

Loopholes in the Research Ethics System?

Informed Consent Waivers in Cluster Randomized Trials with Individual-Level Intervention

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ABSTRACT Individual-cluster trials randomize groups of individuals but deliver study interventions directly to individual participants. We examine three arguments that might justify the perception that the bar for a waiver of consent should be lower in such trials than for individually randomized trials. We contend that if these arguments are treated as sufficient to grant a waiver of consent, then a loophole emerges in research oversight. Such loopholes are morally hazardous for study participants, the integrity of science, and public trust in the research enterprise. We conclude by articulating the standards that research ethics committees should use to evaluate requests for waivers of consent in individual-cluster trials.

KEYWORDS human research ethics, informed consent, informed consent waivers, cluster randomized trials, individual-cluster trials

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In an individually randomized trial, people (often within multiple research sites) are approached with the option of participating in a trial and, if they provide informed consent, are randomized to study or control interventions. In a cluster randomized trial, all the research sites (or clusters) are randomized, and all individuals enrolled at the same research site receive the same intervention. Cluster randomized trials are commonly used when interventions can be delivered only at the group level (for example, testing an alteration to a central dialysis fluid delivery system¹). In such trials, called *cluster-cluster trials*, interventions are not divisible at the individual level, and it is impossible or very burdensome for cluster members to avoid the intervention.² However, in a subset of cluster randomized trials, called *individual-cluster trials*, interventions (such as an antihypertensive drug) are delivered directly to participants, even though groups are randomized (see table 1).³ Individual-cluster trials are noteworthy

because, in principle, individual randomization could have been used.

Individual-cluster trials can serve legitimate scientific purposes but may also be seen as an attractive alternative to the individually randomized trial because the design of the former requires less research-related infrastructure, facilitating the conduct of studies in a wider variety of clinical settings more quickly and at a lower cost. For example, in an individual-cluster trial, there is no need to manage and keep track of the allocations of individual patients, and only one type of treatment needs to be administered in a cluster. In particular, individual-cluster trials may seem considerably less logistically demanding than individually randomized trials if justifying a waiver of consent for the former appears to be easier. One commentator goes so far as to claim that "consent for the intervention is not relevant in a cluster randomized trial because patients receive the same treatment regardless of whether or not they consent."⁴

Table 1.
Types of Randomized Controlled Trials Discussed in This Paper

	<i>Individually randomized trial</i>	<i>Cluster randomized trials</i>	
		<i>Individual-cluster</i>	<i>Cluster-cluster</i>
Unit of randomization	Individuals	Clusters	Clusters
Example	Patients	Primary care physician offices	Municipalities
Unit of intervention	Individuals	Individuals	Clusters
Example	Patient receives antihypertension drug	Patient receives educational brochure	Community public health messages
Unit of observation	Individuals	Individuals	Individuals
Example	Patient medical record	Patient-completed survey	Telephone interview of sample of residents

In what follows, we argue that the perception that it is easier to justify a waiver of consent for individual-cluster trials reflects misconceptions about the conditions under which a waiver of consent should be granted. We argue that the reasons put forth to justify a waiver of consent in individual-cluster trials have the potential to create a loophole in the research oversight system. We define a loophole as the unilateral ability of a researcher to avoid an oversight requirement without altering the substantive research procedures performed on participants. Loopholes in research oversight are morally hazardous not just for study participants but also for the integrity of science and public trust in the research enterprise. We provide guidance for researchers and research ethics committees for avoiding the improper use of waivers of consent in individual-cluster trials.

CLUSTER RANDOMIZED TRIALS WITH INDIVIDUAL-LEVEL INTERVENTIONS

The case for the use of a cluster randomized design to evaluate individual-level interventions is most compelling when there are strong scientific or methodological reasons to prefer cluster randomization. Having a strong rationale for the use of cluster randomization is important because cluster randomized trials are statistically inefficient, which means that they need more research participants than if an individually randomized trial had been used. They are also prone to

additional risks of bias.⁵ One possible rationale may be that there is a substantial risk of between-arm contamination due to having participants in close proximity to each other (or treated by the same provider) randomized to competing interventions.⁶ Another justification may be that the scientific question of interest includes group-level effects, such as herd immunity in vaccine studies.⁷

But the perception that cluster randomized trials have a lower bar for waivers of consent may make cluster randomization an attractive alternative in cases in which an individually randomized design would be scientifically feasible but more costly and logistically more complicated because of the presumed need for informed consent (among other reasons). The push for individual-cluster trials in such cases may increase as funders pressure researchers to produce more research per dollar and as patients, communities, and other stakeholders advocate for pragmatic trials that produce evidence that reflects “real world” settings.⁸

Whether any particular cluster randomized trial enjoys such practical efficiencies relative to an individually randomized trial depends, in part, on whether it can be conducted using a waiver of consent. This is because the process of securing informed consent can be logistically complicated and expensive.

There is a strong presumption that researchers are ethically required to obtain informed consent from study participants. A research ethics committee, how-

ever, may approve a waiver of the informed consent requirement when the research is likely to produce important social value, poses only minimal risk to study participants, and could not feasibly be conducted with informed consent.⁹ Waivers of consent are commonly used in observational studies of people in public spaces, in secondary analyses of previously collected data or biological samples, and in reviews of medical records when adequate confidentiality protections are in place. In our experience, a waiver of consent is rarely used in an individually randomized trial, particularly when the study intervention is a medical intervention such as a drug or vaccine. As informed consent is required ethically and legally for the use of drugs and vaccines in clinical practice, the use of a waiver of consent in such cases would allow research to proceed with a lower standard of consent than in practice. Thus, in an individually randomized trial, the ethical and regulatory presumption is that study personnel at each participating institution will secure informed consent prior to the study's commencement, study interventions, and data collection from all individuals who agree to enroll.

Individually randomized trials can be costly because personnel in each participating center must be trained to identify and recruit eligible patients and to conduct the informed consent process in an ethically acceptable manner. Research personnel must disclose information about the study procedures and interventions, including their risks and potential benefits (either to participants themselves or in terms of the study's social value); the data that will be collected; and the steps that will be used to mitigate physical and psychological risks and risks associated with the disclosure of any medical information that is collected. Research personnel must also be trained to ensure that participants receive the intervention to which they are randomized and that interventions are delivered according to the trial protocol throughout the life of the trial. Trained personnel must be available in sufficient numbers so that they can be positioned in the different study locations and at the various times in which participants may be recruited. Cluster randomized trials granted a waiver of consent avoid the need to recruit individual patients and thus the above difficulties altogether, especially when outcomes are available in the electronic health record.

If a research ethics committee would grant a waiver or a modification of consent for an individually randomized trial of an intervention, then the same moral reasoning would justify the use of a waiver or modification of consent for an individual-cluster trial of the same intervention. Our concern is with the perception that the bar for waiving informed consent is lower in individual-cluster trials than in individually randomized trials because "various forms of cluster randomization offer advantages and may help avoid the need for informed consent."¹⁰ If the bar is lower, a researcher contemplating an individually randomized clinical trial could secure a waiver of consent merely by altering the

Allowing researchers to determine when consent can be waived merely by altering their choice of trial design grants them arbitrary authority that threatens the warrant for trust in research oversight.

design to randomize clusters, without altering any other substantive aspect of the trial. It is this prospect that constitutes a loophole in research oversight.

WAIVERS FOR INSTITUTIONAL ADOPTION?

The adoption of an individual-level treatment as the local "standard of care" for some period of a cluster randomized trial might seem to justify waivers of consent that would not be warranted in individually randomized trials. For instance, Connolly and colleagues report a trial in which centers for interventional cardiology are randomized to provide one of two prophylactic antibiotic regimens for preventing infection after cardiac pacemaker implantation. Opting for an individual-cluster trial (specifically, using a cluster crossover design) means that each institution agrees to adopt only one intervention for this indication for a time before crossing to the alternative. The authors assert that, as it is often not possible for patients to avoid study interventions adopted at the health system level,

“[o]btaining consent is not possible in this study because the antibiotic interventions tested will be adopted as standard procedure for all patients at each of the participating centres during the study.”¹¹

Decisions about which interventions to stock in the formulary, or what practices to adopt as a matter of institutional policy, are not typically the subject of informed consent.¹² Conceptualizing individual-level interventions as “treatment policies” adopted at the institutional level might therefore appear to obviate the need for consent.¹³ However, if the decision to adopt a particular intervention as institutional policy is made to justify the conduct of the cluster randomized trial, then regarding that decision as sufficient to justify a waiver of consent creates a loophole in research oversight. The reason is that the decision to conduct an individual-cluster trial determines whether the condition for a waiver of consent is present.

Alternatively, decisions about which interventions to stock in a formulary can make it more difficult to avoid that intervention. Even if an individual-level intervention is adopted as a policy, however, it must be feasible for the intervention to be avoided by some patients, such as those for whom the intervention is contraindicated. Given that patients who are allergic to a medical intervention will not receive it, we might ask why informed refusal is not also regarded as a contraindication. If the concern to reduce logistical demands on an individual-cluster trial is used as grounds for not providing an analogous accommodation for informed consent or refusal, then, in this case too, a loophole in oversight is created. The reason is that the decision to use a particular study design effectively determines whether the condition for a waiver is met.

BIAS INTRODUCED BY CONSENT?

Another argument holds that, in cluster randomized trials, informed consent can often be sought from cluster members only after randomization and this is a potential source of bias. For instance, Spence and colleagues describe the B-Free trial, an individual-cluster trial (using a multiple period cluster crossover design) of benzodiazepine use in anesthesia.¹⁴ The B-Free trial randomizes hospitals to liberal versus restrictive policies of benzodiazepine use during cardiac anesthesia to evaluate the impact on postoperative delirium. Spence

et al. argue that seeking informed consent from patients would introduce bias, particularly if one study arm were viewed as more desirable by potential participants. The authors maintain that “conducting the B-Free trial would have been impractical without a waiver of individual consent. The unbiased evaluation of alternate cardiac anesthesia policies requires their almost universal application.”¹⁵

Cluster randomized trials are more susceptible to various forms of bias at the levels of both the cluster and the individual.¹⁶ At the individual level, cluster trials are prone to identification and recruitment biases, particularly if researchers and participants are not blinded to allocation. In many cluster randomized trials, clusters are randomized before cluster members can be approached for their informed consent. As the cluster has already been allocated to the study intervention or control, the participant will be aware of the intervention she will receive.¹⁷ If either the study intervention or control is more (or less) desirable, relevant participant characteristics may not be equally distributed between the study arms. If, for instance, healthier participants are more likely to agree to participate when offered the study intervention compared to the control, the trial will be biased to a false-positive result. So, this argument goes, a waiver would be necessary to ensure that study results do not reflect this form of bias.

If the above reasoning is treated as sufficient to justify a waiver of consent, it produces a loophole in oversight. One of the advantages of an individually randomized trial is that informed consent is sought prior to randomization. As a result, neither the researcher nor the participants know to which study arm the participant will be allocated. (This is a reason that the choice of a cluster randomized design must be justified.) The justification for the waiver of consent in the cluster randomized trial is that seeking informed consent after randomization increases the risk of bias when those recruiting and identifying participants have knowledge of the cluster’s allocated intervention. If postrandomization consent poses a sufficient threat to the validity of a trial that it would justify a waiver of consent, then the decision to conduct a cluster randomized trial determines whether the condition for a waiver obtains. All else being equal, a researcher who would be required to secure informed consent in an individually randomized

trial could avoid having to do so by opting for a cluster randomized trial.

FEASIBILITY AND INDIVIDUAL-CLUSTER TRIALS?

A final argument holds that because the sample size needed for cluster randomized trials is often quite large, it is infeasible to seek informed consent without dramatically increasing trial complexity and the necessary personnel and thus inflating study costs.¹⁸

If the difficulty in securing consent from a large number of participants in cluster randomized trials is sufficient to justify a waiver of consent, then this creates another potential loophole in oversight. First, because of intraclass correlation, the number of individuals needed in cluster randomized trials is always larger than would be required for a comparable individually randomized trial. All else being equal, a researcher who would be required to secure consent in an individually randomized trial could secure a waiver of consent simply by opting for a cluster randomized trial.

Second, costs are a legitimate concern in research, and there may be cases in which research simply cannot be carried out without a waiver of consent. But a blanket claim that cluster randomized trials are not feasible without a waiver of consent amounts to the assertion that more research could be carried out if we could avoid the expense of consent. The latter claim is undoubtedly true. But it applies to all research, since eliminating the need for informed consent would increase the resources available for additional studies. Waivers of consent are not justified by the prospect that granting them would permit the conduct of more research.

“The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials” explicitly states that “[a]n inappropriate reason to adopt a CRT is the mistaken belief that the need to seek informed consent can be avoided by using cluster randomization.”¹⁹ The consensus among guidelines and ethical analyses is that informed consent remains a fundamental ethical requirement in cluster randomized trials.²⁰ Waivers of consent must be supported by a compelling ethical justification, and the burden of proof falls to the researcher. Even if a waiver is applicable to some aspects of a cluster randomized trial, “The Ottawa Statement” and guideline 21 of the *International Ethical Guidelines*

for Health-Related Research Involving Humans, from the Council for International Organizations of Medical Sciences (CIOMS), state that consent may nonetheless be required for other interventions or data collection procedures.²¹

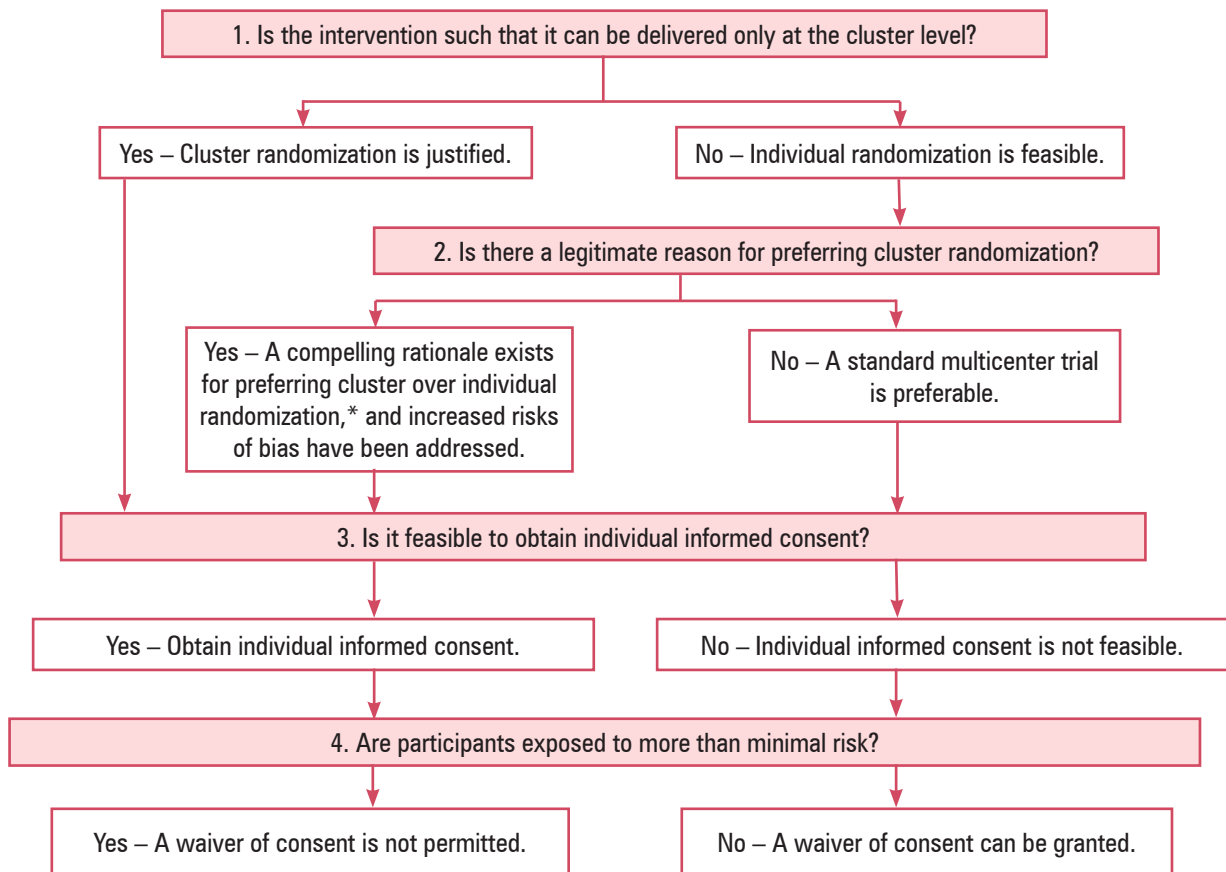
UNDERSTANDING LOOPHOLES

Loopholes in oversight are created if the decision to implement a particular study design and the considerations used to grant a waiver of consent are not independent. The arguments canvassed above have the potential to create loopholes in oversight because they appeal to factors whose presence or absence is determined by the decision of researchers to use individual versus cluster randomized designs. Since the considerations appealed to in these arguments are correlated, some version of each of these arguments can be made in support of the same study. But this does not eliminate the fact that the considerations offered to justify waivers of consent arise from decisions made to facilitate the conduct of that research.

Loopholes in oversight are morally hazardous for study participants, the integrity of science, and public trust in the research enterprise. For participants, the informed consent process protects their right to understand the various factors that influence the care that they receive, including the goals of research, and to make important choices about their lives. In some cases, the need for informed consent represents a “barrier” to research because securing consent to study participation requires additional resources. In other cases, it represents a potential barrier because participants have strong preferences for or against one therapeutic, prophylactic, or diagnostic modality. Such preferences can exist even when treatments are widely used in practice and constitute routine medical care. Facilitating the right of individuals to understand that they are involved in a research study and how this might influence the care they receive respects autonomy and fosters public trust. If individual research teams can circumvent consent by choosing a cluster randomized design, this undermines autonomy and jeopardizes public trust.

If study designs are chosen to circumvent the costs of meeting ethical requirements, there is the potential to undermine the integrity of the scientific enterprise. Clinical trials are instruments for learning and for re-

Figure 1.
Evaluating Requests for Waivers of Consent in Individual-Cluster Trials



*For example, there is a *substantial* risk of treatment contamination that precludes the unbiased estimation of the treatment effect.

ducing uncertainty about specific scientific and clinical questions. The information that they generate is relied on by a variety of stakeholders to make decisions that affect the health of patients, the efficiency of health systems, and the use of scarce resources.²² It is imperative, therefore, that studies implement rigorous methods well adapted to addressing specific knowledge gaps. Cluster randomized trials have a valuable role to play in bridging knowledge gaps for which individually randomized trials are not well suited.

In cases where both study designs are options, cluster randomized trials have significant scientific drawbacks: they require larger sample sizes and are more prone to bias and analytical complexities than are individually randomized trials.²³ In a review of 24 cluster

randomized trials, Brierley and colleagues identified eight trials where the risk of recruitment bias could have been reduced or eliminated by using individual randomization.²⁴ Switching from an individually randomized trial to a cluster randomized trial when the latter is not the optimal design for the question at hand risks substituting a less reliable design for a more reliable one.

All stakeholders in the research enterprise have an interest in ensuring that no stakeholder has the arbitrary power to advance their parochial interests at the expense of the interests of others.²⁵ Allowing researchers to determine when consent can be waived merely by altering their choice of trial design grants researchers arbitrary authority that threatens the warrant for trust in research oversight as an independent check on

researcher discretion and as a safeguard for participant autonomy and study quality.

RECOMMENDATIONS

The Ottawa Statement” holds that a waiver of consent might be granted for cluster randomized trials 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.”²⁶ The CIOMS guideline 10 reiterates these conditions and requires a third point: that “the research has important social value.”²⁷

Research ethics committees should evaluate requests for waivers of consent in individual-cluster trials relative to two standards (see figure 1). The first considers whether a waiver would be warranted in an individually randomized trial of the same interventions. For example, if it would be infeasible to secure consent in an individually randomized trial because of logistical difficulties and if a research ethics committee regards the risks of the study to be minimal, then researchers and research ethics committees could consider whether individual randomization is feasible with a waiver of consent or whether a cluster randomized trial is necessary to generate otherwise unobtainable evidence. In this case, there is credible assurance that opting for a cluster randomized trial does not represent an inappropriate exercise of discretion by researchers.

If a waiver of consent would not be granted in an individually randomized trial of the same interventions, then the research ethics committee must be persuaded that there is a compelling rationale for conducting a cluster randomized trial that is *independent* of the granting of a waiver of consent. This will involve establishing, first, that a cluster randomized trial represents the most scientific and methodologically sound design for the question at hand; second, that a waiver of consent is necessary to preserve the scientific integrity and social value of the study; and third, that the study exposes participants to no more than minimal risk. ♦

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DISCLOSURE

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than minimal risk to the subjects; (ii) The research could not practicably be carried out without the requested waiver or alteration; (iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; (iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

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