

Response ID ANON-5H8E-SHQ-N-M

Submitted to Interim Clinical Policy: Puberty suppressing hormones for children and adolescents who have gender incongruence/dysphoria
Submitted on 2023-10-30 14:55:13

About you

1 In what capacity are you responding?

Other

If you have selected 'Other', please specify::

European Professional Association for Transgender Health (EPATH) and The World Professional Association for Transgender Health (WPATH). The European Professional Association for Transgender Health (EPATH) and the World Professional Association for Transgender Health (WPATH) are deeply concerned over the NHS England Interim Clinical Policy: Puberty suppressing hormones for children and adolescents who have gender incongruence or dysphoria. Transgender and gender diverse young people across the United Kingdom are facing a health care access crisis. The closure of the NHS Tavistock Clinic's Gender Identity Development Service (GIDS), with no new clinical hubs fully operational yet, has left young transgender and gender diverse people and families with no opportunity to obtain care. This is in breach of the main Principles of the NHS Constitution. We urge NHS England to immediately revise the proposed guidelines and work to strengthen equitable access to gender-affirming health care services for transgender and gender diverse youth across the nation.

2 Are you responding on behalf of an organisation?

Yes

If you have selected "Yes", which organisation are you responding on behalf of?:

On behalf of the Associations EPATH and WPATH; The aims of the Associations, which it may pursue at international level in any country, are: (1) to promote mental, physical and social health of transgender people in Europe/globally; (2) to increase the quality of life among transgender people in Europe/globally ; and (3) to ensure transgender people's rights for healthy development and well-being (for further information see The Bylaws at www.wpath.org and www.epath.eu). EPATH and WPATH are concerned about the current situation in the UK for transgender and gender diverse young people, as it significantly risks compromising their health. At present, the former care provider, the NHS Tavistock Clinic's Gender Identity Development Service (GIDS), is not scheduling any new patient appointments for those on the waiting list and the two new proposed (clinical) hubs are not (fully) operational. While the existence of long waiting lists has already compromised the access to transgender healthcare severely, the current situation leaves transgender and gender diverse young people and their families seeking appropriate medical treatments without any possibility to receive such care. Additionally, EPATH and WPATH are concerned about the policy proposition that puberty suppressing hormones are not recommended to be available as a routine commissioning option for the treatment of adolescents who have gender incongruence or dysphoria. EPATH and WPATH support the scientific and consensus-based clinical recommendations of WPATH's Standards of Care Version 8 (SOC8) Adolescent Chapter. We are concerned that the proposed policy proposition is not according to these Standards of Care, which recommend, among other recommendations, the use of puberty blocking hormones and other medical affirming interventions, when certain criteria are fulfilled. The complete lack of access to this treatment will impact the lives of transgender youth in the United Kingdom permanently, as the physical changes from their endogenous puberty are irreversible.

Interim clinical policy

3 Has all the relevant evidence been taken into account?

No

If you selected 'No', please give details::

The National Institute for Health and Care Excellence (NICE) review was published in 2020, which reviewed 9 studies regarding both clinical effectiveness (studies concerning associations of puberty blockers and outcomes regarding gender dysphoria, mental health and quality of life), as well as safety (studies concerning associations of puberty blockers and physical health parameters, based on the PICO format (population, intervention, control, and outcomes). In short, for children and adolescents with gender dysphoria, these address questions regarding: 1) clinical effectiveness; 2) short-term and long-term safety; and 3) cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention.

The selected studies by NICE only focused on the effects of puberty blockers, therefore studies that evaluated a combination of blockers, hormones, and/or surgeries were excluded. This resulted in the inclusion of 9 studies fulfilling the criteria for the defined PICO, while 11 studies were excluded. All selected studies were graded based on the GRADING system as providing 'VERY LOW' evidence. In subsequent stakeholder testing (2023), 8 stakeholders suggested 19 identifiable and unique references that might have been erroneously omitted from the evidence review or literature surveillance report, which were assessed to not fall within PICO and search methodology, with one exception: de Vries et al., 2014. It was concluded that the de Vries et al., 2014 study does fall within the PICO format and search methodology as set out by NICE. It indicates that use of GnRH analogues along with other interventions (e.g., multidisciplinary care) improves body image outcomes after gender affirming surgery. However, this evidence does not materially affect the conclusions of the existing evidence review. (Post-Engagement Evidence Report on Interim PSH Policy for Gender Incongruence or Dysphoria). There are additional studies that are of relevance and should be considered to be incorporated within the NICE review:

Kuper, L. E., Stewart, S., Preston, S., Lau, M., & Lopez, X. (2020). Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics*, 145(4), e20193006. <https://doi.org/10.1542/peds.2019-3006>

Effectiveness studies on blockers, hormones or both.

- Wiepjes et al., (2018).

Wiepjes, C. M., Nota, N. M., de Blok, C. J. M., Klaver, M., de Vries, A. L. C., Wensing-Kruger, S. A., de Jongh, R. T., Bouman, M. B., Steensma, T. D., Cohen-Kettenis, P., Gooren, L. J. G., Kreukels, B. P. C., & den Heijer, M. (2018). The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *The Journal of Sexual Medicine*, 15(4), 582–590. <https://doi.org/10.1016/j.jsxm.2018.01.016>

Report the % of adolescents that stopped blockers (1.9%).

- van der Miesen et al., (2020).

van der Miesen, A. I. R., Steensma, T. D., de Vries, A. L. C., Bos, H., & Popma, A. (2020). Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. *The Journal of Adolescent Health : Official publication of the Society for Adolescent Medicine*, 66(6), 699–704. <https://doi.org/10.1016/j.jadohealth.2019.12.018>

A cross sectional study comparing psychological functioning of transgender adolescents on blockers with baseline transgender adolescents as well as cisgender general population peers; transgender adolescents on blockers functioned better than baseline and comparable to cisgender same age peers.

- Arnoldussen et al., (2022).

Arnoldussen, M., van der Miesen, A. I. R., Elzinga, W. S., Alberse, A. E., Popma, A., Steensma, T. D., & de Vries, A. L. C. (2022). Self-Perception of Transgender Adolescents After Gender-Affirming Treatment: A Follow-Up Study into Young Adulthood. *LGBT Health*, 9(4), 238–246.

<https://doi.org/10.1089/lgbt.2020.0494>

Showing improvement in self-perception on baseline (adolescents) compared to post-treatment (young adulthood).

- van der Loos et al., (2022).

van der Loos, M. A. T. C., Hannema, S. E., Klink, D. T., den Heijer, M., & Wiepjes, C. M. (2022). Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. *The Lancet. Child & Adolescent Health*, 6(12), 869–875.

[https://doi.org/10.1016/S2352-4642\(22\)00254-1](https://doi.org/10.1016/S2352-4642(22)00254-1)

Showing continuation rates of hormone use (98%) after puberty suppression of up to 20 years after it's start.

- Nos et al., (2022).

Nos, A. L., Klein, D. A., Adirim, T. A., Schvey, N. A., Hisle-Gorman, E., Susi, A., & Roberts, C. M. (2022). Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents. *Journal of the American Medical Association*, 5(11), e2239758. <https://doi.org/10.1001/jamanetworkopen.2022.39758>

These findings suggest that clinicians can offer GnRH analogues to transgender and gender-diverse adolescents during pubertal development for mental health and cosmetic benefits without an increased likelihood of subsequent use of gender-affirming hormones.

Other studies concerning safety have also been published. These include:

- Schagen et al., (2020).

Schagen, S. E. E., Wouters, F. M., Cohen-Kettenis, P. T., Gooren, L. J., & Hannema, S. E. (2020). Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. *The Journal of Clinical Endocrinology and Metabolism*, 105(12), e4252–e4263.

<https://doi.org/10.1210/clinem/dgaa604>

During 2 years of GnRHa treatment, Bone mineral apparent density (BMAD) stabilized or showed a small decrease, whereas z-scores decreased in all groups. During 3 years of combined administration of GnRHa and gender-affirming hormones, a significant increase of BMAD was found. Z-scores normalized in transboys but remained below zero in transgirls. In transgirls and early pubertal transboys, all bone markers decreased during GnRHa treatment.

- Boogers et al., (2022).

Boogers, L. S., Wiepjes, C. M., Klink, D. T., Hellinga, I., van Trotsenburg, A. S. P., den Heijer, M., & Hannema, S. E. (2022). Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment. *The Journal of Clinical Endocrinology and Metabolism*, 107(9), e3805–e3815.

<https://doi.org/10.1210/clinem/dgac349>

Growth decelerated during GnRH analogues and accelerated during gender-affirming hormone therapy (GAHT). After regular-dose treatment, adult height was slightly lower than predicted at start of GnRH analogues, likely due to systematic overestimation of predicted adult height (PAH) as described in boys from the general population, but not significantly different from target height. High-dose ethinyl estradiol (EE) resulted in greater reduction of adult height than high-dose estradiol, but this needs to be weighed against possible adverse effects.

- Arnoldussen et al., (2022).

Arnoldussen, M., Hooijman, E. C., Kreukels, B. P., & de Vries, A. L. (2022). Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents. *Clinical Child Psychology and Psychiatry*, 27(4), 1069–1076.

<https://doi.org/10.1177/13591045221091652>

Evaluating associations between baseline IQ (before blockers, hormones and surgeries) and post-treatment young adulthood educational level.

Moreover, WPATH published, as aforementioned, the 8th edition of its Standards of Care for the Health of Transgender and Gender Diverse People.

Coleman, E., Radix, A. E., Bouman, W. P., Brown, G. R., de Vries, A. L. C., Deutsch, M. B., Ettner, R., Fraser, L., Goodman, M., Green, J., Hancock, A. B., Johnson, T. W., Karasic, D. H., Knudson, G. A., Leibowitz, S. F., Meyer-Bahlburg, H. F. L., Monstrey, S. J., Motmans, J., Nahata, L., Nieder, T. O., ... Arcelus, J.

(2022). Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *International Journal of Transgender Health*, 23(Suppl 1), S1–S259. <https://doi.org/10.1080/26895269.2022.2100644>

Regarding the evidence for treatment of transgender and gender diverse adolescents, SOC8 states: "Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood. Therefore, a systematic review regarding outcomes of treatment in adolescents is not possible. A short narrative review is provided instead." While systematic reviews are important in areas of medicine where the evidence is robust, in gender health for minors, our organization believes it is important to simultaneously 1) acknowledge the state of the evidence; 2) develop guidelines that promote a careful and comprehensive approach, while 3) continuing to promote and advocate for continued research and scientific advancements that will further contribute to honed clinical practice recommendations in the future. SOC8 concluded: "although the existing samples reported on relatively small groups of youth (e.g., n = 22 - 101 per study) and the time to follow-up varied across studies (6 months - 7 years), this emerging evidence base indicates a general improvement in the lives of transgender adolescents who, following careful and comprehensive assessment, receive medically necessary gender-affirming medical treatment. Further, rates of reported regret during the study monitoring periods are low. Taken as a whole, the data show early medical intervention - as part of broader combined assessment and treatment approaches focused on gender dysphoria and general well-being - can be effective and helpful for many transgender adolescents seeking these treatments."

Also, regarding the state of the evidence, it is important to stress again that more outcome data are desirable and while controlled trials would provide stronger evidence, they are neither feasible nor ethical. Regarding the feasibility issues, e.g., an untreated control group, this will be highly unlikely since eligible adolescents rarely refrain from treatment. Furthermore, treatment preference may lead to non-participation or withdrawal from a randomized

trial of the group without GnRH. Finally, blinding will be impossible due to the clinically evident effects of treatment (or lack thereof). An alternative might be a waiting-list control group, something that might become feasible with the present long waiting-lists, although still unethical, since puberty develops further while these adolescents will be on the waiting list with life-long (undesired physical) consequences. Other options would be between-clinic comparisons with different treatment approaches, although between-clinic contexts might differ in so many respects that a robust comparison may be extremely challenging. Therefore, the most feasible and preferred option are rigorous longitudinal studies using appropriate outcome measures to provide valuable evidence on the effects and safety of GnRH analogues, of which the Dutch cohort studies are an example.

It is also important to realize that, at present, the NHS is defining the outcome measures for gender affirming medical treatments (improvement of psychological functioning or quality of life), however this falls short. Additional outcomes, such as the improvement of gender dysphoria, satisfaction with care, trends of detransition (and why) are all important to capture in addition to improvement of psychological functioning and/or quality of life. Simply put, for many transgender youth who appropriately receive gender affirming medical care, quality of life may improve, however many other aspects of the human experience can detrimentally impact quality of life in unforeseen ways. It is alarming that the totality of appropriate outcome measures are not being taken into account when making one-size-fits-all policy decisions.

Despite the many areas in medicine where the evidence is low (see e.g., Eating Disorders guidelines of NICE) recommendations are published without the same degree of criticism or scrutiny that gender affirming medical interventions encounter. Considering the definition of low evidence can be subjective and is often based on study biases (due to low numbers or lack of controls), the need for recommendations and guidance is even more necessary in these circumstances. For example, there was low evidence regarding many of the approaches followed during the start of the COVID-19 pandemic, yet careful recommendations were made. All clinical practice guideline recommendations, whether the available evidence is considered as being of high quality or very low quality, require both a judicious consideration of the relevant evidence and consensus from the panel regarding both the interpretation of the evidence and the trade-off between the benefit(s) versus the harm or burden of the recommended health intervention.

Summing up, systematic reviews alone are not enough to make robust clinical recommendations. The Standards of Care version 8, consistent with clinical guidelines in other aspects of medicine, provide recommendations that are based on several factors, including but not limited to the available research. The hallmark recommendation in the Adolescent chapter of SOC8 is for well-qualified and well-trained providers to conduct a comprehensive biopsychosocial assessment in order to determine treatment priorities and sequence, which means medical treatments may or may not be indicated in a particular clinical scenario. This careful recommendation is made because of the limited amount of studies that inform the totality of available evidence, not in spite of it.

4 Does the equality and health inequalities impact assessment reflect the potential impact that might arise as a result of the proposed changes?

No

If you selected 'No', please give details::

While formulating the adolescent SOC8 statements, medical ethics and human rights perspectives were also considered. This seems extremely important in transgender care for adolescents, apart from evidence regarding efficacy and safety. The Adolescent Chapter in the SOC8 refers to, for example, the fact that allowing irreversible puberty to progress in adolescents who experience gender incongruence is not a neutral act given that it may have immediate and lifelong harmful effects for the transgender young person (Giordano, 2008; Giordano & Holm, 2020; Kreukels & Cohen-Kettenis, 2011). From a human rights perspective, considering gender diversity as a normal and expected variation within the broader diversity of the human experience, it is an adolescent's right to participate in their own decision-making process about their health and lives, including access to gender health services (Amnesty International, <https://www.amnesty.org.uk/press-releases/amnesty-international-uk-and-liberty-joint-statement-puberty-blockers>). Giordano S. (2008). Lives in a chiaroscuro. Should we suspend the puberty of children with gender identity disorder? *Journal of Medical Ethics*, 34(8), 580-584. <https://doi.org/10.1136/jme.2007.021097>

Giordano, S., & Holm, S. (2020). Is puberty delaying treatment 'experimental treatment'? *International Journal of Transgender Health*, 21(2), 113-121. <https://doi.org/10.1080/26895269.2020.1747768>

Kreukels, B. P., & Cohen-Kettenis, P. T. (2011). Puberty suppression in gender identity disorder: the Amsterdam experience. *Nature Reviews. Endocrinology*, 7(8), 466-472. <https://doi.org/10.1038/nrendo.2011.78>

5 Are there any changes or additions you think need to be made to this policy?

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It is also important to provide context on systematic reviews and how they inform clinical practice. A systematic review cannot, and should not be used as an exclusive arbiter to determine whether a particular model of care is evidence-based or not. There are many ways of obtaining evidence, which can be obtained both from the scientific literature and expert clinical consensus. While the importance of randomized control trials were stressed in early descriptions of evidence-based medicine, they are rarely performed as it is unethical and impractical to randomize subjects to treatment groups or lack thereof.

Rather, evidence-based medicine is about using the best available evidence to guide clinical decision-making and the development of practice guidelines, which provide guidance on how to ethically use the evidence, whether from randomized trials, observational studies, physiological experiments, case series, case reports, or the experience of individual (or a group of) clinicians, to optimally help patients make the best decisions consistent with their circumstances and values. Thus, all guidelines should be evidence-based, even when the evidence is of very low quality. The guideline development process and the recommendation should include a systematic review of the literature and rigorous assessment of the quality of the evidence. But in addition, the evidence requires interpretation (whether from randomized trials or case reports) and, in the context of guidelines, a consensus process must determine that interpretation. This need for interpretation is important because most observations are theory-laden and conclusions regarding the phenomenon of interest can only be drawn in the context of existing theoretical understanding and shared sets of values.

On occasion, the evidence is so compelling that answers to such questions are obvious and beyond dispute. Far more often, the answers are less obvious and require evaluation and, in the context of guidelines, a series of expert consensus recommendations. Every recommendation in the Standards of Care for the Health of Transgender and Gender Diverse People – Version 8 (SOC8) was agreed upon through a Delphi consensus process (in addition to reviewing the available scientific literature, whether through systematic reviews or short narrative reviews of the existing research), necessitating 75%

agreement from the international and multidisciplinary committee of 120 experts in the field. The hallmark recommendation in the Adolescent chapter of SOC8 is for well-qualified and well-trained providers to conduct a comprehensive biopsychosocial assessment in order to determine treatment priorities and sequence, which means medical treatments may or may not be indicated in a particular clinical scenario.

The proposed NHS Policy regarding Puberty Suppressing Hormones is currently based on decisions that 1) Seems to Assume a treatment model (e.g., "gender affirming model") is the stance driving the WPATH SOC8 Adolescent chapter when it is not; 2) seems to Promote a one-size-fits-all approach when the complexity of the human experience necessitates a broader (yet still careful and ethical) framework, as is the case in SOC8; 3) seems to be Predicated on the notion that a systematic review can be the sole arbiter of what constitutes sufficient evidence for treatment recommendations, when that is not the case in other areas of medicine; and lastly, 4) Isolated cases of regret or rare discontinuance of treatment exist, but do not diminish the validity of treatment for the many transgender and gender diverse adolescents who meet the criteria as specified in the SOC8.

In summary, WPATH and EPATH stress the importance of maintaining access to care for all transgender and gender diverse populations, regardless of age of diagnosis.

Sincerely,

Annelou L.C. de Vries, MD, PhD, EPATH President, on behalf of the European Professional Association for Transgender Health

Marci L Bowers, MD, WPATH President, on behalf of the World Professional Association for Transgender Health

References

- Kuper et al., (2020) Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy
- Wiepjes et al., (2018) The Amsterdam Cohort of Gender Dysphoria Study (1972e2015)/ Trends in Prevalence, Treatment, and Regrets
- van der Miesen et al. (2020) Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers
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- van der Loos et al., (2022) Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence- a cohort study in the Netherlands
- Nos et al., (2022) Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents
- Schagen (2020) Bone development in transgender adolescents treated with GnRH analogues and subsequently gender affirming hormones
- Boogers (2022) Trans girls grow tall- adult height is unaffected by GnRH analogue and estradiol treatment
- Arnoldussen et al., (2022) Association between pre-treatment IQ and educational achievement after gender-affirming treatment including puberty suppression in transgender adolescents