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# Priorities for efficacy trials of gender-affirming hormone therapy with estrogen: collaborative design and results of a community survey

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## Abstract

**Purpose** Treatment guidelines for gender-affirming hormone therapy with estrogen (GAHT-E) recommend specific dosing regimens based on limited data. Well-controlled efficacy trials are essential to tailoring treatment to patient goals as the guidelines recommend. The goal of this study was to take a foundational step toward designing community-centered effectiveness trials for gender-diverse individuals seeking GAHT-E.

**Methods** Our team developed a cross-sectional survey based on broad clinical experience and consultation with our community advisory board. The survey included 60 items covering demographics, transition history, goals and priorities for treatment, indicators of treatment success, sexual function goals, and future research priorities. The survey was distributed during the summer of 2021, primarily through social networks designed for gender-expansive individuals seeking treatment with estrogen.

**Results** A total of 1270 individuals completed the survey. Overall treatment goals most frequently rated "extremely important" or "very important" were the following: (1) improved satisfaction with life (81%), (2) appearing more feminine (80%), (3) appearing less masculine (77%), (4) improved mental health (76%), and (5) being seen as your true gender by others (75%). The three body characteristics most frequently rated "highest priority" or "high priority" among changes were the following: (1) facial hair (85%), (2) breast shape or size (84%), and (3) body shape (80%). The highest-rated research priority was comparing feminization with different routes of estrogen administration.

**Conclusion** The goals and experiences of individuals seeking GAHT-E are diverse. Future clinical trials of GAHT-E should be grounded in the needs and priorities of community stakeholders.

**Keywords** HRT · GAHT · Estrogen · Transgender · Research design

## Introduction

Treatment guidelines for gender-affirming hormone therapy (GAHT) recommend dosing regimens with the caveat that treatment should be tailored to patients' goals; however, there are few data enabling us to ascertain the efficacy of any specific regimen for achievement of patient-centered endpoints [1–3]. Published prospective cohort studies evaluating physical changes achieved via GAHT

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with estrogen (GAHT-E) offer preliminary evidence of efficacy but are limited by uncontrolled variables [4–7].

Despite the increase in the types of evidence acceptable for regulatory decisions in the USA, the existing evidence remains inadequate for approval of drugs indicated for GAHT. Well-controlled clinical trials are the gold standard for assessing safety, absolute efficacy, and comparative efficacy of treatment but as of March 28th, 2023, a PubMed search revealed only one randomized controlled trial of GAHT [8]. Burinkul and colleagues demonstrated the feasibility of comparative efficacy trials for GAHT but did not measure patient-centered endpoints such as anatomical change or patient-reported outcome measures (PROMs) [8]. This low quality and volume of evidence is widely cited in treatment guidelines [2, 3], systematic reviews [1], and reports from stakeholder engagement events [9].

A foundational problem for building the nascent literature was succinctly summarized in a report from an FDA community listening session as follows: "… participation would be dependent on the goal/endpoint of the [study]. [Participants] noted that there isn't a common goal shared by people who identify as trans" [10]. Community members are unlikely to participate in research irrelevant to their treatment goals, and trans and gender-expansive communities have widely varying goals. Thus, investigators must navigate the following two essential decisions: (1) defining and describing appropriately homogenous subgroups for assessing physiological changes and (2) defining "efficacy" to reliably and validly represent their treatment goals [11, 12]. This report describes an initial step in answering these questions in collaboration with community stakeholders.

## Methods

Having chosen to focus first on GAHT-E, our research group designed a cross-sectional survey of experiences, expectations, and priorities of individuals seeking GAHT-E in order to prioritize research questions and treatment outcomes. Because few data and no validated survey measures exist on this topic, our research group developed a novel questionnaire based on clinical experience and in consultation with our institution's community advisory board (CAB). A non-provider team member attended regularly scheduled CAB meetings for advice and feedback. The team subsequently met with two CAB members possessing personal GAHT-E experience to collaboratively review and edit the survey draft, focusing on refining language and broadening the experiences represented; CAB members were paid an honorarium for their time and expertise.

## Population definition

Our research group sought to prioritize affirmation, concision, clarity, and precision in defining the target population. Our goal was to specify a group likely to have relatively similar endogenous hormone environments and treatment responses while affirmatively including individuals of varied identities and experiences. Our study thus focused on the chosen treatment modality over the inherent characteristics of participants by defining the primary inclusion criterion as "seeking GAHT-E." Gender identity and GAHT-E were not referred to as "feminizing" to avoid assumptions or implications of binary gender. Instead, GAHT-E was defined as "medications taken for the purpose of altering your body toward body characteristics such as fat distribution across the body, breast growth, and finer body hair. This can include medications like estrogen, spironolactone, or others."

CAB input and clinical experience indicated that defining this population by natal sex inherently invalidated their lived identities; thus, our research group sought to develop a population definition without reference to natal sex. Our team was unable to develop another approximation of endogenous hormone environment that was as clear and concise—though lacking precision—as the widely used "sex assigned at birth." CAB members suggested "sex listed on your original birth certificate," which was abbreviated to "listed 'male' at birth" or "LMAB," hoping its similarity to the established term "assigned male at birth" or "AMAB" would enhance clarity while reducing invalidating and oppressive connotations.

Our final population definition included individuals listed as "male" on their original birth certificates who were 18 years of age or older and seeking GAHT-E. For initial communication (e.g., flyers), the target population was described as "treatment-seeking trans and gender-expansive people listed as 'male' at birth." GAHT-E was not specified for the sake of concision, reasoning that GAHT-E experience or interest would, in any case, be common among respondents. Additionally, the research group did not want to exclude individuals interested only in other treatments, including androgen blockade monotherapy or surgical therapies.

## Survey design

This study was reviewed and approved by the UCLA South General Institutional Review Board. Our survey of 60 items covering demographics, transition history, treatment goals and experiences, and research priorities was distributed using Qualtrics, an online survey tool. As an incentive and token of gratitude, individuals could enter a raffle for one of eight gift cards regardless of participation. To prevent linking survey

responses to identifiable raffle entries, a separate entry form accessible only through a restricted link provided upon completion or declination of the survey was created.

Prior to any questions, the electronic survey presented study information, including a statement that participation was voluntary and an item requesting consent to continue. To ensure respondents met inclusion criteria, three initial screening items excluded respondents who (1) did not consent, (2) were younger than 18 years of age, or (3) were listed as "female" or "intersex" on their original birth certificates. Built-in tools of the Qualtrics platform were utilized to discourage multiple participation and bot responses as well as to remove identifiers, such as IP address, from the final dataset.

Item text and response options were based on personal experiences, patient reports, and CAB consultation. Given the paucity of existing data to guide scale development, face-valid single items were created to be analyzed individually. Several items included an additional free-text option to solicit additional information where available response items were insufficient. For affirmation and brevity, logic structures were used to avoid displaying questions not applicable to the respondent. For example, participants were asked if they had a penis prior to questions about erectile function, which were then displayed only following an affirmative response. Broadly inclusive definitions of terms were utilized (e.g., defining "sex" as "any activity you use for erotic stimulation whether you are alone or with another person. This includes masturbation, oral sex with a partner, penetrative sex, and a wide range of other activities").

In contrast, some items were designed restrictively to simplify future analyses. For instance, the complex reality of gender identity was balanced with the statistical simplicity of finite, mutually exclusive choices with the item "With which of these gender identities do you *most* identify?" Insight on item acceptability and utility was sought through the "a gender not listed here" option, which included a free-text field.

### Recruitment

The survey was distributed as follows: by (1) emailing patients who previously agreed to receive research opportunities, (2) sharing survey flyers with community allies, and (3) social media and community forum posts. By utilizing our community connections and prioritizing online outreach, the study team hoped to reach a more diverse convenience sample than our institution's primarily white, non-Hispanic, and privately insured population [13]. A team member engaged with relevant online communities led an outreach effort focused on groups created by and for treatment-seeking individuals using relevant terms (e.g., "MtF," "transfeminine," and "GAHT").

### Analysis

Using SAS version 9.4 (SAS Institute, Cary, NC, USA), data was examined for anomalous response patterns such as duplicate responses and outliers. Once data was determined to be free of such artifacts, built-in analysis and reporting tools on the Qualtrics platform were used to produce descriptive statistics. Given our descriptive goal, the study did not include *a priori* hypotheses or conduct significance tests. Instead, we sought to describe response variance and free-text additions. Categorical responses are reported as proportions of responders to respective individual items. For items with many free-text responses, answers were categorized by simple topic (e.g., body part described) and reported by number of respondents addressing each topic. The recommendations in the Checklist for Reporting of Survey Studies (CROSS) were followed in developing this report [14].

## Results

Of 1729 individuals who accessed and responded to at least one screening or consent item, 1270 eligible individuals (73%) completed the survey between June 8 and July 31, 2021. Details for participant eligibility are displayed in Fig. 1.
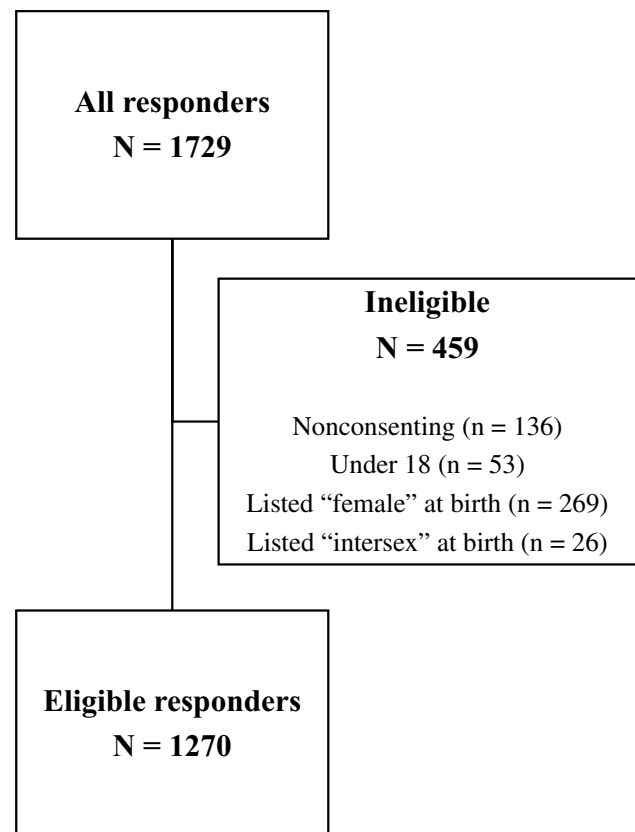


**Fig. 1** Flow diagram for inclusion and exclusion of participants. Note that exclusion criteria were nonexclusive

## Demographics

Respondent demographics are presented in Table 1. Though 90% of respondents reached the survey via social media, our recruitment strategy generally did not meet our goal of a sample more diverse than that of our local program. Predominantly, respondents were white (77%), under age 35 (84%), and residing in the USA (81%).

**Table 1** Demographic characteristics of the study sample (*N* = 1270)

| | % | *n* |
|---|---|---|
| Age | | |
| 18–25 | 41.6 | 528 |
| 26–35 | 42.4 | 539 |
| 36–45 | 9.5 | 121 |
| 46–55 | 3.2 | 40 |
| 56–65 | 2.2 | 28 |
| Most congruent gender identity | | |
| Female | 24.2 | 307 |
| Transgender female | 45.0 | 572 |
| Male | 19.6 | 249 |
| Transgender male | 4.3 | 55 |
| Genderqueer | 0.8 | 10 |
| Genderfluid | 1.2 | 15 |
| Non-binary | 3.5 | 45 |
| A gender not listed here (please specify) | 1.1 | 14 |
| Agender | 0.2 | 3 |
| Location | | |
| United States-West | 32.7 | 410 |
| United States-South | 20.3 | 255 |
| United States-Midwest | 15.0 | 188 |
| United States-Northeast | 13.0 | 164 |
| North America-Canada | 4.7 | 60 |
| North America-Mexico | 0.5 | 6 |
| Europe | 8.8 | 111 |
| Africa | 0.3 | 4 |
| Asia | 0.7 | 9 |
| South America | 0.4 | 5 |
| Australia | 3.3 | 41 |
| Education | | |
| Less than high school diploma | 2.5 | 32 |
| High school graduate (high school diploma or equivalent including GED) | 16.7 | 209 |
| Some college but no degree | 26.7 | 334 |
| Associate degree in college (2-year) | 15.5 | 193 |
| Bachelor's degree in college (4-year) | 27.4 | 344 |
| Master's degree | 7.0 | 87 |
| Doctoral degree | 2.4 | 30 |
| Professional degree (JD, MD) | 1.6 | 20 |

**Table 1** (continued)

| | % | *n* |
|---|---|---|
| Racial identity | | |
| Asian | 3.9 | 51 |
| Native Hawaiian or Pacific Islander | 2.6 | 34 |
| Other | 2.0 | 26 |
| Black or African American | 6.4 | 84 |
| White | 77.3 | 1019 |
| Native American or Indigenous | 7.9 | 104 |
| Spanish, Hispanic, or Latinx | | |
| Yes | 21.0 | 257 |
| No | 79.0 | 966 |
| Insurance coverage | | |
| Yes, I have insurance through my employer | 27.5 | 344 |
| Yes, I have insurance that I pay for myself | 28.2 | 353 |
| Yes, I have state or nationally sponsored coverage such as Medicare or Medicaid | 24.6 | 308 |
| No, I do not have medical coverage | 5.5 | 69 |
| I'm not sure if I have medical coverage | 2.1 | 26 |
| Yes, I have coverage through my parents | 12.2 | 153 |
| Exposure to hormone therapy | | |
| Yes | 81.2 | 1017 |
| No | 18.4 | 229 |
| More than a year | 54.5 | 678 |
| Less than a year | 45.5 | 566 |

Regarding gender identity, one respondent commented that "transgender female" did not make sense because "female" is a sex category, while "woman" is a gender category. Another respondent also added "transgender woman" as free text. Overall, 14 individuals (1%) selected "a gender not listed here." Of associated free-text responses, only "demigirl," listed twice, was listed more than once.

### Treatment goals

Figure 2 displays the overall goals of gender-affirming treatment. Treatments are listed in order of the frequency with which they were rated "extremely important." Similarly, physical features prioritized for change are listed in Fig. 3. Free-text responses are described in Table 2.

### Subjective efficacy indicators

Table 3 lists potential experiences during GAHT-E in the order of frequency endorsed as indicators as to whether GAHT-E was working or not. Free-text positive indicators
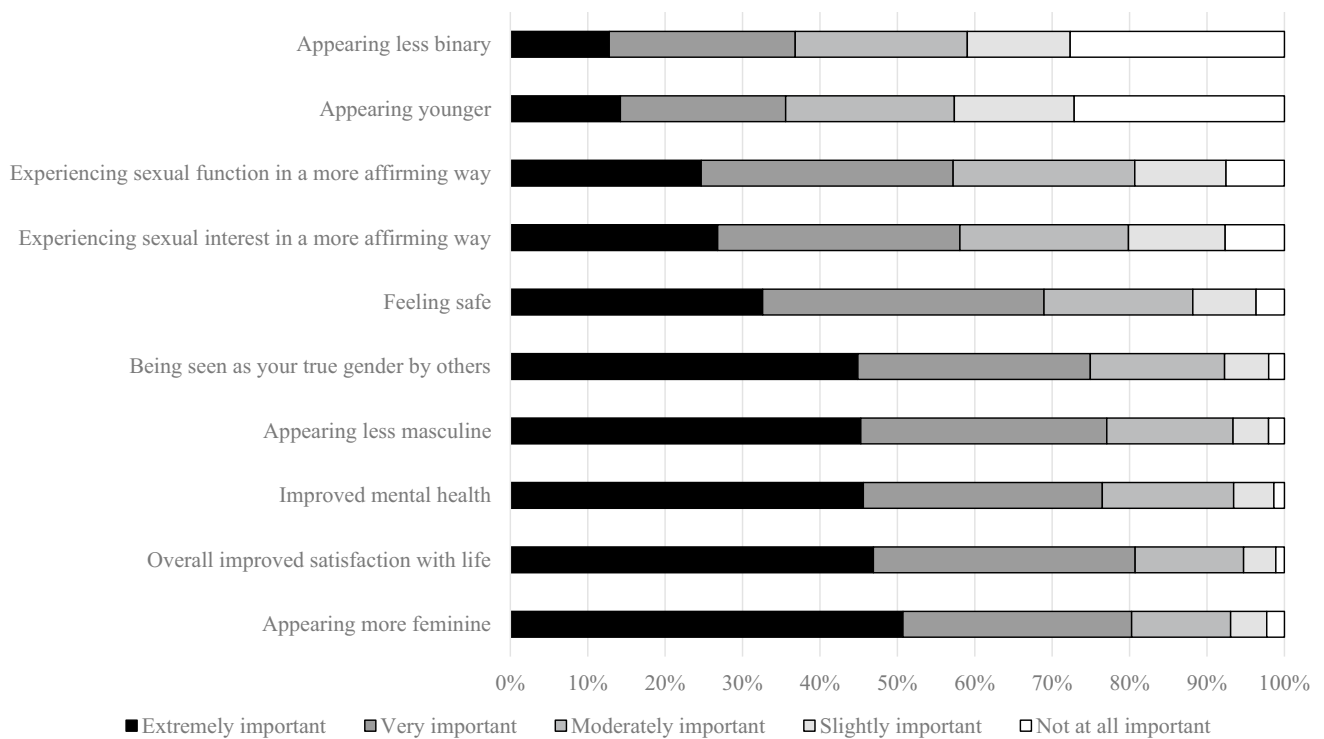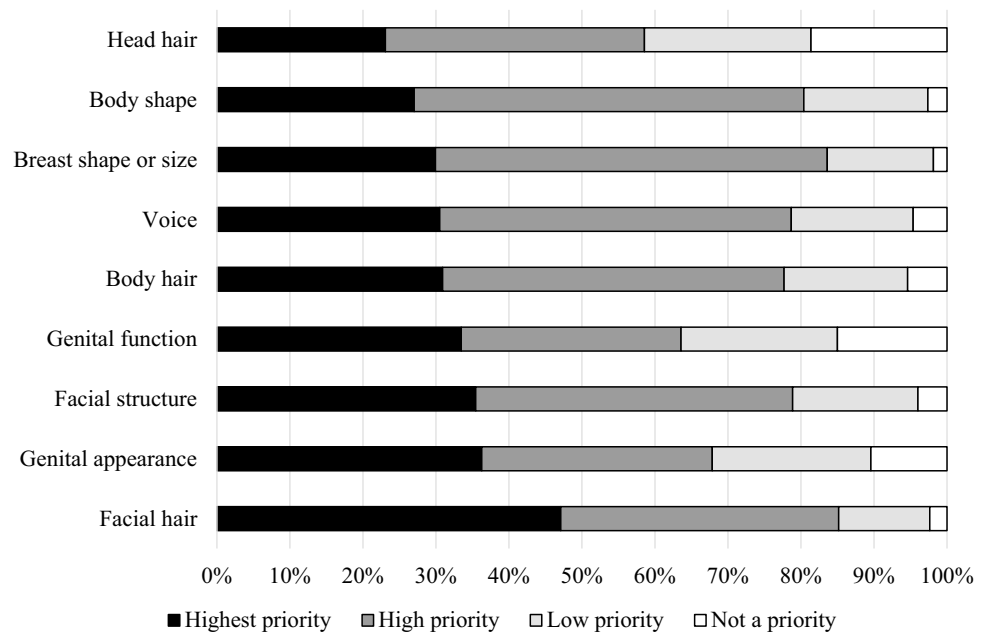
**Fig. 2** Goals when starting gender-affirming treatment

**Fig. 3** Priorities for physical change



added by multiple respondents included qualitative changes to sexuality, changes in body odor, changes to face shape, and reduced head hair loss. Additions to negative indicators were similar to (e.g., changes in body odor) or opposite of (e.g., head hair loss) positive indicators.

## Research priorities

From a list of potential research questions, respondents selected up to three as the most important. These are listed in Table 4 by proportion of respondents endorsing them.

**Table 2** Additional features noted as priorities for change in free-text responses

| Feature | Number of respondents |
|---|---|
| Acne or other skin concerns | 28 |
| Hands, feet, or both | 21 |
| Adam's apple or trachea | 16 |
| Shoulder, chest, or ribcage shape | 15 |
| Overall body shape | 11 |
| Muscle mass | 11 |
| Height | 11 |
| Legs or thighs | 10 |
| Emotional, psychological, or behavioral changes | 10 |
| Hips or buttocks | 9 |
| Facial features | 8 |
| Weight | 6 |
| Odor | 5 |

**Table 3** Subjective indicators of efficacy

| | % | Count |
|---|---|---|
| If your treatment WAS WORKING the way you want, which of these would be important indicators of this? (multiple responses allowed) | | |
| Breast growth | 76.27 | 871 |
| Body shape changes | 71.89 | 821 |
| Decreased body/facial hair | 68.39 | 781 |
| Skin softening | 63.49 | 725 |
| Emotional state | 56.48 | 645 |
| Decreased erectile function | 28.46 | 325 |
| Increased sex drive | 16.46 | 188 |
| Decreased sex drive | 14.10 | 161 |
| Increased erectile function | 8.23 | 94 |
| Other | 2.36 | 27 |
| Total (*n*) | | 1142 |
| If your treatment was NOT WORKING the way you want, which of these would be important indicators of this? (multiple responses allowed) | | |
| Emotional state | 47.20 | 522 |
| Skin changes | 46.56 | 515 |
| Hair thickening | 42.86 | 474 |
| Increased sweating | 40.14 | 444 |
| Increased erectile function | 36.53 | 404 |
| Increased sex drive | 29.75 | 329 |
| Decreased erectile function | 14.74 | 163 |
| Decreased sex drive | 11.75 | 130 |
| Other | 3.80 | 42 |
| Total (*n*) | | 1106 |

Research questions added in free-text responses were similar in their focus on assessing efficacy and safety, additionally suggesting comparing different types of estrogen, testing estrogen monotherapy, and measuring head hair loss as an outcome.

## Discussion

This study emphasizes the immense variance in identities, experiences, and treatment goals among individuals seeking GAHT-E. For example, although respondents rated head hair as a "low priority" or "not a priority" more frequently than any other feature, nearly 60% still rated it as "highest priority" or "high priority." Furthermore, reducing head hair loss was the only specific endpoint listed as a research priority in free-text responses. Similarly, while 16% of individuals felt that *increased* sex drive was a sign of treatment efficacy, 14% reported that *decreased* sex drive was a sign of efficacy. Speaking to the complexity of gender identity, 24% of our respondents identified as male or transgender male, and 87% of that group reported current or former use of GAHT-E compared to 82% of the entire sample. Their GAHT-E use indicates that this group was appropriately included and that centering inclusion criteria on treatment choice allowed us to recruit a group who may not have responded to identity-based recruitment or may have been excluded by identity-based screening items.

Just as informative are the commonalities in our data. Current guidelines for GAHT-E recommend matching treatment regimens with individualized goals, but research evaluating *how* to personalize treatment is lacking [2, 3]. Respondents' highest-rated research priority was comparing routes of estrogen administration in facilitating feminization. Among known outcomes of GAHT-E, respondents most prioritized breast growth, facial and body hair reduction, and body shape changes. The highest prioritized overall treatment goal was "satisfaction with life." These data provide a foundational step toward incorporating the needs of the community into future research and patient care by roughly outlining which treatment goals should be prioritized when designing efficacy studies. While a few prospective cohort studies have attempted to assess some of these differences in physical changes with varying levels or routes of estrogen [4–6], the results have been limited by uncontrolled variables. Active-control trials can provide vital information by varying a single aspect of treatment (e.g., route of administration).

An expansive review of methods to quantitatively assess prioritized outcomes of GAHT-E is outside the scope of this article; however, it should be noted that one substantial

**Table 4** Research question priorities (respondents could select up to three priorities)

| | % |
|---|---|
| Which administration route (patch, injection, pills) of hormone therapy is most effective at feminizing the body? | 54.32% |
| Which administration route (patch, injection, pills) of hormone therapy has the fewest side effects and safety concerns? | 43.01% |
| Does progesterone help with feminizing the body? | 36.87% |
| Do higher levels of estrogen in the blood lead to more feminization or faster feminization? | 36.70% |
| What is the most effective way to block testosterone production or action? | 30.74% |
| Which hormone treatment regimen maintains sexual function most effectively? | 18.31% |
| What is the best way to treat hormone therapy-related painful erections and penile atrophy? | 15.63% |
| How does diet interact with hormone therapy? | 13.73% |
| How does hormone therapy interact with other medications? | 13.39% |

barrier to efficacy trials is that most available measures that were developed with cisgender samples have not been validated in gender-diverse populations, and when used have often been found to be of mixed utility in assessing GAHT-E effects [15–20]. To cite an example, most methods that evaluate breast growth assess volume, which translates easily as a continuous variable for analysis but may not represent patient preferences for overall breast shape [21]. Measurement tools should be grounded in the needs of the relevant population and thoroughly capture the patient experience [22]. The GENDER-Q, for instance, is a modular set of PROMs currently in field testing after development in collaboration with gender-diverse stakeholders which promises to be ideal for GAHT trials [23]. The GENDER-Q may be an ideal model to help update existing anatomical measurement tools to become more patient-centric.

Acknowledging diverse treatment goals is also a requisite for providing an informed, individualized approach to patient care. To illustrate, individuals who view increased libido as a sign of treatment failure may benefit from aggressive testosterone suppression. Conversely, individuals who want to maintain erectile function and libido may benefit from a liberal testosterone goal and early conversations about phosphodiesterase inhibitors. While it is not clear that adjusting testosterone goals directly affects libido, approaching treatment with an open mind, querying specific goals, and allowing patients room to explore such possibilities may improve the doctor-patient relationship, empower patients to be active participants in their care, and ultimately help providers gain understanding of ways to personalize treatment.

Eliciting patient goals at an initial intake visit can also elucidate which adjunctive therapies to utilize. For example, those who rate body hair reduction as a top priority should be referred for laser or electrolysis early in transition, while those who prioritize voice change warrant an early referral for voice therapy. Similarly, if androgenic alopecia is a large source of dysphoria, it may be worthwhile discussing the addition of minoxidil to initial hormone therapy. It is

also important for providers to be mindful that not all individuals with gender incongruence desire hormone therapy. Discussing specific treatment goals may reveal that utilizing exclusively non-hormonal treatments such as scalp hair restoration surgery, laser hair removal, and voice therapy is more suitable for some.

## Limitations

This report describes methods and findings of initial steps toward designing efficacy trials for GAHT and as such is limited in its generalizability. Because the survey was developed based on patient-reported experiences, personal experiences, and the advice of our CAB, our decisions were substantially shaped by our locality and the patients seen at our center. The study team had hoped to reach a broader population via global recruitment within online communities to assess broader validity, but ultimately our sample was substantially similar to those individuals seen in our clinics.

Although it speaks to the efficacy of our recruitment efforts, having 90% of participants recruited from social media may bias our results. Social media offer important spaces for building transgender, nonbinary, and other gender-expansive communities [24–27], but as with physical spaces, access is not always equitable [28, 29]. Further, the online groups from which survey respondents were recruited often focused on *starting* gender-affirming treatments, likely contributing to our sample's relatively short duration of hormone therapy. The groups frequently included such terms as "MtF" or "transfeminine" in titles and descriptions and may have appealed less to nonbinary users; only 3.5% of our respondents reported identifying most with a nonbinary identity, while the Williams Institute estimated that 32.1% of transgender adults in the USA identify as non-binary [30].

Future studies should more directly target communities that our study left out, preferably via qualitative methods that allow participants greater freedom to express experiences

different from those encoded in a structured questionnaire. Additionally, the majority of our study participants were aged 18–35. Future studies should target more specific age ranges to assess whether age affects goals and expectations. Our findings represent only a starting point for characterizing community research priorities; different methods are essential to broadening and deepening our understanding.

## Conclusions

Well-controlled efficacy trials will be essential to gaining regulatory approval for the specific use of GAHT medications, refining clinical care guidelines, tailoring individual treatment plans, and ultimately understanding how to safely and effectively support gender-diverse patients. To best do so, trial designs must be grounded in the needs, priorities, and experiences of actual GAHT users. Based on our collaboratively developed community survey, the medical community should prioritize trials comparing estrogen administration routes in their effects on breast growth, body hair, body shape, and overall well-being. Our findings can serve as a starting point for GAHT-E trials and our methods as one approach to meeting the challenge of their design.

## Declarations

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