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# Roles of Randomized Controlled Trials in Establishing Evidence-Based Gender-Affirming Care and Advancing Health Equity

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## Abstract

This article reviews the design of a recently published randomized controlled trial (RCT) on immediate vs delayed access to gender-affirming hormones for transgender and gender-diverse (TGD) people and outlines key learning points that clinicians should know about how RCTs can and cannot contribute to advancing health equity for TGD people.

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## Questioning the Evidence Base

In recent years, transgender and gender-diverse (TGD) Americans and their clinicians have faced increasing political backlash against gender-affirming care modalities. While attacks on TGD medicine initially targeted youth, adult access to care is now also threatened.[1,2] One tactic used by critics has been to assert that the quality of evidence for gender-affirming care is low[3] and to call for a moratorium on such care until randomized controlled trials (RCTs) are conducted.[4] Calls for additional evidence might seem reasonable on their face: who could object to better evidence? But opponents of TGD health care leverage these calls to justify denying, obstructing, or criminalizing access to such care. And while RCTs are often portrayed as the "gold standard" in evidence-based medicine, a range of logistical and ethical objections make them inappropriate for answering many important questions about TGD medicine. It is critical to understand what researchers and clinicians should know about how RCTs can—and cannot—contribute to advancing health equity for TGD people.

## The Nolan et al RCT

Several limitations of RCTs can be discerned by examining the conditions that made a recent RCT of gender-affirming care possible. In September 2023, *JAMA Network Open* published "Early Access to Testosterone Therapy in Transgender and Gender-Diverse Adults Seeking Masculinization: A Randomized Clinical Trial" by Nolan et al,[5] which examined the effects of testosterone therapy on depression, suicidality, and gender dysphoria (a diagnosis associated with clinically significant distress resulting from

incongruence between one's assigned sex and one's gender identity, which some TGD people object to on the basis that it implies distress is intrinsic to TGD identities) in a sample of 64 Australian TGD adults. The RCT was designed as an open-label study; participants in the study knew whether they had been assigned to an intervention group, which received immediate initiation of testosterone, or to a control group, which received no treatment during a waiting period of 3 months prior to initiation of testosterone—mirroring real-world conditions. The study found a statistically significant decrease in gender dysphoria and a clinically significant decrease in suicidality among the intervention group.

The Nolan et al study was reported as a novel comparative study and the first RCT for gender-affirming hormones.[6] To investigate procedural improvements, the study took advantage of existing structural deficiencies: namely, that Australian TGD patients who seek gender-affirming care often face long wait times at state-funded endocrinology and gender clinics.[7] This context allowed Nolan et al to describe a 3-month waiting period between initial assessment and initiation of testosterone therapy as "standard care." As such, there was no need to assign patients to a nonintervention control group, which would have been ethically untenable.

Nolan et al's explicit project was to develop an evidence base for reimbursement of transition-related costs under the evidentiary standards of the Australian national health system.[6] The authors described their study as a phase 4 efficacy trial[8] because of their intent to extend permitted on-label prescribing of testosterone to TGD people. As in Australia, in the United States prescribing of testosterone for TGD people is always off-label; there is no Food and Drug Administration (FDA) indication for testosterone use in TGD people,[9] so studies such as this one provide an important pathway to improved access. Nolan notes that transgender patients were willing to participate because the 3-month waiting period did not, in this case, constitute an additional burden, as it was already standard care.[6] Other studies designed similarly—to exploit weaknesses in existing procedures and policies—might indeed be a valuable addition to the evidence base for TGD health, but they must be designed to ensure access to affirmative health care with established benefits.

## Limitations of RCTs

Given that it is only ethically permissible to use RCT designs in TGD health research within narrow circumstances and that a robust evidence base of observational studies consistently shows the benefits of affirmative models for TGD adults,[10,11] access to gender-affirming care should not be denied on the basis of an evidence base lacking RCTs. The evidence for gender-affirming care for children and youth is not as strong as that for adults, but the need for research in this population still ought to be met without randomizing pediatric patients to non-intervention groups. Instead, as with adult studies, pediatric researchers should exhaust alternative study methods that explore the potential benefits of access to care and the harms of existing structural barriers (without reinforcing them), at least until such barriers fall away. Nor should researchers underestimate the potential harms of RCT designs on individuals or communities that might depend on research for access to the standard of care. Many TGD people's access to gender-affirming care is severely curtailed by underinsurance, poverty, and medical discrimination[12]; if research participation offers the only accessible path to gender affirmation, decisions about participation may become less voluntary and more coercive.

Furthermore, that this one RCT was possible does not mean that TGD medicine should be subject to critics' contention that only RCTs provide evidence of sufficient quality to justify care. In a 2023 review article in the *International Journal of Transgender Health*, Ashley et al describe a set of problems with RCT study designs that make them inappropriate for TGD mental health research,[13] including the impossibility of masking to which study group a research participant has been assigned due to physiologically evident effects of gender-affirming care, risks of participant nonadherence and withdrawal due to unmasking, and samples of willing participants not being representative of the broader population. Another challenge for RCTs in both the United States and Australia arises from the common practice of self-directed (or "DIY") treatment; recruiting sufficient study samples of treatment-naive participants is resource-intensive, even for established research programs.

Perhaps the most significant challenge to conducting RCTs in TGD health research is the lack of clinical equipoise[14] and expected scientific value: gender-affirming care for adults has been the clinical standard for decades.[15,16] Reviews of observational studies show associations between access to gender-affirming care and improved health outcomes, including reduced suicidality, improved subjective quality of life, decreased incidence of psychiatric diagnoses, and decreased suffering associated with gender dysphoria.[12] RCTs on the pharmacokinetics of testosterone have long since established its safety and effectiveness.[17] Few researchers (or institutional review boards) would consider study designs that deny TGD patients access to widely used, often lifesaving care to be ethical.[18] Similarly, ethics boards may question the time, cost, and risks of study participation to address research questions previously answered.

## A Path Forward

None of this is to suggest there is not a need for research. There are still many things to be learned about TGD medicine, including long-term effects of hormones, hormone blockers, and surgeries; health beyond gender affirmation and throughout the lifespan; and reproductive health care.[19] The broad exclusion of vulnerable populations from research opportunities only further compounds health disparities; clinicians need high-quality research to guide evidence-based medicine. When RCTs can be structured appropriately, they have a place in expanding the evidence base for gender-affirming care. However, other study designs, such as longitudinal observational cohort studies and case-control studies, may be more appropriate for answering many important research questions, given the limitations of RCTs. Good-faith calls for more research should include calls for these other designs, not just RCTs.

Nolan et al cleverly devised a key to fit in the lock of the Australian regulatory system. However, that RCTs are practical and ethical in only some cases renews questions of how regulatory bodies can promote equity in access to care for gender and sexual minorities by accommodating a wider variety of evidence. For example, the FDA could clear a path to expand the list of indications for testosterone therapy by accepting data gleaned from non-RCT studies and other clinical sources such as registries, electronic health records, and claims data sets—so-called "real-world evidence" (RWE).[20] In 2022, the FDA announced an expansion of its program to improve the quality and acceptability of RWE in approval decisions,[21] signaling agency interest in data sources beyond conventional RCT designs and hopefully new opportunities to expand indications for TGD medicine.

## Conclusion

The Nolan et al study delimits both the possibilities and the boundaries of possibility of RCTs in informing TGD health policy. RCTs can be most helpful for studying process improvements and advancing goals of quality improvement. Yet RCTs are unlikely to resolve the underlying ethical tensions between the availability of evidence and the justifications for providing care or to remedy the social conditions that undermine TGD health equity. And they are certainly unlikely to resolve questions raised to stoke political controversies.

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