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

Summary of Recommendations

Recommendation 1: Researchers should provide an acceptable rationale for the use of the cluster randomised design and adopt statistical methods appropriate for this design.

Recommendation 2: Researchers must submit a cluster randomised trial involving human research subjects for approval by a research ethics committee before proceeding.

Recommendation 3: Researchers should clearly identify the research subjects in cluster randomised trials. A research subject can be identified as an individual whose interests may be affected as a result of study interventions or data collection procedures, that is, an individual: (1) who is the recipient of an experimental (or control) intervention; or (2) who is the direct target of an experimental (or control) manipulation of his/her environment; or (3) with whom an investigator interacts for the purpose of collecting data about that individual; or (4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual. Unless at least one of these criteria is met, an individual is not a research subject.

Recommendation 4: Researchers must obtain informed consent from human research subjects in a cluster randomised trial, unless a waiver of consent is granted by a research ethics committee under specific circumstances.

Recommendation 5: When subjects' informed consent is required, but recruitment of subjects is not possible *prior* to randomisation of clusters, researchers must seek subjects' consent for trial participation as soon as possible after cluster randomisation—that is, as soon as the potential subject has been identified, but before the subject has undergone any study interventions or data collection procedures.

Recommendation 6: A research ethics committee may approve a waiver or alteration of consent requirements if (1) the research is not feasible without a waiver or alteration of consent, and (2) the study interventions and data collection procedures pose no more than minimal risk.

Recommendation 7: Researchers must obtain informed consent from professionals or other service providers who are research subjects unless conditions for a waiver or alteration of consent are met.

Recommendation 8: Gatekeepers should not provide proxy consent on behalf of individuals in cluster randomised trials.

Recommendation 9: When a cluster randomised trial may substantially affect cluster or organisational interests, and a gatekeeper possesses the legitimate authority to make decisions on its behalf, the researcher should obtain the gatekeeper's permission to enrol

the cluster or organisation in the trial. Such permission does not replace the need for the informed consent of research subjects.

Recommendation 10: When cluster randomised trial interventions may substantially affect cluster interests, researchers should seek to protect cluster interests through cluster consultation to inform study design, conduct and reporting. Where relevant, gatekeepers can often facilitate such a consultation.

Recommendation 11: The researcher must ensure that the study intervention is adequately justified. The benefits and harms of the study intervention must be consistent with competent practice in the field of study relevant to the cluster randomised trial.

Recommendation 12: Researchers must adequately justify the choice of the control condition. When the control arm is usual practice or no-treatment, individuals in the control group must not be deprived of effective care or programmes to which they otherwise would have access.

Recommendation 13: Researchers must ensure that data collection procedures are adequately justified. The risks of data collection procedures must (1) be minimised consistent with sound design and (2) stand in reasonable relation to the knowledge to be gained.

Recommendation 14: Study clusters may contain within them a proportion of vulnerable subjects. Researchers and research ethics committees should consider whether additional protections are needed.

Recommendation 15: Where individual informed consent is required, and there are individuals who may be less able to choose freely because of their position in a cluster or organisational hierarchy, research ethics committees should pay special attention to recruitment, privacy, and consent procedures for those participants.

Background

Definition of a cluster randomised trial

Cluster randomised trials, also known as group randomised, place-based, or community intervention trials, are an increasingly important design for the evaluation of interventions in health, education, welfare, crime prevention, and policy research as well as economic development in low income countries. In cluster randomised trials, *groups* or "clusters" of individuals—rather than the constituent individuals themselves—are randomly allocated to study arms. Examples of clusters include households, medical practices, hospital wards, schools, neighbourhoods and communities. Study interventions in cluster randomised trials may be delivered at the cluster level (e.g., a community-wide advertising campaign to promote smoking cessation), or at the individual level (e.g., vitamin supplements or leaflets distributed to patients); interventions may also be delivered to individuals at the head of a cluster with the aim to produce an effect on cluster members (e.g., educational messages delivered to health professionals with the aim to promote evidence-based practice).

A glossary is provided at the end of this paper.

Examples of cluster randomised trials

The Community Intervention Trial for Smoking Cessation (COMMIT) used mass education—a cluster-level intervention—to target entire communities in an attempt to reduce smoking rates. Twenty-two (22) communities in the USA and Canada were paired on geographic location, size, and socio-demographic factors. One community in each pair was then randomly assigned to the intervention arm and the other to the control arm (which received no intervention). The trial promoted smoking cessation through a wide range of influences including public education, health care workers, and employers. Given such broad interventions, randomisation of individuals would have been impossible [1].

Lewin and colleagues examined the effect on patient outcomes of a training programme for health workers caring for people with tuberculosis in South Africa [2]. The study targeted primary care clinics in Cape Town that had tuberculosis treatment completion rates of less than 70%. Twenty-four (24) eligible clinics were stratified based on size and were then randomised within each stratum to either the intervention or control arm of the trial. In the intervention arm, nurse clinicians underwent an 18-hour in-service training program that focused on patient-centered care and quality improvement, while no training was offered in the control arm. Study outcomes compared patient treatment completion and patient cure rates before and after the study intervention. As the intervention was targeted at providers who treat many patients, randomisation of individual patients was infeasible.

Kennedy and colleagues studied the effect of patient-centered educational materials—an individual-level intervention—on patient knowledge, anxiety, and quality of life [3]. Patients in the study attended outpatient clinics at six hospitals and were on long term follow-up for ulcerative colitis. As patients attending the same hospital clinic frequently interact with one another, hospital clinics were randomised: three to the intervention arm and three to the control arm. In this trial, randomisation of clinics avoided treatment contamination by ensuring that all patients attending the same clinic were allocated to the same study arm.

Additional examples of cluster randomised trials are provided elsewhere [4].

Ethical challenges in cluster randomised trials

National and international research ethics guidelines are relevant to cluster randomised trials. However, cluster randomised trials pose distinct ethical challenges for several reasons. First, in cluster randomised trials the units of randomisation, experimentation, and observation may differ, meaning that the individuals exposed to the risks of the study interventions may be different from the individuals whose data are collected (and hence, whose privacy may be in question). For example, the intervention may be directed at health professionals, but outcomes are assessed at the patient level. Second, cluster randomised trials often employ communities as the units of randomisation and current understanding of the moral status of communities is incomplete. As a result, the answers to pivotal ethical questions, such as who may speak on behalf of a particular community and on what authority they may do so, are unclear. Third, while risks to individuals may be minor, the risks to the cluster as a whole or to certain subgroups of the cluster may not be apparent, because risks to the group may be underestimated and vulnerable subgroups within clusters may be difficult to identify.

While there is a small but growing literature on the subject [5,6,7,8,9], the ethical challenges raised by cluster randomised trials have yet to be systematically explored. As a result, researchers, research ethics committees, and regulators currently lack dedicated and specific guidelines to help them design, conduct and review cluster randomised trials according to internationally acceptable ethical standards. Predictably, the lack of authoritative and comprehensive guidance has resulted in uncertainty and markedly different interpretations as to permissible ethical practices in cluster randomised trials.

Aim and Scope

The aim of this statement is to provide guidance on the ethical conduct of cluster randomised trials. This guidance is primarily intended for researchers and research ethics committees. It will also be relevant to other groups such as research funders, policy makers, gatekeepers, and journal editors. It builds upon—and does not replace—current published standards of ethical principles for randomised controlled trials and other human subjects research. The guidance will need to be interpreted in light of the applicable laws and regulations of the country or countries in which the research is to be performed, as well as applicable international norms and standards.

Methods

The development of the statement was underpinned by a four year research project funded by the Canadian Institutes of Health Research [10]. The project, conducted by the core Research Team (see Appendix 1), used a mixed-methods approach incorporating both empirical and conceptual work. The empirical work included interviews with key informants, review of the reporting of ethical issues within a representative sample of 300 published cluster randomised trials [11]; surveys of 182 authors of cluster randomised trials; and surveys of 194 research ethics chairs in the USA, Canada, and the UK. Based on the empirical work, as well as the practical experiences of research team members, six ethical questions considered specific to cluster randomised trials and in need of further analysis were identified [4]: (1) How ought research subjects be identified? (2) From whom, how, and when must informed consent be obtained? (3) Does clinical equipoise apply to cluster randomised trials? (4) How do we determine if the benefits outweigh the risks of cluster randomised trials? (5) How ought vulnerable groups be protected in cluster randomised trials? (6) Who are gatekeepers and what are their responsibilities? Each issue was the focus of a normative analysis which led to a discussion paper [12,13,14,15] laying out principles, policy options, and rationale for proposed ethics guidelines.

To develop the consensus statement from this process, a two and a half day meeting of a multidisciplinary Expert Panel was organised. The Expert Panel was composed of four of the members of the Research Team and 14 external members including ethicists, cluster trialists, statisticians, policy makers and journal editors (See Appendix 1 for a full list of membership of the Expert Panel and Research Team). External members were invited as individuals rather than as representatives of their host organisations. The discussion papers were made available to the Expert Panel in advance of the meeting. The first day of the consensus meeting was an open meeting (with simultaneous webcast), at which the results of the empirical studies and ethical analyses of the six issues were presented and commented on by expert discussants and the audience, which included invited representatives from funding agencies, trialists, journal editors, regulators, and chairs of ethics committees. The members of the Expert Panel subsequently met together in closed session for one and a half days to discuss identified issues and to develop recommendations.

A writing group (see Appendix 1) then reviewed the results of the meeting and produced a first draft of the statement. This was circulated to the Expert Panel and was edited in response to their comments. The document was then posted on the project wiki (http://crtethics.wikispaces.com) for comment. Key informants, participants of the open meeting, trialists and ethics review board chairs surveyed in the research project, and other contacts of the Expert Panel were specifically invited to comment. The statement was then edited in response to received comments.

General ethical principles

In this section we present ethical principles that govern the design and conduct of health research generally. Subsequent recommendations in this document consider the application of these ethical principles to cluster randomised trials.

All research involving human subjects should be conducted in accordance with four fundamental ethical principles: respect for persons; beneficence; justice; and respect for communities. The principle of respect for persons requires that: (1) choices of autonomous people, that is, people who can responsibly make their own decisions, are given serious consideration; and (2) people lacking autonomy, such as young children or adults with advanced dementia, are entitled to protection. The principle of respect for persons is the source of the moral rules of informed consent and confidentiality. The researcher is generally obligated to obtain agreement from a research subject (or his or her surrogate decision maker) for study participation. For informed consent to be valid, the research subject must have the cognitive capacity to make the choice, be so situated as to choose freely, have adequate information, and understand what is at stake in the decision. Informed consent may not be required when it cannot feasibly be obtained and study participation poses only minimal risk. Researchers must also take necessary steps to protect the confidentiality of the research subject's personal information.

The principle of beneficence obliges researchers not to inflict harm needlessly and, where possible, to promote the good of research subjects. Health research often contains a mixture of study procedures, some offering reasonable prospect of benefit to research subjects (therapeutic procedures), while others are administered solely to answer the scientific question (non-therapeutic procedures). According to a systematic approach to the ethical analysis of benefits and harms in research called component analysis [16], therapeutic and non-therapeutic procedures must be considered separately. Therapeutic procedures are justified if they satisfy clinical equipoise, which requires that they meet the standard of competent medical practice. In other words, there must be a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment. Non-therapeutic procedures, which generally offer no plausible direct benefit to the research subject, are acceptable if the risks associated with them are minimised consistent with sound scientific design, and reasonable in relation to the knowledge to be gained. When the study involves a vulnerable population, such as children or incapable adults, the risks posed by non-therapeutic procedures must not exceed a minor increase above minimal risk. According to component analysis, one may only conclude that the benefits and harms of a study are acceptable when the moral rules for both therapeutic and non-therapeutic procedures are satisfied.

The principle of justice may be defined as the ethical obligation to distribute the benefits and burdens of research fairly. Researchers have an obligation to ensure that the means used to select research subjects are equitable. Researchers must neither exploit the vulnerable, nor exclude without good reason those who stand to benefit from study participation. In order for proposed eligibility criteria to be evaluated, each criterion must be accompanied by a clear justification in the study protocol. The inclusion of a

vulnerable group (such as children, incapable adults, or prisoners) requires a clear justification to demonstrate they are not being targeted merely as a matter of convenience. Further, in so far as is possible and practicable, the study population ought to mirror the target clinical population. The historical exclusion of children, women, and racial minorities from the benefits of research has led to a variety of contemporary initiatives to promote their inclusion in clinical research. The principle of justice also requires that provisions be in place to compensate research subjects who are harmed as a result of research participation [17].

The principle of respect for communities means that researchers have an obligation to respect communal values, protect and empower communities, and, where applicable, abide by the decisions of legitimate communal authorities. Practically, the researcher-community relationship ought to be viewed as a partnership. Depending upon the degree to which the research affects the community as a whole and the specific features of the community, researchers may productively involve community partners throughout the research process, from defining the study question through the dissemination of results. Community consent ought to be restricted to cases in which the community leader is a legitimate authority who is empowered to speak on behalf of community members. It is important to understand that community consent does not replace the need for the informed consent of individual research subjects [18].

Proportionality

Health research must be reviewed in a manner that ensures that ethical issues receive appropriate consideration. Studies vary in the magnitude and complexity of ethical issues posed. As a result, research ethics committees should adopt a proportionate approach to the review of research. According to this approach, research that poses substantial risk, involves vulnerable subjects, or has major flaws in study design ought to receive intensive scrutiny, while low risk research not involving vulnerable subjects and employing an appropriate design may be reviewed more expeditiously. Many cluster randomised trials pose only low risk to research subjects. For instance, a cluster randomised trial may involve a knowledge translation intervention to promote the uptake of an intervention that is already proven to be effective, or a public health intervention to encourage people to quit smoking. When a cluster randomised trial poses low risk to research subjects, does not involve vulnerable subjects, and is appropriately designed, it may be a candidate for expedited or delegated review by the research ethics committee. These guidelines are intended to ensure robust and appropriate review of cluster randomised trials by research ethics committees, and the following recommendations are intended to guide both expedited and full committee review of cluster randomised trials.

Recommendations

Justifying the cluster randomised design

Recommendation 1: Researchers should provide an acceptable rationale for the use of the cluster randomised design and adopt statistical methods appropriate for this design.

Compared with an individually randomised trial with the same number of individuals, cluster randomised trials are inefficient and have less statistical power. This is a result of the tendency for responses of individuals within a cluster to be more similar than the responses of individuals in differing clusters. Because cluster randomised trials tend to have a smaller number of randomised units than in individually randomised trials (for example, a median of 21 (inter-quartile range 12 to 52) in our review of a random sample of 300 published cluster randomised trials [11]), characteristics for clusters and for individuals within clusters are less likely to be balanced across study arms. Moreover, cluster randomised trials are more susceptible to various forms of bias [19]. For example, selection bias can arise when individual participants are identified or enrolled after clusters have already been assigned. Bias can also arise if consent is sought differently in the intervention and control arms. Furthermore, loss to follow-up is a potentially more serious problem in cluster randomised trials than in individually randomised trials because entire clusters may drop out, resulting in the loss of all the participants in that cluster. Given their inherent statistical inefficiency and these methodological complexities, the use of cluster as opposed to individual randomisation should be methodologically justified**.**

The cluster randomised trial design is used appropriately in several circumstances, including when: (1) the nature of the intervention requires that it be administered at the cluster level (for example, mass media advertising campaigns, or training of health professionals with the aim of improving patient care); (2) it may mitigate the problem of treatment contamination; and (3) it will enhance subject compliance or cooperation of investigators. There may be other practical and logistical reasons for using a cluster randomised design in addition to these [20,21]

Once an acceptable rationale for the cluster randomised design has been established, investigators should adopt statistical methods appropriate for this design. Because multiple observations from the same cluster are usually positively correlated, standard statistical methods for sample size calculation and data analysis are invalid and must be adjusted to allow for the clustered nature of the data. Failure to adopt appropriate sample size calculations may lead to an elevated Type II error (decreased ability to detect an important intervention effect), while failure to adopt appropriate data analysis methods may lead to an elevated Type I error (increased risk of detecting an intervention effect when none exists). Multiple resources are available that can help researchers adopt appropriate statistical methods for cluster randomised trials [21,22,23,24,25,26].

Research ethics committee review

Recommendation 2: Researchers must submit a cluster randomised trial involving human research subjects for approval by a research ethics committee before proceeding.

There is broad agreement in national and international research ethics guidelines that all human subjects research be submitted to and approved by a research ethics committee. Research may usefully be defined as a systematic investigation that is designed to produce generalisable knowledge. Quality improvement initiatives that seek solely to improve local service delivery are (generally) not regarded as research and may not require research ethics committee review. However, cluster randomised trials, including those evaluating quality improvement and knowledge translation interventions, are clearly designed to produce generalisable knowledge and, as a result, must be reviewed and approved by a research ethics committee. While the integrity of researchers is an important protection for research subjects, researchers may have vested interests. Research ethics committees are better placed to ensure that the autonomy and welfare interests of research subjects are protected, and that national and international ethical standards are upheld.

Research ethics committees ought to undertake a proportional approach to the review of study protocols (as discussed above). When a cluster randomised trial poses low risk to research subjects, does not involve vulnerable subjects and is appropriately designed, an expedited review process may be appropriate.

Identifying research subjects

Research subjects bear the burdens associated with the development of generalisable research knowledge. The correct identification of human research subjects is important because it directs the focus of ethical consideration toward the protection of those who may benefit or be harmed in the conduct of a research study. In cluster randomised trials however, the identification of human research subjects is complicated by the fact that the units of randomisation, intervention, and observation may differ within a single study. For example, the unit of randomisation may be a primary care practice, the intervention may be delivered to health professionals, while data may be collected from patients. We offer recommendations to guide the appropriate identification of human research subjects in a cluster randomised trial based on a defining feature of research subjects, namely that their interests are affected by study intervention or data collection procedures.

Recommendation 3: Researchers should clearly identify the research subjects in cluster randomised trials. A research subject can be identified as an individual whose interests may be affected as a result of study interventions or data collection procedures, that is, an individual (1) who is the recipient of an experimental (or control) intervention; or (2) who is the direct target of an experimental (or control) manipulation of his/her environment; or (3) with whom an investigator interacts for the purpose of collecting data about that individual; or (4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual. Unless at least one of these criteria is met, an individual is not a research subject.

The first criterion refers to individuals who are the *direct recipients* of a study intervention. This includes, for example, health professionals receiving an educational intervention designed to promote evidence-based practice, or patients receiving a new therapy for a targeted disease. The second criterion refers to individuals who are directly targeted by an intervention delivered at the cluster level. This includes, for example, smokers targeted by a mass-media smoking cessation campaign. It also includes patients in a cluster randomised trial investigating alterations of health delivery systems or system-wide experimental procedures for diagnosing disease. These two criteria do *not* however, include patients in a cluster randomised trial of an educational intervention delivered to health professionals with the aim to promote evidence-based practice [13].

In some cluster randomised trials, clusters in the control arm are allocated to usual practice or no-treatment, i.e., individuals may not be the recipients nor targets of any study interventions. However, when individuals in the experimental arm of the study are considered research subjects, individuals in the control arm ought to be considered research subjects as their interests may be affected by lack of access to the study intervention or other appropriate care or benefit, and thus, they are entitled to protection (see Recommendation 12).

The third and fourth criteria refer to individuals who provide data. This includes individuals who provide data by interacting with investigators through focus groups, interviews, or additional examinations. It also includes individuals about whom investigators obtain identifiable private information, e.g., through review of patient health records. Individuals who undergo these data collection procedures in the context of a research study are research subjects, even if they are not the recipient or target of the study interventions.

If the study intervention is designed to promote evidence-based practice by health professionals, and does not directly intervene on patients, and if the researchers do not interact with patients or collect their identifiable private information, then those patients are not research subjects [13].

Obtaining informed consent

Recommendation 4: Researchers must obtain informed consent from human research subjects in a cluster randomised trial, unless a waiver of consent is granted by a research ethics committee under specific circumstances.

The obligation to obtain informed consent stems from the ethical principle of respect for persons, which requires that the choices of autonomous individuals be respected. To be valid, such choices must be sufficiently informed, voluntary, and considered. Therefore, researchers must seek the informed consent of potential research subjects, and may only enrol those subjects who consent to participate. In the informed consent process, researchers must provide potential subjects with adequate information about the purpose of the study, study interventions and data collection procedures, the potential benefits and risks of study participation, and alternatives to participation, to enable subjects to make a

reasonable determination about whether study participation is consistent with their preferences and values. Detailed disclosure requirements are enumerated in international and national research ethics guidelines. Generally, informed consent refers to randomisation, study interventions and data collection procedures. However, as discussed below, in some cluster randomised trials different subjects may need to provide consent to different elements. For example, health professionals as the recipients of an educational intervention may need to consent to study interventions, while patients may need to consent to data collection. Moreover, it may not be possible or feasible to seek consent for randomisation, or for specific study interventions or data collection procedures. In these cases, researchers should seek subjects' consent for study interventions or data collection procedures when feasible to do so, or apply for a waiver of consent under specific circumstances.

Recommendation 5: When subjects' informed consent is required, but recruitment of subjects is not possible *prior* to randomisation of clusters, researchers must seek subjects' consent for trial participation as soon as possible after cluster randomisation—that is, as soon as the potential subject has been identified, but before the subject has undergone any study interventions or data collection procedures.

Researchers should strive to identify participants and seek their consent *before* cluster allocation. In some cluster randomised trials, it is not possible to identify and recruit subjects until after randomisation of clusters. For example, patients seeking treatment for a particular disease may need to be prospectively identified after random allocation of medical clinics. In these situations, subjects may be legitimately enrolled *following* randomisation of clusters even though researchers are unable to seek their consent for randomisation. Researchers should, however, seek potential subjects' consent for study interventions and data collection procedures as soon as possible after the subject has been identified, and before administering any study interventions or data collection procedures. Seeking consent in this way after randomisation is consistent with the moral purpose of informed consent, as potential subjects may still freely choose whether or not to participate in the trial [14].

Although seeking consent after randomisation is consistent with the moral purpose of informed consent, researchers should be aware that selection biases can arise in such cases and should adopt design strategies that minimise this bias. For example, identification or recruitment bias can arise when a recruiter is aware of the characteristics of a potential subject as well as the arm to which the subject's cluster has been allocated. Bias can also arise when consent to participation differs in the intervention and control arms, for example, if subjects are given different information during the consent process [27,19]. Hahn and colleagues [28] discuss potential sources of bias that can occur after cluster randomisation and provide recommendations on how to design cluster randomised trials to avoid these biases.

Recommendation 6: A research ethics committee may approve a waiver or alteration of consent requirements if (1) the research is not feasible without a waiver

or alteration of consent, and (2) the study interventions and data collection procedures pose no more than minimal risk.

In some cluster randomised trials, it may not be feasible to obtain individual research subjects' consent for study interventions and data collection procedures. In such cases, a waiver or alteration of consent may apply provided that study and data collection procedures pose no more than minimal risk to research subjects. Minimal risk refers to the risks of daily life, and include the risks associated with routine physical examinations and review of medical records. Additional examples of study interventions and data collection procedures that pose only minimal risk are enumerated in the research ethics literature and ethics guidelines [29,30].

Obtaining individual research subjects' informed consent may not be feasible in cluster randomised trials for several reasons. Firstly, it may be logistically difficult to obtain their consent either because they are not easily identifiable or contactable, or because of resource constraints, particularly in studies randomising large clusters. Secondly, some cluster-level interventions may be unavoidable, making it impossible for potential subjects to refuse the study intervention in a meaningful way. Thirdly, there may be scientific reasons, for example, investigators may be concerned that information provided to potential subjects during the informed consent process will lead to response bias.

The burden of demonstrating the lack of feasibility of obtaining informed consent falls to the researcher. The researcher must adequately justify to the research ethics committee claims that obtaining informed consent is infeasible and that study participation poses only minimal risk.

Some researchers may be concerned that information provided to potential subjects during the consent process will lead to response bias that would undermine a study's validity. For example, by informing physicians that a particular evidence-based guideline is being studied, physicians may alter their behaviour in response to this and if such effects are unbalanced across the study arms, this may bias the estimate of the intervention effect. In such cases, rather than a waiver of consent, the researcher and research ethics committee should consider whether an *alteration* of the consent process (such as incomplete disclosure of the details of study interventions), or adopting design features such as an incomplete block design [31] might adequately address concerns about study validity while still adequately protecting subject's interests. Researchers should be aware that different consent procedures in the intervention and control arms of the trial may lead to selection bias.

If obtaining informed consent is feasible for some but not all procedures (i.e., study intervention or data collection procedures), then researchers should obtain separate informed consent, where possible, for each procedure. For instance, in a cluster randomised trial involving a cluster-level public health intervention for which a waiver of consent for the study intervention has been obtained, informed consent for data collection procedures may nonetheless be required.

In cases in which a waiver of consent has been granted, researchers and research ethics committees may consider providing subjects with the minimum amount of information about the study that is feasible. For example, even though it may not be feasible to seek consent from each potential subject, it may be feasible to publicly disseminate information about the study. This might occur, for example, via distribution of leaflets, placing posters in locations such as schools or physician's offices, or public health bulletins. However, this is not a separate requirement for a waiver of consent. Rather, it is an additional step that researchers and research ethics committees may pursue to respect subjects' autonomy rights.

Recommendation 7: Researchers must obtain informed consent from professionals or other service providers who are research subjects unless conditions for a waiver or alteration of consent are met.

Many cluster randomised trials intervene on professionals or other service providers (e.g., physicians, midwives, teachers) in order to produce an effect on cluster members (e.g., patients, students). These professionals or service providers are research subjects and entitled to ethical protections. This includes the requirement for researchers to obtain their informed consent.

It has been argued that health professionals have an obligation to participate in research that may improve patient care [32]. This *prima facie* moral obligation may indeed provide health professionals with a reason to agree to study participation when approached for informed consent. It does not, however, obviate the need to obtain their informed consent in specific cluster randomised trials when they are research subjects. Consent discussions with these subjects should include career-related risks, including risks due to detection of negligence or incompetence. Data about professional or provider performance should be kept confidential within the research team, unless circumstances arise which mandate disclosure to a professional certifying or licensing body.

Conditions for a waiver or alteration of consent may be met in a variety of circumstances involving professionals in cluster randomised trials. These circumstances include: when the number of professionals allocated to study interventions makes obtaining their informed consent infeasible — either logistically or in terms of the resources required; when cluster-level interventions mean that the professional cannot meaningfully refuse the study intervention (as when study interventions are delivered to entire health care teams as a unit); or, when incomplete uptake of the study intervention or information provided to potential research subjects during the informed consent process would threaten the validity of the study. As with any waiver or alteration of consent requirements (see recommendation 6), the researcher must adequately justify to the research ethics committee claims that obtaining informed consent is infeasible and that the study interventions and data collection procedures pose no more than minimal risk.

Gatekeepers

Gatekeepers are individuals who may be called upon to protect the group-based interests that are affected by enrolment in a cluster randomised trial. In some cluster randomised trials, researchers cannot feasibly obtain individual informed consent due to large cluster sizes, study interventions administered at the cluster level, or the randomisation of clusters before recruitment of individual subjects. In these situations, researchers have historically turned to gatekeepers to perform a variety of roles. These roles include providing proxy consent on behalf of individual cluster members, and giving permission to enrol clusters in trials.

Study interventions in some cluster randomised trials may affect social, communal or other group interests. For instance, the findings of a cluster randomised trial involving a particular community may lead to or perpetuate the stigmatisation of its members. Consequently, gatekeepers have also been used to protect group or cluster level interests, by facilitating consultation with the cluster or declining permission to enrol the cluster when study participation is contrary to its interests.

Recommendation 8: Gatekeepers should not provide proxy consent on behalf of individuals in cluster randomised trials.

In some cluster randomised trials, gatekeepers have served as proxy decision makers on behalf of individual cluster members. However, legitimate proxy consent requires that the proxy decision maker be well acquainted with the potential research subject's values and beliefs, making the proxy decision maker well situated to make decisions consistent with the potential subject's wishes or interests. Further, proxy decision making is typically employed when the potential subject is incapable of making the decision for him- or herself. In cluster randomised trials, neither of these conditions are met, and so gatekeepers are not in a position to provide legitimate proxy consent on behalf of individual cluster members.

Recommendation 9: When a cluster randomised trial may substantially affect cluster or organisational interests, and a gatekeeper possesses the legitimate authority to make decisions on its behalf, the researcher should obtain the gatekeeper's permission to enrol the cluster or organisation in the trial. Such permission does not replace the need for the informed consent of research subjects, when it is required.

Gatekeepers may play an important role in the protection of cluster interests. When a cluster randomised trial may have a substantial effect on a cluster or organisation, the permission of a gatekeeper is one means of protecting the interests of the cluster or organisation.

Gatekeepers may provide or withhold permission to enrol a cluster only when they have legitimate authority to do so. The legitimacy of gatekeepers' authority depends on the extent to which the following conditions are met: (1) their role within the cluster or organisation endows them with the authority to make decisions on behalf of the cluster, e.g., they hold a political office or an administrative position within an organisation that

clearly gives them the relevant decision making authority; and (2) cluster members recognise the gatekeeper's authority. To the extent that cluster members do not clearly accept the gatekeeper's authority to make the particular decision about enrolment, the legitimacy of that authority is questionable. Although a gatekeeper may legitimately give permission for cluster participation, gatekeeper permission is not a substitute for the informed consent of individual research subjects in a cluster randomised trial.

Researchers and research ethics committees should strive to identify situations in which the interests of different stakeholders within a cluster randomised trial may conflict. For instance, the interests of an organisation (such as a health care organisation or school board) may conflict with the interests of clusters within that organisation (such as physician practices or schools), or the interests of individual cluster members (such as patients or students). While requiring permission from a gatekeeper (such as an administrative head, board of governors, or school board) may serve to protect some stakeholders' interests, that gatekeeper may not be in a position to consider the interests of all stakeholders. Researchers and research ethics committees should consider and, where possible, seek to safeguard the interests of all individuals or groups who may be affected by study interventions in a cluster randomised trial.

The decision by a gatekeeper to withdraw a cluster from an ongoing cluster randomised trial may have serious consequences for the subjects as well as the scientific validity of the study. Accordingly, researchers should do what they can to ensure that gatekeepers are unlikely to have reason to withdraw their cluster. As discussed below, consultation with clusters is an important means of facilitating partnership between researchers and clusters, and ensuring that the cluster randomised trial is broadly consistent with group interests. Where possible, cluster randomised trials should be designed to minimise the effect of cluster withdrawal on study validity.

Recommendation 10: When cluster randomised trial interventions may substantially affect cluster interests, researchers should seek to protect cluster interests through cluster consultation to inform study design, conduct and reporting. Where relevant, gatekeepers can often facilitate such a consultation.

Gatekeepers may facilitate consultation between researchers and cluster members about the goals, design, and implementation of the study, as well as consultation about the research findings before they are disseminated. These activities may help to protect and promote group interests by subjecting the study to examination and discussion with those whose interests may be affected, or some set of individuals who are familiar with those whose interests may be affected. Whether and to what extent cluster consultation needs to be undertaken will depend on the particular circumstances of the study.

Assessing benefits and harms within cluster randomised trials

Establishing what constitutes a reasonable balance of harms and benefits is at the heart of central disputes in research ethics. Component analysis provides researchers and research ethics committees with a systematic approach to the ethical analysis of study benefits and

harms (see section on general ethical principles). The distinction between therapeutic and nontherapeutic procedures may not always be clear in cluster randomised trials and, as a result, we refer to the "study intervention", "control condition" and "data collection procedures". Further, the analysis of the benefits and harms of cluster randomised trials must take into account the fact that cluster randomised trials often involve effects on groups, health systems, and society as a whole.

At the heart of clinical equipoise is uncertainty about the comparative benefits and harms of the intervention in the experimental arm versus the control arm, according to a community of experts. In individual patient randomised trials of clinical interventions, the relevant evidence relates to the balance of likely benefits and harms that might be incurred by individual research subjects. Cluster randomised trials may address questions that focus on the effectiveness of interventions solely for individual patients, to which standard clinical equipoise considerations apply; however, they may also address public health questions, health systems questions, and knowledge translation or quality improvement questions. These latter types of questions are of primary interest to a variety of stakeholders, thus, suggesting that the relevant evidence will be broader and will take account of the potential effects on these stakeholders in the justification for these trials.

For example, when researchers and research ethics committees assess the justification of a health system question, they must take into account that benefits and harms might be incurred at the individual citizen, population, and system levels. Determining whether a study is justified would depend, first, on the balance of benefits and harms across these different levels, and, second, on the perceived net balance of the benefits and harms and potential trade-offs between different benefits and harms incurred at different levels. In health systems and knowledge translation cluster randomised trials, the benefits and harms are incurred largely at the system and population levels. There may be comparatively lesser harms (if any) that pertain directly to the individual research subject in such studies.

Component analysis usefully directs the attention of researchers and research ethics committees to the justification of the study intervention, control conditions, and data collection procedures when considering the benefits and harms of a cluster randomised trial.

Recommendation 11: The researcher must ensure that the study intervention is adequately justified. The benefits and harms of the study intervention must be consistent with competent practice in the field of study relevant to the cluster randomised trial.

The ethical concept of clinical equipoise requires uncertainty about the comparative benefits of the intervention in the experimental arm versus the control arm, according to a community of experts. This means that the benefits and harms of the study intervention must be consistent with competent practice in the field of study relevant to the cluster randomised trial. In a cluster randomised trial, study interventions may offer benefits to individual subjects, or they may potentially benefit the clusters, organisations, or

communities to which the research subjects belong. The risks of study interventions may be borne by a stakeholder who may not necessarily derive benefit. So, it is difficult to compare directly the risks and potential benefits of study interventions. Rather, the research ethics committee should ensure that study interventions are consistent with competent practice in the particular field of study relevant to the cluster randomised trial, such as medical practice, public health, health policy, or education. This requires the research ethics committee to appeal to evidence and the opinion of expert practitioners in the relevant field.

Random assignment of study interventions is justified if the relevant community of experts disagrees as to the preferred practice. The community of expert practitioners varies depending on the type of research question. For instance, public health clinicians are the relevant community of expert practitioners for public health questions, and policy makers or analysts are the relevant expert community for health policy questions. The scope of evidence relevant to the benefit-harm analysis may be broad, for example, when outcomes such as equity or costs are key issues for the research question. In the preparation of the study protocol, researchers should undertake a detailed review of the evidence on benefits and harms of the study intervention. Further, researchers may provide evidence regarding the current or imminent disagreement in the relevant community of expert practitioners.

Recommendation 12: Researchers must adequately justify the choice of the control condition. When the control arm is usual practice or no-treatment, individuals in the control group must not be deprived of effective care or programmes to which they otherwise would have access.

The ethical concept of clinical equipoise requires uncertainty about the comparative benefits of the intervention in the experimental arm versus the control arm, according to a community of experts. When the control arm is usual practice or no-treatment, individuals in the control group must not be deprived of effective care or programmes to which they would otherwise have access. Delayed provision of the study intervention to the control group does not justify depriving them of access to effective care or programmes to which they would otherwise have access. As a minimum, the control group should be given usual care within the study context.

Researchers and research ethics committees may consider whether the control group should receive some form of augmented care. In the context of pragmatic health policy or knowledge translation cluster randomised trial that aims to inform local policy, however, augmented care in the control arm may interfere with the scientific validity of the study by increasing the chances of a false negative result, or reducing the study's generalisability. Thus, researchers and research ethics committees need to give careful consideration to the advantages and disadvantages of this approach.

If a study intervention is shown to be effective, the research ethics committee should consider whether and when the control clusters will receive the study intervention.

Recommendation 13: Researchers must ensure that data collection procedures are adequately justified. The risks associated with data collection procedures must (1) be minimised consistent with sound design and (2) stand in reasonable relation to the knowledge to be gained.

Data collection procedures, including interviews, surveys, additional physical examinations, review of the medical record, or the collection of economic information, are unlikely to benefit individuals or clusters directly. Rather, data collection procedures may benefit society in terms of new knowledge gained from the study. Researchers must, therefore, minimise the risks associated with data collection procedures consistent with sound design, and ensure that these risks stand in reasonable relation to the knowledge to be gained.

Protecting vulnerable subjects

Vulnerable research subjects fall into one or more of four broad categories: (1) children; (2) incapable adults; (3) people at undue risk of harm as a result of study participation; (4) people in subordinate positions within social or organisational structures. Cluster randomised trials may legitimately include vulnerable subjects, provided that adequate protections for them are in place. Standard protections for vulnerable groups are discussed in the section on general ethical principles, and are outlined in various national and international ethics guidelines.

Including vulnerable subjects in cluster randomised trials poses the special challenge that their presence within clusters may be hidden, and thus, investigators may fail to employ the required standard protections. The presence of vulnerable subjects may go unnoticed for two reasons: first, clusters may contain within them some individuals who are generally considered to be vulnerable subjects, but who are not considered separately because many other members of the cluster are not vulnerable; and secondly, there may be individuals in a cluster who are not normally thought of as vulnerable, but who become vulnerable by virtue of their cluster membership.

Recommendation 14: Study clusters may contain within them a proportion of vulnerable subjects. Researchers and research ethics committees should consider whether additional protections are needed.

Researchers and research ethics committees should be mindful of the possibility that clusters may contain a mix of vulnerable and non-vulnerable subjects. Where applicable, research ethics committees should ensure that proposed consent procedures are appropriate for vulnerable subjects within the cluster, and that study benefits and harms to such individuals are acceptable. For instance, a cluster randomised trial studying programmes for community treatment of mental illness may affect people living in group homes for the mentally ill. For this vulnerable sub-group, the research ethics committee will wish to ensure that consent procedures, including capacity assessment and the appropriate use of substitute decision makers, is appropriate and it may consult with an independent advocate or committee representing group home clients to ensure that people

living in group homes are not unduly burdened by changes in access to community services.

In some cases, the study intervention may run the risk of exacerbating pre-existing inequalities within clusters [33]. Where applicable, the research ethics committee should take this potential adverse outcome into account in the assessment of study benefits and harms.

The presence of vulnerable subjects within a cluster does not preclude the use of a waiver of consent for all human research subjects in the cluster.

Recommendation 15: Where individual informed consent is required, and there are individuals who may be less able to choose freely because of their position in a cluster or organisational hierarchy, research ethics committees should pay special attention to recruitment, privacy, and consent procedures for those participants.

Some cluster randomised trials are conducted in the setting of clusters or organisations in which some members may be less able to express a free choice about cluster randomised trial participation because of their position within the hierarchy. Examples may include physicians in primary care practices, healthcare workers in hospitals, and employees within organisations. When investigators are recruiting or obtaining consent from these individuals, they should conduct informed consent negotiations in such a way as to limit the potential for coercive influence from cluster or organisational leaders. For instance, consent negotiations should be conducted without the presence of cluster or organisational leaders, and cluster or organisational leaders should not be informed of the identities of those who agree to or decline study participation.

Vulnerability of this type does not preclude the appropriate use of a waiver of consent.

Conclusion

Use of cluster randomised trials is expanding in terms of frequency, geography and range of content areas. The literature around cluster randomised trials is also expanding to address the logistical, methodological and ethical challenges they present. Because of the dynamic nature of this area, we see the ethical principles outlined here as a starting point from which additional work can follow. Such work might include elucidating the special challenges involved in the conduct of cluster randomised trials in low and middle income countries, in the social sciences, and in law enforcement. Another important area for development is the coordination of these ethical principles in the context of other regulations and regulatory agencies. Given the rapidly expanding nature of the field, we would expect that significant revisions and additions to this document may well be needed over the next five years.

Glossary

Beneficence: The ethical principle identifying the moral obligation not to harm needlessly, and when possible, to promote the welfare of research subjects. In the context of clinical research, beneficence gives rise to the moral obligation to provide research subjects with a reasonable balance of harms and benefits.

Cluster Randomised Trial: A study design that randomises to different study arms groups or clusters of individuals (such as households, primary care practices, hospital wards, classrooms, neighbourhoods or communities), rather than independent individuals. Another distinguishing feature of cluster randomised trials is that the units of randomisation, intervention, observation and analysis may be different within a single study. Cluster randomised trials may also be referred to as group randomised, place randomised, or community intervention trials.

Clinical Equipoise: The state of honest, professional disagreement among the community of experts about the preferred policy or practice for a particular problem

Cluster: A group of individuals who share common interests or are associated institutionally, socially, geographically, or in time. Examples of clusters include households, medical practices, hospital wards, schools, neighbourhoods and communities.

Cluster Member: Any individual that belongs to a cluster, regardless of status as a research subject or role in the cluster randomised trial.

Component Analysis: A systematic approach to the ethical analysis of benefits and harms in research according to which therapeutic procedures and nontherapeutic procedures are evaluated separately. Therapeutic procedures must fulfill the requirement of clinical equipoise. The risks of nontherapeutic procedures must be minimised consistent with sound scientific design and stand in reasonable relation to the knowledge to be gained from the study.

Control: That to which a study intervention is being compared, including usual care or no intervention. Some cluster randomised trials may compare two interventions in a head-to-head comparison; in such cases there may be no control.

Data Collection Procedures: Means within the study used to collect information to answer the scientific question at hand. Examples of data collection procedures include interviews, surveys, additional physical examinations, or the collection of information from medical records.

Evidence-based Practice: The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients, health or education policy, or service delivery.

Gatekeeper: Gatekeepers are individuals or bodies that have legitimate authority to protect the interests of clusters, organisations, or communities that are the setting for cluster randomised trials. Gatekeepers may protect group interests in a cluster randomised trial by facilitating cluster consultation or by providing permission for the group to be enrolled in the study. However, permission from a gatekeeper to conduct a cluster randomised trial that involves a particular group is not a substitute for individual informed consent.

The Expert Panel (see Appendix 1) discussed use of the term "gatekeeper", and such variants as "guardian" and "cluster representation mechanism". However, the Panel concluded that the term "guardian", which implies a formal status relationship, as exists between a parent and child or guardian and incapable adult, does not apply to cluster heads. The term "cluster representation mechanism" meanwhile is problematic because "representation" may imply a relationship that confers greater and broader decisional authority than is appropriate.

Interests: The goods that an individual or group would ordinarily seek to protect, including health, welfare, economic, legal, and privacy.

Justice: The ethical obligation to distribute the benefits and burdens of research fairly. Justice gives rise to the need to protect vulnerable subjects in research, and to compensate research subjects who are harmed as a result of research participation.

Legitimate Authority: Refers to the power vested in an individual or body whose role within the cluster or organisation endows them with the capacity to make decisions on behalf of the group. Only gatekeepers with legitimate authority may provide permission to enrol a cluster in a cluster randomised trial. To the extent that cluster members do not recognise the gatekeeper's authority, the legitimacy of that authority is questionable.

Minimal Risk: Minimal risk refers to the risks of daily life, and includes the risks associated with routine physical examinations or psychological testing. Examples of study interventions and data collection procedures that pose only minimal risk are enumerated in the research literature and ethics guidelines.

Moral Status: An individual or group with moral status is recognised as having interests that need to be taken into consideration and that determine whether or not they require protections. The moral status of communities, for example, is a matter of debate, in that opinions differ about whether and to what degree the interests of communities require ethical protections.

Private Information: Personal information that has been collected with reasonable expectation of privacy. Personal information includes any factual or subjective

information, recorded or not, about an identifiable individual. This includes information in any form, such as age, name, ID number, income, ethnic origin, or blood type; opinions, evaluations, comments, social status, or disciplinary actions; employee files, credit records, medical records (Office of the Privacy Commissioner of Canada).

Research Subject: For the purposes of determining ethical protections, any individual whose interests may be affected as a result of study interventions or data collection procedures, that is, an individual (1) who is the recipient of an experimental (or control) intervention; or (2) who is the direct target of an experimental (or control) manipulation of his/her environment; or (3) with whom an investigator interacts for the purpose of collecting data about that individual; or (4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual.

The Expert Panel discussed use of the term "research subject". In other contexts, this term has been abandoned in favour of "research participant", in order to emphasise the voluntary nature of the role. Compared to more common research designs, however, cluster randomised trials may require relatively little participation — in many cluster randomised trials of cluster level interventions, subjects have no active role to play (for instance, when there is a cluster level intervention and a waiver of consent). Given the potential ambiguity in the context of cluster randomised trials, the Panel opted not to use the term "participant" and retained the term "research subject".

Beyond this, there is some confusion in the literature about the origin and meaning of the term "subject". Many take the term as having the connotation of a person who is subject to some authority (as in a royal subject) or one who is subjected to some form of treatment. Our understanding of the origin of the term "research subject" is different. There is a crucial distinction in Kantian moral theory between an object and a subject [14]. An object is a thing that may rightly be treated as a mere means to an end. Rational agents may not be treated this way. Our respect for their capacity to make their own choices and plans (i.e., their autonomy) is the source of a moral duty to seek their informed consent to involve them in our projects. Thus, a research subject is the *moral opposite* of a research object, and the term denotes *a person whose autonomy must be respected* in the conduct of research.

Respect for Persons: The ethical principle requiring that researchers take seriously the choices of autonomous people, that is, people who can responsibly make their own decisions, and protect those who are incapable of making their own choices. This principle is the source of the moral rules of informed consent and confidentiality.

Respect for Communities: The ethical principle that investigators have an obligation to respect communal values, protect and empower communities, and, where applicable, abide by the decisions of legitimate communal authorities.

Study Intervention: A medical treatment, policy change, educational intervention, or complex intervention that is being evaluated in a cluster randomised trial.

Vulnerability: The condition of diminished ability to protect one's own interests in decisions about research participation, which may allow for exploitation by others. Vulnerable populations may include children, incapable adults, people at undue risk of harm as a result of study participation, or people in subordinate positions within social or organisational structures (e.g. prisoners, military personnel). Cluster randomised trials may also include (1) vulnerable individuals within apparently less vulnerable groups, or (2) individuals who are not normally thought of as vulnerable but become vulnerable because of their cluster membership.

Appendix 1. Members of Expert Panel and Research Team

Expert Panel

Martin Eccles MD, FMedSci, FRCP, FRCGP, FFPHM
Trialist, Journal Editor, Research Team Member, Writing Group, Panel Chair
Professor of Primary Care Research and of Clinical Effectiveness, Newcastle University, Newcastle upon Tyne, UK

Jeremy Grimshaw MBChB, PhD, FRCGP
Trialist, Journal Editor, Co-principal Investigator, Writing Group
Senior Scientist, Ottawa Hospital Research Institute; Professor of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Charles Weijer MD PhD
Ethicist, Co-principal Investigator, Writing Group
Professor and Director, Rotman Institute of Philosophy, Western University, London, Ontario, Canada

Fernando Althabe MD MSc
Trialist
Director, Department of Mother and Child Health Research, Institute for Clinical Effectiveness and Health Policy; Professor of Public Health, School of Public Health, University of Buenos Aires Medical School, Buenos Aires, Argentina

Allan Donner PhD FRSC
Biostatistician, Research Team Member
Professor of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

Geneviève Dubois-Flynn PhD
Research Funder
Manager and Senior Advisor of the Canadian Institutes for Health Research Ethics Office, Ottawa, Canada

Sarah Edwards PhD
Bioethicist
Senior Lecturer in Research Ethics and Governance; Centre for Philosophy, Justice and Health, University College London, UK

Diana Elbourne PhD
Biostatistician, Trialist
Professor of Healthcare Evaluation, London School of Hygiene and Tropical Medicine,

David Forster JD, MA, CIP
Research Ethics Perspective
Chief Compliance Officer, Office of Compliance, Western IRB, Olympia, Washington, USA

Melody Lin PhD
Regulator
Deputy Director, Office for Human Research Protections and Director, International Activities, Office for Human Research Protections, Department of Health & Human Services, Rockville, Maryland, USA

Elizabeth Loder MD MPH
Journal Editor
Clinical Epidemiology Editor, BMJ and Associate Professor of Neurology, Harvard Medical School, Boston, Massachusetts, USA

Eileen S. Naughton JD
Policy Maker
Rhode Island Representative, National Institutes of Health Council of Public Representatives, Providence, Rhode Island, USA

Rex J. Polson MD, FRCP
Research Ethics Chair
Chair of West Midlands – Solihull Research Ethics Committee, and Consultant Physician, Solihull Hospital, Heart of England NHS Foundation Trust, UK

Raphael Saginur MD
Research Ethics Chair, Research Team Member
Chief of Infectious Diseases, Ottawa **Abha Saxena** MD
Scientist
Executive Sectretary, Research Ethics Review Committee, World Health Organization, Geneva, Switzerland

Julie Spence MD
Research Ethics Chair
Past Chair, Research Ethics Board, Department of Emergency Medicine, St. Michael's Hospital, Assistant Professor, University of Toronto, Toronto, Ontario, Canada

Gerald White BComm
Policy Perspective
Former Assistant Deputy Minister of Health in Newfoundland and Labrador, Member of

London, UK

Sandra Eldridge PhD
Biostatistician, Trialist
Professor of Biostatistics, Barts and The London School of Medicine and Dentistry, London, UK

Health Council of Canada, Canada

Merrick Zwarenstein MD, PhD
Trialist, Research Team Member
Senior Scientist, Institute for Clinical Evaluative Studies, Toronto, Ontario, Canada

Expert discussants

Catarina Kiefe PhD MD
Trialist, Journal Editor
Professor and Chair, Dept of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts USA

Jonathan Kimmelman PhD
Ethicist
Associate Professor, Biomedical Ethics Unit, McGill University, Montreal, Quebec, Canada

Kathleen Lohr PhD
Distinguished Fellow (Health Services Research)
RTI International, Research Triangle Park, North Carolina, USA

Research team – not in Expert Panel

Monica Taljaard PhD
Biostatistician, Co-principal Investigator, Writing Group
Scientist, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

Ariella Binik PhD student
Research Team Member
Rotman Institute of Philosophy, Western University, London, Ontario, Canada

Judith Belle Brown MSW PhD
Research Team Member
Professor, Department of Family Medicine, Western University, London, Ontario, Canada

Robert Boruch PhD
Research Team Member
Professor of Education and Statistics, Co-Director, Center for Research and Evaluation in Social Policy, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Jamie Brehaut PhD
Research Team Member, Writing Group
Scientist, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

Antonio Gallo BSc
Research Team Member
Rotman Institute of Philosophy and Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

Andrew McRae MD PhD FRCP
Research Team Member, Writing Group
Research Director, Division of Emergency Medicine, University of Calgary, Calgary, Alberta, Canada

Shazia Chaudhry MSc
Research Team Member
PhD candidate, Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada

Angela White PhD
Research Team Member, Writing Group
Rotman Institute of Philosophy Postdoctoral Fellow in Bioethics, Western University, London, Ontario, Canada

1
2

References

[1] The COMMIT Group: Community intervention trial for smoking cessation (COMMIT): I. Cohort results from a four-year community intervention. *Am J Public Health* 1995, 85:183–92.

[2] Lewin S, Dick J, Zwarenstein M, Lombard CJ: Staff training and ambulatory tuberculosis treatment outcomes: a cluster randomized controlled trial in South Africa. *Bull World Health Organ* 2005, 83(4):250–9.

[3] Kennedy A, Robinson A, Hann M, Thompson D, Wilkin D: A cluster-randomised controlled trial of a patient-centred guidebook for patients with ulcerative colitis: effect on knowledge, anxiety, and quality of life. *Health Soc Care Community* 2003, 11:64–72.

[4] Weijer C, Grimshaw JM, Taljaard M, Binik A, Boruch R, Brehaut JC, Donner A, Eccles MP, Gallo A, McRae AD, Saginur R, Zwarenstein M: Ethical issues posed by cluster randomized trials in health research. *Trials* 2011, 12:100.

[5] Edwards SJL, Braunholtz DA, Lilford RJ, Stevens AJ: Ethical issues in the design and conduct of cluster randomised controlled trials. *Br Med J* 1999, 318(7195):1407–9.

[6] Hutton JL: Are distinctive ethical principles required for cluster randomized controlled trials? *Stat Med* 2001, 20(3):473–88

[7] Eldridge SM, Ashby D, Feder GS: Informed patient consent to participation in cluster randomized trials: an empirical exploration of trials in primary care. *Clin Trials* 2005, 2:91–8.

[8] Klar N, Donner A: Ethical challenges posed by cluster randomization. *Wiley Encyclopedia of Clinical Trials* 2007: 1–5.

[9] Mann H, Reyes M: Identifying the human research subject in cluster randomized controlled trials. *IRB* 2008, 30(5):14–8.

[10] Taljaard M, Weijer C, Grimshaw J, Belle Brown J, Binik A, Boruch R, Brehaut JC, Chaudhry S, Eccles MP, McRae A, Saginur R, Zwarenstein M, Donner A: Study protocol: Ethical and policy issues in cluster randomized trials: rationale and design of a mixed methods research study. *Trials* 2009, 10:61.

[11] Taljaard M, McRae A, Weijer C, Bennett C, Dixon S, Taleban J, Skea Z, Brehaut J, Eccles MP, Donner A, Saginur R, Boruch RF, Grimshaw JM: Inadequate reporting of research ethics review and informed consent in cluster randomized trials: review of a representative sample of published trials. *BMJ* 2011, 342:d2496.

[12] Binik A, Weijer C, McRae AD, Grimshaw JM, Baruch R, Brehaut JC, Donner A, Eccles MP, Saginur R, Taljaard M, Zwarenstein M: Does clinical equipoise apply to cluster randomized trials in health research? *Trials* 2011, 12:118.

[13] McRae AD, Weijer C, Binik A, White A, Grimshaw JM, Baruch R, Brehaut JC, Donner A, Eccles M, Saginur R, Zwarenstein, M Taljaard M: Who is the research subject in cluster randomized trials? *Trials* 2011, 12:183.

[14] McRae AD, Weijer C, Binik A, Grimshaw JM, Baruch R, Brehaut JC, Donner A, Eccles MP, Saginur R, White A, Taljaard M: When is informed consent required in cluster randomized trials in health research? *Trials* 2011, 12:202.

[15] Gallo A, Weijer C, White A, Grimshaw JM, Baruch R, Brehaut JC, Donner A, Eccles MP, McRae AD, Saginur R, Zwarenstein M, Taljaard M: What is the role and authority of gatekeepers in cluster randomized trials in health research? Under review.
[16] Weijer C, Miller PB: When are research risks reasonable in relation to anticipated benefits? *Nature Medicine* 2004, 10(6):570–573.
[17] Childress JF: Compensating injured research subjects: the moral argument. *Hastings Center Report* 1976, 6(6): 21–7.
[18] Weijer C, Emanuel EJ: Protecting communities in biomedical research. *Science* 2000, 289(5482):1142–4.
[19] Puffer S, Torgerson D, Watson J: Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. *BMJ* 2003, 327(7418):785–9.
[20] Hayes RJ, Bennett S: Simple sample size calculation for cluster-randomized trials. *Int J Epidemiol* 1999, 28(2):319–26.
[21] Donner A, Klar N: *Design and Analysis of Cluster Randomization Trials in Health Research*. London: Arnold, 2000.
[22] SM Kerry, JM Bland: Trials which randomize practices I: how should they be analysed? *Family Practice* 1998, 15(1):80–83.
[23] SM Kerry, JM Bland: Trials which randomize practices II: sample size. *Family Practice* 1998, 15(1):84–87
[24] Campbell MK, Mollison J, Steen N, Grimshaw JM and Eccles M: Analysis of cluster randomized trials in primary care: a practical approach. *Family Practice* 2000, 17**:**192–6.
[25] Donner A, Klar N: Statistical considerations in the design and analysis of community intervention trials. *J Clin Epidemiol* 1996, 49(4):435–9.
[26] Donner A, Klar N: Methods for comparing event rates in intervention studies when the unit of allocation is a cluster. *Am J Epidemiol* 1994, 140(3):279–89.
[27] Torgerson DJ: Contamination in trials: is cluster randomisation the answer? *BMJ* 2001, 322:355–7.
[28] Hahn S, Puffer S, Torgerson DJ, Watson J: Methodological bias in cluster randomised trials. *BMC Medical Research Methodology* 2005, 5:10.
[29] Kopelman LM: Minimal risk as an international ethical standard in research. *Journal of Medicine and Philosophy* 2004, 29(3):351–378.
[30] Ross LF: *Children in Medical Research: Access versus Protection*. New York: Oxford University Press, 2008.
[31] Eccles M, Grimshaw J, Steen N, Parkin D, Purves I, McColl E and Rousseau N: The design and analysis of a randomized controlled trial to evaluate computerized decision support in primary care: the COGENT study. *Family Practice* 2000, 17:180–6.
[32] Ives J, Draper H, Damery S, Wilson S: Do family doctors have an obligation to facilitate research? *Fam Pract* 2009, 26(6):543–8.
[33] Conrad E, Edwards SJL: Inequalities and fairness in cluster trials. *Research Ethics* 2011, 7(2):58–65.