ICU
MANAGEMENT & PRACTICE

Ethical Challenges With Pragmatic and Cluster RCTs

Traditional explanatory randomised controlled trials (RCTs), often used for drug or device approval, assess interventions under ideal conditions but may not reflect real-world clinical practice, as they typically involve younger patients with fewer coexisting conditions. These trials also struggle to detect treatment effect differences among subgroups and rarely compare alternatives, leaving gaps in decision-making for patients and clinicians.

Pragmatic RCTs aim to provide relevant evidence for real-world decisions by including diverse treatment settings, simplifying recruitment, and using routine data for outcomes. However, they raise ethical concerns, particularly regarding consent and protecting vulnerable populations. The cluster randomisation method adds complexity, as existing ethics guidelines focus on individually randomised trials. Addressing these challenges requires collaboration among bioethicists, biostatisticians, trialists, ethics committees, and community partners, adhering to internationally accepted ethical principles.

The use of pragmatic RCTs raises several ethical concerns, particularly regarding the protection of vulnerable participants. These trials often include a broad range of patients, including older individuals with coexisting conditions, which increases the applicability of results but also the risk of harm. To safeguard vulnerable participants, additional protections, such as assessing decision-making capacity and screening for organ dysfunction, should be implemented while maintaining the trial's pragmatic nature.

Another ethical issue is whether trial participation poses minimal risk. While pragmatic RCTs typically compare routine treatments and fulfill the ethical requirement of equipoise, the treatments involved can still carry significant risks and different benefit-risk profiles. A structured, case-by-case analysis of risks is necessary.

The question of consent is also crucial. Some argue for waiving consent in pragmatic RCTs due to perceived minimal risks, but this perspective is flawed. Informed consent respects participants' autonomy and is essential, especially when drugs or devices are involved. Surveys indicate that patients generally prefer informed consent, highlighting the importance of ensuring participants are aware of potential side effects and can choose whether to participate.

Pragmatic RCTs are often conducted in environments lacking robust research infrastructure, which can complicate obtaining informed consent. Alternative consent methods, such as using electronic devices for information presentation, clinician-led verbal consent documented in electronic health records, and short-form consent documents, are often underutilised in these settings.

Cluster RCTs involve allocating entire communities or hospitals to interventions, making them essential for evaluating public health and health service interventions. While they are rarely used for drug or device approval, some researchers advocate for their use in pragmatic evaluations. However, several ethical questions arise specifically regarding this design.

First, the justification for choosing a cluster design must be carefully considered. Individual randomisation is generally preferred when possible, as cluster RCTs are statistically less efficient and require larger sample sizes, exposing more participants to research risks. While benefits like simplifying logistics and reducing intervention contamination are compelling reasons for cluster randomisation, using pragmatism or avoiding informed consent as justifications is inappropriate.

The question of whether a treatment policy qualifies as a cluster-level intervention is important in the context of RCTs. Cluster-level interventions, like community-wide public health messages, are delivered to the entire cluster and cannot be selectively applied at the individual level, making it

hard for participants to opt out. For such interventions, if participation poses minimal risk, a waiver of consent may be appropriate.

Some argue that individual-level interventions adopted as treatment policies should also be treated as cluster-level interventions, but this is disputed.

Furthermore, there is a common misconception that the criteria for waiving consent are less stringent for cluster RCTs compared to individual RCTs. Consent requirements are determined by the unit of intervention, not the unit of randomisation. Since informed consent is typically required for individual trials involving patient interventions, it remains necessary in a cluster RCT setting as well.

Pragmatic RCTs play a crucial role in promoting evidence-based care for marginalised and underserved communities by providing treatment effect estimates relevant to real-world clinical settings. They enable subgroup analyses to identify differential treatment effects among these populations. Cluster RCTs can evaluate interventions aimed at improving access to and quality of care in these communities.

Patient and public involvement initiatives are essential to ensure that community voices are integrated into the research process, fostering trust and respect between researchers and participants. These initiatives are most effective when community members are engaged from the beginning in formulating research questions and can aid in patient recruitment.

However, advances in RCTs also bring new ethical challenges. Pragmatic RCTs often include diverse patient groups and may be conducted in settings where traditional informed consent methods are impractical. Cluster RCTs, which allocate entire groups to interventions, complicate ethical approaches that focus solely on individual participant protection. Addressing these challenges requires multidisciplinary collaboration and specific ethical guidance tailored to various study designs, offering an opportunity to revisit and deepen the understanding of core research ethics concepts.

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