Common Rule offers the following criteria that identify a research subject. A research subject, according to the Common rule, is a "living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

> *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e. the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects[8]."

Most other regulations that contain definitions of research subjects are narrowly focused on one particular research design, namely clinical trials, and simply define research

subjects as those individuals receiving an experimental intervention in a clinical trial[9,10,12]. One exception is the Australian National Statement on Ethical Conduct in Human Research[11]. The Australian National Statement includes a list of six types of activities that make an individual a research subject, including:

- taking part in surveys, interviews or focus groups;
- undergoing psychological, physiological or medical testing or treatment;
- being observed by researchers;
- researchers having access to their personal documents or other materials;
- the collection and use of their body organs, tissues or fluids (e.g. skin, blood, urine, saliva, hair, bones, tumour and other biopsy specimens) or their exhaled breath;
- access to their information (in individually identifiable, re-identifiable or non-identifiable form) as part of an existing published or unpublished source or database[11].

Four of these criteria describe different kinds of interventions upon, or interactions with, subjects, and are therefore reducible to the first item in the Common Rule criteria. The fourth and sixth item in the Australian National Statement criteria refer to the use of an individual's information, including both identifiable private information and information with personal identifiers removed[11].

Because of its comprehensiveness, and because it is supported by a great deal of historical documentation, we will use the Common Rule criteria as a useful starting point

from which we can attempt to elucidate a principled definition of research subject. We will draw on other guidelines, such as the Australian National Statement, where applicable.

In attempting to develop a definition of "research subject", we will ask whether the components of the Common Rule criteria—obtaining data through intervention or interaction with an individual or the use of identifiable private information—have a common theme. If a common theme that unites the Common Rule criteria can be identified, this may be a foundation on which we can build a principled definition of research subject.

2. Distinctive features of research subjects

In attempting to identify a common theme between the criteria outlined in the Common Rule and other regulations, we will be guided by normative work on the distinction between a subject in clinical research and a patient in clinical practice. To do this, it is first necessary to distinguish between research and clinical practice. In the Appendices to the *Belmont Report*, Robert Levine draws a distinction between research and ordinary medical practice based on the purpose of each activity[18]. Clinical practice, he argues, involves a health professional acting solely for the purpose of ameliorating the health of her patient. Research, on the other hand, is "…a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge"[8]. Research may include interventions that offer benefit to research subjects, but these are not an essential component of an activity whose primary purpose is to benefit society in the form of expanded knowledge.

The insight that the intent of research is different from the intent of clinical practice leads to an important distinction between the physician-patient relationship and the investigator-subject relationship. Elucidating the difference in these two relationships helps us to identify the distinctive feature of research subjects.

In clinical practice, the health professional and patient are in a fiduciary relationship. A fiduciary relationship is characterized by structural vulnerability, in which the beneficiary (in this case, the patient) entrusts the fiduciary (in this case, the health professional) with discretionary powers to act in the beneficiary's interests[19]. Health professionals are empowered and obligated to act in patients' health interests, and are also obligated to protect their privacy interests. Levine points out that in ordinary clinical practice, patients can be confident that their health professionals will act with patients' interests in mind, as the sole purpose of clinical practice is to ameliorate the health of the patient[18].

The relationship between researchers and subjects is somewhat different. Levine[18] and Rothman[20] note that clinician-investigators face a conflict of interests. On the one hand, they have an obligation to act in the best interests of their patient-subjects. On the other hand, clinician-researchers also have obligations to the study, such as ensuring compliance with experimental treatment protocols, that may conflict with their obligations to a patient's welfare. As Rothman writes, "The bedrock principle of medical ethics—that the physician acted only to promote the well-being of the patient—did not hold in the laboratory…The doctor-patient relationship could no longer serve as the model for the investigator-subject relationship." [20] Research regulations evolved specifically to safeguard

the interests of research subjects, as investigators' conflict of interest prevents them from effectively acting in subjects' interests[20].

Research subjects are vulnerable because a clinician-investigator's obligation to protect subjects conflicts with his or her scientific obligations. As Levine puts it, the role of a research subject approximates that of a means to an end[18]. Both the Common Rule and Australian National Statement criteria specify ways in which a subject's interests could be compromised for scientific purposes. When an investigator intervenes on a subject, either with an experimental intervention or in order to collect data, the subject's welfare may be at risk. The same is true if an investigator interacts with a subject. By collecting personal information, the investigator may violate the subject's privacy.

3. A principled definition of "research subject".

As noted above, the Common Rule classifies research subjects as individuals whose interests may be compromised for scientific purposes. We therefore propose using this criterion as the basis for a novel definition of "research subject":

> A research subject is an individual whose interests may be compromised as a result of interventions in a research study.

In this definition, "interests" refer generally to goods that an individual would ordinarily seek to protect. Research ethics regulations are primarily intended to protect subjects' health, welfare and privacy interests. Interests, as far as this definition is concerned, may also include such things as economic interests.

We find historical support for this definition of a research subject in the 1974 US Department of Health, Education and Welfare (DHEW) regulations for human subjects research[21]. These regulations are the immediate predecessor of the Common Rule. Rather than define "research subject", the DHEW regulations refer to "subjects at risk". A "subject at risk" is defined as:

> "any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service.[21]"

4. Evaluating Current Regulations with a Principled Definition of "Research Subject"

The principled definition of "research subject" that we have developed may be used to critically evaluate criteria in current regulations that identify research subjects. We can do this for the Common Rule, the Australian National Statement, as well as other research regulations. Most regulations for clinical trials refer to subjects as individuals who receive experimental or control interventions in a clinical trial. This definition therefore identifies subjects as those who are intervened upon. These regulations are likely adequate for individually randomized clinical trials, but are not sufficiently exhaustive to be applied more broadly as they omit other ways in which individuals' interests could be compromised[9,10,12].

As previously noted, the Australian National Statement offers a six-item list of ways in which an individual could become a research subject. Four of these criteria (1, 2, 3 and 5) identify ways in which researchers may intervene upon or interact with subjects. We can conclude, based on our principled definition of "research subject", that these items are appropriate for inclusion on a list of criteria that identify a research subject. The fourth criterion includes "researchers having access to personal documents or materials" may compromise subjects' privacy interests and merits inclusion[11]. The sixth criterion defines any individual about whom a researcher obtains "information (in individually identifiable, re-identifiable or non-identifiable form) as part of an existing published or unpublished database or source"[11] as a research subject. Yet, the use of non-identifiable information presents no risk to an individual's privacy (or other) interests. Similarly the use of identifiable, publicly available information such as biographical materials or items of public record, presents no risk to an individual's privacy (or other) interests. Our definition of research subject would thus lead us to conclude that this sixth item in the Australian National Statement is too broad for inclusion in a list of ways in which an individual could become a research subject.

We can use our principled definition of research subject reflexively to examine whether all of the components of the Common Rule are germane to a definition of research subject. The Common Rule criteria include interventions on subjects or interactions with subjects, and the use of identifiable private information. These categories broadly describe means by which a research subjects' interests could be compromised, and so merit inclusion in a definition of research subject. The Common Rule definition further defines

interventions as “physical procedures…and manipulations of the subject or the subject's environment”[8]. Physical procedures or manipulations of the subject necessarily involve some degree of risk, and therefore may compromise the subjects’ welfare interests. However, the reference to environmental manipulation is insufficiently explicit and requires further elucidation.

The Importance of Environmental Manipulation

According to the Common Rule, one way an investigator may intervene on research subjects is by manipulating their environment. With respect to healthcare CRTs, Mann and Reyes[5] have interpreted this to mean that an intervention designed to alter a healthcare professional’s practice pattern represents a manipulation of the environment of all patients whose care may be influenced by a professional’s participation in a CRT. Thus, according to Mann and Reyes, every patient of a professional whose care may be influenced by a CRT intervention meets the regulatory definition of a research subject. This claim is understandable, given that much of the literature on the ethics of CRTs assumes that cluster members (in this case, patients) will necessarily be subjects[16,22-25]. If correct, their view has considerable implications for the conduct of CRTs. If, in CRTs targeted at health professionals or health systems, all patients are considered research subjects, the administrative burdens associated with protecting patients as research subjects would threaten the feasibility of many trials. We explore below whether the indirect effects of a research intervention at the group level (such as an educational intervention administered to

health professionals) implies that all individuals within the group (such as the patients of professionals participating in a CRT) must be considered research subjects.

1. Can environmental manipulation make an individual a research subject?

The CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*[14] includes in its definition of research any study that manipulates an individual's social or physical environment, including field studies of pathogenic organisms or toxic chemicals. These guidelines, along with the CIOMS *International Ethical Guidelines for Epidemiological Studies* [17], address issues of informed consent in epidemiologic research and the analysis of harms and benefits for such research. Therefore, without actually defining "research subject" the CIOMS guidelines appear to acknowledge that individuals who may be affected by public health interventions that manipulate the environment such as water fluoridation or pesticide use are, in fact, research subjects [14,17].

A broad interpretation of "environmental manipulation" is untenable, however, because it leads to absurd conclusions. It seems impossible that everyone whose environment is manipulated in the context of a research project must be considered a research subject. The term "environment" refers to "the surroundings or conditions in which a person, animal, or plant lives or operates" [26]. Using this definition, "manipulations of the…subject's environment" would imply that every person on Earth is a research subject in every research study. For example, studies in particle physics at the Large Hadron Collider (LHC) meet the Common Rule definition of research, in that they are systematic investigations designed to develop generalizable knowledge[8]. One concern

regarding the LHC project was that some experiments could create microscopic black holes that might be hazardous to the planet and all of its inhabitants[27]. If we were to employ a broad interpretation of "manipulations of the…subject's environment", the Common Rule would require that particle acceleration experiments at the LHC be considered a manipulation of the environment for all human beings, meaning that everyone on Earth must be considered research subjects. This notion seems patently absurd. We therefore require a better understanding of what environmental manipulations are sufficient to make an individual a research subject.

It is helpful to consider what the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research may have meant when they included "environmental manipulation" in their definition of a research subject. In a paper prepared for the National Commission in 1975 (included in the 1979 Appendix to the *Belmont Report*), Robert Levine defined research as "…manipulation, observation, or other study of a human being--or of anything related to that human being that might subsequently result in manipulation of that human being--done with the intent of developing new knowledge and which differs in any way from customary medical (or other professional) practice."[18] Specific reference to manipulation of an individual's environment did not appear until the National Commission defined a research subject in their 1978 *Report and Recommendations on Institutional Review Boards*, and this language was incorporated into the Common Rule[28]. The Common Rule's reference to manipulation of an individual's environment took the place of Levine's "anything related to that human being that might subsequently result in manipulation of that human being." Exploring the reasons for this

change in regulatory language helps to clarify what kinds of environmental manipulation are sufficiently meaningful to consider an individual a research subject.

Given the sorts of issues being discussed in the research ethics literature at the time, it seems likely that the National Commission was seeking to protect individuals who participated in studies evaluating the psychological effects of various environmental stimuli. Inclusion of environmental manipulation in the definition of research subject seems intended to capture research that deliberately manipulated subjects and placed their welfare at risk without direct intervention or physical contact from investigators.

Examples of this type of research include studies examining the psychological and behavioural effects of habitation in simulated fallout shelters sponsored by the US Office of Civil and Defense Mobilization[29], and studies evaluating the psychological effects of other environmental manipulations such as sensory deprivation[30,31]. Environmental manipulations in the Civil Defense studies includes such things as living in a confined space for prolonged periods, crowding, variable air quality, variable availability of potable water and exposure to variations in temperature. The individuals participating in these studies were subjected to physical or psychological discomfort resulting from the manipulation of their environment in the context of a research study. What these studies have in common, then, is that the study interventions placed the welfare of the subjects in jeopardy by manipulation of their environment rather than via direct intervention or physical touching by the investigators.

These practices support a narrower reading of the environmental manipulation clause. We suggest that environmental manipulation must have a direct impact on an individual in order to make him or her a research subject. In other words, the environmental manipulation must be designed to produce a direct effect on the individuals whose environment is being manipulated. We believe that this interpretation is consistent with the intent of the National Commission. We will therefore expand our definition of "research subject" to include any individual who is deliberately affected *via* manipulation of his/her environment by an investigator (Box 1).

This conclusion is consistent with the language enshrined in the Final Report of the National Bioethics Advisory Commission. In their 2001 Report and Recommendations: Ethical and Policy Issues in Research Involving Human Participants, the Commission agrees that the term "subject" "…connotes the fact that the individual is 'subjected' to an action by the investigator."[32] The Commission specifically recommends that "…Research be considered to involve human participants when individuals 1) are exposed to manipulations, interventions, observations or other interactions with investigators or 2) are identifiable through research using biological materials, medical and or other records, or databases."[32]

2. Do indirect effects of CRT interventions on health professionals or health systems make patients research subjects?

Mann and Reyes have construed a change in physicians' practice patterns that result from educational or quality improvement interventions in a CRT to be a manipulation of

their patients' environment, therefore requiring those patients to be considered research subjects[5]. We respectfully disagree.

First, in order to turn an individual into a research subject, the environmental manipulation must be designed to produce a direct effect on that individual. This is not the case in CRTs that intervene on health professionals. The CRT design is chosen because the interventions under study are cluster-level interventions. The interventions being evaluated in these studies are intended to change health professionals' behaviour by increasing professionals' use of evidence-based strategies to improve care. Patients are not being directly manipulated by interventions administered to their health professionals.

Second, even if a change in a professional's practice pattern did constitute a deliberate manipulation of patients via a manipulation of their environment (a claim that we do not grant), that manipulation does not jeopardize patients' interests and is therefore not sufficient to warrant considering patients as research subjects. Examining the distinction between clinical research and clinical practice is again helpful with respect to this issue. Levine writes,

> "If a physician proceeds in his interaction with a patient to bring what he considers to be the best available technique and technology to bear on the problems of that patient with the intent of doing the most possible good for that patient, this may be considered the pure practice of medicine. By contrast, if a physician interacts with an individual with the intent of developing new

knowledge (not primarily for the benefit of that individual), this activity may be classified as research."[18]

When a health professional participates in a CRT, her patients may still fully entrust their welfare to her because she has no conflicting obligations to the trial itself. Physicians in this situation are subjects themselves, not investigators. Although the professional may have received an intervention aimed at improving practice, the professional is still expected to act in the best interests of her patients and in accordance with professional practice standards. As Henderson puts it, "In the studies in which an administrative intervention does not directly interpose between the physician and the patient, the patient's treatment remains under the direction of the physician and is not removed by the process of randomization[33]." Therefore, effects on practice patterns do not jeopardize the welfare interests of the patients of a health care provider participating in a CRT. Simply being a patient of a professional participating in a CRT of an educational, knowledge translation, or quality improvement intervention does not make one a research subject.

Some studies evaluate patient-level effects as an outcome measure. The fact that a patient-level effect may be measurable is relevant to patients only insofar as their private health information may be used, or they may be asked to submit to surveys or additional examinations to evaluate the outcome of the CRT. Patients of professionals participating in a CRT of an educational or quality improvement intervention need be considered subjects only if they are directly intervened upon by or interact with investigators, or if their identifiable private information is used.

This conclusion does not necessarily hold for patients in CRTs evaluating alternative modes of health service delivery. These CRTs aim to evaluate the effect of different methods of providing care. This is different from CRTs of interventions directed at providers that aim to increase the use of evidence-based care while maintaining the fiduciary relationships that providers have to patients. Examples include CRTs evaluating the effect of employing specialist nurses in asthma management[34] or the use of case managers for the reduction of inpatient length of stay on medical wards[35]. These CRTs are being conducted because the efficacy of the mode of delivery is uncertain. Randomization in clusters is undertaken for logistical reasons and to avoid experimental contamination. A trial evaluating the effect of an experimental mode of delivery is thus akin to a trial that evaluates an experimental treatment. Novel modes of healthcare delivery are therefore best thought of as direct patient-level interventions rather than environmental manipulations. In such studies, the patients would be research subjects because they are directly intervened upon.

3. Implications for CRTs in fields other than healthcare

In some CRTs, particularly in public health, the purpose of the experimental interventions is to deliberately manipulate individuals via their environment. For example, in the COMMIT study, billboards, and mass media ads (environmental manipulations) were intended to produce behavioural change in smokers living in intervention communities[36]. Another CRT evaluating interventions aimed at individuals via environmental manipulation is a CRT comparing rates of diarrheal illness in communities randomly assigned to water treatment with flocculant disinfectant or a control[37]. In these

studies, the purpose of the environmental manipulation is to intervene on individual residents. The residents of communities in such studies are therefore research subjects and entitled to regulatory protections. This does not necessarily mean that informed consent is required from all residents. Rather, many of these studies of environmental manipulations would meet regulatory criteria for a waiver of informed consent[8,15,17].

CRTs in education are roughly analogous to CRTs in healthcare: the teacher-student relationship has many of the characteristics of a fiduciary relationship[19]. If a CRT is used to evaluate the effect of a continuing education intervention for teachers, the indirect effect of the change in teachers' performance on students will not require that students be considered research subjects. However, CRTs of experimental curricular programs may be more similar to CRTs evaluating novel methods of health service delivery, and may require treating students as research subjects.

What is the importance of random intervention assignment?

The importance of random intervention assignment has caused some concern in the literature on the ethics of CRTs. In CRTs, random group assignment is often performed before subjects are enrolled[38]. Indeed, in CRTs of large cluster-level public health interventions clusters may be randomly assigned to interventions that some cluster members may never receive, leading to the concern that the act of random assignment may make these individuals who are not affected by the intervention research subjects[25]. Some of the concern over randomization in CRT stems from how subjects are assigned in individually-randomized trials. In any randomized controlled trial, assignment to the

intervention or control arm (whether individually or in clusters), is determined by a mechanism that is beyond the control of the individual or group being randomized. For example, in healthcare clinical trials, treatment assignment is specified by the study protocol. Treatment is not determined by the clinician-patient dyad. Random assignment has been viewed by some as a research intervention[39], which leads to the conclusion that randomization in and of itself makes an individual a research subject.

We argue that random trial arm assignment is, in and of itself, not sufficient to make an individual a research subject. In any comparative study, regardless of the method of intervention assignment (random or non-random), assignment is out of the control of the individual or group being assigned. For this reason, the use of random intervention assignment is immaterial to the determination that an individual in a trial is a research subject. If some non-random method of intervention assignment were used in place of random assignment, the threats to subjects' liberty and welfare interests would be unchanged. A research subject is an individual whose interests are threatened in the context of a research study. Whether intervention assignment is random or non-random is a moot point.

Random assignment of clusters is, by itself, insufficient to make cluster members research subjects. The fact that, in many CRTs, group assignment is determined before subject enrolment should be acknowledged in consent discussions with individuals who are identified as research subjects according to a principled definition.

Implications for Cluster-Randomized Trials

To summarize our conclusions, we suggest that the following four criteria may be used to define research subjects:

1. An individual who is directly intervened upon by an investigator for research purposes;
2. An individual who is deliberately intervened upon via manipulation of his/her environment by an investigator for research purposes;
3. An individual with whom an investigator interacts for the purpose of collecting data;
4. An individual about whom an investigator obtains identifiable private information for the purpose of collecting data.

A detailed discussion of these criteria and their implications for CRTs follows.

A research subject is an individual whose interests may be compromised as a result of interventions in a research study including:

1. An individual who is directly intervened upon by an investigator for research purposes

Individuals are research subjects if, in the context of a research study, they are the recipients of an experimental intervention (active or control) or if they undergo an intervention to collect data, such as an additional examination.

If an intervention is targeted at individual cluster members but random assignment is done at the cluster level (typically to avoid treatment contamination or for logistical reasons) then the individuals receiving the intervention should be considered research subjects. In healthcare, this would include CRTs evaluating therapeutic or health promotion modalities aimed at individual patients, as well as CRTs evaluating new modes of health service delivery. An example of the former includes a CRT evaluating the effect of individualized exercise prescriptions for patients, randomized by physician practice[40]. An example of the latter includes a CRT evaluating the effectiveness of asthma management using specialist nurses[34]. In these studies, the individuals themselves are being manipulated, and should therefore be considered research subjects.

In healthcare CRTs, the intervention under study is often not administered to patients, but rather to healthcare professionals, and the outcomes are evaluated using patient data. It may be reasonably asked whether the health professionals who receive an educational intervention in a CRT are research subjects or collaborators. Collaborators are individuals who contribute to the design of, or participate in the conduct of, a research study. Collaborators are not recipients of experimental interventions. In healthcare CRTs, the health professionals are receiving an experimental educational or quality improvement intervention. When they are directly intervened upon in this way, health professionals participating in a CRT meet the definition of a research subject[5,6,41].

Some healthcare CRTs evaluate complex interventions that may include combinations of health professional education, novel modes of health service delivery and patient-level interventions. An example is a CRT evaluating a primary care program aimed

at reducing obesity[42]. In this trial, primary care providers in the intervention arm received an educational intervention on motivational techniques and physical activity for obese patients. Patients in the intervention arm were screened for obesity, and obese patients were counseled by the physician and referred to local sports foundations to receive individualized exercise counseling. In determining whether or not patients need be considered research subjects for these CRTs, an ethics committee needs to examine each intervention in such a CRT to determine whether a particular intervention is directed at patients, or whether data collection includes interaction between researchers and patients or the use of identifiable private information. Interventions on health professionals mean that the health professionals will be research subjects. Patients will not necessarily be research subjects because of interventions on health professionals. But, patients will be research subjects if there are patient-level interventions (either therapeutic interventions or direct interventions to collect data) or novel modes of health service delivery are used, if researchers interact with patients, or if the study uses patients' identifiable private information to evaluate outcomes.

2. An individual who is deliberately intervened upon via manipulation of his/her environment by an investigator for research purposes

Individuals who are intervened upon via manipulation of their environment are research subjects. This includes individuals who will be affected by CRTs of public health interventions, whether the unit of randomization is a municipality, a neighborhood, a family, or some other group whose environment may be manipulated. Because these

individuals are research subjects, they are entitled to regulatory protections, including the determination by a research ethics committee that the risks to their interests do not outweigh the potential benefits offered by the CRT. Many of these studies would meet regulatory criteria for a waiver of informed consent because the interventions in these studies pose only minimal risk and would likely be unfeasible without a waiver of consent.

We concluded above that the indirect effects that a CRT may have on an individual are not sufficient to warrant considering that individual to be a research subject. In healthcare CRTs, patients may be indirectly affected by educational or quality improvement interventions that are directed at healthcare professionals or institutions. The physicians under study continue to have an obligation to act in patients' best interests, and have no competing obligations to the study itself. The physician-patient relationship is preserved. If there are no patient-level interventions, if the researcher has no interaction with individual patients, and there is no use of identifiable private information for research purposes, patients are not research subjects.

3. An individual with whom an investigator interacts for the purpose of collecting data

Any individual from whom an investigator, in the context of a research study, obtains data through any kind of interaction should be considered a research subject. Interaction includes any kind of communication or interpersonal contact between investigator and subject, for example interviews, focus groups, or questionnaires. Such modes of interaction may be employed in CRTs when collecting data reported by individual cluster members.

Any data collection through interaction means that the respondents are entitled to protections as research subjects[8,11].

4. An individual from whom an investigator obtains identifiable private information for the purpose of collecting data.

Obtaining identifiable private information about individuals within a cluster will make these individuals research subjects, and therefore make them entitled to protections. Conversely, there is no risk to an individual's privacy if the researchers are only collecting anonymized or aggregate group-level information[43]. Individuals whose data have been anonymized before transfer to the investigators, or whose administrative or health-related information is used to generate aggregate measures for a cluster are not research subjects unless they are manipulated in some other way.

Practical Applications for Ethics Review of CRTs

We will now apply our new definition to the issues raised earlier in 'Examples: Challenges in identifying the research subject in CRTs":

Example 1: The COMMIT Trial

The COMMIT trial[1,2] evaluated a multimodal community-level intervention, including a media and billboard campaign and targeted messaging toward smokers, aimed at reducing cigarette consumption. These interventions did not directly manipulate

individuals, but did intervene on individuals via environmental manipulation. Therefore, individuals in the participating communities are research subjects.

Example 2: A CRT of bed net distribution to reduce malaria prevalence

The distribution of bed nets constitutes a direct intervention on individuals. Therefore, all residents of the intervention communities who received a bed net are research subjects. Individuals contributing blood samples, whether from intervention or control communities, were also directly intervened upon and are research subjects. In this study, no private identifiable information was collected. Therefore, citizens of control communities who did not contribute blood samples, were not recipients of an intervention, were not intervened upon via manipulation of their environment, did not interact with researchers, did not contribute identifiable personal information, and were *not* research subjects.

Example 3: A CRT comparing interventions to improve primary care prescribing

The physicians in this study were recipients of an experimental intervention, and are research subjects. The patients received no intervention from study personnel, had no interaction with the study personnel, and contributed no identifiable private information. Therefore, the patients of physicians participating in this particular study are not research subjects.

Example 4: A CRT comparing modes of educating patients prior to breast cancer surgery

In this study, the patients were recipients of an experimental intervention in that they received one of two candidate modes of education about their surgical options. They responded to questionnaires to generate outcome data, and contributed identifiable medical information. For all of these reasons, they are research subjects. The surgeons delivering the experimental decision tool underwent training, while those in the control group had their practices modified by using additional printed information. These educational interventions and changes in practice are research interventions, meaning that the surgeons participating in both arms of the study are also research subjects.

Conclusions and Future Work

We have defined a research subject as an individual whose interests may be compromised as a result of interventions in a research study, and have specified four ways in which research subjects' interests may be compromised (Box 1). Research subjects are those individuals who are intervened upon by researchers, either by direct interventions or by deliberate manipulations of their environment, those who interact with researchers to provide data, or those whose identifiable private information is used to generate data.

In articulating a principled definition of a research subject, with specifications that help to identify research subjects, this paper represents an essential first step in addressing additional questions on how to protect research subjects in CRTs. The specifications that help define the research subject may be used by investigators and research ethics committees to help ensure that research subjects in CRTs receive necessary protections and

that important research is not hindered by incorrect application of research ethics guidelines and regulations.

Subsequent papers will rely on this novel definition of research subject and analyze the implications of this innovation on such issues as: informed consent; harm-benefit analysis; subject selection and protection of vulnerable subjects; and the role and authority of cluster gatekeepers in CRTs.

Box 1. Definition of a Research Subject

A research subject is an individual whose interests may be compromised as a result of interventions in a research study including:

1. An individual who is directly intervened upon by an investigator
2. An individual who is deliberately intervened upon via manipulation of his/her environment by an investigator
3. An individual with whom an investigator interacts for the purpose of collecting data
4. An individual about whom an investigator obtains identifiable private information for the purpose of collecting data.

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Chapter 6

When is Informed Consent Required in Cluster Randomized Trials?

Introduction

The question of when it is necessary to seek informed consent from subjects in cluster randomized trials (CRTs) has stirred substantial discussion in the CRT literature.

In an article published in the *British Medical Journal* entitled "Ethical Issues in the Design and Conduct of Cluster Randomized Controlled Trials", Edwards et al. describe the difficulties associated with obtaining informed consent in CRTs[1]. The authors suggest that the requirement to seek informed consent is inextricably linked to the type of interventions being evaluated. Their analysis relies on a distinction between two types of CRTs: individual-cluster trials and cluster-cluster trials.

In individual-cluster trials, experimental interventions are directed at individual cluster members but subjects are randomized in clusters in order to avoid experimental contamination[1]. In these studies, it is generally possible to seek subjects' informed consent, just as in an individually-randomized trial.

Cluster-cluster studies, on the other hand, evaluate experimental interventions that target entire clusters[1]. In these studies it may not be possible for cluster members to avoid the experimental interventions, thus making individual refusal of the study interventions meaningless.[1,2] In addition, when dealing with large clusters, it may be logistically impossible to seek consent from all cluster members[1,3].

The relationship between trial type (individual-cluster or cluster-cluster) and the feasibility of obtaining informed consent lies at the heart of the United Kingdom Medical Research Council (MRC) document *Cluster Randomized Trials: Methodological and Ethical Considerations*[4]. The authors of this document conclude that , if seeking consent from individual subjects is feasible, then investigators are obligated to do so. If, on the

other hand, seeking consent from individual subjects is not feasible, authorization to enroll a cluster in the study must be sought from a cluster representation mechanism—an entity or an individual charged with making decisions in the interest of the entire cluster. Thus, according to both Edwards et al., and the authors of the MRC guidelines, whether or not consent is required from individual subjects in CRTs depends on the feasibility of doing so.

The association Edwards and colleagues identify between the type of interventions being evaluated and the feasibility of seeking informed consent from individual cluster members seems intuitively correct. Moreover, their conclusions are reflected in actual practice, in that investigators routinely seek consent in CRTs evaluating individual-level interventions, but not in CRTs evaluating cluster-level interventions[5-7]. Unfortunately, the conclusion that the need to seek consent depends *solely* on the feasibility of doing so fails to follow the general principles guiding human subjects research. If consent cannot be obtained, then other conditions must be satisfied in order to safeguard subjects' interests.

When must investigators obtain informed consent from human subjects in CRTs? This paper seeks to answer this question by examining the challenges related to obtaining informed consent in CRTs through the lens of research ethics. We first examine the ethical principles and moral theories that underpin consent requirements in order to develop a conceptual framework that lays out the fundamental purpose of informed consent requirements. Using this framework, we address the key questions related to informed consent in CRTs, namely: 1) How may CRTs proceed if seeking informed consent is not feasible? 2) Is it permissible to seek informed consent after randomization of clusters? 3) What information must be disclosed to potential subjects? 4) May opt-out,

or passive consent strategies be used instead of seeking informed consent? 5) Do professionals have an obligation to participate in CRTs?

Prior work: Who is a research subject?

Clearly identifying who is a research subject in a CRT—and who is not—helps to address some of the concerns outlined in the CRT literature regarding the feasibility of seeking consent in cluster-cluster trials[1-3,7-9]. In the preceding article in this series, entitled "Who is the Research Subject in Healthcare Cluster Randomized Trials?" we developed a principled definition of "research subject"[10]. We argued that a research subject is an individual whose interests may be compromised in the context of a research study. This includes any individual: 1) who is directly intervened upon by an investigator; 2) who is deliberately intervened upon via manipulation of his/her environment by an investigator; 3) with whom an investigator interacts for the purpose of collecting data; 4) about whom an investigator obtains identifiable private information for the purpose of collecting data[10]. As a general rule, informed consent for CRT participation must be sought from research subjects. Conversely, seeking consent from cluster members who are not research subjects is not required.

The implication of using a principled definition of "research subject" are illustrated using the example of patients managed by primary care physicians in the NEXUS trial [11]. In this CRT, 247 primary care practices were randomly assigned to receive interventions designed to increase general practitioners' compliance with radiography guidelines for patients with nontraumatic back and knee pain. The comparative efficacy of the interventions was evaluated by examining the change in number of lumbar spine and knee

radiographs ordered per thousand patients per year for two years. These data were obtained by abstracting data from patient records from a random sample of primary care practices in each trial arm[11].

The primary care physicians who received the experimental interventions were research subjects, according to the definition of "research subject" outlined above. Consent issues for professionals who are intervened upon in CRTs are discussed further below.

The patients of physicians participating in the NEXUS study were not intervened upon, either directly or via manipulation of their environment, nor did investigators interact with them[10,12]. Investigators obtained identifiable private information from the medical records of a sample of patients. Patients whose private information was used were research subjects. Whether or not consent was necessary for this sample of patients is discussed below. Patients whose medical records were not used were not research subjects. Their consent was not required[10,12].

The remainder of this paper will address consent requirements for research subjects in CRTs. As a general rule, research subjects in a CRT must provide informed consent for trial participation. As will be discussed below, exceptions to informed consent requirements may apply to CRTs in clearly defined circumstances.

Moral Foundations of the Requirement for Informed Consent for Research Participation

Informed consent for research participation is a central ethical safeguard for research subjects[13-15]. This section outlines the moral foundations of informed consent requirements and examines how they apply to CRTs.

In the *Belmont Report* the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research identified three basic ethical principles for research involving human subjects: respect for persons, beneficence, and justice. Consent requirements for research participation stem from the principle of respect for persons[14], which requires: 1) that the wishes of autonomous individuals be respected, and 2) that individuals with diminished autonomy be protected[14].

Autonomous individuals may be understood as those who are capable of self-government and are able to make responsible choices for themselves. Autonomous choices are those that are intentional, substantially informed, and substantially free of coercing influences[16,17].

The principle of respect for persons may be viewed as deriving from deontological moral theory, which defines right action as the satisfaction of moral duties[16-19]. Kantian deontological theory posits that autonomous individuals have intrinsic moral worth in virtue of their capacity for rational decision-making about their ends. Respect for the intrinsic moral worth of others entails respect for their autonomous choices. The famous Kantian dictum exhorts us to always treat others as ends in themselves rather than merely as the means to an end[17,18,20,21].

The requirement to obtain informed consent for research participation is consistent with the kinds of duties owed by investigators to autonomous individuals. According to Freedman, consent requirements arise,

> "…from the right which each of us possesses to be treated as a person, and in the duty which all of us have, to have respect for persons, to treat a person as such, and not as an object. For this entails that our capacities for personhood ought to be recognized by all—these capacities including the capacity for rational decision and for action consequent upon rational decision. [19]"

Research necessarily involves "using" subjects as a means of acquiring scientific knowledge. Why would an individual choose to become a research subject, thereby jeopardizing her privacy or welfare for the sake of science? We suggest that the rational research subject would only agree to such constraints if she agreed with the goals of the study. In consenting to study participation, the research subject adopts the scientific ends of the study as his or her own. Granting one's consent to participate would, therefore, signal that the research participant is treated as an end in and of herself and not merely a means of and was fulfilling the researchers' objectives.

Another way of getting at the essence of informed consent may be by contrasting two operational definitions thereof, namely, autonomous authorization and effective consent. Autonomous authorization is a moral concept according to which a person chooses to adopt the goals of research as his or her own and thereby consents to study participation[17]. The individual must be informed, competent and free from coercion.

Effective consent, by contrast, is a legal concept, relating to a legally or institutionally circumscribed definition of the conditions for valid decision-making[17].

Autonomous authorization and effective consent are often functionally synonymous. However, this is not always the case. For example, a teenager may have the rational capacity to make an autonomous authorization but not to provide effective consent if proscribed from doing so on account of his or her age[17].

We can therefore understand autonomous authorization to research participation practically as the subject's agreement to the interventions that are part of the research protocol, and conceptually as the subject's embracing of the goals of the research study[19]. Ideally, legal or policy criteria for effective consent should be derived from the necessary conditions for autonomous authorization. If the purpose of informed consent regulations is to enable autonomous decision-making i.e., to allow subjects to choose whether or not to adopt the ends of the study as their own, then research ethics regulations and guidelines must be evaluated on the extent to which they accomplish this purpose [17].

Research ethics guidelines lay out the criteria for effective consent for research participation, and thus fulfil the end of enabling autonomous authorization. Informed consent guidelines require that potential subjects have the capacity to decide whether or not to participate in the research study at hand; that their decision be free of coercion; that they be adequately informed of the details of the study's purpose and interventions; and that they understand the information given to them[15,22-24].

Disclosure requirements almost universally include the following: an explanation of the purpose of the study; a description of the study interventions; a description of the risks and potential benefits to subjects from research participation; a description of alternatives available to potential subjects should they choose not to participate; a description of confidentiality protections; a statement assuring potential subjects that participation is

voluntary, that they may withdraw at any time, and that their quality of care will not be affected should they choose not to participate or to withdraw; and information on whom they may contact with questions[15,22-24]. If these disclosure requirements are met, then potential subjects will be able to decide whether or not to embrace the study's ends as their own.

In the remainder of this article, we address the ethical challenges associated with obtaining informed consent in CRTs will be addressed using the following ethical framework:

1) Consent requirements stem from the basic ethical principle of respect for persons, which requires that the choices of autonomous individuals be respected.
2) The principle of respect for persons may be rooted in deontological moral theory, which posits that autonomous individuals have an intrinsic worth and are entitled to respect.
3) Autonomous individuals shall not be used solely as means to an end. They must also be treated as ends in themselves.
4) The purpose of seeking informed consent is to enable potential subjects to embrace the ends of the research study as their own.

Addressing consent challenges in CRTs

Prior to considering specific issues related to seeking consent in CRTs, it is important to be clear about what consent is for. In individually randomized clinical trials, consent is obtained prior to randomization and includes consent for random assignment,

for the experimental interventions in either study arm, and for the interventions used to collect data. In CRTs, all of these may be disaggregated: consent for random assignment, experimental interventions, and for the interventions used to collect data may be sought separately. This disaggregation may be necessary because of the intrinsic features of the CRT design. It may not be possible to seek consent for random assignment if individual cluster members are not identifiable at the time of cluster randomization. In individual-cluster trials, seeking consent for the experimental interventions may be feasible, independent of whether or not it is possible to seek consent for random assignment. In cluster-cluster trials, it may or may not be feasible to seek consent for the experimental interventions. Furthermore, if the interventions are unavoidable, refusal would be meaningless. Even if it is not possible to seek consent for randomization or for experimental interventions, it may be possible—and necessary—to seek consent for data collection procedures such as physical examinations, interviews and the use of identifiable private information.

Specific questions relating to seeking consent in CRTs are addressed in detail below.

1) How may CRTs proceed if seeking consent is not feasible?

Edwards et al.[1], Hutton[2], and Donner and Klar[3] have noted that, in certain circumstances, seeking informed consent from cluster members in a CRT may not be feasible. There are two reasons for this. Firstly, that clusters may be large enough that the logistical difficulties associated with seeking consent from all cluster members would make the study infeasible[3]. Secondly, some cluster-level interventions may be unavoidable, effectively rendering individual refusal meaningless[1,2].

A CRT conducted in India randomly assigned nine geographical sectors in Punjab either to an insecticide spraying program to reduce malaria transmission, or to no intervention[25]. The effect of the spraying program on malaria incidence was evaluated by collecting blood samples from residents reporting a fever and also through cross-sectional surveys in which blood samples were collected from schoolchildren in participating communities. The spraying program intervened on residents via environmental manipulation; therefore all residents of sectors in the intervention arm were research subjects[10,22].

In this case, it would have been exceedingly difficult to seek informed consent from all individuals in intervention sectors. Moreover, even if it were possible to obtain consent, the environmental intervention was unavoidable. What would have been the point of obtaining informed consent? This begs the question: how may such a CRT be performed if seeking subject consent for the experimental intervention is impossible?

Such a trial may qualify for a waiver of informed consent as provided for in many national and international research ethics guidelines[15,22,26]. The moral justification for a waiver of informed consent lies in the relationship between the basic principles of respect for persons and beneficence[14,16,17]. When a conflict between basic principles occurs, we must weigh the relative importance of the competing moral demands of each principle[27,28]. The principle of respect for persons entails the moral requirement to seek informed consent from potential subjects. Beneficence requires that investigators minimize harms while maximizing benefits, and that risks to subjects must be offset by either benefit to the subjects themselves, or to society[14]. We may argue that beneficence entails a requirement to pursue valid research for the betterment of society. Because

neither principle supersedes the other, a moral justification for a waiver of informed consent lies in prioritizing the competing demands of each.

Seeking informed consent from subjects allows them to exercise their autonomy in adopting the ends of the study as their own, and allows them to safeguard their own interests. If subjects' interests can be safeguarded in another way, then there may be cases in which the demands of beneficence—producing valid research to benefit society—may reasonably outweigh the demands of respect for persons—to seek informed consent from subjects. A waiver of consent is only permissible if the risks to subjects' interests, and the consequences of setting aside their autonomy rights, are minor, and if the social benefits that may accrue from the research cannot be otherwise obtained.

This is not a utilitarian argument. A utilitarian might conclude that societal benefit necessitates overriding the autonomous wishes of a small number of research subjects even when consent could be obtained, and where subjects' interests at stake are significant. Rather, this is a principled moral foundation for guidelines permitting a waiver of consent in narrowly-specified circumstances.

Numerous examples exist[22-24,29,30], but the oldest regulation outlining the requirements for an alteration or waiver of informed consent is found in the US Common Rule (45 CFR 46.116d), first published in 1981[22]. The Common Rule requires that following conditions all be met in order for an alteration or waiver of consent requirements to be approved by an ethics committee:

> (i) The research involves no more than minimal risk to the subjects;
>
> (ii) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(iii) The research could not practicably be carried out without the waiver or alteration; and

(iv) Whenever appropriate, the subjects will be provided with additional pertinent information after participation[31].

The majority of national and international guidelines for waivers of consent are based on the protections outlined above, and are substantively similar in both language and application[22-24,29,30]. A detailed discussion of each of these requirements follows.

1.1) The research involves no more than minimal risk to the subjects

According to the rules and regulations governing human subjects research drafted by the US Department of Health and Human Services, minimal risk means that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.[32]" In other words, the risks to subjects from interventions in a CRT must be similar to the risks posed by interventions in routine healthcare, public health or educational practice. Minimal risk interventions for data collection include, but are not limited to, interviews, surveys, physical examinations, and collection of data from patients' medical records[32].

Many CRTs would meet this minimal risk criterion. In healthcare CRT, for example, the interventions being evaluated are generally variations on routine care and do not pose any additional risk. Data collection is often accomplished using subjects' medical records, or by using physical examinations or interviews. Thus, the data-collection interventions in healthcare CRTs often pose only minimal risk.

In the malaria prevention CRT described above[25], geographical districts were randomly assigned either to a pesticide spraying program or to a control. The implementation of a pesticide spraying program is consistent with the kinds of measures that a public health department would ordinarily undertake, so the pesticide spraying is consistent with the risks of daily life for residents of intervention communities. Therefore, the experimental intervention poses only minimal risk to subjects. If it can be successfully argued that seeking consent from individual residents for spraying is not feasible, a waiver of consent for the pesticide spraying intervention is reasonable.

1.2) The waiver or alteration will not adversely affect the rights and welfare of the subjects

The meaning of the second requirement, that the waiver or alteration must not adversely affect the rights and welfare of subjects, is not elaborated on in the text of the Common Rule. So what, exactly, does it mean? The National Bioethics Advisory Commission has suggested that safeguarding subjects' rights means ensuring that investigators and ethics committees adhere to other federal or state statutes that might offer more stringent privacy protections than the Common Rule[33]. This interpretation seems redundant, in that any other regulations with more stringent privacy protections will override the Common Rule.

It seems counterintuitive that a requirement to preserve the rights and welfare of subjects is included in regulations permitting a waiver of consent, which outline precisely when the autonomy rights of research subjects may be set aside. It is, perhaps, more helpful to consider this second requirement as a complement to the first requirement that

risks be minimal. Both of these requirements are aimed at ensuring that subjects' interests (be they welfare interests, financial interests, economic interests or other) are not unreasonably jeopardized in the context of a research study that uses a waiver of consent.

1.3) The research could not practicably be carried out without the waiver or alteration

CRT investigators have suggested that some studies may not be feasible without a waiver of consent for a variety of reasons. These generally relate either to the feasibility of obtaining consent from individual subjects[1,2,8], or to the potential for biased responses because of information disclosed during the consent process[1,2,5,9]. Each of these reasons for seeking a waiver of informed consent will be examined separately.

1.3.1) Seeking consent may not be feasible

In CRTs of cluster-level interventions, it may be impossible for cluster members to avoid the intervention[1,2]. Informed refusal is effectively meaningless if the intervention is unavoidable. Some CRTs may randomize clusters that are so large as to make obtaining consent from all subjects logistically impossible[1,2,8].

The preamble to the Common Rule explicitly states that large scale public health studies in which it is impossible to obtain consent from all individuals who may be affected by the study intervention may be eligible for a waiver[31]. It is reasonable to extend this conclusion to CRTs in other fields of inquiry.

A waiver of consent may be used in studies that do not involve an interaction with or intervention on subjects, but that do use identifiable private information to collect outcome data [33]. This practice has been justified because the logistical effort required to

obtain consent from subjects for the use of their private information is prohibitively difficult[21]. This applies particularly to healthcare CRTs that intervene on health professionals and only use patient information to generate effect measures for the interventions under study. In such studies, it would not be necessary to seek the consent of the patients whose private information is used to generate data. In the NEXUS study cited above, for example, consent was not sought for abstracting identifiable private information from the medical records of patients to evaluate the effect of experimental interventions administered to those patients' primary care physicians[11].

No sharp demarcation exists to determine when seeking consent is practicable or impracticable. This determination, rather, is within the discretionary authority of a research ethics committee. An ethics committee may consider a number of factors in making this determination, including the size of the population, as well as the cost and logistical feasibility of seeking consent from all subjects[34]. If a waiver is desired, CRT investigators must convince the research ethics committee that seeking consent from subjects is not feasible. The ethics committee, in turn, is charged with making the qualitative determination as to whether the risks to subjects are minimal and the societal benefit that may be gained by performing the research without obtaining informed consent outweighs the autonomy interests of individual subjects.

The malaria-prevention pesticide study cited above[25] would likely satisfy the criterion that the study could not practicably be carried out without the waiver. The spraying intervention could not be avoided by residents of intervention clusters. The clusters are also sufficiently large that seeking informed consent from individual residents for the spraying intervention would be so logistically difficult as to make seeking

informed consent infeasible. Therefore, because seeking consent is infeasible and because the spraying intervention poses only minimal risk, the pesticide spraying study would likely be eligible for a waiver of informed consent for the spraying intervention under current research ethics guidelines[15,22,26].

1.3.2) Potential for bias because of information provided to subjects during consent negotiations

It has been suggested that the potential for bias in CRTs as a result of information disclosed in the consent process may be sufficient to justify a waiver of consent[1,9,35,36]. CRTs often evaluate interventions aimed at modifying the behaviors of cluster members. Knowledge of the purpose and nature of interventions offered to the other arms of a trial may bias the outcome of the study. For example, a CRT may evaluate an intervention to improve physician uptake of clinical practice guidelines. If members of the control group know the details and purpose of the intervention, they may choose to familiarize themselves with the guidelines, thus biasing the estimate of the intervention's effect[35]. Some commentators have suggested that the potential biasing effect of the consent process for such trials may justify modifying or waiving consent requirements, because undertaking an experiment that is scientifically invalid is unethical[1,9,35,36].

There is no specific regulatory guidance that provides criteria for determining when concerns for study validity might outweigh obligations to seek subjects' informed consent[34]. Concern for bias is one justification for the use of a waiver[4,34]. Investigators concerned that information disclosed during the consent process might bias study findings may apply for a waiver of consent. An application to the research ethics committee for a

waiver must demonstrate that the CRT meets regulatory criteria for a waiver. Specifically, investigators should provide convincing evidence that disclosure would so bias the study findings as to make the study impracticable. Investigators must also demonstrate that the interventions under study pose only minimal risks to subjects. This approach fits with the moral justification for a waiver of consent: that the societal benefit of research knowledge may not be obtained otherwise and the risks to subjects' interests, and that the consequences of setting aside their autonomy rights, must be minor.

1.4) Whenever appropriate, the subjects will be provided with additional pertinent information

Respecting the research subject as a person, not simply as a means to an end, requires that the nature and purpose of the research be disclosed. Providing subjects with information about the study when a waiver of consent is used is therefore important in ensuring that subjects are respected as persons[19]. Yet, how does this requirement apply to CRTs that use a waiver of consent? If obtaining consent from subjects in large CRTs is logistically impossible, it is likely that providing subjects with additional information is equally impossible. Providing additional information to subjects through the media or signs in healthcare institutions that a study is being conducted, and that they are entitled to seek more information from study investigators may be one way of satisfying this requirement.

Waivers of consent in CRTs with cluster-level and individual-level interventions

It is important to note that a waiver of consent may apply to some, but not all, interventions in a CRT. Some studies evaluating cluster-level interventions evaluate outcomes by collecting data from a smaller sample of each cluster. For example, in the pesticide-spraying example CRT cited above, malaria incidence was ascertained by screening residents and obtaining blood samples of individuals with fevers and from a cross-section of school children[25].

Because each individual who undergoes additional examinations, interviews, or tests to generate data is identifiable and accessible, it is feasible to seek consent for data-collection interventions. In this case, a waiver of consent would only apply to the pesticide-spraying intervention.

Informed consent for data-collection procedures should be sought when doing so is feasible, even if these interventions pose only minimal risk. One example of a data-collection intervention that may be eligible for a waiver is the review of a large number of medical records, as was done for research subjects in the NEXUS study cited above[11].

2) May informed consent be sought after randomization of clusters?

As random assignment of clusters is often done before the intervention is administered, it may be impossible to obtain consent until after randomization has been completed[35]. Hutton notes, "Scientific and logistical constraints associated with [CRTs] imply that consent cannot necessarily be requested before an intervention is assigned to a person…In some cases it is logically impossible to obtain consent for the intervention prior to randomization of clusters. [2]"

An example of such a study is a CRT conducted in Nepal that evaluated the comparative efficacy of three different strategies for umbilical stump cleansing on neonatal mortality and incidence of omphalitis (infection of the umbilical stump)[37]. The units of randomization were geographical sectors of rural Nepal. Mothers were randomly assigned in geographical clusters to use either dry cord care (the standard technique, used in the control arm), to washing the stump with soap and water, or to use a disinfectant solution for stump cleansing. The stump care techniques were performed on the infants by health workers who visited new mothers on a predetermined schedule. Neonatal mortality and incident cases of omphalitis were recorded by the visiting health workers. Each mother gave informed consent for study participation during a prenatal health visit[37]. Enrolling subjects prior to randomization of clusters was not possible because mothers had not yet become pregnant at the time of cluster randomization.

Some commentators have expressed concern that seeking subjects' consent for CRT participation after cluster randomization may not respect subjects' autonomy rights[2,8]. Based on our understanding of the purpose of seeking informed consent, this concern appears unjustified.

The purpose of seeking informed consent is to enable subjects to autonomously embrace the ends of the study as their own. This purpose is still achieved if consent for CRT participation may only be sought after random assignment of clusters, and if subjects are approached for consent at the earliest possible opportunity. If potential subjects are informed that group assignment has already been determined, then they may freely choose whether or not to participate in the CRT. The fact that group assignment has already been determined does not limit potential subjects' autonomy or their ability to

embrace the study's objectives as their own. Potential subjects may freely choose whether or not to participate in the CRT. Thus, it is permissible to seek informed consent for CRT participation after randomization has been done.

In the Nepalese CRT cited above, it was impossible to seek informed consent prior to randomization of clusters. However, mothers were free to decide whether or not to participate in the study. The purpose of seeking informed consent—enabling potential subjects to make autonomous choices to adopt the scientific purpose of the study as an end of their own—was still achieved in this trial, even though consent was sought after random assignment of clusters.

3) What information must be disclosed to subjects?

Potential research subjects must be given sufficient information to allow them to decide whether or not to participate in a study[19]. As outlined above, guidelines for disclosure during consent processes generally include a statement of the study's purpose, a description of the nature, risks and potential benefits of the interventions involved, and the potential subjects' options should they choose not to participate [15,22-24].

If subjects are enrolled after randomization of clusters has taken place because seeking consent prior to randomization is impossible, they must still be informed of: the purpose of the study, detailed information about the trial arm to which they have been assigned, and information about their options should they choose not to participate in the trial.

Information about the purpose of the study is essential to a potential subjects' decision as to whether or not they can embrace the study's scientific ends as their

own[17,18,20,21]. Therefore, the purpose of the study must be described in sufficient detail so as to allow potential subjects to decide whether or not the study's ends are consistent with their values.

Potential subjects must be provided with a detailed description of the interventions administered in the trial arm to which their cluster has been randomly assigned. However, detailed information about other arms in a CRT is not necessary. The choice facing the potential subject is whether to participate in the CRT, in the arm to which their cluster has been assigned, or not to participate in the CRT. Detailed information about the interventions offered in other arms of the trial (i.e. interventions that the subject would not receive) is immaterial to the potential subject's decision whether or not to participate.

In the Nepalese umbilical stump care study cited above[37], a consent form provided to mothers whose clusters were assigned to the chlorhexidine arm, for example, would include the following details:

> "The purpose of this study is to determine whether any of three different techniques for cleaning your infant's umbilical stump is more effective in preventing stump infection or death. Health workers in participating communities were randomly assigned to use one of three different stump cleaning techniques. The health workers from your community who visit you after the birth of your baby will be using a mild disinfectant solution to cleanse your baby's umbilical stump. Specifically, on the 1st, 2nd, 3rd, 4th, 6th, 8th, 10th, 12th, 14th, 21st and 28th day after your baby's birth, you will be visited by a health worker who will cleanse your baby's umbilical stump using the mild disinfectant solution. They will also examine the umbilical stump for infection and examine your baby for signs of

more serious infection. On day 1 and 14, they will also ask you questions about factors that may affect your baby's risk of infection"

One fortuitous effect of the use of tailored disclosure between different arms of a CRT is that the potential for bias may be mitigated. Commentators have expressed concern that, if subjects assigned to the control arm were informed about the content of a behavioural intervention in the experimental arm during the consent process, they may modify their behaviour in such a way that their response to the control interventions may spuriously approximate the response of individuals in the intervention arm[1,9,35,36].

For example, in the umbilical stump care study[37], if mothers assigned to the dry stump care arm surreptitiously used soap and water because they were informed of this technique during the consent process, the study's findings may be biased toward a null effect of the intervention. But, if consent is sought after randomization of clusters, it is not necessary to provide subjects in one arm of a CRT with information about the interventions in other arms. Thus, the potential for bias is minimized.

4) May passive consent be used in CRTs?

In some large CRTs of cluster-level interventions[36,38-40], investigators have used a "passive consent" approach to subject recruitment. In the passive consent approach, investigators take steps to inform potential subjects that a research study is being conducted, and may even provide information about the study itself. If investigators receive no indication from a potential subject that he/she objects to being enrolled in the study, then that subject is presumed to have agreed to participate. This technique is commonly used in CRTs in education. Information about the purpose and interventions in

a study are sent home with students. If the students do not return a document, signed by their parent or guardian, that they decline participation, then they are presumed to agree to study enrolment[38].

In health services research, passive consent is used somewhat differently. In many studies conducted in healthcare settings, notices are posted in patient areas that research is being conducted, although detailed information about the study is not provided. The notices indicate that, if the patients do not wish to participate in the research study, then they may contact the investigators in order to opt out[36,39,40]. It may be impossible for subjects to opt out of some cluster-level interventions, although it may be feasible for subjects to opt out of data collection[1,7].

A passive consent model is best thought of as an alteration of consent processes that are permitted under various waiver of consent guidelines[22,23,26]. When used as described above in healthcare CRTs, an opt-out model satisfies none of the elements of informed consent. Subjects cannot be assumed to have embraced the study's scientific ends as their own. There is no assessment of subjects' decision-making capacity. There is no assurance that potential subjects are making decisions freely. The notices posted typically do not offer sufficient information for potential subjects to make a responsible choice whether or not to participate. There is no assurance that potential subjects understand the information provided in the notice. Indeed, there is no assurance that all potential subjects have even seen the notice.

When passive consent is used in school-based studies, the information sent home with students often contains sufficient information to enable a capable parent or guardian to decide whether or not to allow their child to participate in the CRT[38]. However, there is

no assurance that each child will give the information to their parent. There is no assurance that the parent or guardian understands the information. Nor is there any assurance that the parent or guardian is capable of deciding whether or not to permit their child to participate in the CRT[38].

The use of a passive consent model is subject to the same regulatory demands as the use of a waiver of consent. An investigator must convincingly argue that the research is not feasible without the alteration of typical consent practices. The interventions in a study using a passive consent model must pose only minimal risk. Because passive consent models are subject to the same regulatory requirements as a waiver of consent, passive consent approaches are not any more protective of subjects' autonomy and welfare interests than a waiver.

Although passive consent models do not offer any additional protection beyond that offered under waiver of consent guidelines, the use of passive consent may be justified on pragmatic grounds. For example, in school-based CRTs, passive consent may be required by school administrators or parent groups[38]. A hospital-based CRT evaluating a quality improvement intervention for diabetes care used a passive consent model because "clinicians and the laboratories owned by community hospitals were worried about public concern as patients discovered they were enrolled without consent into a research project.[39]" CRT investigators may choose to use a passive consent strategy for similar pragmatic reasons.

5) Are professionals obligated to participate in CRTs of interventions designed to improve their practice?

In CRTs evaluating an educational intervention on professionals, such as teachers or health care workers, the professionals are the recipients of an experimental intervention[2,10,41,42] and are, therefore, research subjects[10,41,42]. In order to reasonably bear the burdens of research participation, they must be able to embrace the study's ends as their own. Therefore, informed consent must generally be obtained[10,41,42]. However, there may be circumstances in which seeking consent from professionals is logistically difficult. In such cases, CRTs may meet regulatory criteria for a waiver of consent.

The NEXUS study cited above evaluated the comparative efficacy of educational reminder messages or audit and feedback on adherence to clinical practice guidelines for lumbar spine and knee radiography[11]. Two-hundred-and-forty-seven clusters of primary care practices were randomly assigned to receive either reminder messages, audit and feedback, both interventions, or simply a mailed copy of the practice guidelines. The study investigators argued that seeking consent from all physicians in each of those 247 primary care practices was so impracticable as to make the study unfeasible, and that the interventions were sufficiently similar to routine activities that they posed only minimal risk[35]. Similar large-scale studies of interventions designed to improve professional practice may meet regulatory criteria for a waiver of consent for health professionals[15,22,23,26]

Some investigators have argued that professionals may have obligations to participate in CRTs that would override their right to autonomously choose whether or

not to participate[2,5,35]. This suggestion is based on two claims. First, that professional obligations to engage in continuing professional development entail an obligation to participate in CRTs[5,35]. As Hutton claims: "In some cases, the experimental units, that is, professionals, might have a duty to enrol as part of their continuing professional development.[2]" Second CRTs may offer direct or indirect benefits to patients, thereby obligating health professionals to participate[5,35]. According to Hutton and colleagues, "…If a health care professional chooses not to participate in a study, they are in effect denying their patients the potential benefits of participation.[35]" Both of these claims may be refuted.

Health professionals are required to engage in continuing professional development as a matter of professional obligation and as a condition of licensure in many jurisdictions[43]. Physicians, in particular, have a great deal of latitude in determining the means by which the continuing education is completed. Acceptable options may include self study, conference attendance, preparation for teaching, and formal educational programs leading to a degree or diploma[44]. This wide discretion in choosing professional development activities undermines any claim that health professionals have an obligation to participate in CRTs. Participation in a CRT of an educational intervention may be one among many acceptable options for engaging in continuing education. Given the numerous ways in which a health professional may meet their continuing professional development obligations, there is no basis on which an obligation to participate in CRTs of educational interventions can be derived from continuing professional development obligations.

The fact that an educational or quality improvement intervention is being evaluated in a CRT means that its efficacy is unproven[45,46]. If there were certainty as to the efficacy of an educational or quality improvement intervention, a CRT would be unethical[45], and professionals would be able to access that effective intervention through ordinary means. The uncertainty about the efficacy of an educational or quality improvement intervention undercuts any argument that professionals ought to participate in CRTs for the good of those that they serve.

In addition, control groups in CRTs may receive either no intervention or some other intervention that approximates routine practice. This further undermines arguments that professionals ought to enroll in CRTs because of their obligation to act in the interest of those whom they serve.

It is therefore possible to make three conclusions about professionals who are research subjects in CRTs: 1) neither fiduciary obligations nor professional obligations to engage in continuing education require health professionals to participate in CRTs; 2) when it is possible to seek consent from professionals for participation in a CRT, their consent should be sought; 3) some CRTs, in which it is not feasible to seek consent from all professional subjects, and in which the interventions under study pose only minimal risk, may be eligible for a waiver of consent.

Summary

Numerous commentators[1-3,7,9,35] have identified the difficulties associated with obtaining informed consent for participation in CRTs. This paper has addressed these challenges by appealing to basic ethical principles, and to the moral theories that underpin

these principles. Consent requirements stem from the principle of respect for persons, which requires that the choices of autonomous individuals be respected. Seeking informed consent empowers research subjects to choose to adopt the study ends as their own, authorizing interventions that serve a scientific purpose. This conceptual framework leads to specific conclusions about key ethical issues that arise because of the unique methodological features of CRTs. These may be formulated as a set of guidelines for investigators and research ethics committees to identify when consent must be obtained from participants in CRTs:

1. As a general rule, consent must be obtained from all subjects in CRTs. This includes cluster members, as well as individuals who may be the recipients of interventions designed to produce a cluster-level effect such as health professionals or teachers. However, many CRTs may meet the regulatory criteria for a waiver of informed consent.

2. If random cluster assignment occurs prior to subject enrolment, subjects must be informed of the purpose of the study, the nature of the interventions to which they will be exposed in the arm of the study to which they have been assigned, and their options should they choose not to participate.

3. There is no obligation to inform potential subjects of interventions that are exclusive to other study arms and inaccessible by other means. Potential subjects must be informed of the details of the trial arm to which their cluster has been randomized, and of other options should they choose not to participate.

4. Passive consent strategies are not a sufficient substitute for obtaining informed consent, nor do they offer any advantage to subjects beyond the additional protections that are required for a waiver of consent. However, a passive consent strategy may be chosen for pragmatic reasons, provided that regulatory criteria for a waiver of consent are met.

5. Large CRTs that intervene on professionals may be eligible for a waiver of consent from those professionals, provided that seeking consent from all of the professionals is impracticable and that the interventions pose only minimal risk. However, CRT participation cannot be construed as a professional obligation. If seeking consent from professionals who are research subjects is feasible, then such consent must be obtained.

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Chapter 7

Summary and Discussion

Summary of Findings

This dissertation has two principal objectives. The first objective is to empirically describe current practices in addressing ethical challenges in healthcare CRTs, with an emphasis on informed consent. The second objective is to answer two normative questions: 1) Who is the research subject in CRTs? and 2) When is informed consent required from subjects in a CRT?

Empirical Work:

Chapter Three

The empirical evaluation of current research ethics practices began by identifying features of CRTs that are associated with the reporting of obtaining informed consent from patients in a large sample of published CRTs. A sample of 161 CRTs performed in healthcare settings were identified from a random sample of CRTs published between 2000-2008. Both bivariable and multivariable regression analyses were used to examine the relationship between reporting of patient consent and such features as: the date of publication; country of study conduct; journal impact factor; average cluster size; use of patient-level experimental interventions and patient-level data collection interventions; and reporting of the study as quality improvement research.

In our sample of healthcare CRTs, reporting of informed consent from patients was independently associated with the use of experimental interventions directed at patients, with the use of patient-level data collection interventions, with smaller cluster sizes, and

with publication in recent years. Lack of reporting of informed consent from patients was independently associated with publication in lower impact journals, and with study conduct in developing countries.

It is not unreasonable to infer that reporting of patient consent reflects actual consent practices. Therefore, investigators are more likely to seek patient consent in CRTs that use patient-level interventions and in studies with small cluster sizes. These findings are in keeping with published commentaries on the ethics of CRTs which speculate that it may not be possible to seek informed consent in studies evaluating cluster-level interventions[1-5] or in studies with large cluster sizes[1,5].

Consent practices were only described in 60% of CRT reports: consent was obtained in 53%, while consent requirements were waived in another 7% of studies. 40% of study reports do not mention consent practices, in spite of the requirement to document in study reporting guidelines[6]. It may be that a waiver of consent was used in a large proportion of studies that did not report their consent practices. However, this should have been documented. The fact that consent procedures were not described is a significant failure of these reports and the journals that published them.

Chapter Four

A purposive sample of twenty experienced CRT investigators was interviewed with the goal of describing how experienced researchers have addressed ethical challenges in practice. Informants participated in a semi-structured interview, which included questions

on ethical challenges encountered in practice, experiences with the ethics review process, and the need for comprehensive international ethics guidelines for CRTs.

The scope of ethical concerns identified by informants paralleled the scope of ethical concerns identified in the CRT literature. Informants' responses focused largely on consent issues and the role of cluster decision-makers. The analysis of the interviews suggested that, as in the CRT literature, important ethical challenges such as the analysis of harms and benefits of CRTs and justice issues are less important to, or unappreciated by, experienced CRT investigators.

With respect to informed consent practices, the findings of this study were similar to those of the quantitative analysis in the previous chapter. Informants confirmed that whether consent was sought from individual cluster members in practice depended on the kinds of intervention under study. Informed consent is sought more often in CRTs of individual-level experimental interventions than in CRTs of cluster-level interventions.

Informants also offered testimony that ethics review procedures and consent requirements have become more stringent in recent years. This qualitative finding agrees with the quantitative finding that investigators reported seeking patient consent more frequently in studies published 2005-2008 compared to studies published 2000-2004.

Informants had differing views of the impact that the ethics review process has had on their work. Some informants felt that the questions asked by research ethics committees had a positive effect on CRT protocols. Others felt that requirements imposed by research

ethics committees, such as the need to seek subjects' consent, had a negative impact on study validity.

Informants cited variability in research ethics review as an important impediment to the conduct of multicentre CRTs. They also felt that comprehensive international ethics guidelines would be useful in educating research ethics committees about the unique methodological features of CRTs and the ethical issues stemming therefrom. One important purpose for international ethics guidelines for CRTs would be to encourage uniformity in research ethics review.

Normative Work:

Chapter Five

Prior to being able to address issues relating to consent, the analysis of risks and potential benefits, and equitable subject selection, it is essential to be clear about who is the research subject in a CRT. Research subjects in CRTs must be correctly identified to ensure that subjects are adequately protected and that research is not hampered by the inappropriate application of research ethics regulations in situations in which cluster members are not research subjects.

The question of who is a research subject was answered by identifying the features common to different regulatory definitions of "research subject", and evaluating these features in the light of conceptual work describing the distinction between a patient and a research subject in a clinical trial. We define a "research subject" as an individual whose interests are put at risk in the context of a research study. This may occur if the individual

is directly intervened upon, is intervened upon via manipulation of his/her environment, interacts with the research team, or contributes identifiable private information.

This definition of "research subject" has important implications for the ethics of CRTs. First, individuals who receive interventions intended to produce a cluster-level effect are research subjects. This includes health professionals and teachers who receive educational or quality improvement interventions that are being evaluated in the CRT. It is important to recognize that these individuals have interests that may be compromised in the context of a CRT, and that they merit protection as research subjects. This is a separable issue from whether or not consent is required from these subjects—a question considered in chapter six.

Second, some cluster members may not fulfil the definition of "research subject". Cluster members who are not intervened upon, either directly or via manipulation of their environment, who do not interact with investigators, and who do not contribute identifiable private information are not research subjects. This includes patients whose health professionals are intervened upon in a CRT of an educational or quality improvement intervention. They are not intervened upon directly, nor does any indirect effect of the CRT intervention on their care constitute an environmental manipulation. If they do not interact with researchers or contribute identifiable private information, then they are not research subjects. It follows that, if they are not research subjects, their consent for research is not required.

Chapter Six

Working with this definition of "research subject", we then addressed the question of when consent is required in CRTs. We did so by relying on a conceptual framework grounded in the basic ethical principles and a moral theory that supports these principles. This framework outlines the purpose of seeking informed consent and may be summarized as follows: consent requirements stem from the basic ethical principle of respect for persons, which requires that the choices of autonomous individuals be respected. The principle of respect for persons may be viewed as being rooted in deontological moral theory, which posits that autonomous individuals have an intrinsic worth and are entitled to respect. Autonomous individuals must not be used solely as means to an end; they must be treated as ends in themselves. The purpose of seeking informed consent is to enable potential subjects to embrace the ends of the research study as their own.

As a general rule, informed consent must be obtained from all research subjects in a CRT. If it is not possible to obtain informed consent from subjects prior to randomization of clusters, then seeking informed consent after randomization is permissible. Potential subjects may choose to participate in the CRT—or not—knowing the trial arm to which their cluster has been assigned. That cluster randomization has taken place before cluster enrolment does not diminish a potential subject's ability to freely choose whether or not to embrace the study's ends as their own. Nor does it treat a subject solely as means to an end, provided that informed consent is sought at the earliest opportunity—and before any research interventions are performed on that subject.

If subjects are enrolled after clusters have been assigned to different trial arms, then they need only be provided with information material to their choice whether or not to participate in the CRT, namely the purpose of the study; the nature, risks and potential benefits of interventions that they would undergo in the arm to which their cluster has been assigned; and their options should they choose not to participate.

In studies of cluster-level interventions that are impossible to avoid, the use of a waiver of consent for the study interventions may be permissible, although consent for some data collection procedures may still be required. A waiver of consent may be used for CRTs of minimally risky interventions if seeking informed consent from all subjects would make the study unfeasible. This may be the case in very large clusters, or if the only individual-level intervention is the use of identifiable private information that is collected from administrative sources such as medical records. If data collection interventions such as physical examinations, interviews or specimen collections are performed on cluster members, then informed consent should be sought for these interventions.

Professionals cannot be required to participate in a CRT as a consequence of professional obligations. However, circumstances may exist in which a CRT that examines interventions on professionals may meet regulatory criteria for a waiver of informed consent: specifically, if seeking consent is not feasible; if the interventions pose only minimal risk; if rights and welfare are not adversely affected; and (if appropriate) subjects are debriefed after the study is completed.

Discussion

Reflections on the relationship between empirical and normative work

In recent years, there has been a growing academic movement which suggests that answering some research questions requires a methodology that combines both empirical work and ethical analysis[7]. McMillan and Hope offer a cyclical model for the interaction between empirical and normative work. It is not simply that empirical work generates questions for ethical reflection, or that an ethical analysis led to an empirical question. Rather, some problems require both empirical and normative work. The findings of empirical work may stimulate ethical reflection, which may, in turn, drive policy change, the effects of which can be evaluated empirically[7].

Tan and Hope provide an example of how this model is applied to questions around informed decision-making in patients with anorexia nervosa[8]. Tan and Hope sought to determine whether traditional conceptions of decision-making capacity were adequate to guide decisions about when it is appropriate to impose treatment against the wishes of anorexic patients. They began with a qualitative interview study to gain a detailed appreciation of the rationale for choices that anorexic patients make about whether or not to comply with treatment. The data indicated that patients refuse treatment based on values that are related to the disorder itself, such as the sense of control that anorexic behaviour gives to patients. These data conflicted with the traditional conception of lack of decision-making capacity, which assumes that incapable patients make decisions based on false beliefs or faulty reasoning. Therefore, the data prompted further conceptual work that

sought to determine whether or not values closely related to a mental disorder may justify refusal of treatment in the way that other kinds of values justify an informed refusal. Tan and Hope offer that the conclusions of this conceptual work would drive the implementation of policy with regard to the imposition of treatment for anorexic patients[8].

This dissertation fits this cyclical model as proposed by McMillan and Hope[7]: both empirical analysis and normative work is essential in order to comprehensively address important ethical problems in CRTs. The empirical work identified the ethical problems posing the most important challenges to CRT investigators, and described how ethical problems in CRTs are addressed in practice. These findings stimulated reflection on specific ethical questions, namely "Who is the research subject in CRTs?" and "When is consent required in CRTs?" The conclusions of the normative work enabled critical reflection on the empirical data. This included identification and discussion of deficiencies in ethics practices, and the use of a conceptual framework for the ethics of human subjects research to identify important ethical issues that were not reported by CRT investigators. The conclusions of the normative work, and critical reflection on current practice, will guide the development of comprehensive guidelines for the ethical conduct of CRTs

Empirical work identifying normative questions

The interviews done in chapter four documented CRT researchers' views on the ethical problems in CRTs, and asked detailed questions about how these issues were addressed in practice. The principal ethical challenges noted by study informants were related to seeking informed consent from cluster members in CRTs. Namely, they identified issues of feasibility of seeking consent, potential for bias as a result of disclosure

of study details to subjects, and whether or not consent was required from professionals who were intervened upon. Prior to being able to address investigators' concerns over consent issues, normative work was required to clearly identify who is the research subject in a CRT. Therefore, the key question of who is a research subject in a CRT was examined in chapter five.

The question of who is a research subject was addressed by appealing to scholarly work that supports this conceptual framework for research ethics. This scholarly work distinguished clinical research from medical practice, and subjects from patients. These distinctions illuminated our analysis of current regulatory definitions of "research subject", enabling the development of a definition of research subject that is applicable to the entire range of human subjects research. This work has important implications for CRTs. First, in CRTs in which individual cluster members are not intervened upon, do not interact with investigators and do not contribute identifiable private information, these individual cluster members are not research subjects, and therefore, their consent is not required. Second, individuals, such as professionals, who receive an experimental intervention intended to produce a cluster-level effect, are research subjects and, as a result, their consent may be required.

The normative work in chapter six was directly stimulated by the findings of the empirical work in chapters three and four. In addressing the question "When is informed consent required in CRTs?" the relationship between the types of interventions under study and the need to seek informed consent was examined, as well as issues of post-

randomization consent, potential from bias resulting from disclosure of study interventions, and the need for consent from professionals who are intervened upon in a CRT.

We drew on the principle of respect for persons, and on a moral theory on which this principle is based, to address challenges related to seeking informed consent from subjects in CRTs. Consent requirements stem from the principle of respect for persons. This principle, which may be viewed as being rooted in deontological theory, is based on the unconditional worth of autonomous individuals, and demands that the wishes of autonomous individuals be respected. By adequately informing subjects during the consent process, and by allowing subjects to make free choices, subjects are able to freely adopt the scientific ends of the CRT as their own, effectively authorizing interventions that may put their welfare at risk. When it is not possible to seek subject consent prior to random cluster assignment, seeking consent at the earliest opportunity post-randomization is sufficiently respectful of subjects' autonomy, provided that they are informed of the study's purpose and the interventions that they would be subjected to should they choose to participate. If obtaining consent is not feasible, or if the study intervention cannot be avoided, then waiving consent is permitted, provided that risks to subjects are minimal.

Reflecting on empirical work based on findings of normative work

The conclusions of the normative work in this dissertation make it possible to critically reflect on the empirical findings.

Studies with small cluster sizes and that used patient-level interventions were more likely to report seeking patient consent. This fits with the opinions of informants in chapter

three, who related that they only sought consent when feasible to do so. The normative work in this dissertation leads us to conclude that whether consent may be waived for study interventions is related to more than just the feasibility of seeking consent. Waiving consent requirements is only permissible when seeking consent is not feasible and when threats to subjects' welfare interests are minor, i.e. when interventions for which the waiver of consent is sought pose only minimal risk. Thus, we can conclude that researchers and investigators require clear guidelines outlining the necessary conditions for use of a waiver of consent.

Consent issues in CRTs represent a paradigmatic example of how both empirical work and normative work can be used in concert to address key challenges in the ethics of human subjects research. Empirical work identified concern among researchers about consent requirements and a practice of waiving consent that may or may not be sufficiently respectful of subjects' interests. Normative work laid out a moral justification for a waiver of consent, and criteria establishing when a waiver of consent is permissible. These conclusions enabled reflection on current practice, and identified how current practice must be improved. The conclusions of the normative work can also guide the development of policy to ensure that subjects' interests are adequately protected while ensuring that methodologically valid CRTs may be carried out.

This dissertation applied both empirical findings and normative work in reaching other conclusions about how ethical issues in CRTs ought to be addressed. In Chapter four, experienced CRT researchers rarely mentioned issues relating to the analysis of risks and potential benefits, fair subject selection, and the use of vulnerable populations. However,

these issues are critically important in the conceptual framework based on the Belmont Report principles. Thus, the use of a conceptual framework is important in identifying areas that require further education for investigators and research ethics committees, and clear guidelines addressing these issues, to ensure optimal protection of subjects in CRTs.

Implications for Current Practice

The findings of the empirical work and the conclusions of the normative work in this dissertation lead to conclusions about how current practice in CRTs should change.

1. Investigators and ethics committees must recognize that individuals who are intervened upon in order to produce a cluster-level effect (such as professionals) are research subjects. Their consent is required (unless criteria for a waiver are met), the risks and potential benefits to these individuals must be considered, and rules for fair subject selection should apply to these individuals.

2. Investigators and ethics committees should use a principled definition of "research subject" determine whether or not individual cluster members are research subjects. Cluster members who are not research subject need not be approached for consent. Cluster members who are research subjects should be approached for consent unless criteria for a waiver are met.

3. With respect to seeking consent, investigators and ethics committees should consider randomization, experimental interventions and interventions used to collect data separately. Consent for random cluster assignment may be waived if subjects are not identifiable prior to cluster randomization or if clusters are sufficiently large so as to make seeking consent for cluster randomization infeasible. A waiver of consent may be sought for experimental interventions if seeking consent is not feasible *and* if the interventions pose only minimal risk. If seeking consent is feasible or if interventions pose more than minimal risk, then consent for experimental interventions should be sought prior to randomization of clusters (when feasible) or at the earliest possible opportunity after randomization of clusters. The same requirements apply to data collection interventions: consent may be waived if the seeking consent is infeasible *and* the interventions pose only minimal risk. Otherwise consent for data collection interventions must be sought from each subject.

Implications for Ethics Guidelines for CRTs

The empirical and normative work in this dissertation is intended to inform the development of international consensus guidelines for the ethical conduct of CRTs[9]. Ethics guidelines for CRTs should be comprehensive, addressing all of the ethical challenges posed by the CRT design.

Guidelines should address the concerns of CRT investigators and ethics committees, and protect the rights and welfare of research subjects. In order to optimally protect research subjects, guidelines should be comprehensive in scope. The use of a conceptual framework, based on the Belmont Principles, facilitates the identification of ethical challenges that have not been identified by CRT investigators or addressed in literature. In particular, challenges related to the analysis of harms and benefits, and the just selection of research subjects have not been addressed, and require further work in order to inform the development of ethics guidelines for CRTs.

Given the findings in this dissertation, international ethics guidelines for CRTs should include the following:

1. A statement of basic ethical principles: respect for persons, beneficence and justice. These will be derived from the principles articulated in the Belmont Report.

2. A definition of "research subject". A research subject is an individual whose interests may be compromised as a result of interventions in a research study including:

    a. An individual who is directly intervened upon by an investigator

    b. An individual who is deliberately intervened upon via manipulation of his/her environment by an investigator

    c. An individual with whom an investigator interacts for the purpose of collecting data

d. An individual about whom an investigator obtains identifiable private information for the purpose of collecting data.

3. A detailed statement of consent requirements. Generally, consent for CRT participation must be obtained from all individuals meeting the definition of "research subject" in a CRT.

    a. If subject enrolment is done prior to randomization of clusters, information to be disclosed to potential subjects must include the purpose of the study; detailed information about the nature, risks, and potential benefits of the experimental interventions in each study arm; detailed information about the nature and risks of any interventions done solely to collect data; and information about the potential subjects' options should they choose not to participate.

    b. If it is not feasible to seek consent for participation prior to randomization of clusters, seeking a potential subjects' consent for CRT participation in the arm to which their cluster has been assigned is permissible. This consent refers to the experimental interventions in the arm to which the potential subjects' cluster has been assigned, as well as any interventions used to collect data.

    c. If subject enrolment is done after randomization of clusters, information to be disclosed to potential subjects must include the purpose of the study; detailed information about the nature, risks, and potential benefits

of the experimental interventions in the study arm to which that potential subject's cluster has been assigned; detailed information about the nature and risks of any interventions done solely to collect data; and information about the potential subjects' options should they choose not to participate.

d. A waiver of consent for experimental interventions is permissible if:

    i. The interventions pose only minimal risk;

    ii. The study could not reasonably be conducted without the use of a waiver of consent for the experimental interventions.

e. A waiver of consent for data collection is permissible if:

    i. The interventions pose only minimal risk;

    ii. The study could not reasonably be conducted without the use of a waiver of consent for the experimental interventions.

f. Passive consent strategies are subject to the same restrictions as the use of a waiver of consent.

Implications for other fields of inquiry

The findings in this dissertation have implications for CRTs in fields other than healthcare, as well as for nonrandomized studies that examine interventions that are administered in clusters.

In chapter five, a principled definition of "research subject" was developed. Although this definition was developed by appealing to examples in healthcare research, it is intended to be applicable to all fields of human subjects research, including CRTs in other fields. A research subject is an individual whose interests may be compromised in the context of a research study, either by being intervened upon (either directly or by environmental manipulation), by interacting with investigators, or if their identifiable private information is used.

CRTs are widely used in public health, education and a variety of other domains of research. In public health research, research subjects include includes individuals residing or visiting communities participating in a CRT of a public health intervention that cannot be avoided, such as a CRT evaluating water decontamination strategies. In education research, students of a school or school district participating in a CRT of a novel curricular innovation would be considered subjects. These research subjects merit regulatory protections in order to safeguard their interests, including being asked to provide informed consent to study participation (unless criteria for a waiver of consent are met), and the careful review of risks and potential benefits by a research ethics committee.

Our conclusions may also be extended to nonrandomized trials. Consider, for example, a nonrandomized study in which intensive care units in Michigan were assigned to employ either educational and safety interventions intended to reduce catheter-associated bloodstream infections, or to no intervention[10]. The healthcare providers were intervened upon by investigators and are therefore research subjects. The patients were not intervened on, interacted with, nor were they deliberately manipulated via environmental manipulation. No identifiable private information was used to ascertain the relative effectiveness of the educational and safety interventions: only administrative data on infection rates was used. Therefore, the patients in this study are not research subjects, and consent was not required.

Our work on the issue of informed consent in CRTs is also applicable to other fields of inquiry. Our conclusions regarding the timing of consent, disclosure requirements and the use of a waiver of consent is applicable to nonrandomized studies in other fields that employ CRTs, such as public health and education. If group assignment is determined before subject enrolment, and consent could not have been obtained at that time, then seeking consent after group assignment is permissible. Potential subjects must be informed of the study's purpose, the nature, risks and potential benefits of the interventions that they will undergo and their alternatives should they choose not to participate.

The application of waivers of informed consent is the same for nonrandomized studies as for CRTs. Investigators must argue that he research is not feasible without the waiver, and the study must meet the other regulatory criteria for a waiver [11]. Similarly, opt-out consent practices offer no protection to subjects beyond those outlined in waiver of

consent regulations. Investigators may choose to employ an opt-out strategy for pragmatic reasons, but requirements for a waiver of consent must be met before such a strategy is used.

Future Work

Future work will examine how risks and potential benefits to subject CRTs ought to be evaluated by research ethics committees[12]. The definition of "research subject" developed in this dissertation leads to the conclusion that CRTs often include different types of subjects. Subjects may include individual cluster members (who are either intervened upon or contribute identifiable private information), as well as subjects who are intervened upon in order to produce a cluster-level effect, such as teachers or health professionals. The analysis of risks and potential benefits in a single CRT will likely be different for each different type of subject. Furthermore interventions directed at one type of subject may have consequences for another. For instance, interventions directed at health professionals may present both risks and potential benefits for their patients. Conversely, interventions directed at patients may have consequences for their treating professionals, in that they may either contribute to or alleviate professional workload burdens. How ought these indirect risks and potential benefits be considered by a research ethics committees?

Questions associated with the evaluation of risks and potential benefits in CRTs will be the focus of additional papers from the CIHR-funded working group referenced in

chapters one and two[9,12]. The conclusions of this work will inform the development of comprehensive international guidelines for the ethical conduct of CRTs.

The work done in this dissertation will also serve as the basis for my own future work. In particular, the conclusions of this work will be applied to work on the ethics of knowledge translation and quality improvement research, and the methodology involving the joint application of empirical and conceptual work will be used in addressing epistemic questions in clinical trials.

The CRT design is often used in large knowledge translation (KT) or quality improvement (QI) studies. KT is an activity aimed at increasing the uptake of high quality scientific evidence in medical practice and healthcare policy[13]. QI is an activity intended to improve outcomes or the efficiency of processes in health care systems[14]. KT and QI interventions are administered to health care systems or health care professionals. If successful, they lead to improvements in patient outcomes. KT and QI research evaluates the efficacy of these interventions. Research in these fields poses many of the same ethical questions as do CRTs: Who is the research subject? When is consent required? How ought a research ethics committee evaluate the risks and benefits of the interventions being studies? What does it mean to be fair in the selection of research subjects and research populations in KT and QI research? The conclusions of the work in this dissertation are likely to be very relevant to KT and QI research. Both empirical work, in order to evaluate current ethics practices in KT and QI research, and normative work will be required to comprehensively address the range of ethical questions posed by research in these fields.

Thus, future work will involve the application of both the methodology of this dissertation, and its conclusions, to ethical questions raised by KT and QI research.

Epistemic questions raised by clinical trials in medicine can also be addressed by an approach combining both empirical and normative work. One particular challenge amenable to this approach is the question, "When should a clinical trial be stopped in the face of mounting evidence of the superior efficacy of one experimental treatment?"[15] Answering this question is important, in order to ensure that research subjects are not assigned to a treatment that is known to be inferior. In addressing this question, the work of Benjamin Freedman is useful starting point. Freedman writes that a clinical trial should be designed such that, at its completion, its findings will resolve a state of disagreement in the clinical community as to the preferred treatment[16]. In other words, the findings of a clinical trial should be sufficiently convincing as to broadly influence clinical practice. In reality, the results of a single trial rarely change practice[13] (hence the need for knowledge translation interventions), it is an empirical question as to how much evidence is sufficient to be convincing to expert clinicians to stimulate a change in practice. This empirical information may help to set an evidentiary standard that researchers should hope to meet with the design of a clinical trial. The question of when to stop a trial early will then be reduced to "when will accumulating clinical trial data be sufficient to meet this standard?" Answering this question involves both empirical work on the effect of stopping early on the accuracy and precision of estimates of effect[15], and normative work that addresses the ethical implications of enrolling subjects in clinical trials in the face of mounting evidence of the superiority of one trial arm. By combining the findings of both normative and

empirical work on this issue, robust guidelines for early stopping of clinical trials may be formulated. I propose to address this challenge in future work.

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Appendices

Appendix A. Data abstraction form for published CRTs used in chapter two.

1. Study ID (this is the Medline UID number – also the pdf file name) ____
2. Reviewer name ____
3. Publication year ____
4. Journal name ____

General Study Characteristics

5. Country of study recruitment (for identification of developing nations, use World Economic outlook database April 2008 edition at http://www.imf.org/external/pubs/ft/weo/2008/01/weodata/groups.htm#oem):
   - [1] Canada
   - [2] USA
   - [3] UK or Ireland
   - [4] Australia
   - [5] Other **developed** country /countries (specify) (e.g., Canada and USA) ____
   - [6] Other **developing** country/countries (specify)

6. Country of first author (attempt to identify online if not reported):
   - [1] Same as country of study recruitment (or one country of study recruitment)
   - [2] Other (specify) ____

7. Study funding source reported?
   - [1] Yes
   - [2] No

8. If Q7=Yes, specify funding source: (If unclear, confirm online or with author; NA if Q7=No)

	Yes	No	NA
a) Industry	1	2	3
b) Government agency, international development agency, university	1	2	3
c) Foundation, special interest group (e.g., Bill and Melinda Gates Foundation, Alzheimer's society, charitable/non-profit organization)	1	2	3

9. Type of clusters (units of randomization):
   - [1] Primary care practices (intact practices – includes multiple health professionals in at least some practices)
   - [2] Individual primary care physicians (individual GPs)
   - [3] Other individual health professionals (specify) (e.g., dentists, surgeons, nurses, midwives) ____
   - [4] Hospitals
   - [5] Nursing Homes
   - [6] Primary care clinics
   - [7] Units of time (specify setting) (e.g., primary care clinics, nursing homes) ____
   - [8] Households/ families
   - [9] Residential areas (specify) (e.g., villages, neighbourhoods, parishes, hamlets, balozi, household clusters) ____
   - [10] Public health clinics
   - [11] Schools
   - [12] Classrooms

13 Worksites
14 Churches
15 Other (specify) (e.g., teams of health professionals)

Study Design

Note: In order to complete data abstraction, a **single primary outcome** must be identified for each trial. Use the following hierarchy: **First** primary outcome stated by authors; if no primary outcomes specified, use outcome in sample size calculation; if sample size calculation not reported or reported for a sub-study only, use first outcome listed under 'Objectives'; if still unclear, **refer trial to arbitration** before proceeding.). **Note**: Data abstraction pertains to **main study component** (the patient population on which the primary outcome evaluation is carried out), i.e., disregard sub-studies within the main trial, e.g., if a smaller group of patients are enrolled for more intensive follow-up.

10. Were primary outcome measure(s) identified by authors? (Authors clearly distinguished between main (or primary) and secondary outcomes measures?) (Note: Not acceptable if authors merely stated primary **objectives** without operationalizing in terms of specific variables.)
    1 Yes (specify number) ____
    2 No

11. For quality control purposes, state the single **primary outcome** data abstraction will be based on:

12. Trial design at cluster-level:
    1 Parallel trial (clusters independently randomized to different treatments with or without pre-test)
    2 Factorial trial (specify factors and levels) (e.g., 2x2) ____
    3 Cross-over trial
    4 Other (specify) (e.g., latin squares, split-plot, stepped wedge) ____

13. Method of random allocation:
    1 Completely randomized design (unrestricted randomization)
    2 Stratified design
    3 Pair-matched design
    4 Other (specify) (e.g., minimization algorithm) ____

14. a) Data collection schedule for primary outcome:
    1 Posttest only design (primary outcome measure observed post-intervention only)
    2 Pretest-posttest design (primary outcome measure observed both pre- and post-intervention)

    b) Specify number of discrete observation time points or indicate 99="continuous surveillance" (**Note**: Post-test only design with continuous surveillance would typically correspond with a **cohort** design in Q15 (and patient attrition is possible in Q28), whereas post-test only design with one discrete observation time point only would correspond with a **cross-sectional design** (and no patient attrition possible in

Q28). (E.g., patients enrolled at baseline and followed for 30 days to observe hospitalization = continuous surveillance.)

15. Trial design at patient-level (primary outcome):

1 Nested cross-sectional design (each patient measured only once or different patients measured each time point)
2 Nested cohort design (same patients measured at different time points or in continuous surveillance) (NOTE: Patient-level attrition is possible in a cohort design but NOT in a cross-sectional design)
3 Primary outcome evaluated on both cross-sectional and cohort components

Characteristics of Outcomes and Interventions

16. Type(s) of **experimental** interventions (all components of intervention):

	Yes	No
a) Educational/ quality improvement interventions targeted at health professionals (e.g., distribution of educational materials, outreach visits, audit and feedback)	1	2
b) Quality improvement interventions targeted at organization of health care or health services delivery (e.g., financial, shifting of professional roles, multi-disciplinary teams, integration of services, changes in setting or equipment, home visits by nurses)	1	2
c) Patient health promotion or educational intervention (e.g., promotion of breastfeeding, smoking cessation intervention, decision aid, disease screening promotion)	1	2
d) Direct patient therapeutic intervention (e.g., experimental intervention includes specific drug to be prescribed to all patients, vaccines/vitamin supplements, insecticide spraying, surgery, testing of new clinical pathway – distinguish from indirect changes to patient therapies as a result of guideline adherence)	1	2

e) Other (specify)

17. Type of intervention administered in **control** arm (Note: disregard activities administered in all clusters prior to randomization e.g., to ensure similar levels of knowledge before starting the intervention):

1 Not reported
2 No active intervention (i.e., usual care)
3 Scaled down version of active intervention (includes some basic elements of active intervention) (e.g., one educational visit, printed guidelines only)
4 Placebo or sham intervention (e.g., vitamin placebos, education on unrelated medical conditions)
5 Other active intervention (head to head comparison)
6 Other (specify)

18. Typology of trial interventions (options are hierarchical and **based on ability to opt out**): (For more detailed explanation and notes, see notes document or Eldridge ea, 2005, Clinical Trials v2)

1 **Cluster-cluster** (Targeted at cluster organization, health professional, or cluster population - individuals **cannot opt out** of the intervention) (e.g., information on patient population fed back to health professional, change in organization; changes to electronic medical records/ software system; mass media campaign, water fluoridation, insecticide spraying, posters, changes to physical environment) (Primary reason for clustered design is intervention cannot be carried out any other way)
2 **Professional-cluster** (Targeted primarily at health professional – individuals can **decline to have their data used**, but intervention is still likely to have an effect on them) (e.g., physician education intervention to improve detection of dementia) (Primary reason for clustered design is to avoid contamination)
3 **External-cluster** (Additional staff) (Targeted at cluster organization - individuals **can opt out by declining to see** the additional staff) (e.g., specialist nurses) (Primary reason for clustered design is logistical and/or financial)

4 **Individual-cluster** (Targeted primarily at individuals but may be delivered by health professional – individuals **can opt out** in the same way as they would in an individually randomized trial) (e.g., vaccines, vitamin supplements, patient decision aid administered by physician, intervention to promote breastfeeding delivered by midwives, clinical pathway to treat pneumonia in nursing home residents) (Primary reason for clustered design is to avoid contamination and increase individual compliance)

19. Type(s) of **data collection** interventions for primary and secondary outcomes:

	Yes	No
a) Medical record review or use of routinely collected data	1	2
b) Patient specimen collection or physical examination **not required for normal patient care**	1	2
c) Interviewer-administered patient questionnaires (telephone/face-to-face) (Disregard if applied to follow-up non-respondents to the initial postal survey only)	1	2
d) Self-administered patient questionnaires (postal, e-mail, internet)	1	2
e) Health professional survey questionnaires or interviews	1	2
f) Other (specify if none of the above)		
g) Specify which **one** of a) to f) above applies to the **primary outcome**		

20. Primary and secondary outcomes observed:

	Yes	No
a) Patient outcomes (clinical or non-clinical outcomes e.g., morbidity, mortality, depression/anxiety scores, patient satisfaction, quality of life. Note: Length of hospital stay could be either a patient outcome (as an indicator of degree of illness) or a process measure (as an indicator of physician adherence to guidelines).	1	2
b) Process measures ("process measures" refers to actual medical care such as diagnoses, treatment, referral and prescribing, e.g., hospitalization, number of guideline-adherent prescriptions, number of healthcare visits, % visits where guidelines were followed)	1	2
c) Other health professional outcomes (e.g., satisfaction, quality of care, behavioural intentions)	1	2
d) Economic outcomes (even if reported in separate publication)	1	2
e) Other (specify)		
f) Specify which one of a) to e) above applies to the **primary outcome**		

Cluster and Patient Flow

21. Were patients recruited to the study (including recruitment for data collection purposes only)? (Refers to main study component- disregard substudy involving smaller group of patients)

1 Yes
2 No

22. Number of study arms (we need to know if there were multiple intervention or control arms so that patient numbers can be divided up appropriately when assessing imbalances):

a) Intervention arms
b) Control arms

NOTE: In Q23 to 28, combine across arms if multiple intervention or control arms; If head-to-head comparison, choose the reference intervention as control arm. If reference intervention not clear, refer trial to arbitration.
If not reported or unclear, indicate as missing = -1.

23. Number of **clusters** randomized:

a) Total	
b) Intervention arm	
c) Control arm	

24. Number of randomized **clusters** included in **baseline** data collection (assess post-randomization withdrawals) (Note: randomized clusters not identifying any eligible patients at baseline are considered as withdrawals):

a) Total	
b) Intervention arm	
c) Control arm	

25. Number of **clusters** (from those in Q24) that were lost to follow-up (Note: clusters not identifying any eligible patients at follow-up are considered lost to follow-up):
    a) Total
    b) Intervention arm
    c) Control arm

26. Number of **patients** providing data at **baseline**: (As reported in flow diagram or in table describing baseline characteristics of clusters and patients. Will be used to assess average cluster size.)
    a) Total
    b) Intervention arm
    c) Control arm

27. Number of eligible patients invited but **excluded** from baseline data collection (e.g., refusal/ non-response): (Note: If there was no patient recruitment (Q21=2), report as 0; if patients recruited prior to randomization (Q32=2), record b) and c) as NA=-9; if not reported, record as missing = -1.) (Will be used to assess risk of selection bias).
    a) Total
    b) Intervention arm
    c) Control arm

28. Number of patients (from those in Q26) that were **lost to follow-up** at final observation time (or time that was used to assess primary outcome): (Note: Report as 0 if cross-sectional design (Q15=1); disregard in-migration / patients added to clusters after baseline data collection):
    a) Total
    b) Intervention arm
    c) Control arm

Methodological Quality Indicators

29. Sample size / power calculations presented?

1 Not presented or presented for substudy or outcome regarded as secondary only

2 **Patient**-level accounting for ICC ("Sample size was based on a significant effect size of 0.5, incorporated an ICC of 0.05 and was based on enrollment of 4 patients per physician"; "Based on a mean (SD) number of admission days per resident enrolled, within cluster variance of 2 days and between-cluster variance of 3 days and 10 residents per nursing home". Usually will involve stating at least the average cluster size and the ICC/ design effect/ overdispersion factor/within-and between-cluster variance or stated that accounting for clustering without reporting value of ICC.)

3 **Cluster**-level (Should be clear that cluster-level summary data are used for calculation e.g., "sample size was based on the hospital as the unit of analysis…assuming a rate of episiotomy of 42% at baseline, with a standard deviation of 15%, we need 18 hospitals to identify a decrease in episiotomy rate." Use of standard deviation in the case of proportions indicates that binary data was summarized at cluster-level and treated as continuous data for the purpose of sample size calculation.)

4 **Patient**-level without accounting for ICC (usually difficult to tell whether at patient- or cluster-level unless specifically stated)

5 Unclear whether at patient- or cluster-level or whether accounted for clustering (e.g., "sample size was calculated to give a power of 80% of detecting a difference of 1 SD at 5% significance in mean diagnosis concordance score"; "sample size of 500 participants would result in 80% power to detect a difference of 10 points between groups")

6 Other (specify) (e.g., based on intermediate level of clustering)

30. If there was no patient recruitment (Q21=No), assess risk of patient selection ("identification") bias: (**Optional**: use explain field to clarify your choice): (We want to avoid option 6 as far as possible)

1	NA (Q21=Yes)
2	Not possible (patient identification was completed **prior** to randomization)
3	Unlikely (patient identification post-randomization but: done by person **blinded** to group allocation, computerized process without regard to group allocation, or researcher/independent person without knowledge of clinical characteristics of patients; OR eligibility criteria such that unlikely to be subverted by knowledge of random assignment (e.g., all women delivering in hospitals within specified time period were included))
4	Possible (e.g., unblinded individuals with knowledge of clinical characteristics of patients identified participants prospectively after randomization)
5	NA (patient identification is aim of intervention, e.g., intervention to improve detection of dementia in primary care)
6	Unclear (explain) (e.g., not clear who identified patients)

31. If patients were recruited to the study (Q21=Yes), who approached patients?

1	NA (Q21=No)
2	Health professional usually involved in patient's care or regular program staff
3	Member of research team or someone not usually involved in patient care or service delivery
4	Mail questionnaire (specify sent by …) (e.g., researcher, GP)
5	Not reported or unclear
6	Other (specify)

32. If there was patient recruitment (Q21=Yes), assess risk of patient selection ("recruitment") bias: (Optional: use explain field to clarify your choice): (We want to avoid option 5 as far as possible)

1	NA (Q21=No)
2	Not possible (patients were identified and recruited **prior** to randomization and same patients followed over time)
3	Unlikely (identification and recruitment post-randomization but: done by person **blinded** to group allocation, or invitation by mail questionnaire most likely with identical information to patients in different arms)
4	Possible (e.g., identification or recruitment by unblinded individuals with knowledge of clinical characteristics of patients, or possibly different information to patients in different arms)
5	Unclear (explain) (e.g., not clear who recruited patients)

33. Concealment of allocation (secure allocation) (Note: EPOC distinguishes between sequence generation and allocation concealment – however, our eligibility criteria likely will exclude trials subject to bias as a result of sequence generation):

1	Done (Unit of allocation was institution or professional and randomization was performed on all units at the start of the study –this will be the case for most cluster trials; or unit of allocation was by household, patient or episode of care and there was some form of centralized randomization scheme, on on-site computer system or sealed opaque envelopes.)
2	Not done (open list of random numbers/ coin flip was used or security could have been compromised, or allocation was altered by investigators, professionals or patients)
3	Not clear (unit of allocation was by household, patient or episode of care and method of concealment not described)

34. ITEM DELETED

35. Protection against contamination: (EPOC)

1	Done (e.g., allocation by community, institution or practice and unlikely that control arm received the intervention)
2	Not done (likely that control arm received intervention, e.g., cross-over trials or patients within the same cluster allocated to control and intervention arm)

3 Unclear (e.g., professionals allocated within an institution and communication among professionals may have occurred)

36. Analysis for **primary outcome**:

1 At **patient-level** accounting for ICC (e.g., using mixed-effects logistic regression, GEE taking account of clustering by physician, Chi-square statistic adjusted for clustering, random effect for physician, hierarchical modeling, multi-level modeling, alternating logistic regression)

2 At **cluster-level** (clearly stated that analysis at cluster-level, e.g., "analyses performed using patient-level variables aggregated at the provider-level", analysis was based on hospital rates, t-test weighted by inverse variance etc.)

3 At patient-level **not** accounting for ICC (more difficult to distinguish, e.g., multivariable regression analysis of patient-level data with no mention of clustering, or standard 2-sample test on patient-level data without mention clustering or stated that since ICCs were low, clustering was ignored in presentation of results)

4 Unclear whether at patient-level or cluster-level or whether accounted for clustering

5 Other (specify) (e.g., based on intermediate level of clustering, both individual-level and cluster-level analyses used for primary outcome analysis)

37. Primary outcome reported as statistically significant?

1 Yes

2 No

38. Type of test for primary outcome evaluation in Q37: (purpose of item is to distinguish between trials where a significant result is desirable versus not desirable, e.g., equivalence study, intervention is harmful/not safe)

1 Effectiveness/Efficacy

2 Safety/Tolerability (e.g., safety of iron supplementation in malaria-prone settings)

3 Equivalence/Non-inferiority

4 Other (specify) (e.g., descriptive study only)

39. ICC or design effect estimates reported for **any** outcomes recorded at patient-level? (not referring to ICC used for sample size calculation):

1 Yes

2 No

40. Blinding of **health professionals:** (use the following hierarchy to identify relevant HPs: a) HPs targeted by intervention, b) individual HPs that were the units of randomization, c) if HPs were not the units of randomization, the HPs in each cluster involved in administering interventions to patients, d) regular HPs involved in patient care.

1 Yes (stated explicitly that health professionals were blinded/ **not** informed of their allocation status)

2 No (stated explicitly that health professionals could not be blinded to allocation status, or that they were informed of their allocation status or obvious) (e.g., the same specialist nurses/surgeons administered both treatment and control)

3 Not reported or reported but unclear (e.g., reported as "double blind trial" without specifically identifying who was blinded, or "participants" were blinded but unclear whether referred to patients or health professional participants)

41. If Q40=1 or 2, capture **verbatim** the relevant statements including <u>what information was given</u> to different arms (e.g., "physicians were not informed of their study group assignment", "allocation was revealed to surgeons after random assignment") or state "Obvious" and reason.

42. Blinding of **patients:**

1	Yes (stated explicitly that patients were blinded/ not informed of their allocation status OR obvious) (e.g., there was no patient recruitment and patients were clearly unaware of the trial)
2	No (stated explicitly that patients could not be blinded to allocation status or that patients were informed of their physician's allocation status)
3	Not reported or reported but unclear (e.g., patient decision aid and not reported whether patients knew whether they have received the experimental or control intervention; or trial reported as "blinded" without specifically identifying who was blinded)

43. If Q42=1 or 2, capture **verbatim** any relevant statements including <u>what information was given</u> to different arms (e.g., "patients in intervention and control arms received identical information about the trial") or state "Obvious" and reason.

44. Blinding of primary **outcome assessment:**

1	Yes (stated explicitly that primary outcomes were assessed blindly or obvious) (e.g., based on computer algorithm applied to electronic records without regard to random allocation or based on identical postal questionnaires in both groups)
2	No (stated explicitly that outcome assessors / interviewers / data abstractors were not blinded to allocation status or obvious) (e.g., GPs aware of allocation status assessed primary outcomes)
3	Not reported or reported by unclear

45. If Q44=1 or 2, capture **verbatim** the relevant statements or state "Obvious" and reason:

46. Capture **verbatim** any other statements regarding blinding where it is unclear who the blinding refers to (e.g., "participants were not informed of their study group assignment", "double-blind trial")

47. Relevance of blinding for primary outcome measure assessment:

1	Primary outcome measure is **objective** (unlikely to be influenced by knowledge of allocation status; e.g., length of hospital stay, mortality, blood pressure) OR patient identification is aim of intervention (e.g., intervention to improve detection of dementia in primary care)
2	Primary outcome measure is **subjective** (vulnerable to bias from knowledge of allocation status, e.g., patient self-report of health status, depression scales, quality of life measures, subjective diagnoses)
3	Not clear

Ethical Quality Indicators

48. Study reported as "Quality Improvement" / QI anywhere in text?

1	Yes
2	No

49. Stated whether requirements of Declaration of Helsinki followed?
- [1] Yes
- [2] No

50. REB review reported?
- [1] Stated REB approval and identified committees (e.g., "The Ottawa Hospital REB")
- [2] Stated REB approval – did not identify committees (e.g., "local research ethics committees of each study site" and the study sites themselves are not identified)
- [3] Stated REB exempt (specify reason) ____
- [4] Not reported

51. Number of ethics committees involved (indicate as missing if not reported) ____

52. Data and Safety Monitoring Board in place?
- [1] Yes
- [2] No
- [3] Not reported

53. Was a **gatekeeper** identified (separate from the REB) that allowed access to each cluster?
- [1] Yes (specify) (e.g., hospital administrators, lead physicians, nursing home management, "responsible authorities", government initiated program) ____
- [2] No (e.g., "practices agreeing to participate were randomized…", or cluster is individual health professional)

54. Was gatekeeper consent reported? (should be explicitly reported as "consent")
- [1] Yes (e.g., "hospital administrators provided consent to randomization")
- [2] No

55. Capture **verbatim** any statements about **any form** of gatekeeper agreement to participate, including what consent was for (e.g., participation, review of medical records)

____

56. Reporting of any **health professional** consent procedures (requires specific reference to "consent"):
- [1] Reported informed consent was provided including method (e.g., "physicians provided written/ verbal consent")
- [2] Reported informed consent was provided but no details on method (e.g. "consenting GPs were randomized")
- [3] Reported waiver of informed consent (specify reason) (e.g., to avoid Hawthorne type effect) ____
- [4] Not reported (e.g., "physicians agreeing to participate were randomized", "participating physicians were randomized", nursing homes were enrolled in the trial and no report of consent from nurses administering interventions)

57. Capture **verbatim** any statements about any form of health professional agreement to participate, including what "consent" was for (e.g., participation, review of medical records) and use of opt-in versus opt-out procedures:

58. Reporting of **patient** consent procedures (Note: refers to main study component):

1 Reported informed consent was provided including method (e.g., written, verbal)
2 Reported informed consent was provided but no details on method
3 Reported waiver of patient consent (specify reason) (e.g., routine outcome data, no personal identifiers collected)
4 Not reported (e.g., "patients agreeing to participate…", implied by return of survey questionnaire but not reported, or there was no patient recruitment and waiver of informed consent not reported)

59. Capture **verbatim** any statements about **patient** "consent"/agreement to participate, including <u>what consent was for</u> (e.g., participation, review of medical records), and use of <u>opt-in versus opt-out</u> procedures:

60. Capture **verbatim** any statements about attempts to protect **patient confidentiality** or privacy (e.g., "anonymized data were collected", "no personal identifiers were transmitted")

61. Incentives offered? Specify as nr = "not reported" or verbatim (e.g., CME credits, $1000 for computers):

a) Gatekeeper
b) Health professionals
c) Patients

62. Capture **verbatim** any author comments on REB review process or impact of informed consent procedures on study: (e.g., impact on study duration/costs/feasibility/recruitment/scientific validity/ differential process and outcome among centres):

63. Capture **verbatim** any other statements relating to ethical issues (e.g., "patients who declined to participate were offered the successful treatment after completion of the trial"; "individuals in control clusters were not prevented from seeking active treatment")

64. Any other general reviewer comments about ethical or methodological issues? (e.g., trial was stopped early for harm, stopping rules were in place, adverse events reported)

65. Do authors reference a separate publication which may provide further details on items required in this data abstraction form?

- [1] Yes
- [2] No

Appendix B. REB approval from the University of Ottawa and UWO

The Ottawa Hospital | L'Hôpital d'Ottawa

Research Ethics Board
Conseil d'éthique en recherches
798-5555 ext 14146, 14902 or 15072
Fax No. ~ 761-4311
http://www.ohri.ca/ohreb/

Tuesday, December 04, 2007

Dr. Monica Taljaard
Ottawa Hospital - Civic Campus
Clinical Epidemiology Program
F6, Room F650b
1053 Carling Avenue
Ottawa, ON K1Y 4E9

Dear Dr. Taljaard:

Re: Protocol # 2007191-01H **Ethical and Policy Issues in Cluster Randomized Trials, Phase I**

Protocol approval valid until - **Monday, February 04, 2008**

I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved for two months to start recruiting English-speaking patients. Approval is for the Protocol, the English Questionnaire, received on October 26, 2007, and the English Telephone Script, received on October 26, 2007. Upon receipt and review of the French Questionnaire and French Telephone Script, the protocol may be extended to December 3, 2008 (one year from the initial approval date) and the recruitment of French-speaking patients may commence. No changes, amendments or addenda may be made to the protocol or the consent form without the OHREB's review and approval.

The validation date should be indicated on the bottom of all consent forms and information sheets (see copy attached).

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,

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

Encl.

/rf

Office of Research Ethics

The University of Western Ontario
Room 00045 Dental Sciences Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. C. Weijer
Review Number: **13755E** **Review Level:** Expedited
Review Date: November 12, 2007

Protocol Title: Ethical and Policy Issues in Cluster Randomized Trials. Phase 1.
Department and Institution: Medicine-Dept of, University of Western Ontario
Sponsor: CIHR-CANADIAN INSTITUTE OF HEALTH RESEARCH
Ethics Approval Date: December 5, 2007 **Expiry Date:** February 28, 2008
Documents Reviewed and Approved: UWO Protocol, Letter of Information, Telephone script
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. John W. McDonald

Ethics Officer to Contact for Further Information			
☐ Janice Sutherland (jsutherland@uwo.ca)	☐ Jennifer McEwen (jmcewen4@uwo.ca)	☐ Grace Kelly (grace.kelly@uwo.ca)	☒ Denise Grafton (dgrafton@uwo.ca)

This is an official document. Please retain the original in your files.

cc: ORE File

Appendix C. Interview guide used for key informant interviews in chapter four

Key Informant Interview

1. What types of cluster randomized trials have you been involved with?
   [Prompt: We are interested in the type of research that you have done, i.e., primary, secondary or tertiary care, public health, and the types of interventions and outcomes you were looking at]

2. What was your involvement in these trials?
   [Prompt: Clinical investigator, social scientist, statistician, epidemiologist…?]

3. Approximately how many cluster randomized trials have you been involved with?

ethical issues

4. Have you come across any ethical issues in the cluster randomized trials you have been involved with? What were these issues and why did they arise?

5. How did you try to resolve these issues? Were the solutions satisfactory?

6. Tell me about your experiences with obtaining **ethics approval** for the cluster randomized trials you have been involved with.

7. Has the ethics review process had any impact (positive or negative) on the quality of your trials?

8. Can you identify a *particular* trial which presented the most challenging or interesting ethical issues? Tell me more about this trial.
   [Prompt: Nature of the intervention, outcomes of interest, types of clusters, ethical issues…]

9. Has this trial been published? Where?

particular trial.

10. What were the main reasons for using cluster randomization?
    [Prompt: To avoid contamination, cluster-level intervention, ethics, feasibility…?]

11. Now we are interested in the **clusters** that were selected for recruitment to the trial. How were they identified or selected? Who consented on behalf of each cluster and how were the decision-makers identified?

12. Did the decision-makers receive any incentives or benefits from their participation?

13. Were there any ethical concerns with the role of the decision-maker in this trial?

14. Did you experience any difficulties in recruiting clusters to the trial?
    [Prompt: What reasons given for refusing to participate?]

15. Now we are interested in the **individuals** that participated in the trial. How were they identified or selected?
    [Prompt: e.g., through random sampling, had to satisfy eligibility criteria…]

16. Did the individuals consent *prior* to being randomized? If not, why not?

17. Did the individuals consent to receiving the intervention? If not, why was consent not sought?

18. What information was given to individuals about the trial and the interventions involved?
    [Prompt: where individuals aware of the trial?]

19. How were the outcomes assessed?
    [Prompt: telephone survey, in-person interview, secondary data sources…]

20. Did all individuals providing data for analysis consent to data collection? If not, why was consent not obtained?

21. Did you experience any difficulties in recruiting individuals to the trial?
    [Prompt: What reasons given for refusing to participate?]

22. Describe any potential risks or benefits to individuals, and clusters or communities in this trial.

23. What opportunities existed for individuals to withdraw from the trial?

24. Did individuals have access to the intervention outside the trial?

25. Did individuals in the control group have access to the intervention during or after the trial?

26. Do you have any other comments about ethical issues, the ethics review process, or ethics guidelines for cluster randomized trials?

Appendix D. Final coding template for descriptive qualitative analysis in chapter four

Consent from Individuals

- Active vs. passive consent
- Awareness of trial
- Completion of questionnaire as consent
- Consent from individuals with limited capacity
- Consent process as source of bias
- Consent to data collection
- Consent to receive intervention
- Implied consent for data collection within consent for care
- Incentives to individuals
- Individual consent superseding need for cluster or community consent
- Individual (informant's) perception of need for consent
- Information provided to individuals
- Opting out of data collection
- Opting out of intervention
- Subject coercion
- Timing of individual consent re: randomization, Zelen design
- Waiver of consent from individuals/need for consent from individuals

Consent from Gatekeeper

- Alternatives to individual gatekeepers (e.g. advisory boards)
- Gatekeeper authority
- Gatekeeper consent overriding individual consent
- Identification of appropriate gatekeeper
- Incentives to gatekeepers
- Information provided to gatekeepers
- Multiple levels of gatekeepers

Consent from Cluster Participants (e.g. physicians, teachers)

- Cluster level drop-outs
- Coercion of cluster participants
- Compensation for time or activity
- Democratic consent of cluster or practice
- Influence of opinion leader
- Incentives to clusters (financial, infrastructure)
- Need for consent from cluster participants
- Professional obligation for research participation
- Reasons for refusal

Risks and Potential Benefits

- Equipoise between intervention arms

- Intervention as standard or nonstandard care
- Obligations to research subjects
- Overburdening of some clusters
- Perception of no risk to individuals or clusters
- Risks to professional reputation
- Tradeoff of benefits to society vs. risks to individuals
- Uncertainty about intervention safety or efficacy

Privacy
- Access to patient data
- Breaking of privacy protections during trial
- Obstacles from healthcare bureaucracy
- Privacy protections for individual data

Conflicts of Interest

Methodological Concerns
- Contamination
- Selection of clusters
  - Fairness
  - Selection criteria
- Practicality of consent
- Stopping rules

Ethics Board Review Process
- Access to intervention for control groups
- Access to intervention for non-study individuals
- Change in regulations or review over time
- Difference in regulation or review between jurisdictions
- Duration of ethics review process
- Importance of type of intervention for ethics review
- Need to educate ethics boards about cluster trials
- Negative impact of review process
- No impact of review process
- Positive impact of review process

Ethics Guideline Recommendations
- Conflicts of interest with professional obligations
- Distinction between health services research, KT, and QI
- Education about cluster design

- Need for ethics approval
- Reporting standards
- Requirements for valid design and analysis

CURRICULUM VITAE

ANDREW DUNCAN McRAE

Education

Degrees

- Doctor of Philosophy (studies ongoing). Dept. of Epidemiology and Biostatistics. University of Western Ontario, London ON. Sept. 2005-Present. Doctoral Dissertation: An empirical and philosophical analysis of ethical problems in cluster randomization trials. Supervisors: Drs. Charles Weijer and Allan Donner.

- Doctor of Medicine. Dalhousie University, Halifax NS. 2002.

- Bachelor of Science (Medical). Dalhousie University, Halifax NS. Thesis Project: Ethics Problems in Emergency Medicine Research. Supervisor : Dr. Charles Weijer. 2002.

- Bachelor of Science. Dept. of Microbiology and Immunology. Minor in Religious Studies. McGill University, Montreal QC. Graduated with Great Distinction. 1998.

Postgraduate Training

- Royal College of Physicians of Canada Training Program in Emergency Medicine. Department of Emergency Medicine. Queen's University, Kingston, ON. 2002-2007.

Professional Certification

- Fellow of the Royal College of Physicians of Canada. Specialty Certification in Emergency Medicine. 2007.

- Licentiate of the Medical Council of Canada. 2003.

- Advanced Cardiac Life Support Instructor, American Heart Association. 2004.

- Advanced Trauma Life Support Instructor, American College of Surgeons. 2004. ATLS ID #287692

- Pediatric Advanced Life Support Provider, American Heart Association and American College of Pediatrics. 2002.

Academic Appointments

- Assistant Professor. Division of Emergency Medicine, Department of Medicine. University of Western Ontario. London, ON. September 2007-November 2010.

- Assistant Professor. Department of Emergency Medicine. Queen's University, Kingston, ON. July-September 2007.

Employment

- Research Director, Department of Emergency Medicine, Calgary Health Region. Alberta Health Services. Calgary, AB. December 2010-Present

- Emergency Physician. Foothills Medical Centre, Peter Lougheed Centre and Rockyview Hospital. Calgary, AB. December 2010-Present.

- Trauma Team Leader. London Health Sciences Centre. London, ON. February 2009-November 2010.

- Attending Emergency Physician. London Health Sciences Centre and Saint Joseph's Health Centre. London, ON. September 2007- November 2010.

- Attending Emergency Physician, Trauma Team Leader, and RACE Team Physician. Kingston General Hospital. Kingston, ON. July-September 2007.

- Locum Emergency Physician. Sussex Health Centre, Atlantic Health Sciences Corporation. Sussex, NB. December 2004 and December 2005.

Awards

- Western Graduate Research Scholarship. Univ. of Western Ontario (2006-2009)
- Ontario Graduate Scholarship (Declined) (2007, 1998)
- Dr. Robert F. Scharf Award in Emergency Medicine. Dalhousie University (2002)
- Canadian Bioethics Society Student Abstract Award (2001)
- Associated Medical Services, Inc. Bioethics Studentship (2000)
- Dalhousie University Faculty of Medicine Scholarship (2001)
- Ross Stewart Smith Medical Scholarship, Dalhousie University (2000)
- William Isaac MacDougall Scholarship, Dalhousie University (1999)
- Natural Sciences and Engineering Research Council of Canada Postgraduate Scholarship (Declined) (1998)
- McConnell Award, McGill University (1996-97)
- Dean's Honour List, McGill University (1994-95 and 1996-97)

Research Funding

Salary Awards

- Canadian Institutes of Health Research Fellowship Award ($50000/annum salary support, $5000/annum research funding). 2007-2012.

Publications and Presentations

Peer-Reviewed Publications

Journal Articles

- **A McRae**, C Weijer, A Binik. Who is the research subject in healthcare cluster-randomized trials? Manuscript under submission. 2010.

- A Binik, **A McRae**, C Weijer. Does clinical equipoise apply to cluster randomized trials? Manuscript under submission. 2010

- C Weijer, J Grimshaw, M Taljaard, A Binik, R Boruch, J Brehaut, A Donner, M Eccles, A Gallo, **A McRae**, R Saginur and M Zwarenstein. Ethical Challenges Posed by Cluster Randomized Trials in Health Research. Manuscript under Submission. 2010

- M Taljaard, **A McRae**, C Weijer, C Bennett, S Dixon, J Taleban, Z Skea, J Brehaut, M Eccles, A Donner, R Saginur, J Grimshaw. Inadequate Reporting of research ethics review and informed consent in cluster randomized trials: review of a random sample of published trials. Manuscript under submission, 2010

- **A McRae**, M Taljaard, C Weijer, Z Skea, C Bennett, J Grimshaw, A Donner. Features of cluster randomized trials associated with reporting of informed consent from patients. Manuscript in preparation. 2010.

- **A McRae**, M Taljaard, J Belle Brown. Investigators' experience with the ethics review process for cluster-randomized trials: a qualitative analysis. Manuscript in preparation. 2010.

- **A McRae,** C Weijer, A Binik. When is consent required in cluster randomized trials? Manuscript in preparation. 2010.

- A Binik, **A McRae**, C Weijer. The ethical analysis of benefits and harms in cluster-randomized trials. Manuscript in preparation. 2010.

- M Taljaard, J McGowan, J Grimshaw, J Brehaut, **A McRae**, M Eccles and A Donner. Electronic search strategies to identify reports of cluster randomized trials in MEDLINE: low precision will improve with adherence to reporting standards. BMC Medical Research Methodology 2010, 10:15. (Published online 2 February, 2010).

- M Taljaard, C Weijer, JM Grimshaw, J Belle Brown, A Binik, R Boruch, J C Brehaut, S Chaudhry, M P Eccles, **AD McRae**, R Saginur, M Zwarenstein and A Donner. Ethical and Policy Issues in Cluster Randomized Trials: Rationale and Design of a Mixed Methods Research Study. *Trials*. 2009; 10:61 (Published online 28 July, 2009).

- **AD McRae**, H Murray and M Edmonds. Diagnostic accuracy and clinical utility of emergency department targeted ultrasonography in the evaluation of first-trimester pelvic pain and bleeding: a systematic review. *Can J Emerg Med*. 2009; 11(4) 355-364.

- **AD McRae** and C Weijer. US Federal Research Regulations for Emergency Research: A Practical Guide and Commentary. *Acad Emerg Med*. 2008; 15(1): 88-97.

- **AD McRae**, S Ackroyd-Stolarz and C Weijer. Risk in Emergency Research Using a Waiver of Consent: Implications of a Structured Approach for IRB Review. *Acad Emerg Med*. 2005; 12: 1104-12.

- M Pauls, **A McRae**, S Campbell and P Dungey. Ethics in the Trenches Part 2: Case Studies of Ethical Challenges in the Emergency Department. *Can J Emerg Med*. 2004; 6(5): 363-6.

- **AD McRae** and C Weijer. Lessons from Everyday Lives: A Moral Justification for Acute Care Research. *Crit Care Med*. 2002; 30(5): 1146-52.

Other Peer-reviewed Documents

- **AD McRae**. Educational Primer: *Research Ethics*. Prepared for the Royal College of Physicians and Surgeons of Canada Bioethics Education Project. 2006. Available at: http://rcpsc.medical.org/bioethics/extended-primers/research-ethics_e.php

- **AD McRae**. Case Module: Mandatory Reporting by Physicians—Public Safety. Prepared for the Royal College of Physicians and Surgeons of Canada Bioethics Education Project. 2006. Available at http://rcpsc.medical.org/bioethics/cases/case_3_3_3_e.php

- M Jackman and **A McRae**. Case Module: Medical Decision-making by adolescents and older children. Prepared for the Royal College of Physicians and Surgeons of Canada Bioethics Education Project. 2007. Available at http://rcpsc.medical.org/bioethics/cases/case_1_5_2_e.php

Correspondence

- **AD McRae** and C Weijer. Research Without Consent, 2003. *Ann Emerg Med*. 2004; 44(3):278-9.

Published Abstracts

- Ketamine-propofol compared with propofol for procedural sedation in the emergency department. K Church, G Mosdossy, A Shah, S McLeod,K Lehnhardt, M Peddle, **A McRae**. Canadian Association of Emergency Physicians Annual Scientific Meeting. Montreal, QC. June 2010. Can J Emerg Med. 2010: 12(3):229-278.

- **A McRae**, M Edmonds and H Murray. Diagnostic Accuracy of Emergency Department Targeted Ultrasonography for Intrauterine Pregnancy: A Meta-Analysis of Current Evidence. Canadian Association of Emergency Physicians Annual Scientific Meeting. Victoria, BC. June 2007. *Can J Emerg Med*. 2007;

- **A McRae**, M Edmonds and H Murray. Clinical Utility of Emergency Department Targeted Ultrasonography in Symptomatic First-Trimester Pregnancy: A Systematic Review of Current Evidence. Canadian Association of Emergency Physicians Annual Scientific Meeting. Victoria, BC. June 2007. *Can J Emerg Med*. 2007;

- **AD McRae** and C Weijer. The Ethics of Emergency Research: Feasibility and Application of Canadian Guidelines. Canadian Association of Emergency Physicians Annual Scientific Meeting. Hamilton, ON. April 2002. *Can J Emerg Med*. 2002; 4(2): 145. Abstract 73.

- **AD McRae** and C Weijer. Re-thinking Risk in Emergency Research. American College of Emergency Physicians Research Forum. Chicago, IL, USA. October 2001. *Ann Emerg Med.* 2001; 38(4) Suppl: S53. Abstract 193.

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- **AD McRae**. Who is the Research Subject in Healthcare Cluster Randomization Trials?. Canadian Bioethics Society Annual Meeting. Hamilton, ON. June 2009.

- **AD McRae** and C Weijer. Minimal Risk Re-Visited: The Importance of a Risk Threshold for Emergency Research. Canadian Bioethics Society 13th Annual Meeting. Winnipeg, MB. October 2001.

- **AD McRae**. Ethics and Regulation of Acute Care Research. Canadian Bioethics Society 12th Annual Meeting. Quebec City, QC. October 2000.

- **AD McRae**, DI Ginsberg, A Mak, and GS Jensen. Ligation of L-selectin with Different Ligands Induces Distinct Physiological Effects in Peripheral Blood Lymphocytes. 12th Spring Meeting of the Canadian Society for Immunology, Sainte-Adele, QC. March 1998.

- A Mak, **AD McRae**, and GS Jensen. Variant Forms of L-selectin in Human B and T Cell Lymphoma Cell Lines. Presented at the Keystone Symposia: Temporal and Spatial Determinants of Specificity in Signal Transduction, Keystone CO, USA. April 1997.

Other Scholarly Work

- J Anderson, H Braude, A Fuks, K Glass, J Kimmelman, **A McRae**, S Shapiro and C Weijer. McGill Clinical Trials Research Group. Comments on Draft 2nd edition of the Tri-Council Policy Statement. Submitted to the Canadian Interagency Panel on Research Ethics. May 2009. Available at http://www.noveltechethics.ca/pictures/File/Health_Policy_Private/TCPS%20Documents/CTRG_TCPS%20comments09.pdf

- **A McRae**. Subject protections in emergency and critical care research. Submitted to the Canadian Interagency Panel on Research Ethics. May 2009.

Invited presentations

- **AD McRae**. *Assessing Risks and Potential Benefits*. Workshop: Consent in the Emergency Setting. Dept. of Emergency Medicine and Division of Emergency Medical Services. Dalhousie University, Halifax, NS. 26 June, 2006.

- **A McRae**. Ethics and Resuscitation Research: Challenges and Solutions. Ethics for Lunch Seminar Series. Kingston General Hospital. Kingston, ON. Nov. 18, 2004.

- **A McRae**. Practicalities and Pitfalls of Futility Discussions. Grand Rounds. Division of Critical Care Medicine, Queen's University. Kingston, ON. March 2004.

- **A McRae**. Ethical Considerations in Combat Care Research. Conference: Advanced Technological Applications in Combat Casualty Care. United States Department of Defense. St. Petersburg, FL, USA. September 2002.

- **A McRae**. The Ethical Analysis of Risk. Workshop: Ethical Considerations in Emergency Medicine Research. Department of Emergency Medicine, Dalhousie University and Research Ethics Board, QEII Health Sciences Centre. Halifax NS. February 2002.

Other presentations

- **A McRae,** H Murray, M Pauls and C Weijer. Evaluating and Improving REB Review of Emergency Research. Phase I. Emergency Medicine Research Day, Dept. of Emergency Medicine, Queen's University. October 13, 2004.

- **A McRae.** Ethical and Regulatory Challenges in Emergency Research. Grand Rounds. Dept. of Emergency Medicine. Queen's University. June 2004.

- **A McRae.** Advances in the Ethics and Regulation of Emergency Research. Research Day. Dept. of Emergency Medicine, Queen's University. September 2002.

- **AD McRae**. Re-Thinking Risk in Emergency Research. Dept. of Emergency Medicine Research Day, Dalhousie University. May 2001.

- **AD McRae**. Ethics and Regulation of Emergency Research. Summer Research Seminar Series, Dalhousie University Faculty of Medicine. July 1999.