

July 15, 2024

Submitted by the Endocrine Society in response to The National Institutes of Health (NIH) Request for Information (RFI) on NIH-Wide Strategic Plan for Sexual and Gender Minority (SGM) Health Research (NOT-OD-24-122)

The highest priority needs, and emerging areas of opportunity related to SGM health research at NIH.

The Endocrine Society recognizes the progress made under the current version of the Strategic Plan to Advance Research on the Health and Well-being of Sexual and Gender Minorities and many of the current scientific themes are still relevant and require additional research. For instance, chronic disease and comorbidities remain critical drivers of poor overall health in SGM populations and longitudinal studies with registries of transgender individuals should be supported to collect better data on outcomes. We recommend that the following research opportunities be incorporated into the plan:

1. Research evaluating the impact of gender-affirming hormone therapy

Gender-affirming hormone therapy (GAHT) is an essential part of gender affirmation for many transgender individuals, and we maintain that there is an overarching need for outcomes-based research on the effects of GAHT for transwomen, transmen, and non-binary people. Specific areas of emphasis that we recommend for inclusion in the strategic plan are bone health, cardiovascular health, gender dysphoria, psychological well-being, and quality of life (QoL).

Much published research in this field is mostly of low to moderate quality, comprising longitudinal cohort studies and cross-sectional studies, making it difficult to draw clear conclusions. Most studies demonstrate that GAHT reduces gender dysphoria, body dissatisfaction, and uneasiness, subsequently improving psychological wellbeing and QoL in transgender individuals. Additional research could help us understand how external social factors unaffected by GAHT impact dysphoria, well-being, and QoL and confound results.

2. Research on how best to provide or deliver gender-affirming hormone therapy

Additional research is needed to indicate optimal sex hormone levels (estradiol or testosterone) needed for feminization or masculinization, or if sex hormone levels matter at all. International guidelines would benefit from more robust clinical evidence to refine treatment goals, including exploring the effects that estradiol or testosterone concentrations have on clinical outcomes in trans people undertaking GAHT.



While testosterone therapy appears to be reasonably effective at masculinizing physical characteristics, additional research is needed to understand how best to deliver feminizing hormone therapy. In addition to uncertainty regarding optimal estradiol levels, it is not known what doses or formulations of either estradiol or anti-androgens are required for optimal clinical benefit. It is also controversial as to whether progesterone is required for trans people desiring feminizing effects.

3. Research on long-term effects of gender-affirming hormone therapy

The need for high-quality research to determine the long-term safety and efficacy of hormonal medical transition for transgender individuals is critical, particularly as treatment is typically started at a young age and continues lifelong. Sex hormones influence cardiovascular health, malignancy and immune function and play significant roles in many organ systems in the body. Stigmatization has prevented adequate support for transgender health research, consequently not enough is known about the long-term effects of GAHT, although we do have valuable knowledge about long-term effects from retrospective studies. We note that estradiol therapy includes an elevated risk of venous thromboembolic disease, myocardial infarction, and stroke, relative to cisgender populations. Oral estradiol has also been associated with hypertension and migraine. Testosterone therapy is associated with androgenic alopecia, acne, polycythemia, and probable increased cardiovascular risk. However, we do not yet know whether similar adverse effects occur with newer formulations of GAHT, or how to prevent long-term adverse effects.

Partnerships NIH should pursue, both inside and outside of government, to advance SGM health-related research.

Research has shown that gender-affirming hormone therapy (GAHT) improves mental health depression and gender dysphoria. However, partnerships and collaborations aimed at increasing the understanding and adoption of evidence-based care while also helping us understand how best to deliver GAHT for optimal physical and mental health benefit, will help improve access to care. Towards this end, well-designed studies co-created with the patient community, large HMOs (e.g., Kaiser or Geisinger), and industry might be helpful.