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Ethical Challenges Associated with Pragmatic and Cluster RCTs

Charles Weijer, M.D., Ph.D., and Monica Taljaard, Ph.D.

You are part of a discussion at your community hospital about whether your site will participate in a pragmatic, individually randomized, controlled trial (RCT) comparing two antibiotics currently used to treat infections in hospitalized patients. Use of the antibiotics varies widely among physicians, and the drugs are associated with different, potentially serious side effects. Since the antibiotics haven't been compared in an RCT, it is unclear which one is more effective. The investigators don't plan to recruit patients and will use routinely collected data for outcome assessment. They believe that a waiver of consent would be beneficial because it would permit inclusion of hospitals in underserved communities with minimal research infrastructure. During the discussion, the ethics of waiving consent are questioned. A colleague asks, "Would the use of a cluster-randomized design strengthen the case for a waiver of consent?" Conducting a cluster RCT would involve randomly assigning hospitals, rather than patients, to treatment groups, and all eligible patients at a hospital would receive the same antibiotic.

RCTs conducted to support drug or device approval typically use explanatory designs. Explanatory RCTs seek to evaluate an intervention under ideal conditions but provide scant information about its effectiveness in the messy reality of clinical practice. Patients in clinical practice tend to be older and have more coexisting conditions than patients in explanatory RCTs. Furthermore, explanatory RCTs often aren't designed to detect differences in treatment effects among subgroups of patients. Finally, such trials typically don't compare drugs or devices with available alternatives, which can leave patients and clinicians guessing about the best option.

Pragmatic RCTs — which are intended to provide evidence to inform decisions made by patients, physicians, and policymakers — are needed to fill these evidence gaps. Such trials may use various designs. In the proposed RCT, the head-to-head comparison of two antibiotics, inclusion of diverse treatment settings, simplified patient-recruitment method, and use of routinely collected data for outcome assessment reflect pragmatic choices in trial design.

The use of a waiver of consent in the trial is questioned. Pragmatic RCTs also present ethical issues related to assessing research risks and protecting vulnerable people. Moreover, the choice of cluster randomization would create scien-

tific and ethical complications. Since most research ethics guidelines were written with individually randomized explanatory trials in mind, addressing the complex issues presented by pragmatic and cluster RCTs requires collaboration among bioethicists, biostatisticians, trialists, research ethics committees, and — crucially — patient and public partners, using internationally accepted ethical principles.

The use of pragmatic RCTs raises several ethical questions. First, how should vulnerable participants be protected? Pragmatic RCTs often seek to enroll all comers, including patients who are typically excluded from explanatory trials, such as older patients with coexisting conditions, as reflected in minimal restrictions on eligibility. This approach generally leads to results being more widely applicable than results of explanatory trials. But it also poses challenges, since more participants may be at risk for being harmed because of study involvement. Vulnerable participants should generally be included, as long as additional protections are in place. In the proposed RCT, protections might include assessing patients for decision-making capacity and screening for organ dysfunction that may predispose them to antibiotic side effects. When these protections (e.g., ruling out organ dysfunction) are part of the intervention as it is ultimately implemented, pragmatism is preserved. In other cases, protections may be in tension with pragmatism but should nonetheless be retained.

Second, does trial participation pose only minimal risk to participants? Pragmatic RCTs commonly compare routinely used treatments. These trials therefore typically fulfill equipoise — the ethical requirement that study interventions be broadly in keeping with competent care and that it is unknown whether one intervention is better than the other. Comparisons of routinely used treatments may still pose more than minimal risk to participants, however. Treatments may carry substantial risks or have different benefit–risk profiles. In the proposed trial, the two antibiotics are associated with different, potentially serious side effects. The degree of risk posed to participants requires a structured, case-by-case analysis.[1]

Third, is a waiver of consent permissible, and, if not, how should consent be obtained in busy clinical settings? The assumption that pragmatic RCTs pose only minimal risk has led some investigators to suggest that participant consent may be waived. We believe this reasoning is flawed. Informed consent is sought to respect participants' autonomy, not to protect them from risk. When the study intervention is a drug or device, a waiver of consent is rarely appropriate. Indeed, surveys exploring patient and public attitudes about consent in pragmatic RCTs have revealed a consistent preference for prospective, study-specific informed consent. In the proposed RCT, patients may prefer to avoid a particular antibiotic side effect and, as a result, decline to participate.

Pragmatic RCTs are often conducted in settings that lack research infrastructure, however, as in the case of the proposed trial. In our experience, alternative approaches to obtaining consent that may be useful in such settings — such as informed consent by means of electronic devices (e.g., trial information presented on a tablet), integrated consent (clinicians seek verbal consent from patients with the use of a scripted disclosure and document the consent in the electronic health record),[2] and short-form consent (a one- or two-page consent document) — are underutilized in pragmatic trials.

In cluster RCTs, entire communities or hospitals, for example, are allocated to study interventions. Cluster RCTs are necessary for evaluation of cluster-level interventions, such as public health, health services, and knowledge-translation interventions. Although cluster RCTs are rarely used to support drug or device approval, some investigators have recently advocated for their use in pragmatic evaluations of treatments.

Certain ethical questions pertain specifically to cluster RCTs evaluating interventions delivered to patients. First, is the choice of this study design justified? Patient-level interventions, including drugs and devices, can be evaluated in trials with individually or cluster-randomized designs.[3] When an individually randomized design is possible, it is generally preferred. Cluster RCTs are comparatively statistically inefficient, so larger sample sizes are required and more participants are exposed to the risks and burdens of research participation. The scientific and social value of a study could justify the added risks, but bias, which is common in cluster RCTs, threatens to undermine these benefits.

Some reasons for choosing a cluster-randomized design are more compelling than others. Simplifying logistics and reducing the risk of intervention contamination may be the most compelling reasons.[3] Supporting pragmatism isn't a compelling justification,

since cluster RCTs aren't inherently pragmatic. Seeking to avoid the need for informed consent is never an acceptable justification. In the proposed trial, cluster randomization might simplify trial logistics: no randomization would be needed within hospitals, and a hospital's eligible patients would all receive the same antibiotic. But these benefits must be weighed against the need to include more hospitals and the greater risk of bias in a cluster RCT.

Second, is a treatment policy a cluster-level intervention? Cluster-level interventions, such as community-wide public health messages, are delivered to the cluster as a whole and cannot be applied differentially at the individual level. Such interventions are very difficult for cluster members to avoid, thereby undermining the ability to opt out of study participation. Provided that participation poses minimal risk, a waiver of consent is appropriate for cluster-level interventions. Some investigators contend that individual-level interventions adopted as treatment policies should also be considered cluster-level interventions. We disagree. If the proposed RCT used a cluster-randomized design, hospitals would be allocated to a policy of treating all eligible patients with a particular antibiotic. But a patient with a contraindication to the allocated antibiotic would receive a different treatment. Since the treatment policy can be applied differentially at the individual level, it is an individual-level intervention.

An audio interview with Charles Weijer is available at NEJM.org

Third, is informed consent required? A common misperception about cluster RCTs is that the bar for permitting a waiver of consent is lower than it is for individual RCTs. But consent-related issues aren't a function of the unit of randomization; rather, they are driven by the unit of intervention.[4] When interventions are delivered to patients, informed consent is generally required. In the proposed trial, the use of a cluster-randomized design wouldn't bolster the case for a waiver of consent. If informed consent would be required in an individually randomized trial comparing two antibiotics, it would be required in a cluster RCT.[4]

Pragmatic RCTs help promote evidence-based care for marginalized groups and underserved communities. Such trials can provide estimates of treatment effects that are directly relevant to clinical settings. Planned subgroup analyses also permit detection of differential treatment effects among subgroups of marginalized persons. Cluster RCTs can be used to evaluate interventions aimed at improving access to care and the quality of care delivered in underserved communities.

Patient- and public-involvement initiatives seek to ensure that patient and community voices are heard throughout the research process. Such initiatives aim to promote trust between researchers and patients, demonstrate respect for communities, and enhance the social value of research. They are most effective when patients and community members are involved from the outset in choosing research questions, and they could support patient-recruitment efforts.[5] In the proposed RCT, researchers should clearly outline their strategy for engaging with patients and underserved communities, including in formulating the study question, choosing outcome measures, developing setting-appropriate consent materials, and planning to promote practice changes based on results.

Advances in RCTs present new ethical challenges. Pragmatic RCTs, performed with a goal of informing clinical decision making, tend to include diverse groups of patients and may be conducted in settings in which standard approaches to obtaining informed consent are impractical. Cluster RCTs, in which groups are allocated to study interventions, challenge approaches to research ethics rooted solely in the protection of individual participants. Addressing these issues requires multidisciplinary expertise and meaningful collaboration among stakeholders from various disciplines. Ethical guidance on specific study designs is needed. Facing these challenges presents an opportunity to revisit and deepen understanding of core concepts in research ethics.

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From Western University, London (C.W.), and the Ottawa Hospital Research Institute, Ottawa (M.T.) — both in Canada.

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