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

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Abstract

This article is part of a series of papers examining ethical issues in cluster randomized trials (CRTs) in health research. In the introductory paper in this series, we set out six areas of inquiry that must be addressed if the cluster trial is to be set on a firm ethical foundation. This paper addresses the sixth of the questions posed, namely, what is the role and authority of gatekeepers in cluster randomized trials in health research? Gatekeepers (also called guardians or cluster representation mechanisms) are unique to CRTs and are individuals or bodies that represent the interests of cluster members, clusters, or organizations. The need for gatekeepers arose in response to the difficulties in obtaining informed consent due to cluster randomization, cluster level interventions, and cluster size. In this paper, we argue for a more restrictive understanding of the role and authority of gatekeepers.

Previous papers in this series have provided solutions to informed consent in CRTs without the need to invoke gatekeepers. We argued that consent to randomization is not required when cluster members are approached for consent at the earliest opportunity and before any study interventions or data collection procedures. Further, when cluster level interventions or cluster size means that obtaining informed consent is not possible, a waiver of consent may be appropriate. In this paper, we argue that the role of gatekeepers in protecting individual interests in CRTs is limited. Generally, gatekeepers do not have the authority to provides proxy consent for cluster members. When a municipality or other community has a legitimate political authority empowered to make such decisions, cluster consent may be appropriate. However, gatekeepers may usefully protect cluster interests in other ways. Cluster consultation may ensure that the CRT addresses local health needs and is conducted in accord with local values and customs. Gatekeepers play an important role in the protection of the interests of organizations, such as

hospitals, nursing homes, general practices, and schools. In these settings, permission to access the organization turns on resource implications and adherence to institutional policies.

Introduction

This article is part of a series of papers examining ethical issues in cluster randomized trials (CRTs) in health research. CRTs are used increasingly in knowledge translation research, quality improvement research, community-based intervention studies, public health research, and research in developing countries. While a small and growing literature explores ethical aspects of CRTs, cluster trials raise difficult issues that have not been addressed adequately. In the introductory paper in this series, we set out six areas of inquiry that must be addressed if the cluster trial is to be set on a firm ethical foundation [1]. These include identifying research subjects, obtaining informed consent, applying clinical equipoise, benefit-harm analysis, the protection of vulnerable populations, and the role and authority of gatekeepers in CRTs. This paper addresses the sixth of the questions posed, namely, what is the role and authority of gatekeepers in cluster randomized trials in health research?

Gatekeepers, sometimes referred to as guardians or cluster representation mechanisms, are unique to CRTs [2,3]. Gatekeepers may be called upon to protect the interests of individual study participants, clusters, or organizations that are the setting for cluster trials. The use of gatekeepers stems primarily from the difficulty of obtaining informed consent from study participants [2,4]. Previous articles in this series have argued for a more restrictive view of who counts as a research subject, and from whom and when informed consent must be obtained in a CRT [5,6]. This effectively diminishes the number of cases in which it may be necessary to use gatekeepers.

In this article we proceed in a number of steps. First, we outline the development of the use of gatekeepers in the CRT literature. Second, we document the wide variety of roles served by gatekeepers in the protection of individual, cluster, and organizational interests in CRTs.

Third, we provide a detailed ethical analysis of the authority of gatekeepers to fulfill these roles legitimately. Fourth, and finally, we consider the application of our findings using three examples.

Development of gatekeepers in CRTs

In their discussion of CRTs, Edwards and colleagues usefully distinguish between two types of CRTs: individual-cluster and cluster-cluster trials [2]. In individual-cluster trials, interventions are administered to research subjects on an individual basis, although subjects are assigned to each arm of the trial as part of a cluster. For example, research subjects may receive a novel treatment, provide blood samples, or fill out a questionnaire. Cluster-cluster trials, on the other hand, involve interventions directed at groups of study participants, e.g., educational campaigns using media such as billboards or televised information, treatment of water supplies, and pesticide use. Both individual-cluster and cluster-cluster trials may involve difficulties in obtaining informed consent, but greater difficulties are associated with cluster-cluster trials.

As Edwards and colleagues argue, "if the individuals within clusters are given treatments, they can in theory consent individually to the treatment(s) offered within their cluster" [2]. In individual-cluster trials, research subjects must interact directly with researchers on an individual basis at some point in order for the treatments to be administered. This implies that, in general, it will be possible to interact directly with the research subject for the purposes of obtaining informed consent as well.

Nonetheless, aspects of individual-cluster trials may interfere with the ability of researchers to obtain informed consent to all aspects of the CRT [7]. Clusters are often randomized to an arm of the study before it is possible to approach cluster members for informed

consent. In these cases, even when it is possible to obtain informed consent to other aspects of the study, obtaining consent to randomization is not possible. Further, particularly when study interventions seek to produce a behaviour change, researchers may seek to withhold details of interventions in other trial arms from the informed consent process to mitigate the risk of biasing the study outcome.

In cluster-cluster trials, the use of cluster level interventions and cluster size may hamper the ability of the researcher to obtain the informed consent of study participants, with respect to both randomization and study interventions. When clusters are large, perhaps encompassing entire communities, it be impossible for researchers to obtain the consent of all cluster members. Also, when the study intervention targets the entire cluster, it may be difficult for cluster members to avoid the intervention. As a result, individuals may be unable to refuse participation in the trial, so long as they remain a member of the cluster intervened upon in the CRT [2,3].

In response to these difficulties, Edwards and colleagues introduce the idea of gatekeepers. As they maintain, "the decision about whether a particular cluster participates in the trial is taken by an agent who has the power to 'deliver' that cluster" [2]. The role of the gatekeeper differs depending on the particular features of the CRT. In individual-cluster trials, the gatekeeper may provide consent to randomization or "trial entry" of the cluster, while research subjects provide consent to study interventions and data collection procedures [2]. In cluster-cluster trials, the role of the gatekeeper may be more expansive. In these cases, according to Edwards and colleagues, the gatekeeper "must consent to or decline both trial entry and the intervention as a single package" [2]. In effect, the gatekeeper provides proxy consent for cluster members, both with respect to randomization and study interventions.

Others share the view that gatekeepers may make decisions about participation in a trial

on behalf of cluster members. For instance, Donner and Klar mention community leaders and elected and appointed officials as possible gatekeepers who may consent to randomization or study interventions on behalf of cluster members [8]. In their words, "it may be permissible in some studies that the decision regarding random assignment and implementation of an intervention comes from community leaders or decision-makers" [8]. Hutton also defines gatekeepers as "people in either political or administrative positions who are able to give consent for those within a cluster to be randomized" [4].

Hutton suggests that it would be desirable for a gatekeeper to agree to a set of duties to a cluster prior to acting as its representative. However, the gatekeeper may choose not to adopt the role of advocate and, consequently, may prevent the cluster from entering into an otherwise advantageous research partnership [4]. According to Edwards and colleagues, gatekeepers are to act as an advocate for the cluster, to advance its interests and preserve its trust [2]. Thus, whether the gatekeeper should consent to a particular trial on behalf of the cluster will depend on the particular features of the CRT, and whether participation is, on balance, in the interests of the cluster. Additionally, according to Hutton, gatekeepers may play a role in informing researchers about special considerations in the cluster, as well as in informing cluster members about the research project [4].

The views of Edwards and colleagues are also reflected in the document published by the United Kingdom Medical Research Council, *Cluster Randomized Trials: Methodological and Ethical Considerations* ("MRC Guidelines"). As the MRC Guidelines explain, "the ethical principle here is that the [gatekeeper] must act in good faith, and in this regard only in the interests of the cluster represented" [3]. Gatekeepers may give consent on behalf of a cluster, and are to do so solely on the basis of what would be in the interests of the cluster. Gatekeepers are

not to enrol the cluster if the study is contrary to its interests, and they are to remain informed advocates for the cluster throughout the trial. If the gatekeeper does enrol the cluster, it should be withdrawn only if the study no longer serves its interests [3]. The MRC Guidelines also state that gatekeepers must avoid any conflicts of interest, and disclose any unavoidable conflicts [3].

The MRC Guidelines propose several safeguards to ensure that gatekeepers make their decision about whether to enrol the cluster in a way that is analogous to individual consent. For instance, the MRC Guidelines require documentation as evidence that the gatekeeper understands the interests and values of the cluster. This would show that the gatekeeper is able to make decisions about enrolment based on what cluster members would endorse, if they had the opportunity to decide for themselves [3]. Ultimately, however, the MRC Guidelines acknowledge that the gatekeeper's permission to enter the cluster into the study is not "truly equivalent to [individual] consent" [3]. A gatekeeper's agreement may be the best that can be done to protect individuals' interests, given the constraints imposed by study design.

More recently, the role of gatekeepers as proxy decision makers has been discussed in the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Epidemiological Studies* ("CIOMS Guidelines"), which outlines a mechanism for protecting individual interests through consultation between researchers and community representatives. In the words of the CIOMS Guidelines, interactions between researchers and representatives are to be "aimed at obtaining the views of people who are in effect proxies for the potential subjects" [9]. Thus, the guidelines explicitly allow gatekeepers to act as proxies for cluster members.

Variety of roles undertaken by gatekeepers

What roles do gatekeepers undertake in CRTs? In the Table we present a convenience sample of published cluster trials to document the variety of roles undertaken by gatekeepers (see Table) [10–36]. Gatekeepers have been employed in CRTs involving athletic organizations, communities, health centres, nursing homes, schools, and workplaces. Within each type of setting, different people have served as gatekeepers. For instance, in community CRTs, government authorities, community leaders, community advisory boards, medical leaders, and index members have all acted as gatekeepers. In school-based CRTs, the gatekeeper role has been filled by local governments, school districts, and principals. The specific roles undertaken by gatekeepers have also been diverse. Here we outline eight gatekeeper roles described in the study publications.

[INSERT TABLE HERE]

1. Gatekeeper roles relevant to the protection of individual interests

Gatekeepers have undertaken a number of roles that may be understood as primarily protecting individual interests. Gatekeepers have given consent for randomization, provided proxy consent for cluster members, given permission to approach cluster members, and identified cluster members for researchers.

Consent to randomize. In trials that randomly assign clusters to their respective arms before cluster members can be identified, gatekeepers have been asked for consent to randomly assign the cluster to one of the study arms. For example, the Rapid Early Action for Coronary Treatment study investigated the effect of community interventions on patient responses to

symptoms of myocardial infarction [13]. Researchers approached community medical leaders prior to randomization and reported that “[a]ll communities accepted their randomized assignments” [13].

Proxy consent for cluster members. In trials employing a cluster level intervention for which individual consent cannot practically be obtained, gatekeepers have provided proxy informed consent on behalf of study subjects. For example, the “AS!BC” study evaluated the effectiveness of a physical activity program on reducing cardiovascular risk factors in elementary school children [32]. Principals provided permission for the participation of the school, while teachers of Grades 4 and 5 provided consent to receive the study intervention on behalf of students "regardless of whether parents provided consent for their children to be evaluated" [32]. (Data was not collected on children whose parents declined study participation on their behalf.)

Permission to approach research subjects. Gatekeepers have also played a role in determining which cluster members researchers may approach. These gatekeepers, including human resource personnel in worksite settings and physicians in health centre studies, are in positions of responsibility to ensure the well-being and privacy of prospective study subjects. For example, in a CRT studying prevention strategies in health centres, practising internists “were approached for permission to recruit from among their patient pools” [20]. Patients were identified through a central appointment system, and eligibility was determined on the basis of geographic location.

Identification of cluster members. In cases involving clusters whose members are not easily identifiable, gatekeepers have also been used to identify potential research subjects. This role differs from the above role ("permission to approach research subjects") in that the gatekeeper is not in a position of responsibility with regard to cluster members; rather, the

gatekeeper is merely a cluster member who is able to identify other group members. For example, in a study of HIV prevention amongst Roma men, researchers identified an "index" member and asked him to identify members of his social group who were then approached for study participation [15].

2. Gatekeeper roles relevant to the protection of cluster interests

Gatekeepers have undertaken a number of roles that may be understood as primarily protecting the interests of the cluster. Gatekeepers have provided consent on behalf of the cluster, been involved in cluster consultation, and provided protocol approval.

Cluster consent. This role is analogous to community consent, wherein an authority within a cluster determines whether to consent to participation in the trial on the basis of cluster interests [37]. Cluster consent is commonly provided by community leaders, including mayors or other government officials, who are presumed to have the authority to agree to study participation on behalf of the cluster. Cluster consent is independent of but a precondition for informed consent from individual study participants. For example, a CRT investigating a breastfeeding education program in India approached local health system authorities as well as community leaders to obtain permission to conduct the study [18]. Individual consent was obtained from research subjects after cluster consent had been secured.

Cluster consultation. This role is analogous to community consultation, and it may involve discussion between researchers and cluster representatives in order to solicit input on all stages of the research process from study design to publication [37]. In some cases, cluster consultation has been effected through the use of a community advisory board [38]. For example, in a CRT examining a complex intervention for cancer prevention among Hispanic Americans,

members from communities assigned to the intervention arm were recruited to form a community advisory board [14]. An important role of the board was to provide "insights as to the cultural appropriateness of different intervention activities targeted [at] both Hispanics and non-Hispanic Whites" [14]. The community advisory board did not, however, provide consent on behalf of clusters or cluster members.

Protocol approval. Protocol approval is normally the purview of research ethics committees, but it has been undertaken additionally by cluster representatives to ensure that the study is consistent with the values and goals of the cluster. For example, researchers investigating interpersonal psychotherapy for depression in rural Uganda invited local government authorities to review the research protocol after it had been approved by a research ethics committee in the sponsor country [19].

3. Gatekeeper roles relevant to the protection of organizational interests

Gatekeepers have also undertaken a role in the protection of the interests of organizations involved in cluster trials by providing permission on behalf of the organization. In CRTs involving organizations, the organization may or may not be identical to the cluster. In either case, however, it is useful to distinguish between the interests that come into play in decisions about participation.

Organizational permission. Gatekeepers have provided permission to conduct a cluster trial on behalf of organizations that are the setting for the study, including schools and work sites (Table). In providing such permission, the gatekeeper has considered the impact of the study on the organization, including availability of staff, financial implications of participation, and the likelihood that members will be willing to participate. For example, in a school-based cluster

trial evaluating a computerized intervention on dietary fat intake in adolescents, researchers approached principals for permission to include their school in the study [29]. Some principals declined study participation based on organizational interests, e.g., one principal declined citing "a lack of time" [29].

Gatekeeper authority to undertake these roles

As demonstrated in the previous section, gatekeepers in CRTs have fulfilled a variety of roles involving the protection of individual, cluster, and organizational interests. Surprisingly, perhaps, the question as to whether gatekeepers possess the authority to legitimately fulfill these roles remains unexamined. We believe the question pressing because gatekeepers make decisions that have consequences for others. Gatekeeper proxy consent for cluster members may allow a study to proceed thereby exposing people to research risks without their individual informed consent. In other cases, gatekeeper refusal to provide cluster consent or organizational permission may bar access to a potentially beneficial study intervention. Here we undertake an ethical analysis of the authority of gatekeepers to play the roles described above.

1.Gatekeeper authority to protect individual interests

Prior work by our group has significantly restricted the need for gatekeeper consent for study participation and randomization on behalf of cluster members. First, gatekeeper consent is not required when cluster members are not human research subjects. In our paper in this series addressing the identification of research subjects, we present a novel definition of a human research subject as "an individual whose interests may be compromised as a result of interventions in a research study" [5]. We argue that when people are only indirectly affected by

cluster level interventions (and they are not otherwise intervened upon or interacted with, and their private health information is not collected), they are not human research subjects and their informed consent is not required. For instance, knowledge translation studies commonly intervene on health professionals to align practitioner behavior with evidence-based treatment guidelines. In these CRTs, patients may only be affected indirectly by the study intervention and there is no risk of it adversely affecting their interests, i.e., insofar as health professionals' practice is brought more into line with treatment guidelines and standards. When patients are merely indirectly affected by the study intervention, they are not research subjects and neither their informed consent nor that of a gatekeeper is required.

Second, gatekeeper consent on behalf of cluster members is not required when a research ethics committee approves a waiver of consent. In our paper on informed consent, we consider circumstances in which it may be difficult to obtain the informed consent of cluster members due to cluster level intervention or large cluster size [6]. We argue that if study involvement poses no more than minimal risk to cluster members, a research ethics committee may reasonably approve a waiver of consent, meaning that individual informed consent is not required. When the requirement of informed consent has been waived, it is unnecessary for a gatekeeper to provide consent for cluster members.

Third, gatekeeper consent to randomize is not required so long as cluster members are approached for consent as soon as possible and before any study interventions are administered. In our paper on informed consent, we point out that the purpose of informed consent is to allow research subjects to adopt the ends of the study as their own, thereby (partially) justifying exposing subjects to risk for the benefit of others. In individual-cluster trials in which clusters are randomized before individuals can be approached for informed consent, it has commonly been

assumed that gatekeeper consent for randomization is required. We argue, on the contrary, that so long as cluster members are approached for informed consent as soon as possible, and before study or data collection interventions, the moral purpose of informed consent may be fulfilled. Under these conditions, cluster members have the opportunity to adopt the ends of the study as their own and, importantly, they may decline study participation before they are exposed to any risk for the benefit of others. Thus, in these cases, gatekeeper consent to randomize is not required.

The question remains whether gatekeepers may legitimately provide proxy consent for cluster members in studies that do not qualify for a waiver of consent or in which individuals are not approached for consent as soon as possible after randomization of the cluster, and before study or data collection interventions have begun. Generally, in the ethics of research, a proxy decision maker is called upon to provide informed consent on behalf of someone else when the prospective research subject is incapable (that is, lacks the requisite cognitive capacities) of doing so herself [9]. Next of kin usually serve as the proxy decision maker, on grounds that they are likely to know the prospective subject well and be naturally motivated to promote the subject's welfare. A proxy decision-maker is responsible for making decisions that are in accordance with the subject's prior expressed wishes and values, or that are consistent with the individual's best interests [9]. Further, proxy decision makers must strive to avoid any conflict of interest.

The circumstances in which gatekeepers might provide proxy consent in CRTs are not analogous to these cases. In contrast to conventional situations in which proxy consent is required, cluster members will often be competent individuals who are capable of freely choosing whether a study is in accordance with their interests and values. Insofar as cluster

members are competent, gatekeepers would only have the authority to provide proxy consent if cluster members had autonomously authorized them to do so (and we take it this is rarely the case). Further, gatekeepers usually neither have a close personal relationship with cluster members, nor a detailed knowledge of their individual wishes, values, or interests. So not only is gatekeeper proxy consent problematic because it violates conceptions of the importance of autonomy, but conditions for legitimate proxy decision making do not obtain either.

We conclude, therefore, that generally gatekeepers do not have the authority to provide proxy consent on behalf of individual cluster members. As a result, gatekeepers should not provide permission to randomize cluster members nor should they provide consent for individuals. Studies that do not qualify for a waiver of consent or in which individuals are not approached for consent as soon as possible, and before study or data collection interventions begin, should not proceed on the basis of proxy consent from gatekeepers.

Is there any role for gatekeepers to protect legitimately the interests of research subjects in CRTs? We believe so. In certain circumstances, the gatekeeper may legitimately provide permission to approach research subjects and this may protect individual interests in CRTs. When the gatekeeper has fiduciary obligations to individual cluster members, as in a physician-patient or teacher-student relationship, the gatekeeper may be viewed as having an obligation not to allow researchers to approach a cluster member whose interests may be unduly compromised by the approach. Thus, gatekeeper permission from physicians or teachers for researchers to approach individual patients or students is an instance of the legitimate protection of individual interests.

When the relationship between gatekeeper and cluster members is not fiduciary in nature, the gatekeeper does not have the authority to be relied upon to protect the cluster members'

interests. In these situations, the gatekeeper may identify potential research subjects, but not grant permission to approach individuals. The gatekeeper acting in this role should not be relied upon to protect subjects' interests. For instance, consider the role of the index member in the above mentioned study of HIV prevention amongst Roma men. Identification of cluster members may be an important role pragmatically in the conduct of the study, but researchers and research ethics committees should be clear that it does not involve the protection of individual interests.

2. Gatekeeper authority to protect cluster interests

The wide variety of groups studied in CRTs presents a challenge to those trying to determine who has the authority to represent and protect the interests of a cluster. CRTs may involve a variety of clusters, with varying degrees of cohesiveness; clusters may be geographical, political, occupational, religious, or disease-related (see Table). Such clusters may have collective interests that extend beyond and may conflict with the interests of individuals within the group. For example, studies investigating the genetic determinants of breast cancer in Ashkenazi Jews may protect the identity of individual research subjects, yet the community at large may have good reason to fear discrimination on the basis of (perceived) disease susceptibility [37].

Many — indeed, most — clusters participating in research will not have organized structures or legitimate authorities capable of speaking on their behalf. Where organized structures or legitimate authorities exist, these structures may not have been established with the intention of making decisions about research participation [2]. Further, as Hutton points out, a representative may refuse to adopt the functions of a gatekeeper for a cluster [4]. These situations raise the question, “to whom should responsibility for the decision to enter the cluster be passed”

[4]?

The debate in the community-based research literature over a representative's authority to provide community consent may provide some insight into a gatekeeper's authority with respect to clusters. As discussed in the introductory paper in the series, recognition of community-based interests and communities' moral status led to the formulation of the principle of respect for communities [1]. According to Weijer and Emanuel, community consent is appropriate if "the community has a legitimate political authority, which could be a legislative assembly, mayor, or tribal council, that has the authority to make binding decisions on behalf of its members" [37]. The principle of respect for communities relies on identification of community or group characteristics to help determine when community consent is required and when consultation alone is appropriate. Importantly, community consent is not a substitute for individual informed consent.

In the context of a CRT, a gatekeeper may give consent for the cluster to participate in the study if that person has legitimate authority with respect to the individuals involved, and if that authority extends to the decision at hand. Whether the gatekeeper's authority is legitimate depends on whether, amongst the individuals who are significantly affected by the gatekeeper's decisions, there is widespread satisfaction with the gatekeeper's ability to make such decisions. A variety of mechanisms may be used to ensure that the gatekeeper's authority is legitimate, or, in other words, to ensure that the people who are affected by the gatekeeper's decisions are sufficiently satisfied to maintain that authority. However, for the many CRTs that target non-community clusters without organized political structures in place, there is unlikely to be a gatekeeper with the authority to provide consent on behalf of the cluster.

Consider the example of a community-based CRT investigating a breastfeeding education

program in India that sought consent from community leaders and health system authorities to include their communities in the study [18]. Whether those who acted as gatekeepers in this trial had the authority to provide cluster consent depends on two conditions: whether members of the community understood gatekeepers' roles as including the authority to make these decisions, and whether they were largely satisfied with the institutions involved, i.e., the political system used to select community leaders, and the local health system. Individual satisfaction with these institutions will be based not only on past decisions that have been made by the institutions involved, but also on the decisions at hand.

If it is unclear whether an authority figure's responsibilities include decisions about participation in CRTs, one ought to determine what action would likely be conducive to the satisfaction of the people affected by the decision with the institutions involved. It has been reported that the views of community leaders are generally poor substitutes for the views of individual community members [39]. This suggests that any ambiguity about whether a political official's role includes making a decision about participation in a particular CRT may be reason for consultation with cluster members. Cluster consultation is called for because it increases the likelihood that citizens will be more satisfied with the institutions involved, and the continued legitimacy of the institutions involved depends on the satisfaction of the people they purport to represent.

Although the ethical principle of respect for communities has been well received in the community-based research literature, the principle is not substantially applicable to all cluster trials. For CRTs involving well-defined communities, the protections required by the principle of respect for communities may be applied directly. Yet these mechanisms for community protection do not apply to clusters that are not a cohesive group with a common culture, history,

or interests.

In clusters that lack a legitimate political authority, requiring cluster consent is not appropriate, but cluster consultation may still usefully and legitimately protect cluster interests. Cluster consultation involves a partnership between researchers and community members, from research design to publication [40]. The degree to which a cluster can participate will depend on community characteristics and cohesiveness [37]. Cluster consultation may be sought when cluster consent is not appropriate but when the cluster has a common history, common culture, and other characteristics that provide cohesiveness to the group. In these cases there are a variety of aspects of the research endeavor in which cluster representatives may take part: consultation over protocol development; involvement in the conduct of research; dissemination of information; and publication of results [37].

The gatekeeper function of protocol approval relates to the practice of cluster consultation, insofar as cluster members are meant to participate in all stages of the research process, including providing feedback on protocol development. The partnership model requires cluster feedback to ensure the cultural appropriateness of the study in question. To this end, research ethics committees, whose mandate is to review study design and protocols, count community representatives among their members. Further consultation and approval of the study protocol may be especially appropriate when the research ethics committee is not representative of the community in which research is taking place.

3. Gatekeeper authority to protect organizational interests

Another important role of gatekeepers is the protection of organizational interests. Gatekeepers may protect or promote organizational interests by providing permission in the

name of an entire organization, such as a school or hospital, to participate in a study. A gatekeeper's agreement to allow an organization to participate in a CRTs may provide opportunities for individuals within that organization to participate in and benefit from research. On the other hand, a gatekeeper's refusal of permission may mean that individuals within the organization may be denied participation in potentially beneficial research. Thus, the interests of organizations may conflict with the interests of individuals within those organizations. An organization's administrators and managers will be guided by their legal and professional responsibilities to act in ways that promote the safety and privacy of their members, and promote the proper functioning of the organization itself.

Although it may be useful to conceive of these two sets of obligations as distinct, it should be noted that they are not entirely independent of one another. Insofar as being part of the organization serves the interests of its members, presumably serving the interests of the organization also goes some way towards serving the interests of its members. Gatekeepers acting on behalf of organizations may legitimately make the decision about whether the organization will participate in a CRT, insofar as they are well situated to judge organizational interest. This may, in fact, simultaneously serve the interests of those within the organization. However, while an organizational gatekeeper may decide to allow researchers to have access to individual employees, such permission is not a substitute for individual informed consent, since members may also have interests independent of the organization to consider in their decision.

Practical implications

In this section we illustrate the practical implications of our ethical analysis by considering three examples involving CRTs conducted in school-based, community, and

healthcare settings.

Example 1: Improving the recognition of depression in adolescence. The recognition of depression in adolescence is critical to providing mentally ill youth with early access to treatment. This school-based CRT evaluated an intervention aimed at improving the ability of teachers to identify students with depression [31]. The main outcome measure was the ability of teachers to identify depressed students who were independently diagnosed by psychological testing. In the study, 151 teachers in 8 schools in central Scotland were randomized to intervention and control arms. All teachers were given class lists of students and asked to identify students they believed to be depressed. One week later all participated in an educational workshop on the identification of depression. On the day of the workshop, all teachers were again given class lists of students and asked to identify depressed students; teachers in the control arm completed the task before the educational session, and those in the intervention arm completed it after the session. In the same time period, 1,911 students aged 12 to 15 were assessed for depression by a standard questionnaire for depressive symptoms. Those with high scores underwent a structured clinical interview to diagnose depression. Letters of information were sent to all parents and they were given the opportunity to opt their child out of the CRT. Students not removed by their parents then attended an information session, and were invited to provide written, informed consent to study participation. Without any training, about half of the students who were depressed were identified by at least one of their teachers; the study intervention did not improve the identification of depressed students. Who are the gatekeepers in this study? Teachers? Principals? Whose interests do they protect? Do they have the authority to fulfill these roles?

Both students and teachers participating in this CRT are research subjects and their

informed consent is required. It does not appear that clusters were randomized before students were approached for informed consent. Parents were informed of the study and given the opportunity to opt their children out. Insofar as parents' consent was needed, other mechanisms than opt-out forms better serve the goal of providing parents with the opportunity to refuse or consent to their children's participation in research. For example, the researchers could have instead asked the opposite, and required that parents sign and mail back the consent form if they were willing to allow their children to participate. This would have better ensured that the parents understood the aims and methods of the trial, and that they in fact agreed to their children's participation in light of those.

However, researchers also gave students who were not removed from the study the opportunity to provide written informed consent, after attending a 45 minute information session. Thus, on balance student interests were adequately protected by informed consent procedures and research ethics committee review. All of the teachers involved in the study received study and data collection interventions. The study does not report that informed consent was obtained from teachers (an important omission). As the study intervention was directed at teachers and not entire classrooms, there are no prominent cluster level interests at stake in this study. Accordingly, there is no role for the teachers as gatekeepers.

The CRT had substantial implications for participating schools: researchers were granted access to facilities, students, and staff; students were made available for the psychological questionnaire and follow-up interviews; and teachers were given release time for the educational workshop and data collection. Thus, the school principals had an important gatekeeper function in this study in determining the "willingness and ability of the school to conduct the study within the research time frame and on the availability of teachers who could be released to participate in

the teaching intervention" [31]. This decision clearly falls within their ambit as the senior administrator of the school. Thus, on the basis of the study report, the gatekeeper role was a legitimate one for the principals to perform.

Example 2: HIV prevention among women in low-income housing developments. This study sought to reduce risk behaviors for HIV in women who are impoverished, belong to minority groups, and live in low-income, inner city housing developments [42]. The place-based CRT randomized women in 18 low-income housing developments in five cities in the United States to an intervention group or a control group. In the intervention group, opinion leaders were identified, and they participated in a risk-reduction workshop and formed local women's health committees. These committees organized a variety of community events to reach out to all women tenants. The primary outcome measure was change in reported HIV related risk behaviors. Support and approval for the study was obtained from local Housing and Urban Development offices and management of local housing developments. Focus groups were conducted with tenant management organizations, health care providers, political leaders, and others to develop an appropriate and broadly acceptable protocol. All women in the housing developments were invited to fill out anonymous questionnaires about HIV risk related behaviors at baseline, and at the end of the intervention period. The study concluded that community-level behavioral interventions were successful at reducing HIV risk-related behaviors. Who are the gatekeepers in this study? Opinion leaders? Local housing development officials? Whose interests do they protect? Do they have the authority to fulfill those roles?

This study evaluated the effects of a community-level behavior change intervention strategy on reducing HIV risk-related behaviors in women in low income housing developments.

Clusters in this study may also be conceived of as involving communities, since prospective research subjects were selected on the basis of shared geographic and social characteristics. However, no easily identifiable authority existed that could make binding decisions about participation on behalf of cluster members, and on the basis of cluster interests. Therefore, cluster consent would not be appropriate. However, cluster consultation in this study is appropriate. The appropriate role of gatekeepers in cluster consultation includes providing feedback on protocol development, ensuring goals of the study are in accordance with the interests of the cluster, and ensuring the study is sensitive to the concerns of cluster members. We view the focus groups conducted with tenant management organizations, health care providers, political leaders, and others as motivated by the need for cluster consultation in this study.

Organizations, such as the housing developments, also have interests that may require gatekeeper protections. In order to access the buildings and conduct research activities using resources from the housing developments, management may be approached as gatekeepers to provide access for researchers to institutional resources. It is important to disambiguate the interests that managers are to promote and protect in their decisions. Their role is to make their decisions on the basis of organizational interests. Managers are not in a position that gives them the authority to provide proxy consent for cluster members, or to represent cluster interests.

Example 3: Effects of redesigned community postnatal care on women's health 4 months after birth. Despite advances in postnatal care, a substantial proportion of women experience physical and psychological disorders after childbirth. This study evaluated a new model of community postnatal care delivered by midwives in an attempt to improve physical and mental symptoms, including depression, after childbirth [43]. The unit of randomization in the study was

the general practice. A total of 120 practices were identified from a randomly selected list of general practitioners in the West Midlands region in the United Kingdom and approached to take part in the trial. Agreement was obtained from all practice partners as well as from midwifery managers in the local UK National Health Service, before approaching midwives within each practice for participation in the trial [43]. From 36 general practices that agreed to participate (18 randomized to the intervention group and 19 to the control group), 42 and 38 midwives, respectively, recruited women and provided care. Patients were informed of the study between 34 weeks' gestation and the first visit, and their written informed consent was obtained. Midwives in the intervention arm were trained to implement a new model of care that is tailored to the individual needs of patients after birth and is based on 10 evidence based-guidelines that had been developed for the study. Midwives in the control arm provided usual care. Midwives administered a checklist of physical and psychological symptoms at the first visit, 10 days, 28 days, and at the discharge visit at 10–12 weeks. A postnatal depression scale was used to screen patients at 28 days and at the discharge visit. The study intervention significantly improved women's mental health, but it had no effect on their physical health. Who are the gatekeepers in this study? General practice partners and midwifery managers? Midwives? Whose interests do they protect? Do they have the authority to fulfill these roles?

Both patients and midwives participating in this CRT are research subjects and their informed consent is required. In this case, practice clusters were randomized before patients were approached for informed consent. Patients were, however, approached for informed consent as soon as possible (between 34 weeks gestation and the first visit) and before any study intervention or data collection procedures were administered. Thus, gatekeeper consent to randomization is not required. Patient interests were adequately protected by research ethics

committee review and informed consent procedures. The informed consent of the midwives in the study was obtained. The midwives were not, however, gatekeepers. Study interventions and data collection procedures were administered to patients only after their consent was obtained and, as a result, there are no substantial cluster-level interests at stake.

The CRT did have substantial implications for participating general practices. Midwives received training, and researchers required access to patient records. Thus, the general practice partners and midwifery managers had a gatekeeper role with regard to the organizational interests of the practices and the midwives working within them. Gatekeepers had a role to ensure that there were adequate resources, in terms of personnel and finances, for the general practice to participate in the study. Further, the gatekeeper had a role to see that researcher access to confidential patient records is conducted in accord with organizational policies and legal requirements. These decisions fall within the remit of the general practice partners and midwifery managers, and hence they have the authority to fulfill the gatekeeper roles legitimately.

Conclusion

The development of using gatekeepers in CRTs arose from the challenges that design features of cluster trials pose for obtaining individual informed consent. However, using an appropriately restrictive definition of a research subject, determining when a waiver of consent may be allowable, and paying strict attention to those instances in which informed consent may not be required, helps allay many of these concerns and diminishes the need for gatekeepers in CRTs. We have argued that gatekeepers may be called upon to protect the interests of individuals, clusters, and organizations, but that these roles must remain distinct and may conflict. A

gatekeeper may have the authority to protect the interests of one of these groups, but not the others'.

We have argued that gatekeepers cannot legitimately provide proxy consent on behalf of cluster members. The ethical principle of respect for communities and notions of community consent and consultation provides a useful model for the protection of cluster interests. In a restrictive set of cases, a gatekeeper may protect cluster interests legitimately through the provision of cluster consent. It must be remembered that cluster consent does not supplant the need for informed consent from cluster members. Cluster consultation may meaningfully protect cluster interests in cases in which cluster consent does not apply. Finally, gatekeepers may control access to organizations, such as schools, hospitals, or general practices, by granting permission for investigators to conduct CRTs using their facilities, resources, and personnel.

Note

We have created a Wiki webpage to facilitate an open discussion about the ideas expressed in this and other papers published in the series on ethical issues in CRTs. Please enter your thoughts and comments at http://crtethics.wikispaces.com.

Competing interests

JCB, AG, ADM, RS, MT, CW, AW: None declared

RB, AD, MPE, JMG, and MZ have all submitted cluster trial protocols to ethics committees and had difficulty explaining to them the differences between cluster randomized trials and individual patient randomized trials.

Authors' contributions

AG, CW, and AW contributed to the conception and design of the manuscript.

AG, CW, and AW wrote the initial draft and led writing of subsequent versions.

All authors commented on sequential drafts and approved the final version.

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Research Chairs.

Table. Gatekeepers and gatekeeper roles in diverse CRTs in health research.

Setting	Country	Cluster type	Level of intervention	Individual consent reported	Gatekeeper	Gatekeeper role	Ref.
Athletic organizations	Norway	Sports clubs	Cluster	No	Coaches	Agreement to participate[1]	[10]
	Netherlands	Geographic regions	Individual	No	Coaches	Consent for individuals[2]	[11]
	Canada	Athletic teams	Individual	Yes	Head athletic therapist, trainer or sports medicine physician	Identification of cluster members	[12]
Communities	USA	Cities	Cluster	No	Community medical leaders	Permission to randomize	[13]
	USA	Rural communities	Cluster	Yes	Community advisory board	Cluster consultation and partnership	[14]
	Bulgaria	Social circles	Individual	Yes	"Index" member[3]	Identification of cluster members	[15]
	Gambia	Geographic areas/districts	Individual	Yes	Community leaders	Cluster consent	[16]
	Tanzania	Residential areas (Bazoli)	Cluster	Yes	Tanzania Institute for Medical Research	Protocol approval	[17]
	India	Villages	Individual	Yes	Local health system and community leaders	Cluster consultation and partnership/ permission to conduct study[1]	[18]
	Uganda	Villages	Individual	Yes	Local government	Protocol approval	[19]

					authorities and local leaders		
Health centre-based	USA	Health centres	Individual	Yes	Practising internists	Identification and permission to approach cluster members	[20]
	UK	Primary care practices	Cluster/ Individual	Yes	Primary care trust administrative authority	Protocol approval	[21]
	UK	Primary care practice locations	Cluster	Yes	General practitioners	Identification and permission to approach cluster members	[22]
	UK	Midwives	Individual	Yes	NHS trusts[4]	Agreement to participate[1]	[23]
Nursing homes	Canada	Nursing homes	Individual	Yes	Management	N/A[5]	[24]
	Australia	Nursing homes	Individual	Yes	Director of nursing	N/A[6]	[25]
	UK	Nursing homes	Individual	Yes	Management	Agreement to participate[2]	[26]
	New Zealand	Wards within nursing homes	Individual	Yes	Senior management	Informed consent[1]	[27]
Schools	Germany	Classrooms	Cluster	Yes	Responsible local governments	Permission to conduct study[2]	[28]
	Belgium	Classrooms	Cluster	No	Principals	Organizational permission	[29]
	USA	Classrooms	Cluster	No	School district[7]	Protocol approval	[30]
	UK	Teachers	Individual	Yes	Principals	Organizational permission	[31]
	Canada	Schools	Cluster	No	District principals	Individual consent	[32]
Worksites	Sweden	Worksites	Individual	No	Managers and human	Identification of cluster	[33]

				resources	members/ permission to randomize	
USA	Worksites	Cluster	No	Employee advisory board	Cluster consultation and partnership	[34]
USA	Fire stations	Individual	Yes	Department chiefs/ union representatives	Identification of cluster members/ Organizational permission	[35]
USA	Pools	Individual	Yes	Pool managers, community advisors, recreation leaders, pool directors	Cluster consultation and partnership.	[36]

Notes:

1. Several studies report agreement to participate or permission to conduct the study although it remains unclear if these are a form of consent, protocol approval, or another gatekeeper function.
2. Studies that report informed consent from a potential gatekeeper have not specified if this is a form of cluster/community consent or individual consent.
3. “Index” members were defined the “leaders of Roma (gypsy) men's social networks”.
4. Midwives may also have acted as gatekeepers as “all participating midwives were given detailed training on the procedure to identify, recruit, and obtain written informed consent from participants”.
5. Gatekeeper involvement was indicated by the statement that “[n]ursing homes withdrew...based on a decision by the nursing home management”, although a specific function was not given.
6. Researchers reported that directors of nursing “were given the opportunity to participate in the study” without further clarification.
7. This study also used a joint staff service committee (principal, vice principal, and faculty) that was informed and provided support for the study. The committee was not identified as a gatekeeper.

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