OFFICIAL

Women's, Men's, Kid's Health
QB25-000021

ISSUE: CHILD GENDER THERAPY

QUESTION: Increasing stakeholder interest in children displaying gender dysphoria and access to gender affirming treatment.

Topline response:

- Clinical treatment of transgender children and adolescents is a complex and evolving area in which longer term evidence to inform treatment protocols is still developing.
- The provision of public gender dysphoria services to young people in Australia is led by the states and territories, who are responsible for relevant services.
  - Specialist gender services in a number of jurisdictions provide care to young people based on a multidisciplinary approach tailored to individual circumstances and needs.
  - Two independent reviews commissioned by the NSW and Queensland Governments have found their gender services are delivering care that is safe and aligned with international evidence on best practice care.
- Decisions regarding clinical care for minors are shared between the clinicians, the young person and their family. If there is a disagreement about the diagnosis, treatment, or capacity of the minor to provide informed consent, the family court has ruled this requires an application to the court to resolve the dispute consistent with the child's best interests.

Background

- Nearly 1% of Australians (178,900) are trans and gender diverse. This includes trans men, trans women and non-binary people (ABS, 2022).
- Not all trans or gender diverse people choose to affirm their gender medically (gender affirming care), legally and/or socially.
- There is no singular or overarching Medicare Benefits Schedule (MBS) item or group of items that captures all the consultations and surgical procedures involved in gender affirmation.
  - Medicare rebates are available for some surgical procedures, patient consultations with GPs, sexual health practitioners, endocrinologists, psychiatrists and specialists including plastic and reconstructive surgeons, which may occur during patient diagnosis and treatment.
- On 23 March 2023, the Medical Services Advisory Committee (MSAC) received an application from the Australian Society of Plastic Surgeons (ASPS) for the public funding of surgical procedures for gender affirmation in adults with gender incongruence (MSAC application 1754).
  - This application does not seek gender affirming treatment for children.
  - The application is currently undergoing public consultation prior to consideration by MSAC.

  - The clinical evidence component of the application (Stage 1) is scheduled to be considered by MSAC at its meeting on 3-4 April 2025.
  - The MSAC will consider the economic and financial component of the application (Stage 2) at a future meeting. The Committee will provide its recommendations to the Government following this.
- In Australia, the Therapeutic Goods Administration approved the use of gonadotropin-releasing hormone (GnRH) analogues, (or 'puberty blocking' medicines) for certain cancers, endometriosis, anticipated premature ovarian failure and precocious puberty (early puberty), but not specifically for gender affirming care.
- GnRH analogues are only available on Pharmaceutical Benefits Scheme (PBS) for the treatment of certain cancers, assisted reproductive technology, androgen deficiency and precocious puberty under certain circumstances.
  - GnRH analogues may be used '"off label" for patients undergoing gender affirmation; however, will not attract a PBS benefit in this circumstance.
  - Doctors may use medications "off label" where they are satisfied that the benefits outweigh the risks for the patient and have clearly communicated any risks and side effects clearly to the patient and parents/guardians.
- The Medical Board of Australia's 'Good medical practice: a code of conduct for doctors in Australia' states informed consent is an important part of good medical practice. This includes recognising the role of parents or guardians in a young person's treatment and, when appropriate, encouraging the person to involve their parents or guardians in decisions about their care.

MEDIA COVERAGE
Publication: 'Real risks' but sex hormones OK for teen: judge (Attachment A)
Publication date: 11 January 2025
Key issues raised:

- Following a dispute between their parents, a teenager has been granted permission by a Family Court judge to access testosterone as part of their gender affirming treatment.
  - As part of the ruling, the judge noted the risks involved in taking hormones, and highlighted the World Professional Association for Transgender Health guidelines and the Australian Standards of Care and Treatment Guidelines as having – "great weight, because they are models of care arrived at by consensus of the relevant professional bodies".

Publication: Gender stance reviewed (Attachment B)
Publication date: 4 January 2025
Key issues raised:

- The Queensland government will consider expanding the Queensland Children's Gender Service following an independent evaluation confirmed care being provided to children experiencing gender dysphoria was safe, evidence-based, and aligned with national and international guidelines.

- The Queensland Health Minister, Tim Nicholls, has now confirmed a steering committee will oversee the implementation of all 25 review recommendations.

OFFICIAL

Women's, Men's, Kid's Health
QB25-000021

Date last updated by Dept:	17 January 2025	Cleared by Adviser/date:	
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11 JAN, 2025
'Real risks' but sex hormones OK for teen: judge
Weekend Australian, Australia

'Real risks' but sex hormones OK for teen: judge

EXCLUSIVE

ELLIE DUDLEY
LEGAL AFFAIRS CORRESPONDENT

A teenager has been granted permission to access cross-sex hormones despite a Family Court judge conceding there are risks associated with the treatment, and that he cannot be certain the hormones will benefit the teenager in the long term.

Judge Peter Tree, in delivering judgment in the highly contentious legal case, afforded the teenager – known pseudonymously as Ash – the "dignity of risk" to take testosterone and continue transitioning from female to male.

In concluding his decision, Justice Tree said he expected Australian courts in the future to see "regret" cases in relation to cross-sex hormone administration to children. "Nonetheless, I have earnestly tried to ascertain what is best for Ash," he said.

The case, which The Australian has extensively covered over the past year, was brought by one of Ash's parents who wished to obtain sole parental responsibility to approve the administration of hormones. The other parent opposed the treatment.

Justice Tree gave "great weight" to the Australian Standards of Care and Treatment Guidelines, which were developed by the Royal Children's Hospital Melbourne and endorse a gender-affirming model of care.

However, he said the UK Cass Review – a landmark report that recommended limitations on medication for gender-dysphoric children – may have been driven by an "overt political imperative"

Continued on Page 6

Hormones OK for teen, judge rules

Continued from Page 1

and he gave it "little weight" in reaching his decision.

The Family Court continues to grapple with the complexities of gender identity, especially in the context of children, medication and surgery.

In a separate matter, a judge determined a father's refusal to conform with traditional gender norms left his three children "confused" and encouraged them to "question their gender identity" after they all began identifying as non-binary, ruling the two youngest children would not be permitted to see their father for an extended period.

In another case, the mother of a 13-year-old with gender dysphoria abruptly withdrew an application seeking a Family Court order to allow the child to take puberty blockers after trying to have the independent children's lawyer assigned to the matter thrown off the case.

In handing down his judgment, Justice Tree conceded there was a "real risk" the testosterone treatment "may not achieve all that Ash wants it to" and that "he may still be unhappy with having a body ... which he would prefer were different".

"He may therefore still be to some degree dysphoric," the judgment reads. "But overall, the evidence persuades me that there will be some masculinisation, and thus some alleviation of his dysphoria if testosterone were to be administered to Ash, although when, for how long, and to what extent, remains unknown."

Justice Tree outlined various considerations in favour of Ash accessing treatment, including that he had consistently lived as a male, been exposed to "serious transphobic bullying", and has worn a chest binder and layered clothing "so as to conceal the female aspects of his appearance".

He also said Ash had lived "stealth" as a male, meaning he had not disclosed to his classmates that he is biologically female. "(This) has exacted an emotional, social and educational cost on him, including recently having returned to distance education," the judgment reads.

But Justice Tree also acknowledged considerations against the treatment, including that the hormones "may not alleviate his dysphoria, either materially or even at all", and that Ash's cognitive development is ongoing, meaning he may not understand "all the risks". He paid heed to concerns the treatment may not alleviate Ash's gender dysphoria, that it may impair his fertility, and that irreversible changes may

AUTHOR: Ellie Dudley SECTION: GENERAL NEWS ARTICLE TYPE: NEWS ITEM AUDIENCE : 600,000
PAGE: 1 PRINTED SIZE: 408.00cm² REGION: National MARKET: Australia ASR: AUD 21,740
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Anti-Semitism 'on the hallof' as Labor splits

11 JAN, 2025

'Real risks' but sex hormones OK for teen: judge

Weekend Australian, Australia

start about three months after testosterone commences.

Justice Tree found while the possible risks associated with taking testosterone, including infertility or blood disorders, are "real", they are "not unacceptable".

During the hearing, the court was told Ash and his 10-year-old sister, known as Lee, made a pact that Lee would harvest her eggs to ensure Ash could have children if the transition affected his fertility in the long term.

Justice Tree in his judgment said the parent opposing treatment "unduly emphasised" the risks in order to further their case, and said while Ash may become infertile it didn't necessarily preclude him from having children.

"Even if he does become incapable of conceiving a child, if it transpires he forms a relationship with a natal female who is not transgender, or if is, is not infertile, having children is not precluded, although they may not have a genetic connection with Ash," he wrote. "It is likely that most Australians would now think the lack of direct genetic connection between a child and their parent is irrelevant. Likewise there remains the prospect of adoption and surrogacy."

Justice Tree said that in less than two years Ash will turn 18 and therefore "be able to medically do whatever he wants".

"It would obviously be farcical to reject what a 17-year and 11-month-old young person wants to do as being undeserving of weight, when a month later they can do it anyway," he said. "Similar considerations apply – albeit with lesser force – to someone Ash's age."

Justice Tree relied heavily on the evidence of a gender clinician who was a witness for the Independent Children's Lawyer, known to the court as Dr O. Dr O favoured the World Professional Association for Transgender Health guidelines as "by far the best available guidance at this time, and ... informed by decades of expert clinician experience".

Justice Tree agreed, giving the guidelines – as well as the Australian Standards of Care and Treatment Guidelines and state government policy – "great weight, because they are models of care arrived at by consensus of the relevant professional bodies".

He said the Cass Review, a landmark probe that recommended "extreme caution" be taken when prescribing hormones to children, was undertaken "in a vexed environment".

"I do not overlook that there may have been an overt political imperative behind the Cass Review – which was, after all, initiated by the UK executive government," he said.

"Particularly the then UK prime minister is on record of having publicly said on 5 October 2023 – whilst the Cass Review was being finalised: 'And we shouldn't be bullied into believing that people can be any sex they want to be. They can't. A man is a man and a woman is a woman'."

'(This) has exacted an emotional, social and educational cost on him'

JUSTICE PETER TREE
JUDGMENT ON TEEN USING CROSS-SEX HORMONES

AUTHOR: Taylah Fellows SECTION: GENERAL NEWS ARTICLE TYPE: NEWS ITEM AUDIENCE : 407,000
PAGE: 15 PRINTED SIZE: 269.00cm² REGION: QLD MARKET: Australia ASR: AUD 7,162 WORDS: 440
ITEM ID: 1042966595

04 JAN, 2025

Gender stance reviewed

Courier Mail, Brisbane

Gender stance reviewed

LNP accepts all 25 recommendations of panel child psychiatrist slams as 'stacked'

Taylah Fellows

The government will consider expanding Queensland Children's Gender Service, the Health Minister has confirmed, despite the LNP last year voting to ban puberty blockers at its annual national party conference.

Prior to his election, Premier David Crisafulli declared Queensland was taking a "vastly different approach" compared to the rest of the world when it came to gender, but he would need to see scientific evidence before considering a ban on puberty blockers.

His comments came after a review into Queensland's gender service confirmed that care being provided to children experiencing gender dysphoria was safe, evidence-based, and aligned with national and international guidelines.

The independent panel, comprised of experts from across Australia, recommended creating a statewide network in partnership with private providers and NGOs to enhance service delivery, increase standing and add a special credential for gender service doctors to build research and expertise in the gender diversity realm.

Health Minister Tim Nicholls has now confirmed a steering committee will oversee the implementation of all 25 recommendations.

Mr Nicholls will assess the implementation before determining whether there should be another review into the affirmative care model.

"The LNP wants a Queensland free from discrimination where individuals are respected and free to live safely in their communities," he said.

Last week, a fellow of the Royal Australian and New Zealand College of Psychiatrists called on the government to reinstate suspended child psychiatrist Dr Jillian Spencer, who was stood down from the Queensland Children's Hospital in 2023 after she publicly criticised the gender clinic's affirmation treatment approach, including puberty blocker use.

Dr Spencer claimed children and their families were being pressured into affirmation treatment care without adequate mental health assessments and that there was not enough medical evidence to discount long-term effects.

The English National Health Service last year banned puberty blockers after a pediatrician's review.

However, the Queensland review found no evidence of patients being rushed into decisions about their treatment.

Dr Spencer criticised the review, claiming it was "stacked" with gender "activists".

Mr Nicholls was unable to comment on her employment options due to ongoing internal disputes between Dr Spencer and the Children's Hospital.

"Dr Spencer has ... taken action in the Queensland Industrial Relations Commission and has made a claim against CHQHHS under the Public Interest Disclosure Act," he said. "Dr Spencer also has a complaint against her."

About one-third of Queensland gender service patients are discharged into community-based care while another third receive ongoing clinical management and the remainder access medical treatments such as puberty blockers. The waitlist for the service is 12 months.

Des Houghton P64

Australian Government

Department of Health and Aged Care

Information Brief
MB24-003202
Version (1)
Date sent to MO: 17/12/2024

To: Minister Butler

cc: Assistant Minister Kearney

Subject: **URGENT DUE TO COB 16/12 - INFORMATION BRIEF - PUBERTY BLOCKER MEDICATION FOR UNDER 18S**

Comments:			
Contact Officer:	*Tracey Andrews*	*A/g Assistant Secretary, Health Equity Branch*	Ph: s47E(c), s47F Mobile: s47E(c), s47F
Clearance Officer:	*Trish Clancy*	*First Assistant Secretary, Population Health Division*	Ph: s47E(c), s47F Mobile: s47E(c), s47F

Key Issues:

1. Last week the UK Government permanently banned puberty blocker medication to under 18s for gender-affirming purposes on safety grounds. Given this, you have requested advice from the department on options the Australian Government may wish to consider.
    a. The UK ban follows the Independent Review of Gender Identity Services for Children and Young People (The Cass Review), which was commissioned by National Health Services (NHS) England and NHS Improvement in 2020. The final report published on 9 April 2024 (MB24-000896 refer).
    b. The Cass Review determines puberty blockers are successful in supressing puberty but can impact bone density. It found no changes in representations of gender dysphoria, body satisfaction or mental wellbeing.

2. In Australia, the provision of gender services is led by states and territories, who are responsible for the relevant services.
    a. Specialist gender services across several jurisdictions provide care to young people based on a multidisciplinary approach tailored to individual circumstances and needs.
    b. Decisions regarding clinical care are shared between the clinicians, the young person and their family.
        i. This is different from the UK where the NHS uses a largely centralised model with access to services provided through the 'National Referral Support Service for The NHS Gender Incongruence Service for Children and Young People'.

Evidence on the safety of the current access to puberty blockers in Australia

3. In September 2024, NSW Health released their independent evidence review, undertaken by Sax Institute, evidence brief on 'Understanding interventions for children and young people living with gender dysphoria'.
    a. In relation to puberty blockers the review found 'these medications are safe and work well to delay puberty, and their effects can be reversed if stopped. Some studies also suggest that this treatment can help reduce the distress young people with gender dysphoria feel during puberty. However, these medications might decrease bone strength, so doctors need to monitor this during treatment'.

4. Puberty blockers are not the only form of gender affirming treatments. A multidisciplinary care approach is undertaken including through psychological, social, behavioural and other medical interventions.
    a. A July 2024 independent review of Queensland's Gender Clinic found out of the total cohort of children and adolescents who attended an initial session between February 2023 and April 2023, the majority (71%) had not been prescribed medical treatment (gender affirming hormone treatment and puberty blockers) at least 12 months after their initial intake session.
    b. The review also found the service to be safe, evidence-based and consistent with national and international guidelines.

5. The Australian Research Consortium of Trans Youth and Children (ARCYTC) have been funded by the Medical Research Fund to collate the data from over 2,800 young people from gender clinics in Australia. This data can assist to monitor the impact of puberty suppression. This 4-year project commenced in July 2024.
    a. 60 researchers, clinicians and consumers from ARCTYC will come together to conduct interdisciplinary research that develops, implements and evaluates the effectiveness and acceptability of different models of physical and mental health care for transgender children and young people.

Clinical advice on puberty-blockers

6. In Australia, the Therapeutic Goods Administration (TGA) has approved the use of gonadotropin-releasing hormone analogues (GnRA, or 'puberty blocking' medicines) for certain cancers and precocious puberty, but not for gender affirming care.

7. When used for gender affirming care, puberty blocking medicines are prescribed in Australia off label. This is based on a clinical decision of the individuals prescribing physician.
    a. Consent to prescribe puberty blockers in Australia to a person under 18 must be provided by the child's parents or legal guardian. If there is a disagreement about the diagnosis, treatment, or capacity of the minor to provide informed consent, the family court has ruled this requires an application to the court to resolve the dispute consistent with the child's best interests.
    b. Medical practitioners who engage in 'off label' prescribing are required to do so in accordance with Good Medical Practice, the code of conduct published by the Medical Board of Australia, which regulates practitioners in partnership with the Australian Health Practitioner Regulation Agency (Ahpra) to ensure public safety.

8. The TGA monitors the safety of all medicines on the Australian Register of Therapeutic Goods (ARTG).

9. If the TGA identifies a new safety concern that is associated with off-label prescribing, regulatory action may be taken to ensure that the Product Information document clearly communicates the risks and accurately characterises the known safety profile of the medicine.

10. Gonadotropin releasing hormone (GnRH) are not PBS listed for use in gender affirming hormone therapy.

11. GnRH analogues are only available on the PBS for the treatment of certain cancers, endometriosis, anticipated premature ovarian failure and precocious puberty.

12. The Pharmaceutical Benefits Advisory Committee has not received any submissions to consider listing GnRH analogues for use in gender affirming hormone therapy.

13. A ban on puberty blockers would need to consider the impacts on the whole gender affirming care multidisciplinary approach including psychosocial and other medical interventions.
    a. The New Zealand (NZ) Government recently released a position statement on the use of puberty blockers on gender dysphoric adolescents. Their review showed a lack of quality evidence to back effectiveness and safety of puberty blockers. However, the NZ Government's position was to express the need for a more cautionary approach to prescribing puberty blockers including that only clinicians experienced in gender affirming care should prescribe puberty blockers.

Considerations for Australia's approach to puberty blocker

14. In providing advice endorsing Australia's multidisciplinary approach to gender affirming care, to the then Minister for Health, the Hon Greg Hunt MP in 2020 (**Attachment A**), the Royal Australasian College of Physicians (RACP) advised:
    a. 'a national inquiry, or similar, would not increase the scientific evidence available regarding gender dysphoria but would further harm vulnerable patients and their families through increased media and public attention'.

15. While service models for supporting gender dysphoria are a state and territory responsibility, the Commonwealth can play a role in providing national leadership (e.g. clinical guidelines, informational resources for patients and health professionals) and consistency of a best practices approach.

Potential Next Steps

16. Given recent independent evidence reviews into gender-affirming care in both NSW and QLD and the role of states and territories, options focus on updating advice on medical interventions and guideline development (and associated factsheets). Both options could be implemented in sequence.

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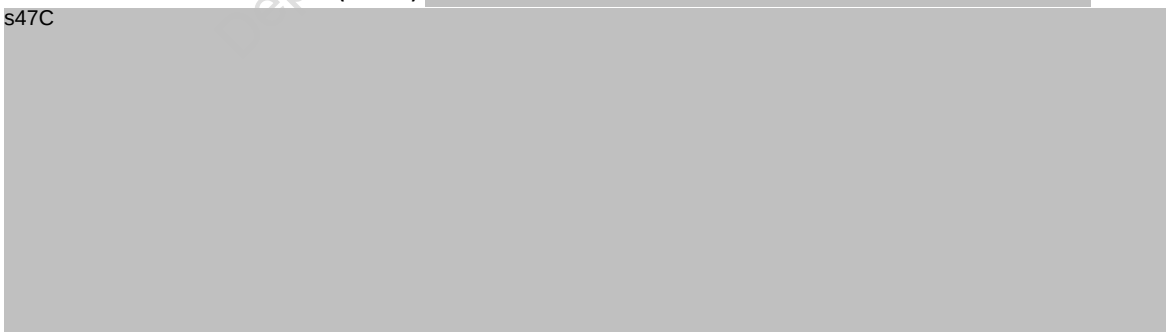
Option 2: Update National Guidelines

19. The Cass Review concludes, of the international clinical guidelines they reviewed, most performed poorly on 'rigour of development, applicability and editorial independence domains'.
    a. This included Australia's standard, the Melbourne Royal Children's Hospital's Australian Standards of Care and Treatment Guidelines for Trans and Gender diverse Children and Adolescents (the Australian Guidelines). These guidelines are endorsed by AusPATH and a number of clinical experts.

20. The Australian Guidelines outline a comprehensive clinical assessment and decision framework for the use of puberty suppressing and gender affirming hormone agents for children and adolescents. The guidelines recommend an individualised approach in which the views of clinicians, the patient and their family are considered.

21. s47C the Guidelines require updating and should be developed according to the National Health and Medical Research Council (NHMRC) Standards for Guidelines (2016) s47C

s47C



Impacts on trans and gender diverse communities

22. Research by the Kid's Research Institute (formerly Telethon Kids) Trans Pathway project (2017) found gender diverse young people were at very high risk for poor mental health, self-harming and suicide attempts. Around 3 in every 4 gender diverse young people reported experiencing anxiety or depression. Four out of 5 gender diverse young people

had ever engaged in self-harm, and almost 1 in 2 gender diverse young people had ever attempted suicide (48%).

23. The NSW Health independent evidence review highlighted the higher mental health risk stating 'Transgender and gender diverse children and young people are at a higher risk of mental health issues and have higher rates of depression, anxiety, suicidal thoughts and suicide than the general population.'

24. In the Government's recently released first National Action Plan for the Health and Wellbeing of LGBTIQA+ People (the Action Plan) under Action 1, it highlighted the need to 'ensure LGBTIQA+ people are engaged on issues that impact them'.
    a. The Cass Review acknowledges a lack of ability to engage trans and gender diverse young people in the study.

s47C [redacted]

Background:

25. The Cass Review was chaired by Dr Hilary Cass, former President of the UK Royal College of Paediatrics and Child Health.

26. Dr Cass made recommendations about the services provided by the NHS to children and young people experiencing gender incongruence.

27. The Cass Review acknowledges difficulty in consulting directly with the trans and gender diverse community in preparing its findings.

28. The Terms of Reference can be categorised into the following areas:
    a. Quality of research data and analysis underpinning current approaches to gender affirming care.
    b. Impact and effectiveness of gonadotropin-releasing hormone analogues (puberty blockers) and gender affirming drugs.
    c. Viability of the assessment models used by clinicians in gender care referrals.
    d. Workforce training and competency.

Consultations: Therapeutic Goods Administration, Technology Assessment and Access Division

Attachments:

A. RACP Letter to Government (March 2020 – available publicly)

Minister	**Minister Butler**
PDR Number	**MB24-003202**
Subject	****URGENT** Due to COB 16/12 - Information Brief - Puberty blocker medication for under 18s**
Contact Officer	Tracey Andrews Ph: s47E(c), s47F Mobile: s47E(c), s47F
Clearance Officer	Trish Clancy Ph: s47E(c), s47F Mobile: s47E(c), s47F
Division/Branch	|Primary and Community Care| Population Health
Has Budget Branch been consulted if there are financial implications?	Not Applicable

Adviser/DLO comments:	Returned to Dept for: REDRAFT ☐ NFA ☐

5 March 2020

The Hon Greg Hunt MP
Minister for Health
Parliament House
CANBERRA ACT 2600

Via Email: Minister.Hunt@health.gov.au

Dear Minister Hunt

Re: Care and treatment of children and adolescents experiencing gender dysphoria

I refer to your letter of 16 August 2019 in which you requested that The Royal Australasian College of Physicians (RACP) provide advice on the treatment of gender dysphoria in children and adolescents.

Following your correspondence, the RACP has consulted with our expert College bodies with relevant clinical expertise in this area, including paediatricians, endocrinologists, and groups with specialist research and bioethics expertise. We have also consulted with several of our affiliated speciality societies, including the Australasian Paediatric Endocrine Group and the Endocrine Society of Australia. It is important to note that our advice is confined to the areas of medical practice in which the RACP's members have expertise. However, this issue is multidisciplinary, and the expertise of other peak groups such as the Royal Australian and New Zealand College of Psychiatrists is also relevant.

What is gender dysphoria?

Trans and gender diverse (TGD) are terms used to describe a person's gender identity when it is different to their birth assigned sex. The term gender dysphoria is used to describe the distress experienced by a person due to incongruence between their gender identity and their sex assigned at birth: it is generally diagnosed at clinical interview, rather than self-defined.

Individuals who have gender dysphoria may require clinical care for psychosocial support and gender transition (social or medical). Children and adolescents who are TGD or have gender dysphoria are a very vulnerable population, experiencing stigma and extremely high rates of depression, self-harm, attempted suicide and suicide.

Evidence supporting therapeutic approaches

Gender dysphoria in childhood and adolescence is an emerging area of healthcare and as such, existing evidence on health and wellbeing outcomes of clinical care is limited. This is due to the relatively small number of studies, the small sizes of study populations, the absence of long-term follow up and the ethical challenges of robust evaluation when control (no treatment) is not acceptable. Similar limitations occur in other health conditions which affect small segments of the population, such as rare cancers. Whilst we believe it a priority to address gaps in the evidence base, further scientific evidence may take a considerable period of time to be produced. It would require consistency in treatment approach and data collection across sites of clinical care, and long-term monitoring of health and wellbeing outcomes of patients with gender dysphoria.

The role of clinical guidelines when evidence is limited

As you are aware, the role of clinical guidelines is to provide recommendations on diagnosis, care and treatment of medical conditions, based on the best available evidence, and expert consensus in areas where evidence is lacking or still emerging. The emergent nature of the evidence in relation to gender dysphoria does not reduce the necessity for clinical guidelines as guidelines can facilitate access to best practice care.

While the National Health and Medical Research Council (NHMRC) guideline development process is often considered 'gold standard', we note that for health issues which are lower in prevalence and where the evidence base is still developing, following the NHMRC guideline development process in its entirety may not be feasible. In these circumstances, guidelines developed using best available evidence and expert clinician consensus are entirely valid.

There are a number of clinical guidelines available to clinicians to guide practice in the care and treatment of children and adolescents with gender dysphoria. These include the American Academy of Paediatrics, the US Endocrine Society, the World Professional Association of Transgender Medicine, the Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents and New Zealand Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa New Zealand.

Our expert groups were asked to consider the care and treatment approach described in the first care and treatment guidelines developed for trans and gender diverse children and adolescents in the Australian context, the Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents. We acknowledge the considerable work, expertise and consultation that took place in the development of these clinical guidelines. The RACP supports the principles underlying these guidelines, specifically the emphasis on a multidisciplinary approach to providing person-centred care which prioritises the best interests, preferences and goals of the patient.

General considerations in clinical care

In considering the issues raised by this consultation, our clinicians identified a number of principles which should be taken into consideration in care and treatment of children and adolescents with gender dysphoria which are discussed in the following paragraphs.

The RACP strongly supports expert clinical care that is non-judgemental, supportive and welcoming for children, adolescents and their families experiencing gender dysphoria. A fundamental principle of medical care is the need to ensure that care and treatment is provided in the best interests of the patient, and that doctors do not harm those who request care through either their action or inaction. The RACP's advice is framed within this context. Patients with gender dysphoria require access to expert care and treatment. Withholding or

limiting access to care and treatment would be unethical and would have serious impacts on the health and wellbeing of young people.

The population under consideration is an extremely vulnerable group who need the support of clinicians, the health system, their families, friends and wider support networks. Treatment should be holistic, developmentally informed, child centred and individualised.
To facilitate a high level of informed consent, patients and families must be provided with information about the limitations of available evidence regarding gender dysphoria. For example, there should be an informed discussion of the burdens and benefits of treatment options in a way each child or adolescent can understand. This is a critical reason why clinicians with expertise in adolescent health are central to guiding care and treatment, because of their expertise in assessing competence to make medical decisions.

Access, funding and delivery of care and treatment for gender dysphoria is variable across jurisdictions and in many areas is lacking. This absence is particularly acute for young people in rural and regional areas, who experience significantly worse health outcomes overall. Unavailability of services and clear referral pathways is impacting on access, equity and continuity of care for trans and gender diverse children and adolescents. Ensuring children and adolescents with gender dysphoria can access appropriate care and treatment regardless of where they live, should be a national priority.

Suggested ways forward

The RACP suggests three ways forward to address these issues. Firstly, the Australian Government work with States and Territories to improve access to and consistency of care within and across jurisdictions. This could be achieved through the development of a national framework for service provision and outcomes monitoring. This framework would serve to support and enable the provision of consistent, high-quality, specialist multi-disciplinary health care in every jurisdiction, across a range of settings, and to guide workforce considerations. It would also guide consistency of outcome data collection across jurisdictions and facilitate long-term monitoring of health and wellbeing outcomes.

Secondly, to facilitate the development of a robust evidence base, the RACP suggests that the Australian Government consider coordinating and providing funding for research on the long-term outcomes for the care and treatment of gender dysphoria, and funds the development of an outcomes database to develop our knowledge and understanding of the long-term outcomes for children and adolescents with gender dysphoria.

Thirdly, the Australian Government should facilitate the development of evidence-based fact sheets aligned to current guidelines which should be made available to all patients and their families to support informed consent. These factsheets should be developed by a multi-disciplinary group of experts in the field including the authors of the Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents, in consultation with patients and their families.

These ways forward would be in line with recommended actions in the National Action Plan for the Health and Children of Young People: 2020-2030.

Need for caution

Finally, our clinicians noted that there are substantial dangers posed by some of the proposals that have been put forward during the recent public debate on this issue, such as holding a national inquiry into the issue. A national inquiry would not increase the scientific evidence available regarding gender dysphoria but would further harm vulnerable patients and their families through increased media and public attention.

Considerations of care and treatment of medical conditions should be based on medical evidence and advice from medical and other health professionals who have specific expertise in the condition in question, as well as the affected patient population. Consequently, the RACP strongly advises that the Australian Government does not establish a national inquiry or similar process.

If you would like any further information, please contact policy@racp.edu.au.

Yours sincerely

s47F

Associate Professor s47F

From: s47E(c), s47F
To: s47E(c), s47F
Cc: s47E(c), s47F ; s47E(d)
Subject: FW: For urgent action by no later than 10am Monday 16 Dec- Advice on safety of puberty blockers [SEC=OFFICIAL]
Date: Monday, 16 December 2024 10:32:31 AM
Attachments: MB24-000896_TL.docx
image001.png
image003.png
image004.jpg
image002.png

Hi s47E(c), s47F

DepSec cleared changes attached (see below).

Given you are editing, if you are able to ensure this is reflected in brief, would be great.

Cheers,
s47E(c), s47F

satisfaction of mental wellbeing.

- In Australia, puberty-blockers have only been ~~indicated~~ authorised for use by the Therapeutic Goods Administration, and are only available on the Pharmaceutical Benefits Scheme (PBS), for certain indications- namely ~~and are only available on the Pharmaceutical Benefits Scheme (PBS)~~ for the treatment of precocious puberty and certain cancers. ~~and precocious puberty.~~
  - When used for gender affirming care puberty blocking medicines are being prescribed off label using private scripts. This is based on a clinical decision of the individual's prescribing physician. When accessed as a private prescription, these medicines attract the full cost of the medication.

s47E(c), s47F
Assistant Director
Men's, LGBTIQA+, Children and Young People's Health Section
Health Equity Branch | Population Health Division
Australian Government Department of Health and Aged Care
Tel: s47E(c), s47F | E: s47E(c), s47F @health.gov.au
GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s47E(c), s47F @health.gov.au>
Sent: Monday, 16 December 2024 10:31 AM
To: s47E(c), s47F @Health.gov.au>
Cc: s47E(c), s47F @health.gov.au>
Subject: FW: For urgent action by no later than 10am Monday 16 Dec- Advice on safety of puberty blockers [SEC=OFFICIAL]

Sorry s47E(c), s47F Please see minor changes from our dep sec. Apologies for the delay.

s47E(c), s47F
Executive Officer A/g

Nick Henderson, First Assistant Secretary

Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health & Aged Care
T: s47E(c), s47F | E: s47E(c), s47F @health.gov.au
MDP 122, PO Box 100, Woden ACT 2606, Australia

From: LAWLER, Tony <s47E(c), s47F @Health.gov.au>
Sent: Monday, 16 December 2024 10:07 AM
To: s47E(c), s47F @health.gov.au>
Cc: s47F, s47E(c) @health.gov.au>; HENDERSON, Nick s47E(c), s47F @health.gov.au>; s47F, s47E(c) @health.gov.au>
Subject: RE: For urgent action by no later than 10am Monday 16 Dec- Advice on safety of puberty blockers [SEC=OFFICIAL]

Thanks s47E(c), s47F
Really minor changes in the attached from me for clarity.
T

From: s47E(c), s47F @health.gov.au>
Sent: Monday, 16 December 2024 9:12 AM
To: LAWLER, Tony <s47E(c), s47F @Health.gov.au>
Cc: s47E(c), s47F @health.gov.au>; HENDERSON, Nick s47E(c), s47F @health.gov.au>; s47E(c), s47F @health.gov.au>
Subject: FW: For urgent action by no later than 10am Monday 16 Dec- Advice on safety of puberty blockers [SEC=OFFICIAL]

Hi Tony,

Please find below information provided this morning to PHD in response to their request on Friday.

Cheers,

s47E(c), s47F

s47E(c), s47F

Executive Officer to Professor Anthony Lawler, Deputy Secretary Health Products Regulation Group and Chief Medical Officer

Health Products Regulation Group
Australian Government, Department of Health and Aged Care
s47E(c), s47F | s47F, s47E(c) @health.gov.au

This email comes to you from Ngunnawal Country
Location: 27 Scherger Drive Fairbairn, Level 2

I may send emails out of hours at a time that suits me. I look forward to receiving your response during your normal working hours.

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s47E(c), s47F @health.gov.au>
Sent: Monday, 16 December 2024 9:09 AM
To: s47E(c), s47F @Health.gov.au>
Cc: s47E(c), s47F @health.gov.au>; HPRG Parliamentary <s47E(d) @Health.gov.au>; s47E(d @health.gov.au>; s47E(c), s47F @health.gov.au>; s47E(c), s47F @health.gov.au>; s47E(d) @health.gov.au>
Subject: FW: For urgent action by no later than 10am Monday 16 Dec- Advice on safety of puberty blockers [SEC=OFFICIAL]

Hi s47E(c), s47F

Please see below input. A massive thank you to the team for getting this together.

- Can you please advise if the information within the attached brief is still current (in relation to 'Efficacy and use of puberty blockers')

  The post-market aspects of the brief are accurate and remain relevant from our perspective. PMAB have confirmed the wording relating to efficacy, and whether any additional GNRAs have been approved since April remains correct. PHD should check the brief and provide input regarding the program aspects (similar to the media last week on the same matter).

- Please advise if you have any additional advice or information you believe should be included to support briefing on safety of puberty blockers or whether the attached contains outdated advice/requires corrections

  - Relevant information to this topic may include safety/efficacy testing of 'puberty blockers' or other relevant information about 'off-label use' of medications for gender affirmation procedures and their safety.

    Suggest consider including the following:

    - The UK's Commission on Human Medicines (CHM) advice that there is an 'unacceptable safety risk in the continued prescription of puberty blockers to children' relates to an identified lack of evidence for these medical treatments for a particular indication, in the UK prescribing context, rather than a specific safety concern related to a particular medicine.
    - The TGA has approved the use of gonadotropin-releasing hormone analogues (GnRA, or 'puberty blocking' medicines) for certain cancers and precocious puberty, but not for gender affirming care.
    - When used for gender affirming care, puberty blocking medicines are prescribed in Australia off label. This is based on a clinical decision of the individuals prescribing physician.
    - The TGA monitors the safety of all medicines on the Australian Register of Therapeutic Goods (ARTG).
    - If the TGA identifies a new safety concern that is associated with off-label prescribing, regulatory action may be taken to ensure that the Product Information document clearly communicates the risks and accurately characterises the known safety profile of the medicine.

The existing sentence in the brief around the different health system context in which these medicines are assessed and prescribed is useful context to our input:

In Australia the care pathways are different then in the UK. The NHS is largely a centralised model, where the government acts as the single-payer and most medical practitioners are employees of the NHS.

I found this webpage of the UK Government's from yesterday very helpful in summarising the recent changes: https://healthmedia.blog.gov.uk/2024/12/11/puberty-blockers-what-you-need-to-know/

Kind Regards

s47E(c), s47F
Executive Officer A/g

Nick Henderson, First Assistant Secretary

Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health & Aged Care
T: s47E(c), s47F | E: s47E(c), s47F @health.gov.au
MDP 122, PO Box 100, Woden ACT 2606, Australia

From: s47E(c), s47F @health.gov.au>
Sent: Friday, 13 December 2024 2:53 PM
To: s47E(c), s47F @health.gov.au>; s47E(c), s47F @health.gov.au>; s47E(d) @health.gov.au>
Cc: s47E(c), s47F @health.gov.au>; s47E(c), s47F @health.gov.au>; s47E(c), s47F @Health.gov.au>; s47E(c), s47F @health.gov.au>; s47E(c), s47F @health.gov.au>; s47E(d) @health.gov.au>
Subject: Fwd: For urgent action by no later than 10am Monday 16 Dec- Advice on safety of puberty blockers [SEC=OFFICIAL]
Importance: High

Hey all,

Please see below request seeking point for the ministers office on ban of puberty blockers in the UK. Grateful if you can please send me any points you have to add by 9:30am monday.

Apologies I am out of the office this afternoon but do have my mobile if you have any questions.

s47E(c), s47F

Sent from Workspace ONE Boxer
---------- Forwarded message ----------

From: s47E(c), s47F @Health.gov.au>
Date: 13 December 2024 at 2:31:36 pm AEDT
Subject: For urgent action by no later than 10am Monday 16 Dec- Advice on safety of puberty blockers [SEC=OFFICIAL]
To: s47E(c), s47F @health.gov.au>,s47E(c), s47F @health.gov.au>,s47E(c), s47F @health.gov.au>,s47E(c), s47F @Health.gov.au>,s47E(d) @health.gov.au>
Cc: s47E(d) @health.gov.au>,s47E(c), s47F @health.gov.au>,s47E(d) @Health.gov.au>

Good afternoon TAAD and TGA colleagues,

We are aware the MO is seeking **urgent** advice following the UKs decision to indefinitely ban the sale and supply of puberty-suppressing hormones - Ban on puberty blockers to be made indefinite on experts' advice - GOV.UK by Monday.

In April 2024, the attached briefing was considered by Minister Butler in relation to the Hilary Cass Review (UK) with a request for information on the Australian health system. Your teams gave input at that time.

For action ASAP (but no later than 10AM, Monday 16 Dec):

- Initial advice is appreciated ASAP, with any proposed, cleared input to come **by 10AM Monday 16 Dec** so we know if we can expect input please
- Can you please advise if the information within the attached brief is still current (in relation to 'Efficacy and use of puberty blockers')
- Please advise if you have any additional advice or information you believe should be included to support briefing **on safety of puberty blockers** or whether the attached contains outdated advice/requires corrections
    - Relevant information to this topic may include safety/efficacy testing of 'puberty blockers' or other relevant information about 'off-label use' of medications for gender affirmation

procedures and their safety.

- In addition, if you are aware of any advice previous to the Minister's Office on this topic or Senate Estimates briefing etc. we would be grateful for a copy and where able, we will refer to this advice rather than duplicate it.

Once we get the formal request from the MO I will advise if there is any additional information.

Apologies again for the urgency of this request. Please feel free to contact me directly to discuss.

Kind regards,

s47E(c), s47F
Assistant Director
Men's, LGBTIQA+, Children and Young People's Health Section
Health Equity Branch | Population Health Division
Australian Government Department of Health and Aged Care
Tel: s47E(c), s47F | E: s47E(c), s47F @health.gov.au
GPO Box 9848, Canberra ACT 2601, Australia

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[SEC=OFFICIAL]

Australian Government

Department of Health and Aged Care

Ministerial Information Request
MB24-000896
Version (1)
Date sent to MO: 16/04/2024

To: **Minister Butler**
cc: Assistant Minister Kearney

Subject/Issue: **CASS review and how the Australian system works**

Comments:			
Contact Officer:	*Belinda Roberts*	*Assistant Secretary, Health Equity Branch*	Ph: s47E(c), s47F Mobile: s47E(c), s47F
Clearance Officer:	*Tiali Goodchild*	*Acting First Assistant Secretary, Population Health Division*	Ph: s47E(c), s47F Mobile: s47E(c), s47F

The Cass Review

- The Independent Review of Gender Identity Services for Children and Young People (The Cass Review) was commissioned by National Health Services (NHS) England and NHS Improvement in 2020 with a final report published on 9 April 2024.
- The Review was chaired by Dr Hilary Cass, former President of the UK Royal College of Paediatrics and Child Health.
- Dr Cass made recommendations about the services provided by the NHS to children and young people experiencing gender incongruence (Full Report - **Attachment A**).
- The Terms of Reference can be categorised into the following areas:
  - Quality of research data and analysis underpinning current approaches to gender affirming care.
  - Impact and effectiveness of gonadotropin-releasing hormone analogues (puberty blockers) and gender affirming drugs.
  - Viability of the assessment models used by clinicians in gender care referrals.
  - Workforce training and competency.

<u>Key Findings and Recommendations of the Review</u>

Quality of research data and analysis

- The Review considered 50 studies that looked at different elements of gender affirming puberty suppression. The report indicates studies generally assessed the success of puberty suppression and there was a lack of robust evidence on the long-term benefits and outcomes of these interventions.

- The Cass Review raised concerns about the quality of available clinical guidelines indicating they have not followed international standards for guideline development. As a result, assessment approaches are inconsistent.
- The Review contends of the clinical guidelines reviewed most performed poorly on 'rigour of development, applicability and editorial independence domains'.
    - This included Australia's standard, the Melbourne Royal Children's Hospital's *Australian Standards of Care and Treatment Guidelines for Trans and Gender diverse Children and Adolescents 2018.*
    - The report recommends clinicians apply an assessment framework to ensure young people referred to gender services receive holistic assessment of needs to inform care plans including screening of neurodevelopment conditions and mental health assessments.
- Further it recommended that gender services must operate to the same standards as other services seeing children and young people with complex presentations and/or additional risk factors. There should be a nominated medical practitioner (paediatrician/child psychiatrist) who takes overall clinical responsibility for patient safety within the service. In Australia the care pathways are different then in the UK. The NHS is largely a centralised model, where the government acts as the single-payer and most medical practitioners are employees of the NHS.
- In Australia, the provision of gender services is led by states and territories, who are responsible for the relevant services (**Attachment B**).
    - Specialist gender services across a number of jurisdictions provide care to young people based on a multidisciplinary approach tailored to individual circumstances and needs.
    - Decisions regarding clinical care are shared between the clinicians, the young person and their family.

Efficacy and use of puberty blockers

- The Cass Review contends the focus on puberty blockers to manage gender-related distress has overshadowed consideration of the effectiveness of other psychosocial and therapeutic interventions.
- The review has recommended standard evidence based psychological and psychopharmacological treatment approaches, including support for parents/caregivers and siblings, be better balanced with greater emphasis on using psychosocial interventions. Not to change a person's perception of who they are but explore their experience of distress and help alleviate this.
- The Cass Review determines puberty blockers are successful in supressing puberty and bone density but found no changes in representations of gender dysphoria, body satisfaction or mental wellbeing.
- In Australia, puberty-blockers have only been authorised for use by the Therapeutic Goods Administration, and are only available on the Pharmaceutical Benefits Scheme (PBS), for certain indications- namely for the treatment of precocious puberty and certain cancers.
    - When used for gender affirming care puberty blocking medicines are being prescribed off label using private scripts. This is based on a clinical decision of the individual's prescribing physician. When accessed as a private prescription, these medicines attract the full cost of the medication.

- Consent to prescribe puberty blockers in Australia to a person under 18 must be provided by the child's parents or legal guardian. If there is a disagreement about the diagnosis, treatment, or capacity of the minor to provide informed consent, the family court has ruled this requires an application to the court to resolve the dispute consistent with the child's best interests.

Viability of the assessment models used by clinicians in gender care referrals.

- Based on the Review's analysis of the impacts of social transition to a different gender, it found no clear evidence on the positive or negative mental health outcomes of social transition in child or adolescent transition. The review raises concerns about the broader impacts of transitional regret and risk of social isolation.
    - The Review Report recommends supporting family to recognise normal developmental variation in gender role and behaviours/expressions as a priority for clinicians in early interventions.
- The long-term outcomes and impacts of interventions of England's 9000 young people who have been through the Gender Identity Development Service (GIDS) was to be assessed by the Review through a longitudinal data linkage study. Dr Cass advises the Review did not receive the cooperation of GIDS and NHS adult gender services to undertake this analysis.
- The Australian Standards of Care and Treatment Guidelines for trans and gender diverse children and adolescents provide a detailed outline of the roles of each member of the multidisciplinary team, for example, mental health professionals, paediatricians, adolescent physicians or endocrinologists, GPs, nurses and bioethicists and some allied health professionals.
- The MBS currently supports some items for surgical procedures if the treating practitioner deems the procedure to be clinically relevant for a patient.
    - For those undertaking gender affirming surgery, they must be over 16 years for top surgery and over 18 years for bottom surgery.
    - Medical Services Advisory Committee, which provides independent advice to Government, is assessing an application by the Australian Society of Plastic Surgeons for the public funding of patient consultations and surgical procedures for gender affirmation in adults with gender incongruence.

Workforce Training and Competency

- The Cass Review highlights the demand in young people and families seeking support for gender incongruence or access to gender affirming care far exceeds the capacity of specialist gender identity services to provide care for. The Cass Review recommends an upskill on competency and training across the broader NHS health workforce in this field to ensure young people and families have improved access to advice and support.
- In Australia, the Royal Australian College of Physicians notes treating gender incongruence in adolescents is an emerging field. In advice to Government in 2020, the RACP recommended:
    - the Australian Government, with states and territories, develop a national framework to guide improved access to and consistency of care across jurisdictions
    - increased funding for research into the long-term outcomes of care and treatment of gender incongruence to support a national database
    - development of evidence-based fact sheets informed by multidisciplinary experts to support families to support informed decision making and consent.

- In Australia, the Royal Children's Hospital Guidelines are widely considered the standard, noting the provision of care for gender services is led by states and territories.
  - The Standards aim to maximise quality and care provision to trans and gender diverse children and adolescents across Australia.
  - The recommendations are based on available evidence including clinical consensus and were developed in consultation with professionals from multiple disciplines working with these young people across Australia and New Zealand, as well as young people and their families.
  - The Royal Australasian College of Physicians (RACP) in March 2020, in consultation with expert college bodies, wrote to the then Minister for Health noting their support for the principles underlying these guidelines and their emphasis of a holistic, multidisciplinary person-centred care approach **(Attachment C**).

Background
Cass Review Terms of Reference

- The Terms of Reference for the Review included:
  - Pathways of care for local services and clinical management for less complex expressions of gender incongruence.
  - Pathways of care into specialist gender identity services including referral criteria.
  - Clinical models and management approaches in specialist interventions.
  - Best clinical approaches for complex representations.
  - The use of gonadotropin-releasing hormone analogues (puberty blockers) and gender affirming drugs.
  - Ongoing clinical audits, data reporting and research priorities.
  - Current and future workforce requirements.
  - Exploration of the increases in referrals and why the increase in the UK has disproportionately been from those assigned female at birth.
- Off-label prescribing refers to the prescription of a registered medicine for a use that is not included in the product information approved by the Australian Therapeutic Goods Administration (TGA)

Attachments:
A: Independent Review of Gender Identity Services for Children and Young People
B: Summary of State and Territory Gender Affirming Care
C: RACP Letter to Government (March 2020 – available publicly.)

Minister	**Minister Butler**
PDR Number	**MB24-000896**
Subject	**MIR: CASS review and how the Australian system works**
Contact Officer	Belinda Roberts Ph: s47E(c), s47F Mobile: s47E(c), s47F
Clearance Officer	Tiali Goodchild Ph: s47E(c), s47F Mobile: s47E(c), s47F
Division/Branch	|Primary and Community Care| Population Health
Has Budget Branch been consulted if there are financial implications?	Not Applicable

Adviser/DLO comments:	Returned to Dept for: REDRAFT ☐ NFA ☐

From: CLANCY, Trish
To: s47E(c), s47F
Cc: s47E(c), s47F ; DEVELIN, Liz; ANDREWS, Tracey; s47E(c), s47F
Subject: Puberty blocker medication for under 18s information brief [SEC=OFFICIAL]
Date: Monday, 16 December 2024 6:43:06 PM
Attachments: image001.png
MB24-003202.docx

Hello s47E(c) s47F

Thanks for your time today.

I've approved the **Puberty blocker medication for under 18s** information brief in PDMS. I assume that it won't get through the system to you until the morning and so am also attaching it here.

You asked about the long-term impacts that the NSW Sax review outlined. The only impact (see the original text below) that was called out in any depth was the potential reduction in bone density.

I hope this helps,

Trish

Puberty suppression treatment (PS) (Number of studies by level of evidence: 3x Level I, 4x Level III-2, 1x Level III-3, 9x Level IV; total 17 studies)

We identified 17 studies pertaining to puberty suppression treatment (PS) in this Evidence Check update. Broadly, the newly identified evidence reinforced the finding of the previous Evidence Check regarding benefits and effectiveness. That is, PS agents (generally referred to as GnRHa) were reported to be safe, effective and reversible. As a counterpoint, this update identified one study describing differential implications of PS for later surgery, with reduced need for mastectomy in trans men but potential complications for genital surgery in trans women as penile inversion may be compromised. Psychological effects of PS on conditions such as depression and anxiety appear modest in comparison with GAHT, with the primary impact being reduction of distress associated with unwanted secondary sexual characteristics; two Level IV studies reflected positive impacts on gender dysphoria.

With regard to risks and potential harms, reductions in bone density remain the primary concern with PS and monitoring of bone mineral density is recommended. However, some newly identified studies suggest maintenance of bone mineral density during PS treatment. Studies reported no indications to monitor liver or renal function in the PS setting. Other reported side effects of PS were also relatively minor. Instances of insufficient suppression of puberty (known as 'pubertal escape') were reported, but satisfaction with PS treatment was reported as good overall. In summary, this Evidence Check update predominantly reinforces the findings of the previous review and adds to the evidence base underpinning these findings; with the qualification that the strength of the evidence remains low.

Evidence for effective interventions for children and young people with gender dysphoria—update (page 10)

Trish Clancy
First Assistant Secretary

Population Health Division | Primary & Community Care Group
Australian Government, Department of Health and Aged Care
Ph: s47E(c), s47F | M: s47E(c), s47F | E: s47E(c), s47F @health.gov.au
Location: Yaradhang 5.N.213

Executive Assistant: s47E(c), s47F | Ph: s47E(c), s47F E: s47E(c), s47F @Health.gov.au
PO Box 9848, Canberra ACT 2601, Australia
The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present

From: DEVELIN, Liz
To: CLANCY, Trish
Cc: s47E(c), s47F ; ANDREWS, Tracey; s47E(c), s47F
Subject: RE: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]
Date: Monday, 16 December 2024 12:49:00 PM
Attachments: image001.png

Team – can I have attachment A please as well.

Then can we set up a Teams meeting at 1 or 130 to discuss.

Thanks
LD

From: CLANCY, Trish <s47E(c), s47F @Health.gov.au>
Sent: Monday, 16 December 2024 12:42 PM
To: DEVELIN, Liz s47E(c), s47F @Health.gov.au>
Cc: s47E(c), s47F @Health.gov.au>; s47E(c), s47F <s47E(c), s47F @health.gov.au>; s47E(c), s47F @Health.gov.au>
Subject: RE: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]

Liz,

Here is our advice re puberty blockers.

Given it's a sub you are not on the official path to the MO hence I'm sending it by email.

We should approve this by 3pm to make the office deadline today.

Thanks to s47E(c) s47F and Tracey who worked on this over the weekend.

Let us know if you have any questions or comments.

Trish

From: DEVELIN, Liz <s47E(c), s47F @Health.gov.au>
Sent: Friday, 13 December 2024 4:02 PM
To: CLANCY, Trish <s47E(c), s47F @Health.gov.au>; ANDREWS, Tracey <s47E(c), s47F @health.gov.au>
Subject: Fwd: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]

FYI.

Sent from Workspace ONE Boxer

---------- Forwarded message ----------

From: s47F @Health.gov.au>
Date: 13 December 2024 at 1:21:11 pm AEDT
Subject: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]
To: DEVELIN, Liz <s47E(c), s47F @Health.gov.au>
Cc: MARTIN, Nick s47F @Health.gov.au>, s47F @Health.gov.au>

Hi Liz

As discussed, following the decision of the UK Government this week to permanently ban puberty blocker medication to under 18s on safety grounds, Minister Butler requests urgent advice from the department on options the Australian Government may wish to consider in light of this development.

Can you please provide a submission to the Minister **by COB Monday** that includes advice on:

- The evidence around the safety of current Australian practice
- The weight of evidence in support of a pause or ban in the Australian context
- If the Minister wanted to commission a review of the evidence and/or clinical guidelines in Australia, the recommended scope and approach for such a review, or another alternative approach to examining the prescribing practices in all Australian jurisdictions
- With regards to the matters above, the potential impacts on the mental health and wellbeing of young Australians, international experience, and the findings of Australian reviews
- Anything else the department considers relevant

Happy to discuss.

Cheers
s47F

s47F
Office of the Hon Mark Butler MP
Minister for Health and Aged Care
P: s47F

[SEC=OFFICIAL]

From: s47E(
To: DEVELIN, Liz; CLANCY, Trish
Cc: s47E(c), ; ANDREWS, Tracey
Subject: RE: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]
Date: Monday, 16 December 2024 12:51:19 PM
Attachments: Attachment A- racp-letter.pdf
image001.png
image002.jpg

Hi Liz

Please find attached Att.A

Kind Regards

s47E(c), s47F
Director – Men's, LGBTIQA+, Children and Young People's Health
Health Equity Branch

Population Health Division | Health Equity Branch
Australian Government, Department of Health and Aged Care
T: s47E(c) | E: s47E(c @health.gov.au
Location: Yaradhang Building 3.S.133
GPO Box 9848, Canberra ACT 2601, Australia

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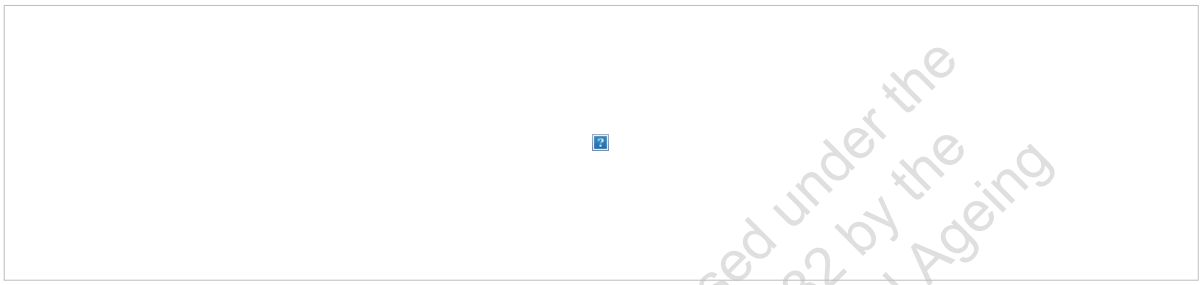

From: DEVELIN, Liz <s47E(c), @Health.gov.au>
Sent: Monday, 16 December 2024 12:50 PM
To: CLANCY, Trish <s47E(c), @Health.gov.au>
Cc: s47E(c), s47F @Health.gov.au>; ANDREWS, Tracey <s47E(c), @health.gov.au>; s22 @Health.gov.au>
Subject: RE: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]

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Sent: Monday, 16 December 2024 12:42 PM
To: DEVELIN, Liz s47E(c), @Health.gov.au>
Cc: s47E(c), s47F @Health.gov.au>; ANDREWS, Tracey s47E(c), @health.gov.au>; s22 @Health.gov.au>
Subject: RE: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]

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( )
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Trish

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Sent: Friday, 13 December 2024 4:02 PM
To: CLANCY, Trish <s47E(c), @Health.gov.au>; ANDREWS, Tracey s47E(c), @health.gov.au>
Subject: Fwd: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]

FYI.

Sent from Workspace ONE Boxer
---------- Forwarded message ----------

From: s47F @Health.gov.au>

Date: 13 December 2024 at 1:21:11 pm AEDT
Subject: For advice Mon please: puberty blocker medication for under 18s [SEC=OFFICIAL]
To: DEVELIN, Liz <s47E(c), @Health.gov.au>
Cc: MARTIN, Nick <s47F @Health.gov.au> s47F @Health.gov.au>

Hi Liz

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- The evidence around the safety of current Australian practice
- The weight of evidence in support of a pause or ban in the Australian context
- If the Minister wanted to commission a review of the evidence and/or clinical guidelines in Australia, the recommended scope and approach for such a review, or another alternative approach to examining the prescribing practices in all Australian jurisdictions
- With regards to the matters above, the potential impacts on the mental health and wellbeing of young Australians, international experience, and the findings of Australian reviews
- Anything else the department considers relevant

Happy to discuss.

Cheers
s47

s47F
Office of the Hon Mark Butler MP
Minister for Health and Aged Care
P: s47F

[SEC=OFFICIAL]

Australian Government

Department of Health and Aged Care

Information Brief
MB24-003236
Version (1)
Date sent to MO: 19/12/2024

To: **Minister Butler**

cc: Assistant Minister Kearney

Subject: ****URGENT** - INFORMATION BRIEF – ADDITIONAL ADVICE – PUBERTY BLOCKER MEDICATION FOR UNDER 18S**

Comments:			
Contact Officer:	*Tracey Andrews*	*A/g Assistant Secretary, Health Equity Branch*	Ph: s47E(c), s47F Mobile: s47E(c), s47F
Clearance Officer:	*Trish Clancy*	*First Assistant Secretary, Population Health Division*	Ph: s47E(c), s47F Mobile: s47E(c), s47F

Key Issues:

1. On 16 December 2024 you were provided with information on puberty blocker medication, following the UK Government's decision to indefinitely block their use to under 18s for gender-affirming purposes on safety grounds (**MB24-003202** refers).
2. Your office asked for the following additional information on the matter:
    a. Prevalence of people seeking gender-affirming care in Australia, and how that has changed over time
    b. The model of care in Australia, including referral pathways and the treatment journey, and the occurrence and role of puberty blocker medications in the treatment journey
    c. More detail on how the above differs or aligns with the situation in the UK
    d. More details on the scope, conduct, findings, and any limitations of the Sax Institute review.

Prevalence of people seeking gender-affirming care in Australia

- Nearly 1 per cent of Australians (178,900) are trans and gender diverse. This includes trans men, trans women and non-binary people.[1]
- The Department can seek data from states and territories on prevalence of people seeking gender-affirming care within their gender clinics noting this was not possible within the timeframe for this briefing.
    - Refer to **Attachment A** for a summary of state and territory gender-affirming care.
- Not all trans or gender diverse people choose to affirm their gender medically (gender affirming care), legally and/or socially.
    - The options for intervention that are appropriate for one person, may not be helpful for another. For example, many trans and gender diverse people may benefit from hormonal intervention and surgery, others may not decide to have either.
- Research indicates low numbers of young people in Australia receive puberty blockers:
    - A national survey of LGBTQ young people found only 4.7% of trans and gender diverse respondents had ever received puberty blockers.[2]
    - Over 10 years, only 23% of those attending a large Victorian clinic started puberty blockers.
- It is not possible to quantify the extent to which Medicare Benefits Schedule (MBS) items are claimed for gender affirmation purposes, including for people under 18.
    - The MBS Items that may be deemed clinically relevant by medical practitioners for trans and gender diverse people can be used for a range of clinical indications.
    - Medicare data for the billing of an MBS item does not record the reason why a service has been performed.
- In addition, medications used for gender affirming care are listed on the Pharmaceutical Benefits Scheme (PBS) for a number of indications including central precocious puberty, assisted reproductive technology, androgen deficiency, and others.
    - When used for gender affirming care, puberty blocking medicines are prescribed in Australia off label through private prescriptions and do not attract a PBS subsidy.
    - PBS data collection includes information on prescription medicines that qualify for a benefit under the *National Health Act 1953* and for which a claim has been processed. As medications used for gender affirming treatment are used off-label (private scripts), data is not collected and therefore cannot be used to determine how usage has changed, over time.

[1] 19/12/2024 ABS releases first ever estimates of LGBTI+ Australians https://www.abs.gov.au/media-centre/media-releases/abs-releases-first-ever-estimates-lgbti-australians

[2] Amos N, Lim G, Buckingham P, et al. Rainbow Realities: In-Depth Analyses of Large-Scale LGBTQA+ Health and Wellbeing Data in Australia.; 2023

The model of care and referral pathways in Australia versus the UK

- In Australia, the care pathways are different than in the UK.
  - The National Health Service (NHS) has been a largely centralised model and most medical practitioners are employees of the NHS. Gender affirming care is provided for free under the NHS as a primarily public health system.
    - Following recommendations of the Cass Review, puberty blockers will only be prescribed to children attending gender identity services as part of clinical research. Licensed uses of the medicine continue in the UK for children (precocious puberty) and certain cancers.
    - Professor Ian Hickie AM noted in April 2024 the UK Cass Review of the gender services provided to adolescents and young people was developed against the backdrop of criticisms of the UK's now closed nationally centralised Tavistock clinic.[3]
      - The Tavistock approach was criticised over concern it was prescribing puberty-blockers without adequate interrogation through more holistic care of the young person's co-existing medical conditions including mental health, and/or neurodiversity.
      - Professor Hickie argued the movement to a multidisciplinary, regionally based model, which the UK is transitioning to now, is consistent with the approach being applied across Australia for the last decade.
  - In Australia, the provision of gender services is led by states and territories, who are responsible for the relevant services.
    - Gender affirming care in Australia is primarily provided through the relevant gender service in the state system and is a mix of public and privately delivered care by a multidisciplinary team of specialists. This often incurs high costs for the family of the young person.
    - Decisions regarding clinical care (including decisions to commence or cease gender affirmation treatment) are shared between the clinicians, the young person and their family. If there is a disagreement on the diagnosis, treatment or capacity of the minor to provide informed consent, the Family Court of Australia has ruled this requires an application to the Court to resolve the dispute consistent with the child's best interests.
- In Australia, MBS items that may be used for gender affirmation purposes do not contain direct restrictions around age. Rather, the MBS points to relevant clinical guidelines in the delivery of services and clinical judgement.
  - There are a range of guidelines available for clinicians, including the *Australian Standards of Care and Treatment Guidelines* which move away from treatment recommendations based on chronological age. [3]
    - Instead, these guidelines recommend timing of medical transition and surgical interventions are dependent on the adolescent's capacity and competence to make informed decisions, duration of time on puberty suppression, coexisting mental health and medical issues, and existing family support.

[3] Professor Ian Hickie, 2024, Australia is not the UK': Major reviews into gender affirming care' ABC Health https://www.abc.net.au/listen/programs/healthreport/gender-puberty-blockers-hormones-evidence/103689784?fbclid=IwZXh0bgNhZW0CMTAAAR0te5t_HKX97XULVIezMgsOMDDevWuHRMCWtWwFkMSj9RZniKs02ox8S5s_aem_AZF0Xc8vgpf7hgGzZ4S13>

- Like for other areas where a change in clinical eligibility occurs, this would flow through to MBS items for example, such as the definition of infertility recently updated by the Australian and New Zealand Society of Reproductive Endocrinology and Infertility (ANZREI).
  - It is important to therefore note, such requirements are not set by Government in the context of the MBS, these are set by clinical groups, unless specific restrictions are introduced.

Role of puberty blocker medications

- Puberty blockers are one of a range of gender affirming treatments. A multidisciplinary care approach is undertaken including through psychological, social, behavioural and other medical interventions, as deemed appropriate by the multidisciplinary health team.
- Puberty suppression is indicated under the *Australian Standards of Care and Treatment Guidelines* (see below for further details on ASCTG) when an adolescent with gender dysphoria experiences significant distress with the onset or progression of pubertal development.
  - Puberty suppression involves use of gonadotrophin-releasing hormone agonists which suppress the endogenous oestrogen and testosterone responsible for induction of secondary sexual characteristics and is most effectively used when commenced in the early stages of puberty.
  - Puberty suppression is reversible and typically relieves distress for trans and gender diverse adolescents by halting progression of physical changes such as breast growth and menstruation in trans males and voice deepening and facial hair development in trans females. [4]
  - Other physical changes such as linear growth and weight gain continue while on these medications, and the adolescent is given time to develop emotionally and cognitively before making decisions on gender-affirming hormone use that have some irreversible effects.
  - The main concern with use of puberty suppression from early puberty is its impact on bone mineral density owing to the absence of the effect of oestrogen or testosterone on bone mineralisation.[5]
    - Research indicates low numbers of young people in Australia receive puberty blockers.
    - Regular monitoring of bone mineral density during treatment is recommended and good nutrition and weight bearing exercise are encouraged, to optimise bone health. [3]

[4] Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2017; **102**: 3869–3903.

[5] Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol* 2006; **155**(suppl 1): S131–S137.

- Oestrogen and testosterone are used as gender affirming hormone treatment, to either feminise or masculinise a person's appearance by inducing the onset of secondary sexual characteristics of the desired gender.[6,7]
    - Some of the effects of these medications are irreversible, while others have a degree of expected reversibility that is likely, unlikely or unknown.

Additional background on the *Australian Standards of Care and Treatment Guidelines*

- The *Australian Standards of Care and Treatment Guidelines* aim to maximise quality care provision to transgender and gender diverse children and adolescents across Australia, while recognising the unique circumstances of providing such care to this population. [8]
    - The *Australian Standards of Care and Treatment Guidelines* include general principles for supporting trans and gender diverse children and adolescents using an affirmative approach, as well as separate guidelines for the care of pre-pubertal children and trans and gender diverse adolescents, along with discipline-based recommendations for mental health care, medical and surgical interventions, fertility preservation, and speech therapy.
    - The *Australian Standards of Care and Treatment Guidelines* are based primarily on clinician consensus, along with previously published standards of care, treatment guidelines and position statements, and data from a limited number of non-randomised clinical studies and observational studies.[3]
        - The final document was endorsed by the Australian and New Zealand Professional Association for Transgender Health, the peak organisation in the region which actively promotes communication and collaboration among professionals of all disciplines involved in the health care, rights and wellbeing of people who identify as trans and gender diverse.[3]
        - The recommendations provided in the guidelines are based primarily on expert consensus. The guidelines acknowledge scarcity of high quality published evidence on the topic prohibited the assessment of level (and quality) of evidence for these recommendations. Where evidence exists, it has been referenced.[3]
    - Increasing evidence demonstrates with supportive, gender-affirming care during childhood and adolescence, harms can be ameliorated, and mental health and wellbeing outcomes can be significantly improved. [3]

Safety of medicines in the UK versus Australia

- The UK's Commission on Human Medicines recommended indefinite restrictions on the prescription of puberty blockers to children, citing an 'unacceptable safety risk in the continued prescription of puberty blockers to children'.
    - This recommendation stemmed from a lack of evidence for these medical treatments being used for gender incongruence and/or gender dysphoria in the UK prescribing context, rather than a specific safety concern related to particular medicines used in the gender affirmation process.

[6] Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2017; **102**: 3869–3903.

[7] Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol* 2006; **155**(suppl 1): S131–S137.

[8] Telfer M, Tollit M, Pace C, Pang K. Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents.; 2023.

- Puberty blockers will only be prescribed to children attending gender identity services as part of clinical research. A formal review of the evidence and the legislation will be conducted in 2027.

- The UK's Dr Hilary Cass Review (Cass Review) raised the issue of capacity of the young person and the concerns about the consent process for both parents and patients potentially leading to poor decision making in pursuing medical treatments for gender dysphoria when a comprehensive assessment is not performed.
  - Dr Cass reasoned the decision making in the NHS had been binary (i.e., pursuing a medical pathway and ignoring other options) rather than offering a wide range of potential pathways.
  - This differs from models of care in Australia where the provision of gender services is led by states and territories, who are responsible for the relevant service and they are primarily provided by a multidisciplinary team of specialists.
    - Decisions regarding clinical care (including decisions to commence or cease gender affirmation treatment) are shared between the clinicians, the young person and their family. If there is a disagreement on the diagnosis, treatment or capacity of the minor to provide informed consent, the Family Court of Australia has ruled this requires an application to the Court to resolve the dispute consistent with the child's best interests.
- In Australia, the Therapeutic Goods Administration (TGA) approved the use of gonadotropin-releasing hormone analogues (GnRA, or 'puberty blocking' medicines) for certain cancers, endometriosis, anticipated premature ovarian failure and precocious puberty, but not specifically for gender affirming care.
  - When used for gender affirming care, puberty blocking medicines are prescribed in Australia off label and do not attract a PBS subsidy.
  - This is based on a clinical decision of the individual's prescribing physician.
  - The Pharmaceutical Benefits Advisory Committee has not received any submissions to consider listing GnRH analogues for use in gender affirming hormone therapy.
- The TGA monitors the safety of all medicines on the Australian Register of Therapeutic Goods.
  - If the TGA identifies a new safety concern associated with off-label prescribing, regulatory action may be taken to ensure that the Product Information document clearly communicates the risks and accurately characterises the known safety profile of the medicine.
  - The TGA is not aware of any regulatory action being considered for off-label use of GnRH analogues for use in gender affirming hormone therapy.

Sax Institute review overview

- The Sax Institute review, 'Understanding interventions for children and young people living with gender dysphoria', provides NSW Health with access to the latest information on specific treatments for children and young people with gender dysphoria.
- A copy of the Sax Institute's Evidence Brief Summary is at **Attachment B** and the full report is available at **Attachment C**.
- The Sax Institute looked for research published in the scientific literature between 2019 and 2023 and provided NSW Health with an updated report on what they found. This work builds on a previous report provided to NSW Health summarising the research published between 2000 and 2019.

- The Review recommends three main directions for research to improve the quality of research and our understanding of treatments for gender dysphoria:
    - Improving Study Design
    - Long-Term Follow-Up
    - Collaboration and Multi-Centre Studies
- Findings will guide NSW Health's various projects designed to gather more information from experts and people with lived experiences, with the aim of providing safe and effective psychological and medical treatment services for young people with gender dysphoria. *Sax Institute Review findings*
- The Sax Institute review found it was difficult to draw definitive conclusions about interventions for gender dysphoria in children and young people from the available research (see limitations below, for more details).
- The review found 82 new research studies published since 2019. This represents a rapid growth in research in this field.
- Various methods of varying quality were used to gather information in these studies.
- Interventions and their relevant findings include:
    - Puberty suppression
        - These medications can delay the physical changes of puberty, giving young people more time to explore their gender identity without the added stress of unwanted changes to their body.
        - The research shows these medications are safe and work well to delay puberty, and their effects can be reversed if stopped.
        - Some studies suggest this treatment can help reduce the distress young people with gender dysphoria feel during puberty. However, these medications might decrease bone strength, so doctors need to monitor this during treatment.
    - Hormone therapy
        - Hormone therapy, using either oestrogen or testosterone, can help older teens develop physical traits that match their gender identity.
        - Research indicates this treatment can improve the mental health and well-being of young people with gender dysphoria.
        - Although some people may experience side effects like headaches, nausea, and vomiting, serious problems are rare.
    - Psychological support
        - The research shows emotional and social supports (therapy, family therapy and crisis support) are safe and well-received by people living with gender dysphoria (and their families), with no reported risks or harms.
    - Chest surgery
        - Chest surgery, often called "top surgery," is a procedure that helps people living with gender dysphoria by changing their chest to better match their gender identity.
        - For transgender men or non-binary individuals who want a more masculine chest, this surgery involves removing breast tissue to create a flatter chest.
        - For transgender women or non-binary individuals who want a more feminine chest, this surgery involves enhancing the chest with implants.
        - The research shows this surgery can significantly improve a person's confidence and comfort with their body, helping to reduce feelings of distress related to gender dysphoria.

        - As with any surgery, there are risks like infection or scarring, but many people feel the potential benefits outweigh these risks.
    - Preservation of fertility
        - Preservation of fertility means taking steps to preserve a person's ability to have biological children in the future.
        - Research on saving fertility for people with gender dysphoria before starting medical or surgical treatments shows that freezing sperm for transgender women and eggs for transgender men are effective methods.
        - However, there are some risks, such as potentially lower-quality sperm from those who have had puberty suppression or hormone treatments and the physical and emotional challenges of these fertility preservation procedures during adolescence, which might worsen gender dysphoria

Sax Institute Review limitations

- The Sax Institute note to date, research on treatments for gender dysphoria have faced several challenges, including:
    - Comparing Groups:
        - It is difficult to design research studies that compare people receiving treatment with those not receiving treatment because it is not ethical to deny treatment to those who need it.
        - Without a comparison group, it is difficult for researchers to confidently determine a treatment's effects.
    - Long-term and Mixed Treatments:
        - Gender dysphoria treatments often take a long time and involve a mix of medical, surgical, and psychological care. This makes it tough to determine the impact of a single treatment on its own.
    - Small and Single-Centre Studies:
        - Many research studies have only a small number of participants and are conducted at a single medical centre.
        - This makes it uncertain whether the results would be the same for a larger, more diverse group of people in different locations.

Consultations: Therapeutic Goods Administration, Technology Assessment and Access Division and Medical Benefits and Digital Health Division

Attachments:

A. Summary of state and territory gender-affirming care
B. Sax Institute - Evidence Brief summary: Understanding interventions for children and young people living with gender dysphoria
C. Sax Institute - Full report: Evidence for effective interventions for children and young people with gender dysphoria—update

Minister	**Minister Butler**
PDR Number	**MB24-003236**
Subject	****URGENT** Due to MO COB 19/12/24 - Information Brief – Additional Advice – Puberty blocker medication for under 18s**
Contact Officer	Tracey Andrews Ph: s47E(c), s47F Mobile: s47E(c), s47F
Clearance Officer	Trish Clancy Ph: s47E(c), s47F Mobile: s47E(c), s47F
Division/Branch	|Primary and Community Care| Population Health | Health Equity
Has Budget Branch been consulted if there are financial implications?	Not Applicable

Adviser/DLO comments:	Returned to Dept for: REDRAFT ☐ NFA ☐

Attachment A

Summary of State and Territory Gender Affirming Care

	Age and Service Restrictions	National Criteria, including Family Court
National	There are **no age restrictions for gender affirming care in Australia**, regardless of jurisdiction. Jurisdictional limitations relate to the availability of services.	**Trigger points for referral to the family law courts** • Where there is a dispute or disagreement between the young person, parents and/or medical practitioners as to diagnosis, treatment, or the young person's competence to consent to treatment for gender dysphoria, a court exercising family law jurisdiction may hear matters relating to the welfare of children, including medical matters. • When deciding gender affirming care, the court will make a determination as to what is in the best interests of the child. • Evidence must be given to satisfy the court that a proposed major medical procedure is in the child's best interests, and includes medical, psychological or other expert evidence. • How a court determines what is in a child's best interests is subject to a range of considerations that are provided for in the Family Law Act, and include: the views of the child; the nature of the relationship between the child and the parents; and any other matters the court thinks relevant. • This power for the court to consider matters about the welfare of a child is provided in the *Family Law Act 1975* (s. 67ZC).
AUSTRALIAN CAPITAL TERRITORY (ACT)	Canberra Hospital Paediatric Endocrinology Clinic (Gender Clinic) caters for children up to **16 years old**. A GP referral is required. Patients are then triaged by a specialist Doctor to determine what priority they will be given. The ACT government has developed guidelines for supporting the mental health of trans and gender diverse (TGD) people.	
NEW SOUTH WALES (NSW)	NSW Health is developing a coordinated, state-wide Specialist Trans and Gender Diverse Health Service (TGD Health Service) to provide gender affirming health care for people until they are 25 years old. TGD Health Services will be delivered through a Rural and Regional Hub, and Sydney metropolitan hub, which are under development. Sydney Children's Hospitals Network will provide support at The Children's Hospital at Westmead for people under 16, and South Eastern Sydney Local Health District will support people over 16.	
NORTHERN TERRITORY (NT)	The Northern Territory **does not have a publicly funded Gender Clinic service for children and young people**, however there are health specialists and non-government services who may assist. Surgical interventions must be referred to interstate providers.	

QUEENSLAND (QLD)	Children and young people **under 17** can access the gender service at Queensland Childrens Hospital if they live in Queensland. To use this service, you must have a referral from your GP or other medical provider.	• The Federal Circuit and Family Court of Australia is the usual court of choice in resolving disputes concerning the medical treatment of children with gender dysphoria, due to its experience and expertise in dealing with such applications. However, the Family Court of Western Australia also hears gender dysphoria matters, as well as State and Territory supreme courts, which may hear matters concerning the welfare of children as part of a common law *parens patriae* jurisdiction (inherent authority to intervene to protect persons unable to act on their own behalf, for example children). • Otherwise, the court has held that treatment for gender dysphoria is therapeutic – that is necessary for the treatment of a bodily malfunction, disease, or psychiatric disorder, and that, in the absence of dispute, parents can consent to treatment without the need for court intervention.
SOUTH AUSTRALIA (SA)	The Women's and Children's Hospital Gender Diversity Team accepts new referrals for people **up to 17 years old** with gender identity concerns from General Practitioners, Psychiatrists, Psychologists, and Mental Health Professionals. The team offers specialised fertility support and supports young people seeking puberty suppression and gender affirming hormones. Adolescents who are under 16, or who lack decision-making capacity, require a parent/legal guardian to be aware of the appointment and to attend with them.	
TASMANIA (TAS)	The Tasmanian Gender Services (TGS) is for people **17 years and under**. Those over 17 years can access Transgender support services through the Sexual Health Service. TGS offers advice, assessment, and treatment for children and young people experiencing significant difficulties with being gender diverse.	
VICTORIA (VIC)	The Royal Children's Hospital Melbourne (RCH) Gender Service sees children and adolescents for a new assessment **up to their 16th birthday**. Adolescents who are 16 years or over may be eligible to access adult services. The initial consultation for gender dysphoria for children 8 years and under will entail a review by a psychologist or child psychiatrist. They may be referred later to a paediatrician who specialises in adolescent medicine and gender diversity if required. Children and adolescents up to 16 years require a parent to attend a referral appointment regarding gender identity.	

WESTERN AUSTRALIA (WA)	WA **does not provide publicly funded gender affirming services for children under 17 years old.** Oestrogen/anti-androgen and testosterone treatment can be provided to more mature adolescents with long-term stable gender identity, who have developed the capacity to give informed consent to these treatments, including appreciation of the risk of regret. This requires repeated consultations, and specific counselling regarding fertility. The Gender Pathways Service (GPS) is a state-wide service located within YouthLink, Youth Mental Health (North Metro Health Service), which provides specialist clinical psychology assessment for young people aged 17-24 years seeking medical and/or surgical gender affirmation treatment, who are experiencing significant barriers to accessing this through other pathways. Referrals are accepted for young people aged 17 to 24 years.	

Evidence Brief

SaxInstitute

This Evidence Brief summarises the findings of an Evidence Check rapid review brokered by the Sax Institute

Understanding interventions for children and young people living with gender dysphoria

What is gender dysphoria?

Gender dysphoria is a condition where a person experiences discomfort or distress because their gender identity differs from the sex they were assigned at birth. This can affect children and young people significantly, impacting their mental health and overall well-being.

What did we do?

We looked at the latest research from around the world to understand what knowledge was being used to inform the care of children and young people living with gender dysphoria.

We looked for research published in the scientific literature between 2019 and 2023 and provided NSW Health with an updated report on what we found. This work builds on a previous report we provided to NSW Health summarising the research published between 2000 and 2019.

We made recommendations for further research that could fill gaps in knowledge.

Why it matters

Not everyone who identifies as transgender or gender diverse experiences gender dysphoria. However, those who do are especially vulnerable to discrimination, bullying, social exclusion, and physical assault, which can lead to poor health outcomes.

Transgender and gender diverse children and young people are at a higher risk of mental health issues and have higher rates of depression, anxiety, suicidal thoughts and suicide than the general population.

To help reduce the impact of these problems, it's crucial that transgender and gender diverse young people, including those living with gender dysphoria, have access to high-quality, safe, inclusive, and responsive support and services based on the best research available. Appropriate gender affirming interventions may help reduce distress and improve quality of life.

Interventions we looked at

Puberty suppression

Hormone therapy

Psychological support

Chest surgery

Preservation of fertility

What did we find?

Overall, it is difficult to draw definitive conclusions about interventions for gender dysphoria in children and young people from the available research. We found 82 new research studies published since 2019. This represents a rapid growth in research in this field. Various methods of varying quality were used to gather information in these studies. While we found that there hasn't been a significant increase in the use of gold-standard methods (such as, randomised controlled trials (RCTs)) in this emerging field of research, we were still able to draw out meaningful insights into the effectiveness and risks of gender dysphoria treatments. The research we found provides a starting point for discussing critical issues with patients, caregivers, and healthcare providers, including deciding where to invest in future research.

In NSW, children and young people need to meet additional consent requirements and obtain a diagnosis to access medical treatments for gender dysphoria. These treatments are considered after careful assessment and discussion. For more information see the NSW Health Framework for the Specialist Trans and Gender Diverse Health Service for People Under 25 Years: www.health.nsw.gov.au/lgbtiq-health/Publications/tgd-framework.PDF

Puberty suppression:

These medications can delay the physical changes of puberty, giving young people more time to explore their gender identity without the added stress of unwanted changes to their body. The research shows that these medications are safe and work well to delay puberty, and their effects can be reversed if stopped. Some studies also suggest that this treatment can help reduce the distress young people with gender dysphoria feel during puberty. However, these medications might decrease bone strength, so doctors need to monitor this during treatment.

Hormone therapy:

Hormone therapy, using either oestrogen or testosterone, can help older teens develop physical traits that match their gender identity. Research indicates that this treatment can improve the mental health and well-being of young people with gender dysphoria. Although some people may experience side effects like headaches, nausea, and vomiting, serious problems are rare.

Psychological support:

We reviewed the research on emotional and social support for people with gender dysphoria and their families. This includes:

- Therapy: Sessions with a trained mental health professional to help children and young people explore their gender identity and deal with any distress.
- Family therapy: Sessions designed to help families understand and support their child.
- Crisis support: Help for those experiencing extreme distress.

The research shows that these types of emotional and social supports are safe and well-received by people living with gender dysphoria (and their families), with no reported risks or harms.

Chest surgery:

Chest surgery, often called "top surgery," is a procedure that helps people living with gender dysphoria by changing their chest to better match their gender identity. For transgender men or non-binary individuals who want a more masculine chest, this surgery involves removing breast tissue to create a flatter chest. For transgender women or non-binary individuals who want a more feminine chest, this surgery involves enhancing the chest with implants.

The research shows this surgery can significantly improve a person's confidence and comfort with their body, helping to reduce feelings of distress related to gender dysphoria. As with any surgery, there are risks like infection or scarring, but many people feel the potential benefits outweigh these risks.

Preservation of fertility

Preservation of fertility means means taking steps to preserve a person's ability to have biological children in the future. Research on saving fertility for people with gender dysphoria before starting medical or surgical treatments shows that freezing sperm for transgender women and eggs for transgender men are effective methods. However, there are some risks, such as potentially lower-quality sperm from those who have had puberty suppression or hormone treatments and the physical and emotional challenges of these fertility preservation procedures during adolescence, which might worsen gender dysphoria.

Recommendations for further research

To date, research on treatments for gender dysphoria has faced several challenges:

- **Comparing Groups:**
  It's difficult to design research studies that compare people receiving treatment with those not receiving treatment because it's not ethical to deny treatment to those who need it. Without a comparison group, it's difficult for researchers to confidently determine a treatment's effects.
- **Long-term and Mixed Treatments:**
  Gender dysphoria treatments often take a long time and involve a mix of medical, surgical, and psychological care. This makes it tough to determine the impact of a single treatment on its own.
- **Small and Single-Centre Studies:**
  Many research studies have only a small number of participants and are conducted at a single medical centre. This makes it uncertain whether the results would be the same for a larger, more diverse group of people in different locations.

We recommend three main directions for research to improve the quality of research and our understanding of treatments for gender dysphoria:

1. **Improving Study Design:**
   Develop innovative study methods that include well-chosen comparison groups. Traditional randomised controlled trials (RCTs) may not be practical or ethical, however comparison might still be possible by drawing on siblings, cisgender adolescents, population datasets, or historical reference control groups.
2. **Long-Term Follow-Up:**
   Research teams could track existing groups of participants over time to learn about long-term outcomes, including checking for health risks, benefits and costs.
3. **Collaboration and Multi-Centre Studies**:
   Research teams starting new studies in Australia should work with established teams to create studies involving multiple medical centres. This approach can combine data to better understand how people use services and improve models of care.

Conclusion

Our review of current research provides NSW Health with access to the latest information on specific treatments for children and young people with gender dysphoria. The report suggests directions for further research, and does not make any recommendations.

This review's findings will guide various projects designed to gather more information from experts and people with lived experiences, with the aim of providing safe and effective psychological and medical treatment services for young people with gender dysphoria.

For more information on NSW Health's services for trans and gender diverse people see https://www.health.nsw.gov.au/lgbtiq-health/Pages/tgd-health-service.aspx

About the Sax Institute

The Sax Institute is an independent, not-for-profit organisation that improves health and wellbeing by driving better use of evidence in policies, programs and services.

About Evidence Checks

An Evidence Check review is a synthesis, summary and analysis of the best and most relevant research evidence to inform policy making and program development. Evidence Check is used by a range of agencies, including government agencies, non-government organisations, and other policy making agencies.

Additional resource

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Evidence Check

Evidence for effective interventions for children and young people with gender dysphoria—update

An Evidence Check rapid review brokered by the Sax Institute for the NSW Ministry of Health—February 2024

An Evidence Check rapid review brokered by the Sax Institute for the NSW Ministry of Health.
February 2024.

This report was prepared by: Bragge, P, Ngo C, Delafosse V, Goldberg E, Temple-Smith M, Sanci L.

February 2024

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Evidence Check: Evidence for effective interventions for children and young people with gender dysphoria—update

Supporting the statewide Specialist Trans and Gender Diverse Health Service to deliver best practice care and treatment

An Evidence Check rapid review brokered by the Sax Institute for the NSW Ministry of Health. February 2024.

This report was prepared by Bragge P, Ngo C, Delafosse V, Goldberg E, Temple-Smith M, Sanci L.

Contents

List of Abbreviations

AFAB	assigned female at birth	Hb	haemoglobin
AMAB	assigned male at birth	HbA1c	haemoglobin A1c
ALT	alanine aminotransferase	Hct	haematocrit
ALP	alkaline phosphatase	HDL	high-density lipoprotein
AST	aspartate aminotransferase	K+	potassium
BC	Bicalutamide	L	lynestrenol
BMAD	bone mineral apparent density	LDL	low-density lipoprotein
BMD	bone mineral density	LH	luteinising hormone
BMI	body mass index	LS	lumbar spine
BP	blood pressure	MPA	medroxyprogesterone acetate
CA	cyproterone acetate	NHMRC	National Health and Medical Research Council
CASP	Critical Appraisal Skills Program	NOS	not otherwise specified
CGAS	Children's Global Assessment Scale	OC	oral contraceptive pill
CSHT	cross-sex hormone treatment	QtC	heart-rate corrected QT interval (time taken for ventricular depolarisation and repolarisation) on an electrocardiogram
DEXA	dual-energy X-ray absorptiometry	PS	puberty suppression treatment
ED	eating disorder	RCHGS	Royal Children's Hospital Melbourne Gender Service
FA	fractional anisotropy	RCT	Randomised controlled trial
FN	femoral neck	SSC	spermatogonial stem cell
FP	fertility preservation	TAYAs	transgender adolescents and young adults
FSH	follicle-stimulating hormone	TE	testosterone esters
GAC	gender-affirming care	TESE	testicular sperm extraction
GAHT	gender-affirming hormone therapy	TG	transgender

GAS	gender-affirming surgery	TGD	trans and gender diverse
GD	gender dysphoria	TGNB	transgender and nonbinary
GICT	gender identity conversion therapy	TSH	thyroid-stimulating hormone
GID	gender identity disorder	TTC	testicular tissue cryopreservation
GnRH	gonadotropin-releasing hormone	TVQ	Transsexual Voice Questionnaire
GnRHa	gonadotropin-releasing hormone agonist	UGDS	Utrecht GD Scale
GRADE	Grading of Recommendations Assessment, Development and Evaluation	WM	white matter
GRS	gender reassignment surgery	WPATH	World Professional Association for Transgender Health

Foreword

This Evidence Check report, commissioned by the NSW Ministry of Health through the Sax Institute, provides a comprehensive update of research evidence pertaining to interventions for young people aged under 18 experiencing gender dysphoria and published between 2019 and 2023. The purpose of this review is to provide an objective summary of the available literature on this topic.

The review builds on a previous Evidence Check, also commissioned by the NSW Ministry of Health through the Sax Institute, which covered the years 2000–2019. The research team that conducted this Evidence Check includes members involved in the previous Evidence Check.

This Evidence Check identified 82 new studies encompassing five gender dysphoria interventions—puberty suppression treatment, gender-affirming hormone therapy, gender-affirming chest ('top') surgery, fertility preservation and psychosocial therapies.

The increased volume of research evidence identified in this Evidence Check compared with the previous Evidence Check of the same topic (which identified 46 studies) reflects considerable growth in research in this field.

This Evidence Check systematically identified, tabulated, evaluated and described research regarding the effectiveness, risks and key characteristics of research on gender dysphoria interventions. Recommended best practice approaches to research evidence synthesis were consistently applied and transparently reported. As is standard practice for research evidence synthesis, we summarised the strengths and limitations of the body of research identified based on findings from analysis and the reported conclusions of authors of the research papers reviewed. This information informed recommendations for further research in this field.

This report does not make recommendations for policy and clinical practice.

Although knowledge of the state of the research evidence is an important input, policy decision making and the development of clinical practice guidelines are separate activities requiring a range of other inputs and consultation activities that were not within the scope of this project.

Therefore, this report is not designed to support policy or clinical practice decision making in isolation from other inputs and consultation activities.

We encourage readers of the report to consider its findings alongside credible policy, health service, clinical and other information sources relevant to their setting.

Definitions used in this Evidence Check

The language used in this field is evolving. Consequently, terms used in past research will vary. Additionally, terms preferred by members of the community and clinicians may vary and carry different meanings. As such, we provide the following summary of the definitions used in this report.

Transgender / trans and gender diverse are umbrella terms referring to people whose assigned sex at birth does not match their internal gender identity. Transgender / trans or gender diverse people may identify as nonbinary (that is, not exclusively as either gender); as both genders; as neither gender; they may move between the gender binary; or they may reject the idea of gender altogether. Transgender / trans or gender diverse people may or may not modify their body, dress or legal status, and may or may not seek medical treatment.[1]

Gender dysphoria is defined as *"clinically significant distress arising from the incongruence between birth-assigned sex and gender identity"*.[2(p3)]

Gender-affirmative healthcare refers to a broad array of psychological, social, behavioural and medical interventions that aim to support and affirm an individual's gender identity. These interventions include, but are not limited to, interventions provided to people with gender dysphoria.

Gender-affirming chest surgery ('top surgery') is the surgical alteration of physical characteristics of the chest, including breast reduction (mammoplasty), breast augmentation or other types of chest reconstruction such as alterations to the chest wall. Additionally, both transgender men and women may have facial masculinisation or feminisation surgery as well as surgery to alter their vocal cords and related organs.[3]

Gender-affirming hormone therapy (GAHT) refers to medicines prescribed to help a person gain the outward characteristics that match their gender identity.

Puberty suppression treatment involves medicines that delay the physical and physiological changes associated with puberty.

Fertility preservation is the process of saving or protecting eggs, sperm or reproductive tissue so that a person can use them to have biological children in the future.

Executive summary

Background

Transgender and gender diverse healthcare is an emerging and complex area. In 2020, the Sax Institute published an Evidence Check review commissioned by the NSW Ministry of Health on the effectiveness of interventions for children and young people under 18 years old with gender dysphoria[2], defined as *"clinically significant distress arising from the incongruence between birth-assigned sex and gender identity"*.[2(p3)] In 2023, the NSW Ministry of Health commissioned the Sax Institute to provide a comprehensive update of the research evidence on this topic published between 2019 and 2023. This updated review followed the same research questions as the previous Evidence Check. This Evidence Check synthesises and appraises the newly identified evidence about the effectiveness of a range of gender dysphoria interventions that can be delivered in public hospitals and community settings in NSW, as well as any risks or safety issues associated with each component of care. This report does not make recommendations for policy and clinical practice. Information provided in this report on the state of the available research evidence will inform a range of activities and consultations to be undertaken by the NSW Ministry of Health.

Research questions

This Evidence Check update aimed to address the following set of umbrella and sub-questions, developed in consultation with the NSW Ministry of Health:

Question 1—Effective clinical medical interventions for transgender and gender diverse young people under 18 years old with gender dysphoria

Question 2—Effective psychosocial interventions for transgender and gender diverse young people under 18 years old with gender dysphoria

a: What have been shown to be the most effective medical interventions and psychosocial interventions for treating transgender and gender diverse young people **under 18 years old** with gender dysphoria?

b: What have been shown to be the risks or potential harms from medical interventions and psychosocial interventions for treating transgender and gender diverse young people **under 18 years old** with gender dysphoria?

c: Is there variation in the effectiveness or risks associated with medical interventions and psychosocial interventions for treating transgender and gender diverse young people with gender dysphoria?

Summary of methods

Our team undertook a search and selection process to identify peer-reviewed literature that responded to the research questions and was published between January 2019 and September 2023. We selected 82 eligible studies for inclusion in the Evidence Check update. All citations were ranked according to the established National Health and Medical Research Council (NHMRC) Levels of Evidence to assess the robustness of the included studies. We critically appraised all included studies using appraisal tools appropriate for the study design type. The proportionate levels of evidence identified were:

- 16 studies (20% of 82 included studies) Level I evidence (systematic reviews of level II studies—noting that although this is the technical NHMRC classification, the included systematic reviews did NOT review level II studies)
- 1 study (1%) Level II evidence (a randomised controlled trial)
- 12 studies (15%) Level III-2 evidence (comparative studies with concurrent controls)
- 5 studies (7%) Level III-3 evidence (comparative studies without concurrent controls)
- 48 studies (57%) Level IV evidence (case series or cross-sectional studies).

We performed a narrative synthesis of the results. In this process we mapped the updated review outputs against the findings of the first Evidence Check.[2] Studies examining multiple interventions for gender dysphoria were categorised based on their stated primary aim.

Key findings

Results of searching and study characteristics

Eighty-two studies met criteria for inclusion in this update review, comprising the following proportionate volumes of research by intervention type:

- 39 studies (48%) pertaining to gender-affirming hormone therapy (GAHT)
- 17 studies (21%) relevant to puberty suppression treatment
- 8 studies (9%) focusing on gender-affirming chest surgery
- 7 studies (8%) relevant to psychosocial therapies
- 6 studies (7%) relevant to fertility preservation.

There were also five studies (6%) that reported on care use (the proportion of participants who discontinued gender-affirming medical treatment); however, no firm conclusions can be drawn from this evidence about care use as it was an incomplete set of studies and was not a primary focus of this review. This section is therefore contained in Appendix 1.

The 82 eligible studies represented a considerable increase in volume of research examining gender dysphoria interventions from 2019–2023 with only 46 studies eligible for the previous review covering the years 2000–2019. Overall, the evidence about gender dysphoria interventions remains weak due to poor study designs, low participant numbers and single-centre recruitment. Additionally, there was variability in study characteristics such as included populations, specifics of interventions and outcome measures used. Therefore, readers with specific interests are encouraged to access the relevant evidence tables detailing individual study characteristics. While studies in this Evidence Check update generally report favourable outcomes for gender-affirming care initiatives, the limitations in the evidence need to be borne in mind when interpreting these findings. Notwithstanding these caveats the findings for key interventions of interest showed general congruence with those of the previous review of this topic.

Key findings by intervention

Question 1—Effective clinical medical interventions for transgender and gender diverse young people under 18 years old with gender dysphoria

As in the 2020 Evidence Check, the following clinical interventions were evaluated: two types of pharmaceutical intervention (puberty suppression and gender-affirming hormone therapy), surgical intervention (chest or breast surgery), and cryopreservation of gametes (sperm or oocytes).

Puberty suppression treatment (PS)

(Number of studies by level of evidence: 3x Level I, 4x Level III-2, 1x Level III-3, 9x Level IV; total 17 studies)

We identified 17 studies pertaining to puberty suppression treatment (PS) in this Evidence Check update. Broadly, the newly identified evidence reinforced the finding of the previous Evidence Check regarding benefits and effectiveness. That is, PS agents (generally referred to as GnRHa) were reported to be safe, effective and reversible. As a counterpoint, this update identified one study describing differential implications of PS for later surgery, with reduced need for mastectomy in trans men but potential complications for genital surgery in trans women as penile inversion may be compromised. Psychological effects of PS on conditions such as depression and anxiety appear modest in comparison with GAHT, with the primary impact being reduction of distress associated with unwanted secondary sexual characteristics; two Level IV studies reflected positive impacts on gender dysphoria.

With regard to risks and potential harms, reductions in bone density remain the primary concern with PS and monitoring of bone mineral density is recommended. However, some newly identified studies suggest maintenance of bone mineral density during PS treatment. Studies reported no indications to monitor liver or renal function in the PS setting. Other reported side effects of PS were also relatively minor. Instances of insufficient suppression of puberty (known as ‘pubertal escape’) were reported, but satisfaction with PS treatment was reported as good overall. In summary, this Evidence Check update predominantly reinforces the findings of the previous review and adds to the evidence base underpinning these findings; with the qualification that the strength of the evidence remains low.

Gender-affirming hormone therapy (GAHT)

(Number of studies by level of evidence: 7x Level I, 5x Level III-2, 2x Level III-3, 25x Level IV; total 39 studies)

This Evidence Check update identified a considerable volume of evidence (39 studies) pertaining to GAHT, reflecting an overall rise in research into interventions for gender dysphoria since 2019–20. The newly identified studies support the conclusions of the previous review, which reported that GAHT was effective in producing changes in body composition that align with the desired sex. Increases in BMI were reported; however, this remained in the healthy range and did not appear to be long term. There does not appear to be a significant impact on adult height and it appears that GAHT recovers the bone mineral density losses that occur during PS.

Additionally, there were mixed results on menstrual suppression (albeit in Level IV studies) with some studies reporting good achievement of amenorrhea and others reporting breakthrough bleeding. A number of studies provided new evidence pertaining to the psychological benefits of GAHT. The identified studies reported positive results across the domains of body image, gender dysphoria, depression, anxiety, suicide risk, quality of life and cognitive function. However, neutral and some negative findings were also reported in these domains. Additionally, two Level IV studies reported no changes in mental health care use following gender-affirming pharmaceutical care. Although studies reporting positive mental health outcomes following GAHT outnumber those with neutral or negative findings, considerable flaws remain in the evidence because of generally low participation rates of target groups, inadequate representation of young people and / or poor study designs and conduct. The relevant systematic reviews identified underline this observation. Several studies support the finding of the previous review, which reported that GAHT appears to increase bone density following the negative impact of puberty suppression treatment on bone density.

We observed similar increases in research volume in studies reporting on the risks and potential harms of GAHT. Findings on overall safety, cardiometabolic risk, kidney and physiological parameters support the previous review's findings that serious adverse outcomes associated with GAHT are rare. One Level I study flagged risk of meningioma associated with cumulative dose exposures of cyproterone acetate greater than 3g and therefore quoted recommendations that daily doses should be 10mg or less. This study also reported increased prolactinoma risk, which may reflect increased monitoring, with symptomatic prolactinoma risk not elevated. Minor changes in physiological parameters were reported, for example, blood pressure and elevated potassium—in the case of potassium, none of the subjects had symptoms of hyperkalaemia, and all elevated measurements were normal when repeated. Newly identified primary studies reported a range of less serious side effects (for example, headaches, nausea and vomiting), consistent with the previous review. There was some evidence regarding fertility impacts of GAHT, although only from two Level IV studies. Overall, despite increases in research volume, the conclusions of the previous review with respect to GAHT are largely unchanged as the increased number of studies is offset by generally poor study designs.

Gender-affirming chest surgery ('top surgery')

(Number of studies by level of evidence: 1x Level I, 3x Level III-2, 4x Level IV; total 8 studies)

This update identified eight studies evaluating surgery including one systematic review, therefore expanding the evidence base from the previous review. With regards to benefits / effectiveness, the

updated evidence reports generally positive findings for gender dysphoria, psychosocial outcomes and sexual function and quality of life. However, there were neutral findings on psychosocial outcomes in transgender men as well as mixed positive / negative findings on quality of life.

The irreversible nature of surgery remains a key risk / potential harm, although regret rates were low where reported. Complication rates for chest surgery were also reported to be low. In contrast with the previous review, several studies reported on outcomes in adolescents referred for chest surgery at 16–17 years of age. Findings were generally positive across these studies on sexual function, gender incongruence and chest dysphoria. One Level I study reported low regret rates and two Level III-2 studies reported low complication rates. Although the evidence base is expanded and generally supports chest surgery, confidence in findings is low because of a lack of studies and / or poor study quality, use of mixed surgery populations and the confounding effect of hormone and other therapies, which almost always precede surgery. Offsetting these limitations are three high quality comparative studies with positive findings specific to adolescents. In summary, this update provides some additional evidence that supports chest surgery; however, further studies are required that focus on the effect of surgery in adolescents.

Fertility preservation (cryopreservation)

(Number of studies by level of evidence: 2x Level I, 2x Level III-2, 3x Level IV; total 6 studies)

This update has added two systematic reviews and a further four primary studies to the evidence base pertaining to cryopreservation (noting that three of the four primary studies were included in the two Level I reviews). Desire to have children among transgender adolescents is relatively high; however, uptake of fertility preservation treatment remains low because of cost barriers, late referral and low awareness. One Level I review found evidence for another factor contributing to low uptake of fertility preservation, identifying that most people who expressed an interest in having children did not see biological offspring as their preferred option. Although the newly identified evidence generally reports favourable benefits and effectiveness outcomes for both semen and oocyte cryopreservation, some risks or potential harms warrant mention. Studies consistently reported that semen was of lower quality if patients had received puberty suppression and / or GAHT. Furthermore, harvesting semen can be challenging in early puberty and / or due to discomfort with masturbation. There is emerging evidence that testicular sperm extraction can mitigate these limitations, although this research is in its infancy and semen cryopreservation remains the dominant approach. Oocyte preservation was reported as generally effective with no adverse events; however, cryopreservation procedures are invasive and psychologically challenging and can worsen gender dysphoria.

In summary, while additional evidence supporting fertility preservation was identified, both reviews and primary studies remain limited by small sample sizes, single centre recruitment, study design limitations and variation in use of hormones in participant cohorts. Notwithstanding this, outcomes reported are predominantly positive and very few adverse effects were described in identified studies.

Question 2—Effective psychosocial interventions for transgender and gender diverse young people under 18 years old with gender dysphoria

Psychosocial therapies

(Number of studies by level of evidence: 3x Level I, 1x Level II, 1x Level III-3, 2x Level IV; total 7 studies)

This Evidence Check update has added considerably to the volume of evidence evaluating psychosocial interventions such as such as psychotherapy, family therapy and mental health / crisis support. The previous review identified only three studies, with one a single case study; this Evidence Check has identified three systematic reviews and four primary studies including a randomised controlled trial. The newly identified studies report benefits and effectiveness across numerous outcome domains including suicidal ideation, psychological distress, depression, anxiety and gender minority stress. Furthermore, most studies report that interventions are both acceptable and safe, with no risks or potential harms reported.

Although the existence of an RCT is unique to this intervention category, it should be noted it was of a mixed population of sexual and gender-minority youth—the number of people experiencing gender dysphoria is not reported and no subgroup analysis of this group is presented. Furthermore, considerable limitations were identified in this body of literature. In addition to the previously observed limitations of small sample sizes and lack of diversity in participant cohorts, these included a large number of psychological interventions with additional variability in delivery mode; and studies of mixed populations with no subgroup analysis of adolescents and / or transgender participants. Therefore, although study designs are stronger relative to other intervention areas in this Evidence Check update, a number of limitations that are applicable to studies of psychological therapies should be borne in mind when interpreting findings of studies of psychological interventions.

Gaps in evidence

We assessed the extent to which gaps in the evidence base reported in the previous Evidence Check[2] have been addressed by newly identified studies, with the following observations:

- The studies examining the characteristics of transgender and gender diverse young people within the context of treatment interventions in Australia are limited to descriptions of those attending a Melbourne-based gender-affirming care clinic. Knowledge of characteristics of cohorts in other Australian jurisdictions remains limited to poor.
- The evidence base was dominated by studies without control or reference group comparisons. This limitation was compounded by the complex nature of gender-affirming models of care for people experiencing gender dysphoria, which may involve multifaceted interventions that are often concurrent and/or delivered over a long period of time. This makes evaluation of specific treatment effects for individual therapies challenging. Hence the gap remains (as previously identified) for proof of effectiveness of the discrete interventions, medical or psychosocial. While it is acknowledged that ethical limitations preclude the conduct of randomised controlled trials for many gender dysphoria interventions, further comparative studies (i.e. Level III-2 and III-3 designs) would be of more value than uncontrolled (Level IV) studies in addressing this gap.
- The previous review noted that further studies were needed to explore the potential for the TGD child undergoing puberty suppression to experience the (increasing) social isolation proposed by some authors. As we found no newly identified evidence pertaining to social isolation during puberty suppression in this update, this gap in the evidence base remains.
- This Evidence Check update identified only one study targeting the relationship between puberty suppression, GAHT and surgical outcomes—confirming a persisting lack of research attention.

- Studies examining the effects of exercise and diet on bone density inadequately controlled for confounding (for example, due to exercise and vitamin D levels) and this remains a gap in knowledge.

There was a welcome increase in the volume of studies identified in this Evidence Check update, with a wide breadth of outcomes examined; however, there was inconsistent to low use of validated measures.

Likewise, the evidence base for psychosocial interventions has been augmented by a number of newly identified studies, although confidence in the findings remains low. Further research is required to explore specific effects of therapies at different ages and to expand the evidence beyond association (correlation) to firmer conclusions regarding causation and factoring in the influence of mediating variables.

Recommendations for further research

Analysis of persisting research gaps indicated three main recommendations for research directions:

1. **Long-term follow-up and cohort tracking:**
   Existing identified cohorts from longitudinal studies should continue regular periodic follow-up to improve understanding of longer-term outcomes, including risks, benefits and potential economic-related insights.
2. **Collaboration and multicentre cohorts:**
   Newly established research studies in Australia should collaborate as much as practicable with established research teams to build multicentre cohorts. Such multisite cohorts may also harness the power and promise of data linkage to understand, for example, service use behaviours and best investments for models of care.
3. **Generalisability and bias reduction**
   Innovative study designs are needed that offer controls via appropriately recruited reference groups. The traditional RCT approach is unlikely to be feasible and ethically acceptable for many of the key intervention areas; however, in addition to other comparative study designs, one promising direction may be the application of hybrid designs emerging in the field of implementation science.

Discussion and conclusion

Gender-affirming medical and psychosocial interventions can be considered a complex intervention, defined as comprising numerous interacting components; a corresponding number and variability of outcomes; and requiring flexibility and tailoring in delivery.[4] Complex interventions are resource-intensive to deliver and evaluate.

It can be challenging in the field of research into interventions for gender dysphoria to design studies that compare those receiving treatment with a well matched control group to ascertain the effect of the treatment. Ethical concerns arise regarding withholding of treatment to people experiencing gender dysphoria because of perceptions that this may cause greater distress. In addition, the nature of some gender dysphoria treatments themselves can make the selection of control groups difficult. It is

therefore not surprising that Level IV studies account for 57% of the total research volume in this Evidence Check update, with proportionally fewer comparative studies than in the previous Evidence Check. It is likely that these differences in part reflect dedicated efforts to report outcomes or 'snapshots' of clinical interest for cohorts over time as they progress through management at specialist gender dysphoria clinics. Examples include the programs led by the Royal Children's Hospital in Melbourne[5,6] and in Amsterdam.[7,8]

Moreover, the inherent limitation of research into interventions for gender dysphoria, independent of study design, is that gender dysphoria management is undertaken over a long treatment period during which various interventions may overlap. This makes it difficult to study the differential effect of individual interventions, even when a control group is used. For example, PS and GAHT, two interventions in 70% of all included studies in this Evidence Check update, often overlap; of the 57 primary studies examining these therapies, 40 contained cohorts that had received both therapies during the period of the study, including 21 of the 23 Level IV studies examining GAHT. The complex nature of gender dysphoria treatment, in addition to these factors, should be considered when interpreting the findings of this Evidence Check.

Notwithstanding the above considerations, there was some consistency in the findings between the original Evidence Check and this update. Several newly identified studies, including reviews and controlled empirical studies, supported previous conclusions that gonadotropin-releasing hormone agonists are the most effective treatment for puberty suppression. Similarly, a relatively large number of studies reported positive impacts of GAHT on a range of psychosocial outcomes including gender dysphoria, depression, anxiety and suicide risk. Evidence identified in this Evidence Check update also reported that both semen and oocyte cryopreservation were successful approaches to fertility preservation.

This update added considerably to the evidence base about psychosocial therapies from the previous Evidence Check. Newly identified studies reported a range of benefits across suicidal ideation, depression and anxiety. Both the confounding effects of hormonal therapies and the wide range of disparate psychological therapies evaluated should be borne in mind when interpreting findings of psychological interventions.

While there has not been a rapid growth in the conventionally accepted gold standard designs of RCTs in this field, this Evidence Check offers important insights into the effectiveness and risks associated with gender dysphoria interventions. The combined total of 128 studies (of varying quality) provides a platform for engaging patients and carers in dialogue on key issues, including defining directions for future research investment.

Finally, it is important to emphasise that this Evidence Check provides a synthesis of reported findings of eligible studies, the strength of the study design and how each study has been conducted. This review is not designed to guide policy or clinical practice. Although knowledge of the state of the research evidence is an important input into policy and clinical practice guideline development, these activities involve considerable additional processes, consultations and inputs. Therefore, this report should not be used in isolation to guide policy or practice.

Background

Not all people who identify as transgender / trans or gender diverse experience gender dysphoria.[9] However, people who do experience persistent gender dysphoria are a uniquely vulnerable group at high risk of harm from discrimination, bullying, social exclusion and physical assault, which can contribute to poorer health outcomes.[10] Transgender individuals experience an elevated prevalence of mental health problems that negatively impact wellbeing and quality of life[11], including higher suicidal ideation and suicide rates than the general population.[12]

To address these impacts, it is important that transgender and gender diverse people, including those experiencing gender dysphoria, have access to supports and services that are informed by the best available research evidence. NSW Health's current LGBTIQ+ Health Strategy 2022–2027 reflects this principle with a stated vision that *"LGBTIQ+ people in NSW receive high quality, safe, inclusive and responsive healthcare that delivers outcomes that matter to them"*.[13] Accordingly, a Framework for the Specialist Trans and Gender Diverse Health Service for People Under 25 Years was published by NSW Health in July 2023. This is designed to guide *"how evidence-based trans and gender diverse health care will be delivered through the Specialist Trans and Gender Diverse Health Service (the TGD Health Service) to NSW Local Health Districts (LHDs) and Speciality Health Networks (SHNs)"*.[1]

A previous review of evidence pertaining to the effectiveness of interventions for children and young people with gender dysphoria commissioned by NSW Health through the Sax Institute was published in 2020.[2] It identified 46 papers, comprising 34 empirical studies, six reviews and six guidelines or consensus statements.

The previous Evidence Check concluded that *"the available evidence of the benefits and harms of treatment for this age group is of low quality"*.[2(p11)] Specific limitations highlighted included small sample sizes, an absence of RCTs from ethical concerns, lack of standardised outcome measures and failure to control for confounders (variables that can influence measured outcomes). Although the quality of evidence was described as low, the review outlined a range of benefits and risks associated with puberty suppression treatment and gender-affirming hormone therapy (GAHT). In contrast, the review reported very little evidence for either benefits or risks associated with gender-affirming surgery or psychosocial interventions.[2]

The current Evidence Check was commissioned by NSW Health through the Sax Institute to inform a range of projects to ensure delivery of high quality responsive services, including but not limited to:

- Development of clinical guidance for the TGD Health Service by a Clinical Advisory Group to support consistent and high-quality care
- Development and implementation of monitoring and evaluation mechanisms to track outcomes, embed quality improvement and contribute to the wider evidence base
- Development of accessible resources to ensure young people and families have the information they need to make informed decisions about treatment and care options.

The questions for this Evidence Check are:

Question 1—Effective clinical medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria

1. Question 1a—What have been shown to be the most effective medical interventions for trans and gender diverse young people **under 18 years old** with gender dysphoria?
2. Question 1b—What have been shown to be the risks or potential harms from medical interventions for trans and gender diverse young people **under 18 years old** with gender dysphoria?
3. Question 1c—Is there variation in the effectiveness and risks associated with medical interventions for trans and gender diverse young people **under 18 years old** with gender dysphoria by factors listed below?

Question 2—Effective psychosocial interventions for trans and gender diverse young people under 18 years old with gender dysphoria

1. Question 2a—What have been shown to be the most effective psychosocial interventions for treating trans and gender diverse young people **under 18 years old** with gender dysphoria?
2. Question 2b—What have been shown to be the risks or potential harms from psychosocial interventions for treating trans and gender diverse young people **under 18 years old** with gender dysphoria?
3. Question 2c—Is there variation in the effectiveness or risks associated with psychosocial interventions for treating trans and gender diverse young people **under 18 years old** with gender dysphoria?

The Evidence Check was undertaken between August 2023 and February 2024 and focused on research on this topic published since the previous Evidence Check. We therefore limited searches for evidence to the years 2019–2023. All searches were conducted on **19 September 2023.**

In reporting the results of this Evidence Check, we made reference to the key conclusions from the previous 2020 review[2]; the commentary focused on what the new evidence from 2019 onwards has added to these previous conclusions. Readers interested in the evidence tables and further details from the 2020 review are encouraged to access the previous report.[2]

Methods

The methodology of the Evidence Check update included:

- Identifying peer-reviewed articles for each research question
- Screening for relevant studies
- Characterising the studies
- Grading the level of evidence of peer-reviewed articles for selected questions (strength of study design) and evaluating their methodological quality (conduct of study)
- Reporting the results of selected studies and summarising key findings for each question by intervention
- Identifying evidence gaps and providing recommendations for future research that might address the gaps.

Peer-reviewed literature search

As this is an update of a previous review, an *a priori* review protocol was developed based on the parameters of the original Evidence Check, with testing and refinement in consultation with the NSW Ministry of Health and the Sax Institute.

The peer-reviewed literature search was conducted using electronic databases including the Cochrane Library, Joanna Briggs Institute, Medline, Embase, PsycINFO, CINAHL and Scopus. All databases were searched on September 19, 2023. Following screening and selection of relevant articles from the database search, references cited in five clinical practice guidelines supplied by the NSW Ministry of Health (listed in Appendix 2) were cross-checked against the yield from the database search for eligible articles not captured in the search[*].

Eligibility criteria

Citations, abstracts and full-text articles were screened independently by two members of the research team, with disagreements resolved via consensus discussion. The study inclusion and exclusion criteria were co-developed with the NSW Ministry of Health based on the previous Evidence Check (Table 1).

[*] Note the inclusion of the clinical practice guidelines was not within the scope of this review Evidence Check update as the focus of the review was on the underlying evidence rather than clinical practice recommendations.

Table 1—Study selection: Inclusion and exclusion criteria

	Include	Exclude
Publication type	• Systematic reviews focused on gender dysphoria or contained a section focused on gender dysphoria • Primary studies conducted in Australia and countries with comparable health services: New Zealand, Canada, US, UK, Western Europe [Luxembourg, Germany, Netherlands, Spain, Portugal, Ireland, Monaco, Switzerland, Belgium, Liechtenstein, Andorra, UK, France, Gibraltar, Isle of Man] and Scandinavia [Denmark, Sweden, Norway, Iceland, Finland, the Faroe Islands].	• Systematic reviews without a focus or specific section on gender dysphoria—for example, more broadly focused on LGBTQI+ • Non-systematic reviews, as these are subject to article selection bias • Clinical practice guidelines are out of scope for the review, which focuses on the evidence base rather than clinical practice recommendations • Qualitative studies, as these focus on care experience rather than effectiveness of interventions • Primary studies not conducted in Australia or the listed countries with comparable health services • Book chapters • Theses • Conference presentations that are not full peer-reviewed papers • Expert or consensus opinion papers, commentaries • Case reports / small case series with fewer than 10 participants as these are not generalisable • Preprints as these are not peer-reviewed.
Language	English	Non-English
Population	• Children and young people (including prepubertal) ⩽ 18 years of age experiencing gender dysphoria, defined as *"clinically significant distress arising from the incongruence between birth-assigned sex and gender identity"*.[14] This includes those with variations of sex characteristics or differences in sex development at birth who were assigned a gender that differs from their gender identity	• Adults aged over 18, unless treatment was received when ⩽ 18 years of age • Mixed-age populations with no sub-analysis of people ⩽ 18 years of age or where the proportion of participants ⩽ 18 cannot be determined • *Studies of mixed age populations ⩽ 25 years of age will be tagged as 'of interest' as this is the relevant age range of the sponsoring health service; however, the search strategy will not capture all such studies*

	Include	Exclude
	• Studies reporting on interventions for transgender adolescents up to the age of 25 where the mean age was 17 years or younger and mean age is reported in the study, or if more than 50% of the sample was 17 years or younger • Studies of mixed age groups where there is sub-analysis of children ⩽ 18 years of age • Where participant follow-up was reported beyond 18 years, studies in which the intervention was commenced at 18 years or younger.	• Studies of stakeholder and community views, including those of parents of children and young people (including prepubertal) ⩽ 18 years of age experiencing gender dysphoria, as the primary focus is the effects of treatment on this group rather than wider impacts and perceptions.
Study focus	• All studies evaluating interventions for gender dysphoria including: • Fertility preservation • Psychological and psychosocial interventions • Puberty suppression treatment • Contraception in the context of management of gender dysphoria • Gender-affirming hormone therapy, sometimes referred to as cross-sex hormone therapy • 'Top' surgery.	• Non-interventional studies • Contraception outside of the context of gender dysphoria (for example, to manage menstruation problems in cisgender adolescents) • Conversion therapy • HIV prophylaxis • Ethics papers, e.g. regarding consent practices • Legal papers regarding gender dysphoria laws / rulings • 'Bottom' surgery (genital surgery).
Outcomes	All outcomes including costs, side effects, adverse outcomes, harms of not providing treatment, non-deterioration and benefits.	
Date Range	2019–2023	Studies published before 2019.

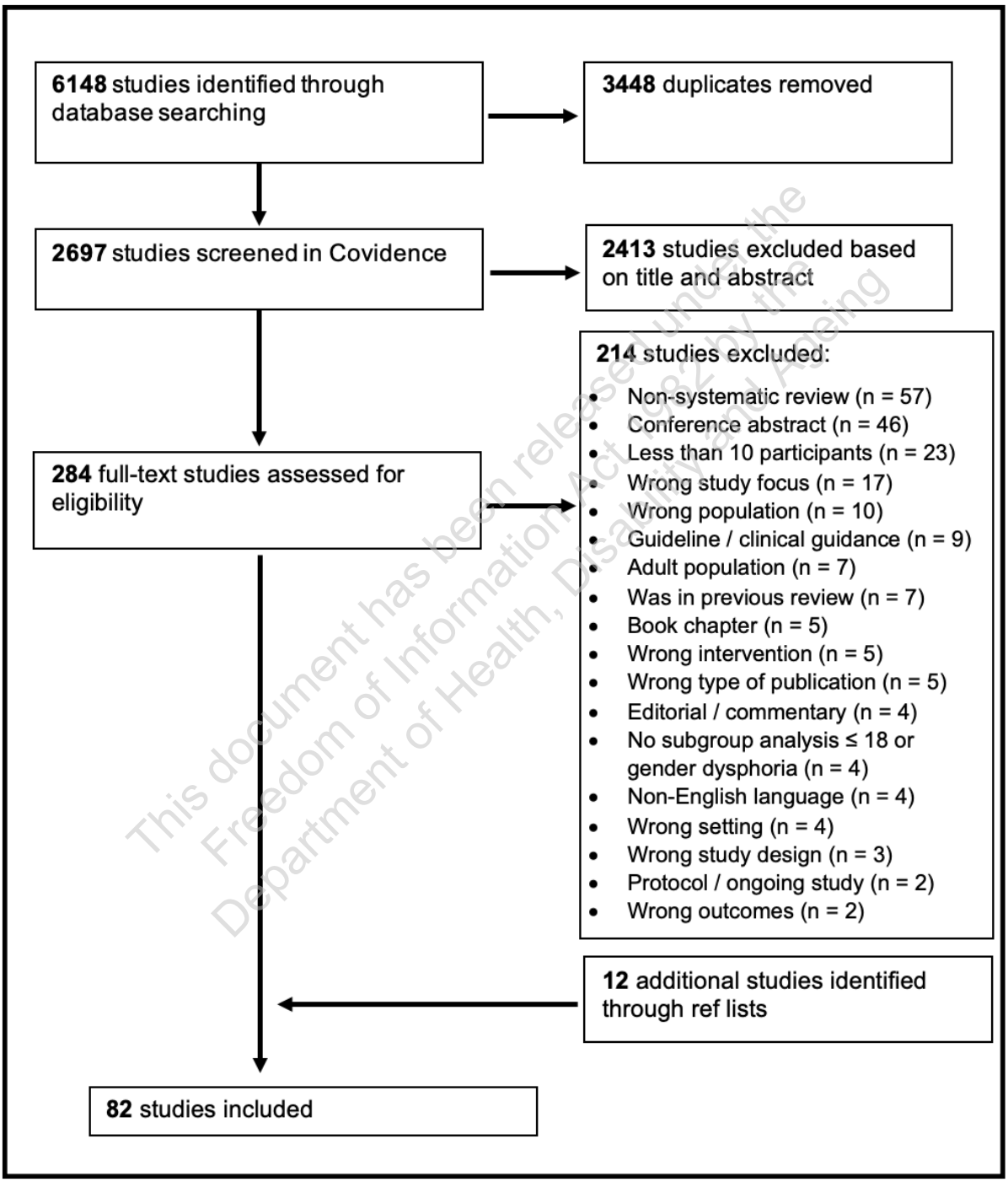
Included studies

After removal of duplicate citations, we identified 2697 citations in the initial databases search. Using Covidence, we screened the studies by title and abstract and excluded 2413 citations based on study inclusion and exclusion criteria (Table 1). The remaining 284 citations were progressed to full-text review, where a further 214 studies were excluded. We identified an additional 12 citations from the reference lists of studies and clinical practice guidelines. The full texts of these additional citations

were examined and they were subsequently included in this Evidence Check. In total, 82 reports met the criteria for consideration in this Evidence Check update. The flow diagram for the literature search and selection phases is detailed in Figure 1.

Figure 1—Flow diagram for the literature search and selection process

The literature was included or excluded in three phases: identification, title and/or abstract screening and full-text screening. The number of records considered at each stage is indicated in brackets.



Evidence grading and quality appraisal

Consistent with the previous Evidence Check, we assessed the quality of included studies using the National Health and Medical Research Council (NHMRC) levels of evidence and grades for recommendations for guideline developers.[15] We critically appraised all 82 included studies using appropriate appraisal tools for each study design. Appendix 2 details the characteristics of studies by NHMRC level of evidence, study design, appraisal approach and number of identified studies.

Data analysis and reporting

We categorised studies that examined multiple interventions for gender dysphoria using their stated primary aim. Further details of the review protocol, including search strategies and yields by database, plus results of cross-checking of clinical practice guidelines, are contained in Appendix 2.

As with the previous Evidence Check, meta-analysis was not a valid approach to synthesise the findings because of the heterogeneity of the included studies. The most appropriate approach was a narrative synthesis of findings, which included consideration of the level of evidence of the studies. It should be noted that some review papers among the included studies may have sourced the same primary studies, and this Evidence Check update may have encompassed primary studies included within those systematic reviews. Care has been taken in interpreting the findings of such reviews to ensure results or certain primary sources are not overstated.

To support comparison, we compiled the findings across the five intervention categories covered by the previous Evidence Check:

- **Puberty suppression treatment**
- **Gender-affirming hormone therapy**
- **Gender-affirming chest surgery**
- **Fertility preservation**
- **Psychosocial interventions.**

As in the previous review, the findings for each of these intervention categories reported across eligible studies were compiled under the following headings:

- Context—treatment information (e.g. definition, various medications)
- Benefits—benefits / effectiveness of treatment across key outcomes
- Risks—adverse events and risks of treatment, including side effects
- Variation in the effectiveness and risks—information about how benefits and risks may vary according to age, treatment stage or other relevant domains
- Strengths and limitations of evidence
- Conclusions of Evidence Check update.

We created detailed data extraction tables in order to capture a more detailed summary of the parameters of individual studies relevant to each intervention category. Reflecting the variability in the characteristics of the studies included in this Evidence Check, readers with specific interests are encouraged to access the relevant evidence tables detailing individual study characteristics.

For *systematic reviews,* we extracted the following data:

- Author, date, aims, number of quality criteria met, and number applied
- Groups targeted by the intervention in the included studies
- Intervention
- Age or stage of puberty
- Benefits
- Risks
- Key conclusions reported by study authors (headline findings, headline conclusions on strength of evidence contained in the review).

For *primary studies,* we extracted the following data:

- Author, date, aims, number of quality criteria met and number evaluated
- Country, design, setting
- Intervention (primary intervention of interest as reported by the study authors)
- Sample size, age and gender identity of subjects
- Main outcomes
- Benefits
- Risks
- Key conclusions reported by study authors (headline findings, strengths /limitations of the study).

We ordered the data extraction tables on two levels; first, from highest to lowest level by study design (i.e. Level I to Level IV) and then from highest to lowest based on the number of quality criteria met using the appropriate quality appraisal tool. For example, the findings of systematic reviews are presented first in each intervention category (Level I on the NHMRC level of evidence) and each systematic review is then ordered from highest to lowest according to the number of quality criteria met based on appraisal using the AMSTAR 2[16] critical appraisal tool for systematic reviews, in the data extraction tables.

With respect to interpreting the results of the quality appraisal analyses, it is important note that the denominator for the same quality appraisal tool varies as a count of which items are applicable to an individual study. Additionally, some quality appraisal tools (e.g. the AMSTAR 2) do not recommend creating a summed measure of 'quality criteria', because each individual criterion is not necessarily considered 'equal'. Therefore, the ranking of study designs has taken primacy when interpreting the findings of this Evidence Check, with the ranking by quality criteria used as an indicative guide to relative quality only.

In the years since the previous Evidence Check there has been increased focus on gender detransition, defined as *"the process of reidentifying with one's birth sex after having undergone a gender transition"*.[17(p270)] To this end, a short narrative summary of identified evidence relating to care use has been included in this Evidence Check in Appendix 2. This reflects that **care use was not a primary focus of this review, which focused on intervention effectiveness. Where studies included in this review also reported on care use, that information has been extracted, but it does not represent all the available evidence on this topic.**

Table 2 shows the distribution of the 82 included studies by evidence grade (rows) across the five intervention areas and the additional category of care use (columns).

Table 2—Included studies by NHMRC evidence grading[15] and intervention

Level and study design	Puberty suppression treatment (n = 17)	Gender-affirming hormone therapy (n = 39)	Gender-affirming surgery (n = 8)	Fertility preservation (n = 6)	Psychosocial interventions (n = 7)	Care use (n = 5)
I. A systematic review* (n=16)	3	7	1	2	3	
II. A randomised controlled trial (n=1)					1	
III-1. A pseudo-nonrandomised controlled trial (n=0)						
III-2. A comparative study with concurrent controls (n=12) • Non-randomised experimental trial • Cohort study • Case-control study • Interrupted time series with a control group	4	5	3			
III-3. A comparative study without concurrent controls (n=5) • Historical control study • Two or more single arm studies • Interrupted time series without a parallel control group	1	2		1	1	
IV. Case series / cross sectional study (n=48)	9	25	4	3	2	5

While level I evidence is strictly classified as systematic reviews of RCTs (Level II studies), almost no RCTs have been conducted in this area to date. The systematic reviews enumerated here have used systematic principles, and so provide the best quality evidence in the absence of reviews of RCTs.

Findings

All included studies were analysed according to their NHMRC level of evidence grading. The appropriate tools for each study design were used to assess the quality of the studies. A summary of this process is presented in Table 3.

Table 3—Level of evidence grading and critical appraisal tool used by study

NHMRC evidence grading, study design definitions, number and citations of included studies by study design and critical appraisal tools and processes used are summarised below.

Level	Study design and definition	N	Critical appraisal tool and approach
I	**A systematic review of level II studies** *"Systematic location, appraisal and synthesis of evidence from scientific studies".*[14(p20)] NOTE: The NHMRC definition specifies that systematic reviews are focused on Level II studies (randomised controlled trials). The systematic reviews in this Evidence Check did NOT review Level II studies.	16 studies[3,11,12,18–30]	The AMSTAR 2 tool for evaluating quality of systematic reviews.[16] We appraised all systematic reviews in duplicate, with disagreements resolved through discussion.

II	**A randomised controlled trial** *"Experimental studies meet three conditions: manipulation, control and random assignment. Specifically, the researchers manipulate the intervention of interest and the control condition and they randomly allocate the participants to the intervention or control group (Shadish et al. 2002). Random allocation refers to an authentically random process such as the toss of a coin or use of a table of random numbers (Shadish et al. 2002)".*[31(p72)]	1 study[32]	The revised JBI critical appraisal tool for the assessment of risk of bias for randomised controlled trials[33]: appraised in duplicate with disagreements resolved through discussion.
III-1	**A pseudo-nonrandomised controlled trial (i.e. alternate allocation or some other method)** *" … allocation may not use an authentically random process. For example, if investigators use alternate group allocation like even and odd dates, they cannot ensure that each participant has an equal chance of landing in either group. Experimental studies without authentic random allocation but using systematic alternate group allocation methods mentioned above are experimental studies with pseudo randomisation, or pseudo-RCTs".*[31(p72)]	0	N/A
III-2	**A comparative study with concurrent controls**		
	Non-randomised experimental trial: "*Quasi-experimental studies are studies where the intervention of interest and the control condition are controlled (manipulated) by the researchers, however, the allocation of participants is not a*	1 study[34]	JBI checklist for quasi-experimental studies (non-randomised experimental studies)[35]: appraised by one reviewer.

	random, systematic or pseudo-random allocation. Frequently, participants self-select into groups or the researchers decide which persons should get the intervention and which persons should get the control (Shadish et al 2002)".[31(p72)]		
	Cohort study: *"… outcomes for groups of people observed to be exposed to an intervention, or the factor under study, are compared to outcomes for groups of people not exposed".* Prospective = followed prospectively with further outcomes recorded as they happen; retrospective = defined at a point of time in the past and information collected on subsequent outcomes [NHMRC 2008].[14]	11 studies[36–46]	JBI checklist for cohort studies[47]: appraised by one reviewer with a second reviewer also undertaking two appraisals as a quality check.
	Case-control study: *"… people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/non-exposure to the intervention or factor under study"* [NHMRC 2008].[14]	0	N/A
	Interrupted time series with a control group: *"… trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and then compared to the outcomes at the same time points for a group of people that do not receive the intervention (factor under study)"* [NHMRC 2008].[14]	0	N/A

III-3	**A comparative study without concurrent controls**		
	Historical control study: *"… outcomes for a prospectively collected group of people exposed to the intervention (factor under study) are compared with either (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (i.e. control group/usual care), or (2) the outcomes of a previously published series of people undergoing the alternate or control intervention"* [NHMRC 2008].[14]	3 studies[48,49,50]	JBI checklist for case control studies[51]: appraised by one reviewer with a second reviewer also undertaking one appraisal as a quality check.
	Two or more single arm studies: *"… the outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared"* [NHMRC 2008].[14]	0	N/A
	Interrupted time series without a parallel control group: *"… trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and compared*" [NHMRC 2008].[14]	2 studies[52,53]	JBI checklist for quasi-experimental studies (non-randomised experimental studies)[35]: appraised in duplicate with disagreements resolved through discussion.
IV	**Case series** with either post-test or pre-test/post-test outcomes.	42 studies[5–8, 54–91]	The National Institutes of Health (NIH) quality assessment tool for before-after (pre-post) study with no control group.[92] Appraised by one reviewer with a second reviewer also undertaking four appraisals as a quality check.

	Cross-sectional study: *"… a group of people are assessed at a particular point (or cross-section) in time and the data collected on outcomes relate to that point in time"* [NHMRC 2008].[14]	6 studies[93–98]	JBI checklist for analytical cross-sectional studies.[99] Appraised by one reviewer with a second reviewer also undertaking one appraisal as a quality check.

Question 1—Effective clinical medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria

Question 1a—What have been shown to be the most effective medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria ?
Question 1b—What have been shown to be the risks or potential harms from medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?
Question 1c—Is there variation in the effectiveness and risks associated with medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?

Puberty suppression treatments

Context

Puberty suppression treatments, also referred to as puberty blockers, are designed to delay the development of secondary sexual characteristics such as breasts in trans males and deepening voice and laryngeal prominence in trans females. Gonadotrophin releasing hormone analogues (GnRHa) are used to achieve puberty suppression.[24,26,27]

Puberty suppression is intended to relieve distress associated with the onset and development of secondary sexual characteristics in people experiencing gender dysphoria, and to give time to discuss and explore less reversible interventions.

Puberty suppression treatment may be undertaken in conjunction with psychological counselling and may be followed by the use of gender-affirming hormone therapy (GAHT: the use of hormones to induce development of physical sex characteristics consistent with preferred gender identity).[25] Therefore, studies examining the effectiveness of puberty suppression may have recruited participants who received both puberty suppression treatment and GAHT. This is especially the case for retrospective research designs or studies conducted over long time periods of clinical interventions. In this Evidence Check, we have classified studies according to their stated primary focus. This means *participants in the studies listed in this section may have received both puberty suppression treatment and GAHT, but their stated primary focus is the effectiveness of puberty suppression*.

This Evidence Check update identified 17 studies focusing on puberty suppression treatment—three systematic reviews (Level I evidence); four comparative studies with concurrent control (Level III-2); one comparative study without concurrent control (Level III-3); and nine case series and cross-sectional studies (Level IV).

The additional information about the benefits of puberty suppression provided by this Evidence Check is summarised below (Table 4). It covers the overall effectiveness of treatments, reversibility, safety and tolerance, and psychological outcomes.

Table 4a—Benefits of puberty suppression treatment

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
A gonadotropin-releasing hormone agonist (GnRHa) is the most effective treatment to suppress puberty.	**Overall effectiveness for suppression of puberty** Eight studies reported positive findings regarding effectiveness of GnRHA for puberty suppression. Two Level I studies reported that GnRHa is well tolerated by the target population[26,27] and one of these also reported that GnRHa is preferred for puberty suppression.[27] Two comparative studies with controls (III-2)[42,46], one comparative study without concurrent controls (III-3)[49], and three Level IV studies[64,84,85] reported that GnRHa was effective for puberty suppression. One Level IV study reported eight cases of pubertal escape in a sample of 49 patients using histreline.[84]
Puberty suppression treatment for TGD adolescents appears to be **effective, safe, well tolerated and reversible**, thus allowing the adolescent to explore their gender identity before embarking on irreversible, or partially irreversible, treatment (eight references, NHMRC levels III-2 to IV).	**Reversibility** Two systematic reviews (I) reported that puberty suppression treatment is reversible.[26,27] **Safety and tolerance** Seven included studies reported that puberty suppression treatment is safe, well tolerated, or has few side effects. These comprised two systematic reviews (I)[26,27], one comparative study with a control group (III-2)[39] and four pre-post cross-sectional studies (IV).[69,84,85,97] One Level IV study examined the effects of GnrHa on the heart by measuring the electrocardiographic QTc interval. It found no significant effect for the GnRHa drug leuprolide acetate (noting no other GnRHa drugs were explored in this study).[91] One III-2 study reported mixed findings—while puberty suppression reduced breast development and lessened the need for or extent of chest surgery in trans men, the subsequent reduction in penile development in

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	trans women could result in the need for more extensive genital surgery.[46]
Puberty suppression treatment reduces emotional and behavioural problems associated with gender dysphoria (one reference). A key psychological benefit associated with puberty suppression treatment is the prevention of future psychological distress that TGD adolescents may experience when they develop the secondary sexual characteristics of the sex they were assigned at birth (one reference). However, it is also possible that puberty suppression treatment may increase social isolation for adolescents, who remain in a prepubertal state and thus out of synchrony with their age-group peers.	**Psychological outcomes** The review undertaken by the National Institute for Health and Care Excellence (NICE) (2020)[24] reported that GnRHa had positive effects on psychosocial functioning and may reduce depression; Rew (2021)[27] reported improvements in affect and social life and decreases in depressive symptoms, emotional and behavioural problems and suicidal ideation. Ramos (2021)[26] reported improved mental health. Additionally, two Level IV studies reported lower odds of lifetime suicidal ideation (Turban 2020)[97]; and reduced emotional and behavioural problems (van der Miesen 2020).[98] NICE (2020)[24] also reported that GnRHa had no impact on gender dysphoria, anger, anxiety or body image. Similarly, one Level IV study

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	reported no change in psychological functioning, quality of life or gender dysphoria.[64]
To achieve the appearance of the desired sex, the outcomes of gender-affirming hormone therapy (GAHT) and surgery are better among individuals for whom puberty was suppressed compared with those who initiated physical transition after puberty had been completed (one reference, NHMRC level III-2).	No relevant information pertaining to this finding was identified in this update.

Table 4b—Costs and risks of puberty suppression treatment

The additional information on the costs and risks of puberty suppression provided by this Evidence Check is summarised below. It covers treatment costs, bone density and other side effects.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
GnRHa is the most effective treatment for puberty suppression; however, it is also the most expensive.	**Treatment costs** One Level III-2 study reported that two puberty suppression treatment implants (Vantas and SupprelinLA) were equally effective—with Vantas being approximately 10% of the cost of SupprelinLA.[42] Similarly, the Level III-2 study by Eitel (2023)[39] found intramuscular Lupron and subcutaneous Eligard were equally effective in suppressing clinical puberty progression, with Eligard approximately 25% of the cost of Lupron. Additionally, Eligard was superior for *biochemical* puberty suppression. Little data about costs was provided in the updated studies, although some compared more and less expensive forms of puberty suppression treatment.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
For young people with needle phobia, GnRHa may not be acceptable as it is delivered via injection.	No relevant information pertaining to this finding was identified in this update.
Some adolescents experience a loss of bone density mineralisation from a lack of oestrogen or testosterone, which is a concern as it increases the future risk of osteoporosis and bone fractures. More research is needed to understand whether the bone density mineralisation changes are fully reversible, and why only some adolescents experience this adverse side effect (four references, NHMRC levels III-2 to IV). Other side effects such as hot flushes, weight gain, acne and mood changes are common but are generally well tolerated.	**Bone density** The Level I study by NICE (2020)[24] reported that while three studies had found GnRHa reduced bone density, the observed reductions were largely within one standard deviation of normal. Another Level I study by Ramos (2021)[26] reported either maintenance or reduction of bone mineral density across three studies, two of which reported that addition of cross-sex hormones tended to re-establish BMD. The Level I study by Rew (2021)[27] reported reduced turnover and bone mineral density with use of GnRHa, particularly in young trans women. Three Level IV studies reported mixed findings on bone density: • No significant change over three years, but significant fall in first year; baseline measures were lower in trans boys compared with trans girls[74] • Negative effects on bone mineral density were reported; however the majority of participants were deficient in Vitamin D. Spinal X-rays of four participants with significant decreases in bone mineral density revealed no fractures.[79] **Other side effects** A range of side effects was reported across included studies. These are listed below with reference to study design. • Headache (Level I: NICE 2020[24], Level IV: Carmichael 2021[64]) • Pain (Level I: NICE 2020[24], Level IV: Schwartz[85]) • Changes in body fat (Level I: Ramos 2021, Rew 2021[26,27])

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	• Mood swings and emotional lability (Level I: Rew 2021[27], Level IV: Schwartz 2023[85]) • Reduced height velocity if starting later in puberty / at later Tanner stages (Level III-2: Schulmeister et al. 2022[43]) • Histrelin implant can be difficult to remove / replace but this is a rare complication (Level IV: Pine-Twaddle 2023[84]) • Hot flush (Level IV: Carmichael 2021[64]). Two Level IV studies showed no effects • Withdrawal of sex hormones had no effect on body composition of trans boys; unexpected decrease in height and lean mass in trans girls (Ghelani 2020)[69] • Body fat redistribution (android vs. gynoid) was in keeping with participants' affirmed gender (Navabi 2021).[79]
Fertility may be compromised in individuals who start puberty suppression treatment at a young age because the treatment impairs the development of sperm cells (spermatogenesis) and egg formation in the ovary (oocyte maturation) (one reference). Fertility preservation options should be discussed with patients and their caregivers before starting GnRHa. We found no empirical evidence for fertility compromise in adolescents in any empirical studies but recommendations for discussion of fertility preservation prior to medical intervention for TGD children and adolescents were given in guidelines, reviews without meta-analyses and position statements (six references).	No identified studies provided updates to this finding.
There is a theoretical potential for increased social isolation for TGD adolescents as they undergo treatment because the timing of puberty may be out of synchrony with their age-group peers (one reference—NHMRC level ungraded: clinical practice guideline).	No identified studies provided updates to this finding.

Table 4c—Variation in the benefits and risks of puberty suppression treatment

As summarised below, this Evidence Check produced no additional information on variation in the benefits and costs and risks of puberty suppression.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
There is no minimum age to start puberty suppression treatment; rather, the pubertal stage is used to determine what is most appropriate for each child or adolescent. The recommendation is for trans males to start at Tanner stage 2 and trans females at Tanner stage 2–3 (three references) depending on individual circumstances (NHMRC level of evidence ungraded: standards of care and clinical practice guidelines). For example, a trans female who has already gained desired height may wish to begin GnRH earlier than a trans girl who has not gained their desired height, as long as they have reached Tanner stage 2.	No identified studies provided updates to this finding (noting that clinical practice guidelines were out of scope for this Evidence Check update).
Careful monitoring is required regarding bone density. Where loss of bone density is evident, it is recommended that a shorter use of GnRHa or an earlier start of GAHT be considered (three references—NHMRC level of evidence ungraded: clinical practice guideline and reviews without meta-analyses).	No identified studies provided updates to this finding (noting that clinical practice guidelines were out of scope for this Evidence Check update).

Strengths and limitations of evidence

All three systematic reviews commented on limitations in the design of included studies, mitigating against firm conclusions. Additionally, Rew et al.[27] emphasised limitations in diversity of study participants, with the vast majority being Caucasian or white.[27] Limitations of small sample sizes, weak study designs and lack of diversity in participants were also acknowledged across the included primary studies.

Conclusions of Evidence Check update—puberty suppression treatment

We identified 17 studies pertaining to puberty suppression treatment (PS) in this Evidence Check update. Broadly, the newly identified evidence reinforced the previous finding regarding **benefits and effectiveness.** That is, PS agents (generally referred to as GnRHa) were reported to be safe,

effective and reversible. As a counterpoint, this update identified one study describing differential implications of PS for later surgery, with reduced need for mastectomy in trans men but potential complications for genital surgery in trans women as penile inversion may be compromised. Psychological effects of PS on conditions such as depression and anxiety appear modest in comparison with GAHT, with the primary impact being reduction of distress associated with unwanted secondary sexual characteristics; to this end, two Level IV studies reflected positive impacts on gender dysphoria.

With regard to **risks and potential harms,** reductions in bone density remain the primary concern with PS. Although findings pertaining to bone density were mixed in newly identified studies, monitoring of BMD was recommended. Conversely, studies reported that there appeared to be no indications to monitor liver or renal function in the PS setting. Other reported side effects of PS were also relatively minor. Instances of pubertal escape were reported, but satisfaction with PS treatment was reported as good overall. In summary, this Evidence Check update predominantly reinforces findings of the previous review and adds to the evidence base underpinning these findings; with the qualification that the strength of the evidence remains poor.

Table 5 below summarises the main features of each of the reports on PS included in this Evidence Check.

Included studies in this Evidence Check update—puberty suppression treatment

Table 5a—NHMRC Level I. Systematic reviews—puberty suppression treatment (n = 3)

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions reported by study authors
National Institute for Health and Care Excellence (NICE) 2020[24] Examined clinical effectiveness, safety, cost-effectiveness, subgroups for whom benefits are higher or lower, criteria used to define GD, age when treatment commenced and treatment duration for GnRH analogues.	9 observational studies: 5 retrospective observational; 3 prospective longitudinal; 1 cross-sectional. People aged 18 years or less.	**GnRHa** GD defined by DSM criteria (reported in 6/9 studies). Treatment started age 11–18 years. Duration of treatment not reported in 6 studies and ranged from a few months to 5 years.	Reduction in depression, positive psychosocial impact. No impact on GD, anger, anxiety, body image.	No difference in bone density Changes in cognitive function not statistically tested. No effect on renal or liver function. Reports of sterile abscess (1), leg pain and headache (1), weight gain (1). One study reported 9/143 stopped treatment—5 no longer wanted therapy, 4 had side effects; one study	Little change with GnRH analogues from baseline to follow-up on mental health (depression, anger and anxiety), body image and psychosocial impact. GnRH analogues may reduce the expected increase in bone density (which occurs during puberty). *"A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies … the studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions reported by study authors
Score on quality criteria = 8.5 / 13.				reported 11/26 stopped treatment.	*of very low certainty using modified GRADE … Many of the studies did not report statistical significance or confidence intervals."*
Ramos 2021[26] To review treatment of gender incongruity with GnRHa analogues. Score on quality criteria = 6 / 13.	11 studies mostly conducted in centres assisting transgender children and adolescents.	**GnRHa + GAHT (GnRHa focus)** Some study participants also received gender-affirming hormones (testosterone, oestradiol, triptorelin, among others).	Reversible treatment and allowed time for patients to experience social transition first. Seemed to be well tolerated by the target population. Improved mental health reported in three studies.	Individual studies reported on side effects (aseptic abscesses, pain in the lower limbs, headaches, weight gain); and changes in body fat with a decline in lean mass and waist-hip index. Three studies reported BMD maintenance and one showed reduction; two reported that addition of cross-sex hormones tended to re-establish BMD.	*"The use of GnRHa seems to be well tolerated by the studied population. When started … In addition to preventing the irreversible phenotypic changes that occur in cross-hormonal therapy, the use of GnRHa can equally contribute to the mental health of these adolescents."* *"Studies found are heterogeneous (different definitions, population and evaluation techniques) and sometimes based on small sample size, restricting statistical power. Even fewer studies accessed long-term consequences of puberty blockage with or without posterior cross hormone therapy."*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions reported by study authors
				One study reported 9 / 84 cases of discontinuation; another reported 1 / 84 cases of discontinuation.	
Rew 2021[27] To review literature about the practices of administering gonadotropic-releasing hormone agonists (GnRHa) for children and the outcomes and risks. Score on quality criteria = 5.5 / 12.	9 studies: 4 retrospective chart reviews, 2 case reports, 1 cross-sectional and 1 prospective study.	**GnRHa + GAHT (GnRHa focus)** Some study participants also received gender-affirming hormones. Children eligible for puberty suppression treatment if they were diagnosed with gender dysphoria.	Benefits described across studies included anthropometric measurements returning to normal limits in adulthood; positive changes in secondary sexual characteristics along with lack of sustained creatinine or LFT abnormalities; improvement in affective and social life; improvements in general functioning; and	Known risks and adverse outcomes of using GnRHa in children included mood swings and emotional lability. Other adverse risks described included slow growth, decrease in lean body mass, increased fat, decreased height velocity, and decrease in bone turnover markers.	*"The evidence to date supports the finding of few serious adverse outcomes and several potential positive outcomes.* *" … large long-term studies with diverse and multicultural populations have not been done … The need for additional well-designed longitudinal and mixed methods studies is critical to support and even improve current practice for this very vulnerable population."*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions reported by study authors
			decreases in depressive symptoms, emotional and behavioural problems and suicidal ideation.		

Table 5b—NHMRC Level III-2. Comparative studies with concurrent control—puberty suppression treatment (n = 4)

Author, date, aims, quality criteria score	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions reported by study authors
Olson-Kennedy 2021[42] To investigate the effectiveness of histrelin implant	US Case series: retrospective chart review study. Center for Transyouth Health and	**GnRHa only** Histrelin implants N=66 M age = 11.3 years, Tanner stage 2–3, 32	Changes in gonadotropin, sex steroid levels.	Both implants (Vantas and SupprelinLA) were successful in suppressing puberty progression among early	No apparent side effects reported.	*"… both Vantas and SupprelinLA are equally effective at reducing gonadotropin and hormone levels into a pre- or early pubertal range".* *"Limitations of this study include a relatively small sample size. Future*

Author, date, aims, quality criteria score	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions reported by study authors
for puberty suppression. Score on quality criteria = 7 / 9.	Development at Children's Hospital Los Angeles (CHLA).	trans females, 34 trans males.		and mid-adolescent patients.		*studies with larger sample sizes will assist in validating these findings."*
Schulmeister 2022[43] To quantify the growth of TGD youth starting GnRHa therapy. Score on quality criteria = 6 / 8.	US Comparative with control. Four multidisciplinary transgender clinics based at academic medical centres.	**GnRHa only** N=55 transgender adolescents. Mean age: 11.5 ± 1.2 years.	Growth and height velocity (HV),	Individuals who initiated GnRH agonist at a later Tanner stage / chronological age had significantly lower height velocity (HV) in the first year.	Those starting treatment in late puberty had a lower HV range compared with prepubertal children (not statistically significant).	*"Overall, TGD youth treated with GnRHa have HV similar to that of prepubertal children, but TGD youth who start GnRHa later in puberty have an HV below the prepubertal range. Ongoing follow-up of this cohort will determine the impact of GnRHa treatment on adult height."* *"Limitations of this study include a relative lack of diversity of participants and lack of data on bone age and pretreatment HV."*
van de Grift 2020[46] To investigate the long-term	Netherlands Single-centre retrospective	**GnRHa + GAHT (GnRHa focus)**	Physical sex characteristics (e.g. height, weight, breast	Less breast development among trans men, indicating	Shorter penile length among trans women, increasing	*"PS effectively reduces the physical development of sex characteristics … Transgender girls and women, especially, should be*

Author, date, aims, quality criteria score	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions reported by study authors
effect of PS on development of sex characteristics and gender-affirming surgical implications. Score on quality criteria = 6 / 8.	cohort study (comparative with control).	GnRHa, gender-affirming surgeries N=300 M age: 23 years ±2.9. Tanner stage 2–5; 184 trans men; 116 trans women.	development, penile length).	less invasive mastectomy (or becoming unnecessary).	possibility of intestinal (rather than penile inversion) vaginoplasty.	*informed that they might require more extensive, centralized surgical care with long-term aftercare."* Reported limitations included small subgroup sample size; potential for selection bias (non-enrolled candidates not followed up; missing data due to retrospective design).
Eitel 2023[39] To compare the effect of Eligard and Lupron in assisting puberty suppression. Score on quality criteria = 4 / 8.	US Case series (retrospective chart review). Seattle Children's Gender Clinic 2016–2021.	**GnRHa + GAHT (GnRHa focus)** Intramuscular **Lupron** and subcutaneous **Eligard** N=48 Mean age at start: 13.7 years (50% also concurrently	Sex hormone levels (one hour after injection) and clinical PS outcomes (i.e. menarche or breakthrough bleeding in those AFAB).	All patients experienced clinical puberty suppression; biochemical suppression rates were superior with Eligard (90% vs 69%).	No apparent adverse effects reported.	*"Eligard and Lupron were both effective in suppressing clinical puberty progression."* Limitations of this study include small sample size, retrospective nature and limited Tanner staging data due to telemedicine visits conducted during the COVID-19 pandemic. In addition, 50% of patients were receiving concurrent GAH.

Author, date, aims, quality criteria score	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions reported by study authors
		receiving GAHT).				

Table 5c—NHMRC Level III-3. Comparative studies without concurrent control—puberty suppression treatment (n = 1)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions reported by study authors
Mejia-Otero 2021[49] To investigate the effectiveness of GnRH for puberty suppression among transgender youths.	US Case series: retrospective chart review GENder, Education and Care Interdisciplinary Support (GENECIS).	**GnRHa only** (leuprolide and histrelin) N=60 (n=30 transgender adolescents with mean age (SD) of 13.0 ± 2.1;	Suppression of hypothalamic-pituitary gonadal (HPG) axis.	GnRHa produces a similar effect on transgender and children with CPP.	A higher oestradiol level was observed in transgender group after treatment.	*"GnRHa are effective in suppressing the HPG axis in transgender youth"* "Our study has important limitations … different doses of leuprolide and histrelin", small number of patients to compare the effectiveness of each dose, data from "different laboratories", and

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions reported by study authors
Score on quality criteria = 6 / 10.		n=30 children with central precocious puberty (CPP) with mean age of 7.7 ± 2.3). 50% of the trans group at Tanner stage 4–5.				"significant ethnic and racial differences between groups".

Table 5d—NHMRC Level IV. Case series / cross-sectional—puberty suppression treatment (n = 9)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
***Turban 2020**[97] To examine the association between pubertal suppression (PS) access	US Cross-sectional survey 2015 US Transgender	**GnRHa + GAHT (GnRHa focus: GAHT examined as a confounder)** GnRHa	Mental health outcomes (psychological distress, binge drinking, drug use, suicidal	Access to PS treatment associated with a lower odds of lifetime suicidal ideation when compared with	No apparent adverse effect reported.	Transgender adults *"who received treatment with pubertal suppression, when compared with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation".*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
and mental health outcomes. Score on quality criteria = 7 / 8.	Survey (USTS) conducted by National Center for Transgender Equality (NCTE).	N=20,619 Mean age = 23.4 years (45.2% assigned male at birth).	ideation and attempts).	those who wanted PS but did not have access to it.		*"Limitations include the study's cross-sectional design, which does not allow for determination of causation."*
Ghelani 2020[69] To examine the effect of sudden sex hormone withdrawal on body composition of late pubertal adolescents. Score on quality criteria = 8 / 10.	UK Pre-post design University College London Hospital (UCLH) Gender Identity Development Service.	**GnRHA only** Triptorelin sex hormone, administered for at least one year. N=36 (n=11 trans male, n=25 trans female) aged 15–17 years with GD.	Body composition; height, weight and BMI measured at 0, 6 and 12 months.	Withdrawal of sex hormones does not seem to affect body composition of trans boys, with no significant differences in any variable from baseline to 12 months.	*"There is a significant slowing of height and lean mass in transgirls. This could, however, be potentially detrimental if the patient decides not to go ahead with transition."*	*"GnRH analogues do not appear to have significant harmful effects on body composition when used in healthy postpubertal adolescents … Effects of the treatment on anthropometry and body composition were gender-specific…"* *"The main limitation of our study was the relatively small sample size, especially for the transgirls … we were not able to measure bone mass which would also be of relevance in these patients."*
Pine-Twaddell 2023[84]	US Pre-post	**GnRHa + GAHT (GnRHa focus)**	Pubertal suppression outcomes (i.e.	The use of HI over one year has been found	1 patient did not react well to GnRHa and	*"Extended use of HI (>= 17 months) in TG/NB and CPP youth was efficacious and resulted in*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
To examine the impact of histrelin in a longer time (>12 months). Score on quality criteria = 8 / 10.	Two US paediatric centres.	GnRHa, histrelin implant (HI). N=49 Mean age = 11.6 years ± 2.4 Tanner stage 2–5. Transgender or nonbinary (TG/NB) youth. • Group A (n=25): HI • Group B (n=15): GAHT + HI • Group C (n=2): no treatment + HI • Group D (n=7): central precocious	increase in Tanner stage, hormonal concentration).	to be safe and efficacious for patients. Adoption of HI is associated with few surgical procedures and lower costs.	discontinued suppression at 15 months. 8 cases of pubertal suppression escape. Can be difficult to remove or replace the implant.	*sustained biochemical and clinical pubertal suppression in majority of our study subjects."* *"Limitations of the study include retrospective design, nonstandardization of assays used, timing of laboratory and clinical examinations, and lack of GnRH stimulation testing."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
		puberty (CPP).				
van der Loos 2023[7] To investigate the continuation rate of adolescents starting PS and GAHT. Score on quality criteria = 8 / 10	Netherlands Pre-post Amsterdam UMC.	**GnRHa + GAHT (GnRHa focus)** GnRHa for a minimum of three months and then GAHT. N=720 (n=220 trans girls, 69%, median age: 14.1 years. n=500 trans boys, median age: 16 years).	Continuation of GAHT (based on prescription of gender-affirming hormones).	High rate of continuation from PS with GnRH to GAHT (98%).	Discontinuation rate appears to increase with older-age trans females.	*"This study confirmed a steep increase of referrals to our gender identity clinic … Novel findings are that detransition was very rare and that the majority of people starting GnRHa continued with subsequent GAH."* Study limitations: *"… the results may be different for centers following a different treatment approach … Due to the retrospective design, data might be lacking … calculated proportions in the most recent years are likely an underestimation."*
Joseph 2019[74] To investigate the impact of GnRHa on bone density in	UK Pre-post Early Intervention	**GnRHA only** GnRHa for one year or ongoing until they reach 16 years old. N=31:	BMD for lumbar spine and femoral neck (hip), z-scores for birth sex and age.	No significant change in the absolute values of hip or spine BMD or lumbar	Progressive fall in BMD and BMAD z-scores, most rapid in the first year of	*"… although there is an immediate drop in BMD and BMAD Z-scores, we have shown that absolute BMD and BMAD does not change substantially over a 3-year period in*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
adolescents with GD. Score on quality criteria = 7 / 9.	program national endocrine clinic.	• Trans girls (n=10), mean (SD) age at first, second and third scan: 13.0 (1.1), 14.5 (1.2) and 15.8 (1.3) • Trans boys (n=21), mean (SD) age at first, second and third scan:12.9 (3.0), 14.3 (3.3) and 15.6 (3.5). A further 39 had two scans; main analysis on 31.		spine BMAD over 3 years. Lower fall in BMD / BMAD z-scores in the longitudinal analysis group in the second year (i.e. *"31 subjects who had three DXA [dual energy X-ray absorptiometry] scans").*	treatment for both groups.	*transgender adolescents on GnRHa treatment".* *"… results have come from a retrospective analysis of clinical scans which were not acquired for the sole purpose of this study … Although 70 is a large sample size for the first-year data, the pure longitudinal data set is smaller (n=31)."*
Schwartz 2023[85] To compare the effectiveness of	US Pre-post	**GnRHa + GAHT (GnRHa focus)**	Method choice, continuation, bleeding patterns,	Overall satisfaction with menstrual	Patients taking norethindrone acetate reported more side	*"Most of our patients achieved amenorrhea, or at least improved menstrual bleeding, as well as improved menstrually related*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
various menstrual management methods. Score on quality criteria = 7 / 9.	Nemours Children's Hospital Delaware Gender Wellness Program.	Oral norethindrone acetate or a 52-mg levonorgestrel (LNG) intrauterine device (IUD). N=101 Transgender and gender diverse adolescents.	amenorrhea rates, effect on moods and dysphoria, and side effects.	management methods. Almost all patients had improved bleeding and high rates of amenorrhea at the second follow-up.	effects (e.g. pain, mood swing) compared with those using IUD.	*dysphoria, with fairly low rates of side effects."* *"The main limitation is its retrospective design, which relies on adequate documentation and resulted in missing data."* Also, it *"may have limited generalizability"* as the *"patients were all seen in a specialized gender clinic, and the majority had a dedicated visit with a pediatric gynecologist, which introduces selection bias and may overestimate the degree of gender dysphoria in general".*
Navabi 2021[79] To examine evidence on effects of GnRHa on bone health and body composition among adolescents.	Canada Pre-post Children's Hospital of Eastern Ontario (CHEO).	**GnRHa focus (scan within 90 days of starting treatment)** GnRHa, starting with 3 doses of 7.5 mg every 4 weeks, followed by 11.25 mg	(1) Bone mass—measured with dual energy radiograph absorptiometry (DXA); (2) body composition.	No change in BMI and is below obesity risk (85% cutoff). No bone fracture detected.	GnRHa negatively affects bone mineral density. However, the majority of transgender youth had vitamin D	*"GnRHa monotherapy negatively affected bone mineral density of youth with GD without evidence of fractures or changes in BMI z score."* Study limitations: *"Lack of consistent records of physical activity at baseline and follow-up visits limited analysis of physical*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Score on quality criteria = 6 / 8.		every 12 weeks after confirmation of puberty suppression. N=172 (< 18 years old): • 119 (69.2%) transgender males: M age 15.2 ± 1.8 [SD] years; 90.7% Tanner 4–5) • 51 (29.7%) transgender females (M age 15.4 ± 2.0 years; 80.3% Tanner 4–5) • 2 (1.1%) youth as nonbinary.			insufficiency or deficiency. Transgender youth body fat redistribution (android vs. gynoid) was in keeping with patients' affirmed gender.	*activity's role as a potential contributing factor to bone health and body composition. The small sample size of youth in early puberty prevented comparison of GnRHa effects in early versus late puberty."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Carmichael 2021[64] To examine the short-term outcomes of pubertal suppression on adolescents with GD. Score on quality criteria = 8 / 11.	UK Pre-post Gender Identity Development Service (GIDS), London.	**GnRHa only** GnRHa with psychological support and therapy. N=44 Age: 12–15 years Persistent GD.	Bone mineral content (BMC) and bone mineral density (BMD); Child Behaviour CheckList (CBCL) total t-score; Youth Self-Report (YSR) total t-score; CBCL and YSR self-harm indices.	All patients achieved PS by 6 months. No change identified in psychological functioning, quality of life or degree of GD.	Expected adverse events were prevalent during the initial two years, notably mild headaches or hot flushes, with reported incidences of 25% at 0–6 months, 23% at 7–12 months, and 22% at 13–24 months. One patient ceased PS and did not start gender-affirming hormones.	*"Treatment of young people with persistent and severe GD aged 12–15 years with GnRHa was efficacious in suppressing pubertal progression. Anticipated effects of withdrawal of sex hormones on symptoms were common and there were no unexpected adverse events."* *"The study size and uncontrolled design were key limitations. The small sample size limited our ability to identify small changes in outcomes. This was an uncontrolled observational study and thus cannot infer causality."*
Waldner 2023[91] To examine the rate of gender-diverse adolescents	Canada Pre-post	**GnRHa + GAHT (GnRHa focus)**	The rate-corrected QT interval (QTc) prolongation.	None of the patients experienced clinically	QTc prolongation appears to be more prevalent in trans girls;	*"This retrospective review of ECGs in gender-diverse youth on leuprolide acetate demonstrated that none of 33 subjects had clinically significant QTc*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
with QTc prolongation on leuprolide acetate therapy. Score on quality criteria = 7 / 10.	Stollery Children's Hospital Pediatric Endocrinology Gender Clinic.	N=33 (10 trans girls, 23 trans boys). Mean age (SD): 13.7 (SD 2.1) years. Range 9–18 years.		significant QTc prolongation.	however, the study was unable to conduct a subgroup analysis due to the limited sample size in this group.	*prolongation, using a conservative cutoff value of 460 ms."* *"The limitations of this investigation include the small sample size and retrospective nature."*
van der Miesen 2020[98] To examine the effect of receiving gender-affirming care (GAC) on transgender adolescents' psychological wellbeing. Score on quality criteria = 6 / 10.	Netherlands Pre-post Center of Expertise on Gender Dysphoria of the VU University Medical Center (VUmc) in Amsterdam.	**GnRHa only** N=1101 • n=651 cisgender adolescents, mean age 15.39 (1.36) years. • n=272 transgender at referral, mean age 14.47 (2.18) years. • n=178 transgender	Internalising, externalising, suicidality and peer relations.	Emotional and behavioural problems of transgender reduced when receiving GAC at a similar level to their cisgender peers.	No apparent adverse events or effect reported.	*"Our study also showed that transgender adolescents receiving gender-affirmative care involving puberty suppressing treatment not only have less emotional and behaviour problems than transgender adolescents who have just been referred to gender-affirmative care but also reported similar rates of mental health problems as their nonclinical cisgender peers on internalizing problems (with a lower clinical range percentage) and self-harm/suicidality but not on peer relation problems."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
		using PS, mean age at 16.75 (1.24) years.				Limitations: *"… this study did not make use of a random nonclinical national probability sample … the cross-sectional design of this study with different participants in the groups before and after puberty suppression may potentially limit the results with participants being different on characteristics not measured and controlled for."*

*This article was subject to an Erratum—"The following disclosure was omitted: Dr JM Carswell has received an advisory board stipend from Endo Pharmaceuticals."

Gender-affirming hormone therapy

Context

Gender-affirming hormone therapy (GAHT, also referred to as cross-sex hormone treatment) aims to induce development of the physical sex characteristics congruent with an individual's gender expression.[25] For transgender men testosterone is used; for transgender women oestrogen is used in conjunction with anti-androgen agents, as oestrogen is insufficient to suppress testosterone to female levels.[18,28] In addition to its effect on physical sex characteristics, GAHT aims to improve mental health and quality of life.[21,25]

Because GAHT may follow puberty suppression treatment, studies examining its effectiveness may contain participants who have also received puberty suppression. In this Evidence Check, we have classified studies according to their stated primary focus. This means that *studies contained in this section may contain participants who have received both puberty suppression treatment and GAHT, but their stated primary focus is the effectiveness of GAHT*.

This Evidence Check update identified 39 studies focusing on GAHT, comprising seven systematic reviews (Level I); five comparative studies with concurrent controls (III-2); two comparative studies without concurrent controls (III-3); and 25 case series or cross-sectional studies (IV).

The additional information about the benefits of GAHT provided by this Evidence Check is summarised below (Table 6). It covers the overall effectiveness of treatment for changes in body composition, BMI, growth and bone maturation, amenorrhoea (menstrual suppression), body image, gender dysphoria, overall effects on psychological health, depression, anxiety, suicide risk, behavioural problems, quality of life and wellbeing, mental health care use, cognitive and brain function and bone density.

Table 6a—Benefits of gender-affirming hormone therapy

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
GAHT promotes changes in body composition in ways that align with the desired gender.	**Overall effectiveness of changes in body composition** One Level I study concluded that *"the body of available data on GAHT in trans people is steadily increasing, and short-to-midterm outcomes are quite reassuring in relation to effectiveness and safety"*.[20(p587)] **Body mass index (BMI)** One Level III-2 study of 124 transgender males reported that GAHT increased BMI; however, this study noted possible confounding due to

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	racial differences between groups.[45] A further Level III-2 study of 85 adolescents reported increases in BMI after initiation of GAHT.[41] One Level IV study of 46 trans male adolescents reported that although testosterone increased BMI within 6 months of initiation, no significant change in BMI was recorded between baseline and 12 months.[86] **Growth and bone maturation** One Level III-2 study reported that bone maturation and growth rate reduced during GnRHa and increased during GAHT in 161 trans females, with an adult height lower than predicted prior to GnRHa but not to a statistically significant degree.[37] One Level IV study of 154 transgender masculine youth reported that early treatment with oxandrolone was associated with increased adult height.[71] **Amenorrhea or menstrual suppression** Overall evidence about amenorrhea was mixed across four Level IV studies. These encompassed several different agents including the contraceptive pill. One Level IV study reported a menstrual cessation rate of 54% with a dose of 140mg subcutaneous testosterone, rising to 97% with a 200mg dosage[76]; another reported high effectiveness (94%) with menstrual suppression in a cohort of more than 500 patients receiving oral contraceptive pills (47% of cohort), norethindrone (30%) or intramuscular medroxyprogesterone (15%).[6] However, one Level IV study of 220 patients on GnRHa and GAHT reported less than 50% achieved amenorrhoea within six months[54]; and Grimstad (2021b)[70] reported breakthrough bleeding in 58 out of 232 patients after 12 months of testosterone therapy. Longer duration of time receiving testosterone and endometriosis

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	were associated with breakthrough bleeding in this study.
GAHT is associated with improved body image, decreased body dissatisfaction, reduced gender dysphoria and improved psychological wellbeing (five studies referenced, levels III-2–IV).	**Body image** One Level I study reported unclear evidence about body image.[25] One Level III-3 study of 38 transgender young people reported improved satisfaction with body image following GAHT.[52] One Level IV study of 42 transgender adolescent boys reported improved body satisfaction following testosterone treatment.[93] **Gender dysphoria** One Level I study[25] and one Level III-3 study of 38 transgender young people[52] reported that GAHT reduced gender dysphoria. A further Level IV study of 315 transgender participants reported that GAHT improved appearance congruence.[65] However, one Level IV study of 530 patients reported menstrual suppression therapy (including GAHT) was not associated with a change in gender dysphoria.[6] **Overall effects on psychological health** Findings across two Level I studies regarding overall effects of GAHT on psychological health were inconclusive or neutral, with Ludvigsson (2023)[22] unable to reach conclusions owing to bias and small participant numbers in included studies and Baker (2021)[19] reporting there was no evidence of harm to mental health from GAHT. **Depression** Findings pertaining to depression were generally positive for higher-ranked study designs, with two Level IV studies reporting no change in depressive symptoms.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	Two Level I studies reported GAHT reduced depression.[25,28] Five Level IV studies reported GAHT reduced depression.[65,75,82,89,94] One Level IV study of 80 transgender youth reported no improvement in depression at 4-month follow up after GAHT.[63] A further Level IV study of 530 patients reported that menstrual suppression therapy (including GAHT) was not associated with a change in depression symptoms.[6] **Anxiety** Two Level I studies (NICE 2020b, Rowniak 2019)[25,28] and three Level IV studies[65,75,82] reported GAHT reduced anxiety. A further Level IV study of 42 transgender adolescent boys reported reductions in social anxiety.[94] In contrast, three Level IV studies reported no change in anxiety following GAHT[6,63,89] and one Level IV study reported that two participants out of 315 experienced severe anxiety during clinic visits.[65] **Suicide risk** One Level I study[25], one Level III-3 study[52] and six Level IV studies[55,75,89,80,93,94] reported reductions in suicidality following GAHT. However, one Level IV study[63] reported no change in suicidality and a further Level IV study[65] reported that 11 of 315 participants had suicidal ideation and a further 2 died by suicide. **Behavioural problems** One Level I study reported reductions in behavioural problems following GAHT treatment.[25] **Quality of life / wellbeing** Two Level I studies[25,28] reported increased quality of life following GAHT, and a further Level I study[19] reported no evidence that GAHT harms quality of life.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	Two Level IV studies reported positive affect and life satisfaction[65] and enhanced wellbeing[55] following GAHT. One Level IV study reported no change in adolescent development (i.e. relationships, living situation, peer contacts) following GAHT.[75] **Mental health care use** One Level IV study reported that mental health care visits overall did not significantly change following gender-affirming pharmaceutical care. However, TGD participants were more likely to have a mental health diagnosis at baseline compared with controls (siblings).[73] A further Level IV study reported no change in psychiatric treatment needs for any reason (i.e. overall), but reductions in need for treatment for depression, anxiety and suicidality.[75] **Disordered eating** One Level IV study reported no significant improvement in disordered eating following gender-affirming care including GAHT.[83] **Cognitive and brain function** One Level IV study reported no impact on IQ scores / educational achievement compared with the general population in a sample of 72 adolescents.[56] One Level IV study of transgender youth reported better executive function in patients undergoing GAHT but poorer executive function with long-term puberty suppression treatment (however these patients had ASD and anxiety symptoms).[87] One Level IV study demonstrated stronger functional connectivity between the right amygdala (involved in processing emotional content) and the ventromedial prefrontal cortex (involved in cognitive control of emotion processing) in 36 transgender youth receiving GAHT compared with 46 transgender youth not

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	receiving GAHT. The amygdala–ventromedial prefrontal cortex can be disrupted in multiple psychiatric disorders, including anxiety and depression.[94]
GAHT appears to increase bone density following the negative impact of puberty suppression treatment on bone density (three studies, levels III-2–III-3).	**Bone density** One Level I study[22] reported that children with gender dysphoria have lower group mean values for bone mineral density (BMD) prior to puberty suppression (GnRHa) treatment; that puberty suppression treatment delays puberty-induced BMD gain; and that this is almost fully compensated by subsequent GAHT. A further Level I study[25] reported mixed evidence on bone mineral density, with two studies reporting that GAHT may increase bone density (measured in lumbar spine and femoral neck) and one reported no significant difference following GAHT treatment. One Level III-3 study of 121 transgender youth[53] reported decreases in bone mineral apparent density (BMAD) during GnRHa therapy followed by increases with GAHT. While trans boys had normal z-scores at baseline and study end, trans girls had relatively low z-scores at baseline and after three years of oestrogen treatment. Implications for adverse outcomes such as increased fracture risk for trans girls as they grow older were reported as uncertain. One Level IV study of 87 adolescents[60] reported that 6 mg oestradiol or 100–200 µg ethinyl oestradiol resulted in greater increases in bone mineral density compared with 2 mg oestradiol.
Where GnRH has not been used for puberty suppression in trans girls, anti-androgen medications such as cyproterone acetate or spironolactone may be used in addition to GAHT to also relieve gender dysphoria (one study, NHMRC Level III-2).	No identified studies examined cyproterone use independent of puberty suppression: • One Level I study reported that **cyproterone acetate**, leuprolide and medroxyprogesterone acetate may be more effective than **spironolactone** or oestradiol alone for suppression of serum total testosterone concentration.[18]

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	• A further Level I study reported that although **cyproterone acetate** (commonly used alongside oestrogen therapy) may cause increases in depression, there was no evidence for overall harms to mental health or quality of life.[19] • One Level IV study[93] included patients receiving spironolactone as monotherapy, although no subgroup analysis of this cohort was conducted. • A further Level IV study[77] examined the effect of spironolactone on hyperkalaemia; however, participants were also receiving GnRHa and / or oestrogen and no subgroup analysis was conducted.

The additional information on the risks of GAHT provided by this Evidence Check is summarised below. It covers overall safety, cardiometabolic effects and thrombosis, risk of meningioma and prolactinoma, kidney diseases, physiological and mixed effects, physical side effects and fertility.

Table 6b—Risks of gender-affirming hormone therapy

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
Rarely, other serious adverse outcomes, including breast and ovarian cancer among trans boys receiving androgen therapy, have been reported in the literature. However, there are too few cases to suggest a causative link between GAHT and gynaecological malignancy (one reference to committee opinion).	**Overall safety** One Level I study[28] reported that the limited GAHT research identified few long-term risks. A further Level I study[20] reported short-to-medium outcomes as 'reassuring' in relation to effectiveness and safety. **Cardiometabolic effects and thrombosis**

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	Rowniak (2019)[28] also quoted a previous review reporting low-quality evidence that GAHT increased triglyceride levels in both trans men and trans women, could have a minor effect on high density lipoprotein (HDL) and systolic BP in trans men; however, this evidence was from before 2010). A further Level I study reviewing more than 80 studies on cardiometabolic risk and thrombosis[21] concluded that *"although the currently available literature lacks power and is at moderate risk for bias, most of the studies reported no increase in cardiovascular morbidity for transgender people taking HT in short-to-medium (10 years) follow-up periods"*.[21(p131)] One Level III-2 study reported that GAHT reduced HDL; however, this study noted possible confounding due to racial differences between groups.[45] A larger Level III-2 study (4172 transgender youths vs. 16,648 controls) reported that oestradiol and GnRHa alone did not appear to relate to cardiometabolic diagnoses.[44] The same study found higher odds of overweight / obesity vs. controls in the overall group; higher odds of dyslipidaemia and liver dysfunction in those taking testosterone with or without GnRHa; and higher odds of overweight / obesity and hypertension if taking testosterone alone[44]; however, the time of diagnosis in relation to the initiation of GAHT could not be determined. One Level IV study of 611 transgender adolescents[78] reported no incidental occurrence of arterial or venous thrombosis associated with GAHT. **Meningioma / prolactinoma risk** One Level I study[18] reported that use of cyproterone acetate in transgender women has been associated with a four times higher incidence rate of meningioma when compared with a female reference population, with this risk

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	associated with cumulative dose exposures greater than 3g. Additionally, this review reported that hyperprolactinaemia was associated with cyproterone acetate, which is reversible following discontinuation. Although a fourfold increase in prolactinomas in transgender women has been observed, the review conclusion was unclear regarding the significance of this result as it may reflect increased prolactin monitoring; the incidence of *symptomatic* prolactinomas was not elevated. **Kidney** One Level III-2 study[41] reported changes in serum creatinine among a cohort of 286 transgender patients within 6 months of treatment. In transgender males the increase was to levels similar to baseline measurements for those designated male at birth. In transgender females, the increase brought levels above baseline measurements for those designated female at birth. When compared with a reference group of adolescents, serum creatinine was more similar when compared by gender than when compared by designated sex. These changes are likely related to changes in body size and composition. Although there were no changes in mean serum creatinine for the entire cohort beyond 12 months of GAH, two transgender males out of 194 had estimated glomerular filtration rate (eGFR) rises between 12 and 24 months that were potentially indicative of chronic kidney disease using accepted thresholds; however these rates were below these thresholds when the male formula for eGFR rather than the female formula was used. **Physiological / mixed** One Level I study[25] reported small increases in blood pressure and body mass index (BMI) as well as non-significant changes in creatinine and alkaline phosphatase (ALP). A further three cases of erythrocytosis on testosterone were

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	reported (one due to incorrectly high testosterone dosage). Four patients had elevations in alanine aminotransferase (ALT) on oxandrolone and two had elevations in aspartate aminotransferase (AST) on oxandrolone. These elevations resolved either spontaneously or after switching to testosterone. One Level IV study of 85 adolescents[77] reported hyperkalaemia (defined as serum potassium concentration above 5.0 mmol/L) in 5 participants. None of the subjects had symptoms of hyperkalaemia, and all elevated measurements were normal when repeated.
Side effects such as acne, weight gain, mood swings and hot flushes are common with GAHT but rarely lead to cessation of therapy. Scalp hair loss may also occur in trans boys (three references NHMRC level III-2).	**Physical side effects** One Level III-2 study reported nausea and vomiting associated with GAHT.[37] One Level III-2 study reported higher odds of headache in trans feminine and trans masculine youth receiving GAHT vs. those who had not received GAHT[40]; another Level III-2 study also reported headaches as a side effect of GAHT.[37] One Level IV study[5] reported almost 25% of 158 of patients with GAHT (testosterone) reported pelvic pain, with higher rates if using additional agents for menstrual suppression.
GAHT is only partially reversible. Voice deepening, facial hair growth and reduction in scalp hair growth may be irreversible for trans boys. Reversing the effects of breast development in trans girls may require surgery (two references, clinical guideline and committee opinion).	No relevant updated information identified.
Because GAHT may affect future fertility, recommendations to discuss fertility preservation before medical intervention for TGD children and adolescents were given in guidelines, reviews without meta-analyses and position statements (six references).	**Fertility** One Level IV study of 214 transgender women reported that commencing GAHT early in puberty (Tanner stage 2–3) reduces mature spermatozoa production, resulting in reduced ability to collect mature spermatozoa for assisted reproduction later in life. However, more than 85% of the

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	cohort had the option of harvesting spermatogonial stem cells. Furthermore, fertility preservation options were not influenced by cessation of GAHT prior to genital gender-affirming surgery or duration of GAHT prior to surgery.[66]

This Evidence Check found no additional information on variation in the benefits and risks of GAHT.

Table 6c—Variation in the benefits and risks of gender-affirming hormone therapy

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
Historically, GAHT has rarely been started before 16 years of age. However, recent studies and expert consensus suggest the most appropriate stage at which to begin treatment should not be decided on age alone. Comorbidities such as mental health issues and medical conditions should be taken into account when considering medical interventions, as well as psychosocial factors such as parental support and the readiness of the adolescent for informed consent (one reference—NHMRC level of evidence: ungraded; clinical practice guideline).	No identified studies provided updates to this finding (noting that clinical practice guidelines were out of scope for this Evidence Check update).
A multidisciplinary team may include a paediatrician, adolescent physician, endocrinologist, general practitioner, fertility counsellors, nurse, counsellors, speech pathologists, family workers, psychiatrists and psychologists (five references—NHMRC level of evidence ungraded: reviews without meta-analyses and clinical practice guidelines).	No identified studies provided updates to this finding (noting that clinical practice guidelines were out of scope for this Evidence Check update).

Strengths and limitations of the evidence

The seven Level I studies (systematic reviews) ranged in quality, with four of moderate-to-high relative quality[19,22,25,28] and three of lower relative quality.[18,20,21]

The Level I studies collectively highlighted a range of limitations in the literature that they discussed in their conclusions. Two Level I studies[22,25] noted numerous limitations in study design that meant firm conclusions about reported effects could not be made. More specific observations across the Level I studies encompassed:

- Treatment: variations in hormone dosage, route of administration and length of time using hormones[28]
- Bias and confounding: uncontrolled confounding factors[19,25,28]; recruitment bias (clinics)[19,20]; lack of RCTs[22]; small sample sizes[18,19]; failure to enumerate drop-outs[22]
- Outcome measurements: validity of quality-of-life measures questioned[28]; validity of psychological outcome scales[19]; group-level analysis where intra-individual change was more appropriate[22]; many different scoring tools with conflicting results[25]; lack of distinction between statistical and clinical significance[25]; serum testosterone level not a suitable surrogate marker of therapy as the mechanism of many GAHTs is through androgen receptor antagonism[18]
- Lack of long-term studies.[21,22]

A number of these issues were acknowledged as limitations in the included primary studies. Most frequently these were small sample sizes, retrospective study designs, lack of diversity in participant cohorts and use of a single-centre cohort.

Additionally, 25 of the 39 included studies were Level IV, which is the weakest study design in the NHMRC hierarchy.

Conclusions of Evidence Check update—GAHT

We identified a considerable volume of evidence pertaining to GAHT in this Evidence Check update, reflecting an overall rise in the research into interventions for gender dysphoria since 2019–2020. Although the newly identified studies support the conclusions of the previous review, which reported that GAHT was effective for changes in body composition, evidence was mixed for changes to body mass index (BMI) and growth and bone maturation. Additionally, mixed results were reported for menstrual suppression, albeit in Level IV studies. The largest volume of new evidence pertains to the psychological benefits of GAHT. The identified studies reported positive results across the domains of body image, gender dysphoria, depression, anxiety, suicide risk, quality of life and cognitive function. However, neutral and some negative findings were also reported in these domains. Additionally, two Level IV studies reported no changes in mental health care use following gender-affirming pharmaceutical care. Although studies reporting positive mental health outcomes following GAHT outnumber those with neutral or negative findings, considerable flaws remain in the evidence because of generally low participation rates of target groups, inadequate representation of adolescents and / or poor study designs and conduct. The relevant systematic reviews identified underline this observation. Several studies support the finding of the previous review, which reported that GAHT appears to increase bone density following the negative impact of puberty suppression treatment on bone density.

Similar increases in research volume were observed in studies reporting on the risks and potential harms of GAHT. Findings on overall safety, cardiometabolic risk, kidney and physiological parameters support the previous review's findings that serious adverse outcomes associated with GAHT are rare. One Level I study flagged the risk of meningioma associated with cumulative dose exposures of cyproterone acetate greater than 3g, as well as prolactinoma risk, which may reflect increased monitoring, with symptomatic prolactinoma risk not elevated. Minor changes in physiological

parameters were reported. For example, blood pressure and elevated potassium—in the case of potassium, none of the subjects had symptoms of hyperkalaemia and all elevated measurements were normal when repeated. Newly identified primary studies reported a range of less serious side effects (for example, headaches, nausea and vomiting), consistent with the previous review. Some evidence was identified regarding the fertility impacts of GAHT, although only from two Level IV studies. Overall, despite increases in research volume, the conclusions of the previous review with respect to GAHT are largely unchanged as the increased number of studies is offset by generally poor study designs. Table 7 summarises the main features of each of the reports about GAHT included in this Evidence Check.

Included studies in this Evidence Check update—gender-affirming hormone therapy

Table 7a—NHMRC Level I. Systematic reviews—gender-affirming hormone therapy (n = 7)

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
Rowniak 2019[28] Evaluate effectiveness of use of gender-affirming hormones in improving quality of life, depression and anxiety in transgender individuals. Score on quality criteria = 12.5 / 13.	N = 7 studies (all observational: 1 case-control, 2 cross-sectional, 4 case series).	**GAHT** Hormones not specified. All patients in hospital setting seeking gender transition. Predominantly adult cohorts but no age restrictions at level of search. Studies that included participants who had gender-affirming surgery were excluded.	Studies reported significant improvement in scores on validated scales for quality of life, anxiety and depression compared with transgender participants not yet on cross-sex hormones. Three studies reported significantly higher QOL in hormone vs. no hormone transgender patients.	*"The review found low-quality evidence suggesting that the hormones could increase triglyceride levels in both trans men and trans women, and could have a minor effect on high-density lipoprotein cholesterol levels and systolic blood pressure in trans men."*	*"The included studies found improvement in the scores for the outcomes and concluded that the hormones were responsible for this improvement. However, the certainty of these conclusions is low at best, and the reason for this improvement is not completely understood, nor is it explored in any of the included studies."* Limitations of included studies: *"The greatest risk of bias was related to the lack of clarity concerning differences in the*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
					intervention as related to hormone dosage, route of administration and length of time using hormones prior to assessment … The other risk of bias was regarding confounding factors. Although all of the studies reported possible confounders, only two stated that they used linear regressions to control for the confounding variables …[O]ne question that arose while conducting this review was the validity of the quality-of-life measures with regard to the actual lived experience of the transgender population being surveyed."
Baker 2021[19] To review the effects of gender-	N=20 studies (1 RCT, 2 pre-post trials, 12	**GnRHa: 3 studies** **GAHT: 17 studies**	Improved quality of life and decreases	No reported adverse effects of hormone therapy on patients' mental health.	*"… our review indicates that gender-affirming hormone therapy is likely associated*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
affirming hormone therapy on psychological outcomes of transgender people. Score on quality criteria = 8.5 / 13.	prospective cohorts, 1 retrospective cohort and 4 cross-sectional studies.	Three studies focused on adolescents; mean age was over 25 in most studies.	in depression and anxiety symptoms. Associations were similar across gender identity and age.	*"… some evidence indicates that cyproterone acetate, a common anti-androgen assessed in many studies alongside estrogen therapy, may increase depression".*	*with improvements in QOL, depression, and anxiety. No studies showed that hormone therapy harms mental health or quality of life among transgender people."* Limitations of included studies: *"Certainty in this conclusion is limited by high risk of bias in study designs, small sample sizes, and confounding with other interventions … Uncontrolled confounding was a major limitation in this literature. Many studies simultaneously assessed different types of gender-affirming care and did not control for gender-affirming surgery status, making it difficult to isolate the effects of hormone therapy ...*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
					Another source of potential bias was recruitment of participants from specialized clinics that impose strict diagnostic criteria as a prerequisite for gender-affirming care. Most studies used well-known scales for measuring psychological outcomes. None of these scales, however, have been specifically validated for use in transgender populations."
Ludvigsson 2023[22] To evaluate the impact of hormone treatment on psychosocial and physical outcomes in children diagnosed with gender dysphoria.	N=24 studies (All observational).	**GnRHa: 8 studies** **GnRHa + GAHT: 13 studies** **GAHT: 3 studies** Age range: 11–15 years; treatment usually continued for approximately two years.	Some studies reported improved global function and quality of life; however, the long-term effects of hormone treatment on psychosocial health (i.e. global function, suicide ideation, gender	*"… lower group mean values for BMD already prior to GnRHa treatment, and that GnRHa treatment delays the physiologically occurring BMD gain during pubertal sex hormone stimulation. However, this GnRHa-induced delay in BMD gain is almost fully compensated for by later*	*"… the long-term effects of hormone therapy on psychosocial health could not be evaluated. Concerning bone health, "GnRHa treatment delays bone maturation and bone mineral density gain, which, however, was found to partially recover during*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
Score on quality criteria = 8.5 / 13.			dysphoria, depression, anxiety, cognition, quality of life) could not be evaluated.	*ensuing (cross-sex hormone treatment) CSHT. Although study participants were followed up to 22 years of age, the observed remaining deficit may depend on the limited study group size or on too short an observation time."*	*CSHT when studied at age 22 years."* *"Our review highlights several specific knowledge gaps … randomised controlled trials are lacking in gender dysphoria research …* *… observational data have frequently been analysed at a group level where intra-individual changes would have been more appropriate …* *… many studies only present data on chronological age but fail to account for puberty stage and biological age …* *… long-term studies are lacking …* *… individuals who stop GnRHa treatment before the start of CSHT need to be*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
					described and followed up … *… some of the findings underlying this review are old …* *… we could not evaluate the frequency of individuals who drop out from GnRHa treatment and no longer wish to continue with gender transition."*
National Institute for Health and Care Excellence (NICE) 2020[25] Examined clinical effectiveness, safety, cost-effectiveness, subgroups for whom benefits are higher or lower, criteria used to	10 observational studies 7 retrospective observational; 3 prospective longitudinal. People aged 18 years or less.	**GAHT was the primary focus; included studies had participants who had also received GnRHa** GD defined by DSM criteria (reported in 5/10 studies). GAHT treatment started aged 16–17	Reduction in GD, depression, anxiety, suicide risk, behavioural problems. Increase in quality of life. Unclear effect on body image. Mixed evidence on family function unchanged vs.	Reduction in people with normative peer contacts between baseline assessment and 1 year after starting GAHT. No evidence of de-transition, defined as ceasing treatment. Glucose, insulin, insulin resistance, cholesterol unchanged; HbA1c, AST, ALT, GCT unchanged; ALP increased at some time	*"Results from 5 uncontrolled observational studies suggest that in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
define GD, age when treatment commenced and treatment duration for gender-affirming hormones. Score on quality criteria = 8.5 / 13.		years old (range 14–19). Duration of treatment was between 1 and 5.8 years.	reductions in participants living with parents / guardians. May increase bone density (mixed evidence).	points but not sig. at 24 months; creatinine increased but within UK reference range. BP increased (absolute increases small). BMI increased (most participants in healthy weight range). Minor complications were severe acne (n=7), androgenic alopecia (n=1), mild dyslipidaemia (n=3) and significant mood swings (n=1).	*treatment on body image is unclear."* *"The key limitation … is the lack of reliable comparative studies. All the studies included in the evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE ...* *… many different scoring tools and methods were used to assess the same outcome, often with conflicting results."* *"… most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult the determine*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
					whether any statistically significant changes seen are clinically meaningful."
Angus 2021[18] Review effectiveness of 'antiandrogens' in feminisation. Score on quality criteria = 6.5 / 12.	N=4 studies, (all retrospective) Women aged 16+ were eligible, but all included studies had adult women.	**GnRHa + GAH** 'Antiandrogens' (GnRHa, progestogens, 5α-reductase inhibitors, androgen receptor antagonists).	CPA, GnRH analogues and MPA are more effective than spironolactone at suppressing testosterone.	Use of CPA in transgender women has been associated with a four times higher incidence rate of meningioma when compared with a female reference population. While meningiomas are rare, both the European Medicines Agency and the United Kingdom Medicines and Healthcare Products Regulatory Agency advise against use of CPA at doses of ⩾ 10 mg daily unless there are no other treatment options. CPA use has been associated with hyperprolactinaemia of	*"[T]here are inadequate data to support enhanced feminization with any particular antiandrogen … The comparative effects on breast development, body fat redistribution and reduction in facial and body hair are unclear."* *"Existing studies are mostly retrospective analyses of clinic data, with a small number of study participants, lacking clinically relevant endpoints and without adequate comparison to different treatment groups. Instead, the serum total testosterone concentration is typically*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
				uncertain clinical significance—reversible. Fourfold increase in prolactinomas was also observed in transgender women—this may reflect increased prolactin monitoring in this population.	*reported as a surrogate marker of therapy, a significant flaw given some commonly prescribed antiandrogens work predominantly via androgen receptor antagonism rather than decreasing testosterone levels."*
Defreyne 2019[21] Review effects of gender-affirming hormone therapy on cardiometabolic risk and thrombosis. Score on quality criteria = 6.5 / 13.	77 included studies, including 11 reviews. 4 studies on cardiovascular mortality; 12 on cardiovascular morbidity; 12 on blood pressure; 25 on lipids; 24 on body composition; 19 on markers of increased thrombosis.	**GAHT** Transgender people without age limitation.	N/A—focus of review was on risks.	CV mortality: Several reviews inconclusive, with no long-term prospective follow-up studies. CV morbidity: Meta-analysis reported no increased risk of myocardial infarction, stroke or venous thromboembolism (VTE) but may be due to lack of reported outcomes. Conflicting findings in primary studies. Conflicting findings on diabetes possibly	*"Although the currently available literature lacks power and is at moderate risk for bias, most of the studies reported no increase in cardiovascular morbidity for transgender people taking HT in short-to-medium (10 years) follow-up periods. Known biochemical markers of CVD show conflicting results for transgender people prescribed HT."*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
				confounded by screening prior to hormone therapy.	*"We must acknowledge the fact that our data* [i.e. the included studies in the review] *are limited by a relatively short follow-up duration, without data on older transgender people."*
D'hoore 2022[20] The focus of this paper is to give an update on hormone treatments from recent data in larger cohorts, when available. Score on quality criteria = 5.5 / 12.	91 studies from 2015–2021 Adults n=69 Adolescents n=21 Both adults and adolescents n=1.	**Studies examined GnRHa and GAHT** (oestrogens, antiandrogens, testosterone, progestational agents).	GAHT reduces mental health problems in trans people and helps obtain the desired physical features. In trans men, BMD was found to increase during GAHT; in trans women, it was less conclusive. Blood pressure is not significantly changed by GAHT.	In trans women there is a significantly increased risk of VTE (1 study in comparison to cis controls; 1 study compared with both reference cis women and cis men; 1 study associated with recent progestin prescriptions). The use of oestrogens in transgender women is associated with an elevated risk of myocardial infarction and stroke. Trans men have an increased risk of elevated hematocrit levels, but this is manageable.	*"The body of available data on GAHT in trans people is steadily increasing, and short-to-midterm outcomes are quite reassuring in relation to effectiveness and safety."* *"For this review we relied on published data from a limited group of clinical research teams that are active in this field. Per definition, this is biased literature, with participants having access to well-organized research centers."*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
			In general, lipid profile is favourably changed in trans women in contrast to trans men. But in trans women treated with CPA, a negative effect is seen in HDL levels. There is no evidence of elevated cancer risk of breast, endometrium or prostate.	There is a small but higher risk of prolactinoma occurrence in trans women and a small increased risk of meningioma in trans women on CPA.	

Table 7b—NHMRC Level III-2. Comparative studies with concurrent control—gender-affirming hormone therapy (n = 5)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Valentine 2021[45] To examine changes in BMI and lipids in adolescent transgender males undergoing testosterone treatment. Score on quality criteria = 5 / 7.	US Retrospective chart review study. A large Midwestern paediatric academic centre.	**GAHT only** Testosterone N=124 Transgender male adolescents (n=42), M age: 16.6 years (14–19). Cisgender males (n=82): 15.5 years (14–21).	Body mass index (BMI) and lipid profile changes.		Significant increase in BMI in transgender males over time. A reduction in high-density lipoprotein in the transgender males.	*"… exogenous testosterone administration in adolescents who were assigned female at birth may lead to increased body mass over time."* Study limitations: *"… racial discrepancy and limitations related to retrospective study design, small sample size, single site data collection, and variable length of follow-up."*
Valentine 2022[44] To determine the probability of cardiometabolic-related	US Retrospective, cross-sectional study. Five children's hospital / health	**GnRHa + GAHT** GAHT (oestradiol, testosterone), GnRHa.	Odds of having cardiometabolic-related diagnoses.	Oestradiol and GnRHa alone not associated with cardiometabolic-	Treatment group w/ testosterone and/or GnRHa had higher odds of overweight / obesity,	*"TGDY have increased odds of overweight / obesity compared to matched controls. Screening and tailored weight management, sensitive to the needs of TGDY, are needed."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
diagnoses in transgender and gender diverse youth (TGDY). Score on quality criteria = 5 / 7.	services in the US.	TGDY (n=4172) Controls (n=16 648).		related diagnoses.	dyslipidemia and liver dysfunction. Testosterone group had higher rate of overweight / obesity and hypertension.	*"We were not able to determine if cardiometabolic-related diagnoses occurred before or after receiving a prescription for GAHT given limitations of the data set."*
Boogers 2022[37] To investigate the effect of GnRH and GAHT on growth of height. Score on quality criteria = 5 / 8.	Netherlands Retrospective cohort study Center of Expertise on Gender Dysphoria in Amsterdam.	**GnRHa + GAHT** N=161 (transgender girls).	Height, weight, bone age.	Bone maturation and growth rate reduced during GnRHa (but increased with GAHT). All patients had lower than predicted adult height (PAH), with the group treated with EE having the	Side effects of high-dose oestradiol and EE were not examined; nausea, vomiting and headache are commonly reported side effects.	*"Growth decelerated during GnRHa and accelerated during GAHT. After regular-dose treatment, adult height was slightly lower than predicted at start of GnRHa, likely due to systematic overestimation of PAH as described in boys from the general population, but not significantly different from target height."* Study limitations: *"A limitation is the retrospective character of*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
				largest difference (3cm).		*the study with some missing data. Another limitation is the delayed introduction of the growth-reductive treatment in some individuals and the difference in baseline characteristics between the 3 treatment groups."*
Millington 2022[41] To investigate the effect of GAHT on serum creatinine in transgender and gender diverse youth. Score on quality criteria = 5 / 9.	US Prospective longitudinal observational study Boston Children's Hospital, Benioff Children's Hospital, Lurie Children's Hospital and Children's	**GAHT only** (oestradiol, testosterone) N=286 TGD individuals aged between 12 and 22 years. 92 trans girls; 194 trans boys.	Serum creatinine level.	Serum creatinine level of trans boys treated with GAHT increased to a similar level to cis boys. Serum creatinine levels in TGD youth closely resembling those of the reference population when matched by gender identity.	After 12 months of treatment, mean serum creatinine in trans girls decreased but still remained above that of participants designated female at birth at baseline.	*"We observed significant changes in serum creatinine and corresponding eGFR within 6 months of GAH treatment in TGD youth."* Study limitations: *"Direct measurement of GFR and analysis of body composition were not performed as part of this study, presenting significant limitations to the study. Additionally, information regarding the method and precision of serum creatinine measurements was not*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
	Hospital Los Angeles.					*collected. Lack of racial diversity in the cohort is an additional limitation."*
Hranilovich 2023[40] To investigate the potential side effect of GAHT causing headache among transgender and gender diverse youth (TGD). Score on quality criteria = 4 / 7.	US Retrospective case-control study Boston Children's Hospital Gender Multispecialty Service (GeMS).	**GAHT only** N=763 TGD adolescents • Trans feminine (n=273) • Trans masculine (n=490) 10–20 years old.	Headache prevalence.	N/A	Higher rate of headache in patients receiving GAHT. Of those with headache, 28 received testosterone and 13 did not; 9 received oestrogen and 2 did not.	*"Among transfeminine and transmasculine youth, those who received gender-affirming hormone therapy had higher odds of headache compared to those not taking gender-affirming hormone therapy."* Study limitations: *"… reliance on incidental reports of headache in medical record"* and *"a risk of both transfeminine and transmasculine adolescents who received GAHT having more documentation of headache".*

Table 7c—NHMRC Level III-3. Comparative studies without concurrent control—gender-affirming hormone therapy (n = 2)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Lavender 2023[52] To investigate the impact of hormonal treatment on gender diverse young people's psychological functioning and behaviours. Score on quality criteria = 6 / 8.	UK Retrospective observational study An endocrine clinic.	**GnRHa + GAHT** N=38 gender diverse young people n=28 assigned female at birth and n=10 assigned male at birth. Aged 12–15 years, at >= Tanner stage 2, and treated with GnRHa followed by GAHT.	Sexual characteristics, social motivation, behaviours, gender dysphoria (GD) experience.	Improved satisfaction with body image, GD and social motivation. Reduced self-harm and suicidality concerns and internalising behavioural problems.	No information on side effects.	*"Improvements over time were noted in GD, primary sexual characteristic satisfaction, and social motivation. Caregiver reports of improvements in internalizing and externalizing behaviors were most evident with GnRHa, while young person reporting indicated improvements in externalizing behaviors with GnRHa, which increased with GAH."* *"Due to the uneven distribution of young people assigned male and assigned female at birth, although consistent with UK and international referral trends, we were unable to compare groups statistically … In addition, data were available from a small number of individuals, and thus, generalizability should not be assumed."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Schagen 2020[53] To investigate the impact of hormonal treatment on bone development in transgender adolescents. Score on quality criteria = 6 / 8.	Netherlands Observational prospective study Setting: not mentioned.	**GnRHa + GAHT** (Sustanon, 17beta-oestradiol, testosterone-esters) n=51 trans girls and 70 trans boys receiving GnRHa; of this cohort, n=36 trans girls and 42 trans boys subsequently received GAHT. GnRHa initiation at 12.6 (12.1–12.8) years old for trans girls and 12.7 (11.9–14.0) for trans boys.	Bone mineral apparent density (BMAD), age- and sex-specific BMAD z-scores, and serum bone markers.	BMAD z-scores increased during GAHT treatment.	BMAD z-scores decreased during GnRHa treatment. Bone markers reduced in trans girls and early pubertal trans boys while on GnRHa. "The consequences of lower BMD for long-term bone health in these individuals remains unclear."	*"Gender-affirming hormone treatment increases bone accretion and normalizes the age- and sex-specific BMAD z-scores in transboys."* *"An important limitation of this study is the lack of an untreated control group."*

Table 7d—NHMRC Level IV. Case series / cross-sectional—gender-affirming hormone therapy (n = 25)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Grannis 2021[93] To assess the effect of GAHT on internalising symptoms, body image satisfaction. Score on quality criteria = 7 / 8.	US Cross-sectional A large children's hospital.	**GnRHa + GAHT** N=42 Transgender adolescent boys • n=19 receiving testosterone cypionate (T) • n=23 not receiving GAH (UT) Aged 9–21 years.	Anxiety, social anxiety, depression, suicidality, body image dissatisfaction and brain activation.	Lower level of mental health issues and less suicidal ideation in the past year and a higher body satisfaction level.	No apparent side effects reported.	*"A primary finding of this study is that symptoms of anxiety, depression, and suicidality were lower in testosterone-treated transgender adolescents than in a comparable group of transgender adolescents not receiving GAH."* *"The present study's most important limitation was our modest sample size … Notably, our sample size precluded the analysis of other potential factors related to internalizing symptoms, such as duration of T treatment or dose-dependent responses … Second is the cross-sectional design and lack of randomization."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Grannis 2023[94] To explore the applicability of GAHT benefits to both transgender and nonbinary populations, and examine the associations among body image satisfaction, neural circuitry, and internalising problems. Score on quality criteria = 7 / 8.	US Cross-sectional A large children's hospital.	**GnRHa + GAHT** GAHT (i.e. testosterone or oestrogen) N=82 transgender and nonbinary youth. AFAB: • Receiving GAHT (treatment): mean age 17.04 (1.18) • No GAHT: mean age 15.24 (1.72). AMAB: • Receiving GAHT+: M age 17.64 (0.86)	Mental health (anxiety, depression and suicidal ideation in the past year). Brain activation (i.e. amygdala response and amygdala-vmPFC co-activation).	GAHT treatment associated with lower levels of social anxiety, depression and suicidality among trans boys. Enhanced functional connectivity observed between the amygdala and vmPFC.	No apparent side effects reported.	*"Exploratory analyses revealed that GAHT duration was associated with internalizing symptoms, such that longer duration of GAHT was negatively associated with body image dissatisfaction and symptoms of depression and suicidality."* *"… the study is limited by its cross-sectional design, small sample size, and omission of mental health related considerations, such as length of mental health interventions and information regarding psychiatric cooccurrences (e.g. autism). … [A] further limitation is the decision to include youth receiving puberty blockers or Spironolactone as monotherapy in the GAHT group."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
		• No GAHT: M age 16.27 (1.49).				
Boogers 2023[60] To investigate the dose-dependent impact of oestrogen on bone mineral density. Score on quality criteria = 8 / 10.	Netherlands Pre-post Centre of Expertise on Gender Dysphoria in Amsterdam.	**GnRHa + GAHT** GnRHa, followed by GAHT and then gradually increased doses of oestradiol. N=87 adolescents Mean age 13.5 ± 1.2.	Bone mineral density (BMD) z-scores.	Higher doses of oestrogen associated with increased in lumber spine BMD z-scores.	High dose group had slightly lower vitamin D concentrations compared with the regular group. No evaluation of side effects.	*"In conclusion, individuals treated with 6 mg estradiol, and with 100-200 µg EE especially, had a greater increase in BMD compared to trans girls treated with the regular dosage of 2 mg estradiol that resulted in low serum estradiol concentrations. This indicates a dose-dependent effect of estrogen on BMD."* *"However, the number of individuals in the growth reductive treatment groups was relatively small. Due to the retrospective character of the study, missing data were inevitable … Since the type of treatment schedule was based on participants' characteristics, the three*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						treatment groups were not similar at baseline."
Hisle-Gorman 2021[73] To examine the use of mental health services in transgender youth who received gender dysphoria care, including pharma-ceuticals. Score on quality criteria = 8 / 10.	US Pre-post Data extracted from the Military Healthcare Data Repository (MDR).	**GnRHa + GAHT** N=10,357, mean age at 8.5 years: • Transgender and gender diverse adolescents (n=3754), median age 10 [8–13] • Control cisgender siblings (n=6603), median age 9 [4–14].	Number of mental health diagnoses and appointments, psychotropic medication prescriptions.	N/A	Those receiving gender-affirming care, including pharma-ceuticals, continue to need mental health support. There was an increase in psychotropic medication prescriptions in transgender patients.	*"Results strongly support clinical recommendations for screening of mental health conditions in TGD youth and availability of healthcare for those in need."* Study limitations: *"… limited by the use of healthcare data in the form of ICD-9/10 codes which cannot indicate the severity of diagnoses or the full breadth of complex TGD identities" … "the short duration of care following gender-affirming pharmaceutical treatment, which may be insufficient to observe any clinically significant change"*, and *"unable to control for differing, regional, family level, and care provider acceptance".*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Laurenzano 2021[76] To describe the impact of subcutaneous testosterone (SC-T) on menstrual cessation rate and other health outcomes in trans masculine and gender diverse (TM/GD) youth. Score on quality criteria = 8 / 10.	US Pre-post Rady Children's Hospital San Diego (RCHSD).	**GnRHa + GAHT (GAHT focus)** GAHT (testosterone), started at 25–50mg biweekly and increased at provider's prescription. N=119 TM/GD) youth Mean age 16 years (10.1–19.8).	Menstrual cessation.	High successful rate of menstrual cessation at 54% at 140 mg monthly and 97% at 200 mg monthly. Testosterone was found to be an effective and safe choice providing gender-affirming care for (TM/GD) youth.	Reduction in high-density lipoprotein and an increase in hematocrit detected from baseline to follow-up. Other side effects can include mild acne (common), injection site reaction, hypertension, transaminitis, and dyslipidaemia (less common).	*"This study, to date the largest pediatric study of SC-T, adds to the currently limited literature supporting the efficacy and safety of SC-T as an alternative to IM testosterone injections for GAHT in TM/GD youth."* *"The primary limitations of the study are its retrospective nature and single-center cohort. Detailed information on exact timing of blood draws was not always possible to ascertain retrospectively, so separation of the cohort into mid-injection or trough T levels based on treating providers may not have been accurate in all cases."*
Moussaoui 2022[5]	Australia Pre-post	**GnRHa + GAHT (GAHT focus)**	Prevalence rate of pelvic pain.	Not discussed as this study evaluated pelvic	Almost a quarter of patients	*"In conclusion, we report here—in what is to our knowledge the first time—the prevalence rate of*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
To examine the prevalence of pelvic pain in trans adolescents treated with testosterone. Score on quality criteria = 8 / 10.	Royal Children's Hospital Gender Service (RCHGS).	GAHT with testosterone. N=158 trans masculine adolescents (n=121 no pelvic pain, n=37 with pelvic pain) Median age: 16.6 years.		pain prevalence rate.	reported pelvic pain. The risk of having pelvic pain increased >5 times for those treated with additional agents for menstrual suppression (26.3%) compared with those who were not (4.8%, p = 0.028).	*pelvic pain in trans adolescents on gender-affirming testosterone treatment, and observe that a quarter of them described pelvic pain."* *"Limitations of our study include its retrospective nature, which is likely to be associated with under-reporting of pelvic pain, and the limited documentation of the nature and likely causes of this pain within the medical records."*
Allen 2019[55] To evaluate the effectiveness of gender-affirming hormones for enhancing	US Pre-post Children's Mercy Hospital Gender	**GnRHa (8 patients) + GAHT** N=47 adolescents and young adults	Wellbeing, suicidality.	Enhanced wellbeing and reduced level of suicidality.	No information on side effects.	*"To our knowledge, this is the first study to demonstrate that levels of suicidality decrease, and general well-being increases, among adolescents diagnosed with GD after receiving GAH."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
mental health in transgender adolescents. Score on quality criteria = 7 / 9.	Pathway Services (GPS) clinic.	(mean age 16.59, SD 1.19).				*"Confounding variables of this study may include level of familial support, whether a patient is actively receiving psychotherapy, or differences in the specifics of gender-affirming medications (e.g. dosage)."*
Grimstad 2021a[71] To examine the effect of oxandrolone on trans male adolescents. Score on quality criteria = 7 / 9.	US Pre-post A paediatric academic medical centre.	**GnRHa + GAHT** (oxandrolone + testosterone) N=154 (transgender masculine youth) including 34 receiving oxandrolone with M age 14.5 (1.7). + Other groups (n = 120): M age	Height	Greater heights for patients treated with oxandrolone.	Transient elevations in aspartate amino-transferase (AST) or alanine amino-transferase (ALT) detected in 2 participants and erythrocytosis in 3 participants while on testosterone.	*"Our retrospective review of height in TM youth suggests that early therapy with oxandrolone with or without GnRHa is associated with increased adult height … Our findings highlight the importance of early individualization of therapy and the need to include height in transition-related care discussions."* Study limitations: *"The cohort is predominantly White, so*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
		at 120 16.8 (1.6).				*generalizability to those of other races or ethnicities may be limited. In addition, multiple possible selection biases may have influenced our findings. Treating physicians may have been more likely to be proactive with height-preserving therapies if the patient showed evidence of continued growth potential."*
Pham 2023[83] To explore disordered eating in transgender and nonbinary adolescents after receiving gender-affirming care, including pharma-ceuticals.	US Pre-post Seattle Children's Gender Clinic (SCGC).	**GnRHa + GAHT** N=91 transgender and nonbinary adolescents: 61% trans boys, 30% trans girls, and 7% nonbinary / gender-fluid Mean age (SD): 15.2 years (2.1).	Disordered eating thoughts and behaviours.	N/A	There was no significant improvement in disordered eating after receiving GAC.	*"There were no significant changes in disordered eating after initiating gender-affirming medical care, possibly due to the limited study time frame of 12 months. Given the high prevalence of disordered eating behaviors, clinicians should consider screening all TGNB adolescents for disordered eating thoughts / behaviors throughout gender affirming care."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Score on quality criteria = 7 / 9.						*"Main study limitations include that generalizability is difficult given the homogenous sample size of mostly white and gender binary adolescents … Although analyses included age, we did not gather information on participants' pubertal stages; this is likely a confounding variable … Additionally, the shortened version of the EDE-Q we used in this study has not been validated."*
Sequeira 2019[86] Effect of GAHT on body mass index (BMI) in trans masculine adolescents. Score on quality criteria = 7 / 9.	US Pre-post An adolescent medicine clinic at a large urban children's hospital for gender-affirming hormone therapy.	**GAHT only** Testosterone BMI of patients measured at 6 and 12 months. N=46 trans masculine adolescents aged 13–19 years.	(BMI) z-score.	Increased BMI measured at 6 months after GAHT initiation.	No significant change in BMI between baseline and 12 months, which conflicts with prior literature; further research needed to explore the cause.	*"Additional study is needed to understand the full short- and long-term impact of testosterone use on BMI z-score in transmasculine adolescents to provide appropriate informed consent and develop interventions to improve health outcomes."* *"This study is limited by its small sample from a single academic*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						institution and use of retrospective electronic health record data."
Grimstad 2021b[70] To examine the breakthrough bleeding patterns of transgender and gender diverse adolescent and young adults (TGD AYA) on GAHT > 1 year. Score on quality criteria = 6 / 8.	US Pre-post Tertiary-care children's hospital.	**GnRHa + GAHT** (testosterone) > one year N=232 TGD AYAs: Without breakthrough bleeding (BTB), mean age at 16.3 ± 1.8 With BTB: n=58, mean age at 16.3 ± 2.2.	Prevalence of breakthrough bleeding.	N/A	Patients experiencing breakthrough bleeding were receiving GAHT longer (25%), potentially worsening GD experience. They were also more likely to have endometriosis.	*"Breakthrough bleeding is relatively common (25%) on T-GAHT despite early amenorrhea. Most cases do not have an identifiable cause. Our data did not show superiority of any 1 method for managing breakthrough bleeding on T-GAHT."* *"The limitations of this study include its retrospective nature, limited statistical power, and the inability to control which medications were used, as much of the choice of whether to initiate, change, or stop medications was due to patients' goals and provider preferences. In addition, many patients initiated menstrual suppression therapies in advance*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						of T-GAHT and continued them through testosterone initiation."
Nos 2022[81] To evaluate whether GnRHa use increased the likelihood of using GAHT among transgender and gender diverse adolescents. Score on quality criteria = 6 / 8.	US Pre-post US Military Health System (MHS).	**GnRHa + GAHT** GnRHa, GAHT N= 434, mean (SD) of 15.4 (1.6) years at the time of their first TGD-related encounter • n=312 (71.9%) trans girls • n=122 (28.1%) trans boys.	Initiation of GAHT	GnRHa use was not found to be associated with increased subsequent GAH use.	N/A	*"In this cohort study of TGD adolescents, GnRHa use was not associated with increased subsequent GAH use. These findings suggest that clinicians can offer the benefits of GnRHa treatment without concern for increasing rates of future GAH use."* Study limitations: *"It is a retrospective cohort analysis of administrative data from patients enrolled in the US military health plan program, TRICARE. The children of active duty or retired service members identified in our study are different from the general population in several ways (e.g. higher socioeconomic standing, higher parental*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						education, better healthcare coverage, higher geographic mobility)… We also did not capture information on individual patient, parent, and clinician factors that may influence decisions about starting or stopping gender-affirming medical treatments, or to seek out these treatments at all."
Olsavsky 2023[82] To examine the interaction between GAHT and social support and its effect on psychological wellbeing.	US Pre-post A gender-affirming multidisciplinary clinic.	**GnRHa + GAHT** GAHT, transgender and nonbinary (TNB) adolescents. N=75 TNBs Mean age: 16.39 years.	Anxiety and depressive symptoms, non-suicidal self-injury (NSSI) and suicidality in the past year, and social support.	GAHT associated with better mental health outcomes (i.e. anxiety and depression).	Information on side effects not reported.	*"TNB adolescents had better mental health outcomes in the context of receiving gender-affirming hormonal interventions and having greater support from family and friends. Findings highlight the important role of quality family and friend support for TNB mental health."* Study limitations: *"… all adolescents in this study were receiving care through a gender-*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Score on quality criteria = 5 / 7.						*affirming multidisciplinary clinic where they had access to counselors and therapists, and therefore, likely represent a more supported population than a community sample … Finally, this study was cross-sectional, which means we could not investigate causality, and our sample was primarily White with a greater proportion of transmasculine participants."*
de Nie 2022[66] To assess the impact of puberty suppression treatment on exocrine testicular function by determining the most advanced	Netherlands Pre-post Center of Expertise on Gender Dysphoria of Amsterdam UMC between 2006 and 2019.	**GnRHa + GAHT (GAHT focus)** GAHT, gGAS N = 214 transgender women (6 subgroups at Tanner stage 2–3, Tanner stage 4–5, adult).	Fertility preservation possibility: preservation of spermatozoa, preservation of spermatogonial stem cells or absence of germ cells.	The options for fertility preservation appear independent of whether GAHT is ceased before surgery and the duration of GAHT prior to gender-affirming	Commencing GAHT in early pubertal adolescence (Tanner stage 2–3) restricts the ability to collect mature spermatozoa suitable for direct use in	*"The results of this study show that there may still be options for fertility preservation using orchiectomy specimens obtained during gGAS. … In addition, the vast majority (>85%) of transgender women in our cohort could still opt for cryopreservation of testicular tissue harboring spermatogonial stem cells. A complete absence of germ cells*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
germ cell type orchiectomy specimens obtained during genital gender-affirming surgery (gGAS). Score on quality criteria = 7 / 10.				genital surgery (gGAS).	assisted reproductive techniques.	*was only observed in a small number (7%) of transgender women in our cohort, who all commenced GAHT as adults."* *"A limitation of this study is the lack of data on serum hormone levels on the day of gGAS. We were therefore unable to verify if the transgender women who were asked to temporarily stop hormonal treatment four weeks prior to surgery actually did so, and if people with complete spermatogenesis were compliant to treatment … We were therefore unable to assess if different estrogen formulations have different effects on testicular histology and spermatogenesis."*
Cantu 2020[63]	US Pre-post	**GnRHa + GAHT** N=80	Not stated	No changes in depression, anxiety or	No improvement in acute distress	*"Neither distance from medical center nor initiation of hormone therapy was associated with*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
To examine changes in anxiety, depression and suicidality from initial appointment to first follow-up. Score on quality criteria = 6 / 9.	An academic medical centre.	Young adults, mean age 15.1 (1.8) Trans female (n=15), trans males (n=58), nonbinary (n=7).		suicidality were identified within the average 4-month time frame from initial visit to first follow-up.	level at 4-month follow-up. Hormone initiation not related to the mental health outcome.	*symptom changes. While research shows decreased distress with initiation of hormones, study findings suggest changes may actually take longer to occur."* Study limitations: *"Data collected were limited to one clinic, with a relatively small sample size and only two time points examined. Power analyses revealed that the current sample would have been well powered to detect large effects, but not small-to-moderate effects, which are more likely when looking at shorter time frames. Due to sample size, we could not examine how age, affirmed gender, or initiation of hormone blockers were associated with changes in symptoms of distress. Sample size also limits the ability to*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						examine differences among those with genderqueer and nonbinary identities."
Millington 2019[77] To investigate the likelihood of having hyperkalaemia when taking spironolactone for gender transition. Score on quality criteria = 6 / 9.	US Pre-post A specialty gender clinic at a tertiary care paediatric hospital.	**GnRHa + GAHT (GnRHa focus)** spironolactone N=85 adolescents 16.6 ±1.7 years.	Incidence of hyperkalaemia.	Low rate of hyperkalaemia, detected in 5 participants (2.2%).	One subject discontinued spironolactone after an elevated potassium measurement.	*"Hyperkalaemia in patients taking spironolactone for gender transition is rare and when present is transient and asymptomatic. In the absence of other medical comorbidities, routine electrolyte monitoring in this population may be unnecessary."* *"The generalizability of this study is limited by the relatively small sample size and the use of only one study site. Its retrospective nature introduces potential selection bias; for example, clinicians may have avoided spironolactone use in patients*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						with premorbid conditions or prior hyperkalemia."
Chen 2023[65] To examine the effect of GAHT on psychological functioning in transgender youths at two-year follow-up. Score on quality criteria = 7 / 11.	US Pre-post Ann and Robert H. Lurie Children's Hospital.	**GnRHa + GAHT (GAHT focus)** N=315 transgender and nonbinary participants: 190 participants (60.3%) trans males Mean [±SD] age at 16±1.9 years.	Psychological outcomes (anxiety, depression, gender congruence, life satisfaction).	Improved mental outcomes, including enhanced gender congruence, positive affect, and life satisfaction, and reduced anxiety and depression.	Adverse events: 11 participants (3.5%) had suicidal ideation, 2 severe anxiety when visiting clinics, and 2 deaths by suicide. Elevated anxiety and depression and low life satisfaction persisted in some patients.	*"In this 2-year study involving transgender and nonbinary youth, GAH improved appearance congruence and psychosocial functioning."* *"Because participants were recruited from four urban pediatric gender centers, the findings may not be generalizable to youth without access to comprehensive interdisciplinary services or to transgender and nonbinary youth who are self-medicating with GAH … Finally, our study lacked a comparison group, which limits our ability to establish causality."*
Kaltiala 2020[75]	Finland Pre-post	**GAHT 1+ years**	Adolescent development,	Proportion requiring	No change pre-post in	*"Medical gender reassignment is not enough to improve functioning*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Assess how adolescent development progresses and psychiatric symptoms develop among transsexual adolescents after starting cross-sex hormone treatment. Score on quality criteria = 5 / 8.	Two gender identity service facilities for minors in Finland.	Transsexual adolescents presenting for treatment prior to age 18. N=52.	psychiatric symptoms.	specialist level psychiatric treatment *"during the so-called real-life phase of living in the desired role"* was similar. Treatment needs due to depression, anxiety and suicidality / self-harm had diminished.	proportion progressing age-appropriately in school / work; dealing with matters outside of home; being involved in dating / steady relationships. Proportion of those functioning age-appropriately in peer relationships decreased.	*and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development."* Study limitations: *"Collected from medical files, the data is as accurate as clinical documentation can be …The follow-up period was approximately only a year, which inhibits drawing conclusions on long-term outcomes."*
Moussaoui 2023[6] To investigate the	Australia Pre-post	**GnRHA and GAHT** Oral contraceptive	Effectiveness of menstrual suppression, satisfaction,	High rate of effectiveness (93.8% of	No apparent adverse effect reported.	*"Effectiveness of and satisfaction with menstrual suppression were high in TGD adolescents receiving this treatment ...*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
effectiveness of menstrual suppression in transgender and gender diverse (TGS) adolescents. Score on quality criteria = 5 / 8.	A paediatric tertiary referral clinic for TGD children and adolescents younger than 18 years.	pill, norethindrone, intramuscular medroxy-progesterone. N=530 (GD patients assigned female at birth) M age: 15.2±1.3 years.	distress related to menstrual bleeding.	participants) and satisfaction. No difference in risks of GD, depression and anxiety between those receiving menstrual suppression or not.		*However, menstrual suppression was not associated with any difference in gender dysphoria, depression, or anxiety symptoms in this cross-sectional study, and longitudinal studies are required to better investigate this."* Study limitations: *"Firstly, information on menstrual suppression was retrospectively retrieved … and was limited by missing data. Secondly, the findings of this study may not be generalizable to all TGD adolescents, because participation was restricted to adolescents presenting to a specialized gender service in a tertiary pediatric hospital … Thirdly, the cross-sectional design does not provide information on longitudinal follow-up and does*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						not allow any conclusions about potential causality."
Arnoldussen 2022[56] To examine the potential effect of gender-affirming care treatment (GAHT) on cognitive development and educational achievement. Score on quality criteria = 6/10.	Netherlands Case series pre-post Center of Expertise on Gender Dysphoria (CEGD) of Amsterdam University Medical Center.	**GnRHa + GAHT (GAHT focus)** Puberty suppression, GAHT, affirming surgeries. N=72 adolescents; trans boys = 45 trans girls = 27 Mean age: 12.78 years.	IQ, educational achievement.	IQ scores and educational achievements pre and post GAC were not significantly different. Cognitive development of adolescents receiving GAC is similar to the general population.	Not reported in this study.	*"… gender-affirming medical treatment including puberty suppression does not negatively affect the association between IQ and educational achievement."* *"Limitations in this study were the lack of a control group, the small sample size (N=72) and the heterogeneous study population (e.g. age, treatment duration). In addition, since the demographic characteristics of our sample and the methods used to examine IQ and educational achievement were not similar to the studies that have examined this association in the general population, the comparison of the results of these*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						studies should be interpreted with caution."
Strang 2022[87] To investigate whether executive function (EF) is overrepresented in transgender youth and those under GD medical treatment. Score on quality criteria = 6 / 10.	US Pre-post A multi-component study of cognitive, mental health, and neurological development.	**GnRHa + GAHT (GAHT focus)** N = 124 transgender youth Mean age (SD): 16.67 (2.03), aged 11–21 years: • Female (n=41) • Male (n=81) • Nonbinary (n=2).	Global executive functioning (EF).	Patients undergoing GAHT reported better EF.	Poorer EF detected in patients on long-term puberty suppression treatment.	*"Regarding gender-affirming medical interventions, gender-affirming hormonal intervention status was associated with EF, where youth receiving GAH had fewer parent-reported EF problems when accounting for age, gender, assigned sex, mental health and ASD diagnostic status."* *"Although our sample was intentionally recruited from both clinical and community sources, it was not representative in terms of race or ethnicity. Further, we did not assess socioeconomics, which is itself a predictor of EF.. The study includes treatment durations, but the cross-sectional assessments preclude*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						interpretations of causal influences on EF."
***Turban 2022[90]** To examine the relationship between access to gender-affirming care and mental health outcomes. Score on quality criteria = 5 / 9.	US Case series: cross-sectional online survey Community organisations.	**GnRHa + GAHT (GAHT focus)** N=21,598 transgender adults, who had access to GAC: • During early adolescence (n=119, 0.6%), aged 13–15 years • During late adolescence (n=1.7%), aged 16–17 years • In adulthood (n=12,257, 56.8%)	Psychological distress, binge drinking, illicit drug use, suicidal ideation.	Access to GAC associated with improved mental health outcomes (i.e. lower odds of past-year suicidal ideation).	The study mentioned (but did not evaluate as an outcome) the potential delayed bone development due to long-term use of pubertal suppression.	*"Access to GAH during adolescence and adulthood is associated with favorable mental health outcomes compared to desiring but not accessing GAH."* *"Limitations include its non-probability cross-sectional design, which reduces generalizability and limits determination of causality."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
		• Never had access (8860, 41.0%).				
Mullins 2021[78] To assess the risk of thrombosis among trans adolescents. Score on quality criteria = 4 / 8.	US Pre-post Cincinnati Children's Hospital Medical Center (CCHMC) Transgender Health Clinic.	**GnRHa + GAHT (GAHT focus)** GAHT (oestrogen, testosterone) N=611 Trans adolescents Median age 17 years (15–19).	Thrombosis risk.	No arterial or venous thrombosis associated with GAHT detected in the study cohort.	More studies needed to explore thrombosis risk when exposed longer to GAHT.	*"GAHT in youth, titrated within physiologic range, does not carry a significant risk of thrombosis in the short term, even with the presence of preexisting thrombosis risk factors."* *"Our study has several limitations. First, the study was conducted at a single institution; however, the study included all youth who were started on GAHT since the inception of the Transgender Health Clinic. Second, as a retrospective study, the data were limited to that available through extraction of existing records in the electronic medical record (EMR). On the basis of the EMR, it was sometimes not possible to*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
						determine if a subject had discontinued GAHT or was lost to follow-up."
Tordoff 2022[89] To examine impact of gender-affirming care on mental health of transgender and nonbinary youths. Score on quality criteria = 5 / 10.	US Pre-post Seattle Children's Gender Clinic.	**GnRHa + GAHT** N=104 transgender and nonbinary (TNB) youths Mean [SD] age at 15.8 [1.6] years: n=63 trans males, n=27 trans females, n=10 nonbinary / gender fluid, n=4 opted for 'I don't know'.	Mental health outcomes: depression, anxiety and suicidal ideation.	Improved depressive symptoms and reduced suicidal ideation over 12 months.	No association between GAC and anxiety. No data on long-term outcomes.	*"This study found that gender-affirming medical interventions were associated with lower odds of depression and suicidality over 12 months."* Study limitations: *"This was a clinical sample of TNB youths, and there was likely selection bias toward youths with supportive caregivers who had resources to access a gender-affirming care clinic … Our sample also primarily included White and trans masculine youths, limiting the generalizability of our findings."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Alaniz 2023[54] To examine the time to cessation of menses in adolescent and young adult transgender males. Score on quality criteria = 3 / 7.	US Pre-post Tertiary children's hospital.	**GnRHa + GAHT** Testosterone, norethindrone acetate, depot medroxy-progesterone acetate, progestin). N=220 (n=211 trans males, n=6 gender fluid / nonbinary, n=2 'something else', n=1 'male' Median age 15.8 years.	Time needed to reach menstrual cessation under the treatment conditions.	Shortest time to cessation of menses observed in group treated with testosterone and norethindrone acetate (NETA).	Less than 50% patients were able to achieve amenorrhea within a 6-month period.	*"Patients used a variety of different hormonal regimens for menstrual suppression. Less than half achieved cessation of menses within 6 months. NETA and depot leuprolide users reported the most rapid cessation of menses."* *"The study is limited by a relatively small sample size of predominantly white patients and is further limited by the retrospective study design, which might have overestimated time to menstrual cessation."*

*This article was subject to an Erratum—"Concerns were raised, post-publication, regarding common publications of the handling Academic Editor and some of the authors. A second and independent member of the *PLOS ONE* Editorial Board has reevaluated the manuscript and reviews, and has confirmed that the article is scientifically sound and meets *PLOS ONE*'s Publication Criteria. They also confirmed that there are no concerns with the original reviews. The authors discovered an error in the original manuscript. Specifically, throughout the article, the "early adolescence" group was mislabelled and inadvertently included all participants who accessed GAH prior to age 16, including some respondents who accessed GAH at ages younger than that recommended in the most recent Endocrine Society

Guidelines. Analyses for this “early adolescence” group have been updated to include only those who accessed GAH during the younger adolescent age group outlined by the most recent Endocrine Society guidelines (i.e. ages 13–15) [2]. The following specific errors have been corrected:

- The early adolescence group age (14–16) appears incorrectly throughout the article. The correct group age is (13–15). The Endocrine Society Guidelines note an age of 13.5, and the authors chose age 13 as a lower cutoff to include individuals who would have accessed GAH at this age.
- The number and percentage of the early adolescent group reporting access to GAH appears incorrectly through the article. The correct values are 99 (0.5%).
- The sample of individuals ever desiring GAH appears incorrectly throughout the article as 21,598. The correct value is 21,578, now that those reporting access to GAH younger than age 13 have been excluded.

The following sentence has been added to the first paragraph of the Methods section: We additionally excluded any participants who reported accessing GAH prior to age 13, as this would represent an age lower than the current threshold mentioned in the most recent Endocrine Society Guidelines.

Gender-affirming chest surgery ('top surgery')

Context

Gender-affirming surgery is undertaken to affirm preferred gender identity by altering physical characteristics. In the case of transgender men this can involve breast reduction (mammoplasty) or other types of chest reconstruction such as alterations to the chest wall, and genital surgery to create a penis (metoidioplasty) and scrotum, and removal of the vagina, uterus and ovaries. Transgender women may undergo breast augmentation and genital surgery to create a vagina, clitoris and labia. Additionally, both transgender men and women may have facial masculinisation or feminisation surgery as well as surgery to alter their vocal cords and related organs.[3]

Given the focus of this Evidence Check update on children and young people, genital surgery was considered out of scope. **Therefore, only studies pertaining to chest and other 'top' surgery were eligible for inclusion in this update.** Studies pertaining to chest surgery are summarised in Tables 8a–8c and outlined in Tables 9a–9c. Tables 9a–9c also contain some additional information about facial surgery, Adam's apple surgery and vocal cord surgery from the included systematic review.

This Evidence Check update identified eight studies focusing on gender-affirming surgery, comprising one systematic review (Level I); three comparative studies with concurrent control (Level III-2); and two case series / cross-sectional studies (Level IV).

The additional information about the benefits of chest surgery provided by this Evidence Check is summarised below (Table 8). It covers psychosocial outcomes, sexual function, quality of life and gender incongruence.

Table 8a—Benefits of gender-affirming chest surgery (top surgery)

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
Few studies have examined gender-affirming surgery in children and adolescents, and clinical guidelines rely heavily on expert opinion. We identified only three studies, all focusing on chest surgery in trans boys. The paucity of studies is to be expected given the age restrictions on gender-affirming surgery and the inclusion criteria of this Evidence Check for studies of young people, where treatment was undertaken under the age of 18 years. The evidence for the effectiveness of this chest surgery is very weak (NHMRC Level IV) and should be considered preliminary.	**Psychosocial outcomes** One Level I study[3] reported positive findings for psychosocial wellbeing in transgender women and no difference pre- and post-surgery in transgender men. One Level IV study of 75 adolescents[58] included 10 who received surgery. The surgery group reported emotional and behavioural problems similar to the population-based German norm mean. One Level IV cross-sectional study of 288 transgender adults[95] reported positive outcomes of gender-affirming care, including surgery, on

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	suicidal ideation, anxiety, depression and stress symptoms. However, as the mean age in this survey-based study was 32.8 years (SD 13), it has limited relevance to adolescent population. **Sexual function** One Level I study[3] reported positive findings for sexual wellbeing in transgender women and no difference pre- and post-surgery in transgender men. One Level III-2 study[38] of 113 transgender people aged 18–25 receiving a combination of PS, GAHT and various surgical procedures (vaginoplasty = 38; breast augmentation = 9; mastectomy = 63; metoidioplasty = 6) reported a significant increase in sexual activity one year post-surgery (noting transgender people were also less experienced in all types of sexual activities compared with the general population). **Quality of life** One Level IV study of 75 adolescents[58] included 10 who received surgery. The surgery group reported physical quality of life scores similar to the German norm mean.
Keeping in mind the preliminary nature of the evidence, existing studies suggest trans boys have a high level of satisfaction with chest surgery and that chest surgery is associated with a reduction in gender dysphoria.	**Gender incongruence** One Level III-2 study[36] of gender-affirming mastectomy in 36 adolescents and young people compared with 34 controls reported that top surgery was associated with improved chest dysphoria, gender congruence and body image satisfaction. However, 11 patients were lost to follow-up.
It has been suggested that clinical protocols for gender-affirming treatments need adjustment to meet the specific needs of nonbinary adolescents (NHMRC ungraded: qualitative).	No evidence pertaining to this finding was identified in this update.

The additional information on the risks of gender-affirming chest surgery provided by this Evidence Check is summarised below. It covers satisfaction and safety.

Table 8b—Risks of gender-affirming chest surgery (top surgery)

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
Top surgery (mastectomy for trans boys and breast contouring for trans girls) is considered to be irreversible (4 references—NHMRC ungraded: position statement, standard of care and guidelines).	No evidence pertaining to this finding was identified in this update; however, the irreversibility of surgery is generally self-evident.
While the majority of young people who had top surgery experienced high levels of satisfaction, varying degrees of satisfaction with the outcome have been reported (2 references—NHMRC level of evidence IV).	**Satisfaction / regret** One Level I study[3] reported long-term satisfaction with chest surgery in both transgender men and women. Regret / dissatisfaction was reported as rare, with two cases of regret out of 182 transgender men in one study and dissatisfaction in transgender women rare (usually relating to breasts perceived as being too small).
	Safety One Level III-2 study[38] of 113 transgender people aged 18–25 receiving a combination of PS, GAHT and various surgical procedures reported no adverse events. One Level III-2 study[36] of gender-affirming mastectomy in 36 adolescents reported low complication rates (1 haematoma, 2 seromas, 1 instance of nipple loss). However, 11 patients were lost to follow-up.

Table 8c—Variation in the benefits and risks of gender-affirming chest surgery (top surgery)

This Evidence Check found several Level IV studies reporting on variation in the benefits and risks of gender-affirming chest surgery, these are reported in the table below.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
Top surgery is not generally performed before 18 years of age because of the irreversibility of these procedures (5 references—NHMRC level of evidence ungraded: clinical practice guidelines, standards of care and position statements).	The Level IV study of Tang (2022)[88] recruited 209 adolescents undergoing gender-affirming mastectomy. The median age at referral was 16 (range 12–17). This study reported that two patients expressed regret; prevalence of any complication was 7.3% and revision rate was 10.9% for those with at least a one-year follow-up. This study also observed a 13-fold increase in this surgery over a seven-year period (2013–2020). One Level III-2 study[34] of 10 patients undergoing reinnervation of the nipple-areolar complex recruited patients with a mean age of 17.5 (range 16–19). This study reported significant improvement in sensation compared with a control group (mean age 36.6, range 18–59). One Level IV study[61] of chest reconstruction enrolled 153 patients including 59 adolescents with a mean age of 16.7 (SD 0.8) at initial assessment. This study reported improved gender and appearance congruence and decreased chest dysphoria in both nonbinary and binary patients for both the total sample and the adolescent subgroup. The remaining studies did not report exclusively on patients aged under 18. The Level III-2 study of Bungener (2020)[38] recruited 113 participants with a mean age of 20.8 and a mean time since surgery of 1.6 years; Ascha's Level III-2 study of mastectomy (2022)[36] had participants with a mean age of 18.6 (SD 2.7); Becker-Hebly's study[58] containing 75 adolescents had only 11 who had received surgery, with a mean age of 16 at baseline and 19 at follow-up. No conclusions specific to this group were made. The mean age in Hughto's study (2020)[95] was 32.8.

Strengths and limitations of the evidence—gender-affirming chest surgery (top surgery)

The Level I review[3] identified limitations in the evidence consistent with research into puberty suppression treatment and GAHT—retrospective study designs, small sample sizes, lack of diversity in participants and limitations in validity of quality of life measures. These limitations—especially small

sample sizes and retrospective designs—were acknowledged in the primary studies, with further limitations of single-centre recruitment, loss to follow-up and potentially inadequate length of follow-up also described.

It is also important to note that the *volume* of evidence pertaining to chest surgery is relatively low; most studies (49 / 79) in the Level I review pertained to genital surgery, which was out of scope of this Evidence Check update.

Conclusions of Evidence Check update—gender-affirming chest surgery (top surgery)

This update identified eight studies evaluating surgery including one review, thus expanding the evidence base from the previous Evidence Check. With regards to **benefits / effectiveness,** the updated evidence reports generally positive findings for gender dysphoria, psychosocial outcomes and sexual function and quality of life. However, neutral findings on psychosocial outcomes in transgender men were reported as well as mixed positive / negative findings on quality of life. The irreversible nature of surgery remains a key **risk / potential harm**; however, regret rates were low where reported. Complication rates for chest surgery were also reported to be low. In contrast with the previous Evidence Check, several studies reported on outcomes in adolescents referred for chest surgery at 16–17 years of age. Findings were generally positive across these studies on sexual function, gender incongruence and chest dysphoria, with relatively few reported rates of regret or complications. Although the evidence base is expanded and generally supportive of top surgery, confidence in findings is low because of a lack of studies and / or poor study quality, use of mixed surgery populations and the confounding effect of hormone and other therapies, which almost always preceded surgery. Offsetting these limitations are three high-quality comparative studies with positive findings specific to adolescents. In summary, this update provides some additional evidence supporting top surgery; however, further studies focusing on the specific effect of surgery in adolescents are required.

Table 9 summarises the main features of each of the reports on gender-affirming surgery included in this Evidence Check.

Included studies in this Evidence Check update—gender-affirming surgery

Table 9a—NHMRC Level I. Systematic reviews—gender-affirming surgery (n = 1)

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
Javier 2022[3] To conduct a systematic literature review into the longer-term (i.e. ⩾ 1 year) surgical satisfaction and quality of outcomes following various forms of gender-affirming surgery in transgender populations. Score on quality criteria = 8.5 / 13.	79 studies, most retrospective: 9 studies on chest surgery; 49 studies on genital surgery; 6 facial surgery; 8 vocal cord surgery.	Chest, genital, facial, vocal cord, and Adam's apple removal surgeries. No age restrictions. Note: genital surgery information not extracted.	Chest surgery, transgender men (4 studies)—positive for satisfaction, no difference pre-post for psychosocial function. Chest surgery in transgender women (5)—positive for satisfaction and psychosocial function. Facial feminisation surgery (6)—positive for	Chest surgery in transgender men: 2 cases of regret out of 182 patients across two studies. Chest surgery in transgender women: dissatisfaction was rare and generally was that breasts were too small.	*"Overall, the findings in this literature review suggest both transgender men and women who undergo gender-affirming surgery report being satisfied with their surgery in the longer term, with very few reporting regret."* Limitations of included studies: *"… most of the studies examined in this review were retrospective (i.e. involving participants reflecting upon outcomes of their surgeries; see Appendix for more detail) …* *… employed very small sample sizes, with findings for several quality of life outcome constructs being classified as having low strength of evidence due to its studies sampling fewer than 100 participants in total …*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage of puberty	Benefits	Risks	Key conclusions and limitations reported by study authors
			satisfaction and health-related QoL, reduced gender incongruence. Vocal cord surgery in transgender women (8 studies)—satisfaction with surgery but mixed findings on quality of life.		*… employed non-validated self-report measures when measuring transgender men and women's quality of life …* *… findings generally come from countries that are Westernized, and generally accepting of transgender people."*

Table 9b—NHMRC Level III-2. Comparative studies with concurrent control—gender-affirming surgery (n = 3)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Bungener 2020[38] To describe the sexual and romantic development during and after receiving GAC. Score on quality criteria = 8 / 9.	Netherlands Retrospective study Centre of Expertise on Gender Dysphoria at the Amsterdam University Centres.	**PS, GAHT and GAS** N=113 transgender adolescents • 38 trans women • 75 trans men. Mean age 20.79 years, SD 1.36).	Sexual experiences.	One-year post surgery, young transgender adults reported a significant increase in experiences with all types of sexual activities.	No apparent adverse events or effect reported.	*"This study on the sexual and romantic experiences of young transgender adults during and after early GAT reveals an increase in sexual activity after gender-affirmative surgeries."* Study limitations: *"… the data on sexuality during GAT (before surgery) were collected retrospectively."*
Rochlin 2020[34] To explore the effect of a new technique to reinnervate the nipple–areolar complex (NAC)	US Prospective study Setting not stated.	Gender-affirming top surgery: • Treatment / surgery group undergoing	NAC sensory restoration.	Significant improvement in the NAC sensation areas, including nipple, areola	Adverse events or effect not stated.	*"This proof of concept study suggests that immediate reinnervation of the NAC after mastectomy enhances recovery of NAC sensation in patients undergoing female-to-male mastectomy."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
after mastectomy. Score on quality criteria = 8 / 9.		NAC reinnervation (n=10); Mean age at 17.5 years (range: 16–19 years) • Control group (n=10): Mean age at 36.6 years (range: 18–59 years).		and peripheral breast skin, for treated patients.		*"The limitations of our study include the small study size … In addition, the placebo effect is a potential bias, as knowledge of neurotization may have impacted the treated group's perception of sensation."*
Ascha 2022[36] To determine whether top surgery enhances chest dysphoria, gender congruence,	US A nonrandomised prospective cohort study 3 institutions in a large	Gender-affirming top surgery (mastectomy). 81 transgender and nonbinary (TGNB) adolescents and young	Chest dysphoria, gender congruence, and body image satisfaction.	GAC top surgery is related to enhanced chest dysphoria, gender congruence, and body	1 haematoma (3%), 2 seromas (6%), and 1 instance of nipple loss (3%).	*"Top surgery is associated with low complication rates. Top surgery is associated with improved chest dysphoria, gender congruence, and body image satisfaction in this age group."* Study limitations: *"Analyses omit 11 patients whose outcomes were not measured due to attrition … patients in*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
and body image. Score on quality criteria = 7 / 9.	metropolitan location.	adults (AYA) designated female at birth (DFAB). Mean [SD] age, 18.6 [2.7] years. Surgical patients n=36; Control: n=34; 11 lost to follow-up.		image satisfaction.		*the treatment group who were able to access surgery may have greater socioeconomic status and parental support, possibly introducing sampling bias … We were unable to achieve a high degree of balance on baseline measures between surgery and control groups, even after propensity score adjustments."*

Table 9c—NHMRC Level IV. Case series / cross-sectional—gender-affirming surgery (n = 4)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Hughto 2020[95] To investigate prevalence of self-reported suicidal ideation, suicide attempts, and nonsuicidal self-injury (NSSI) before and after initiating the gender affirmation process. Score on quality criteria = 8 / 9.	US Cross-sectional Survey data from the Transgender Stress and Health Study.	**GAHT + GAS** N=288 transgender adults (234 trans males and 54 trans females) Mean (SD) age 32.8 (13) years.	Depressive, anxiety and stress symptoms.	Social and medical GAC associated with lower risk of suicidal ideation and improved mental health outcomes (including improved anxiety, depression and stress symptoms).	Not stated.	*"Overall, in the present study, we provide evidence in support of the significant association between social and medical gender affirmation experiences and the mental health of U.S. transgender adults …[O]ur findings add to the collective body of evidence suggesting that multiple sources of gender affirmation may help to curb self-harm and poor mental health symptoms in transgender people."* Study limitations: *"Given our study's cross-sectional design, it is not possible to make causal inferences. Given that our measures were self-reported, it is possible that biases in recollection or reporting influenced the results."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Boskey 2023[61] To examine the effect of chest reconstruction surgery (CRS) on gender congruence and chest dysphoria. Score on quality criteria = 6 / 9.	US Pre-post Centre for Gender Surgery at Boston Children's Hospital.	Chest reconstruction surgery. N=153, trans masculine and nonbinary adolescents and young adults: • Subgroup of adolescents (n=59, mean age 16.7 (0.8).	Chest dysphoria and gender congruence.	Significant differences in gender congruence, appearance congruence, and chest dysphoria between at least two assessment points for the total sample and each subgroup (binary / nonbinary and adult / minor).	Medical, social and behavioural assessment undertaken to reduce potential regret given changes are irreversible.	*"The results of our longitudinal cohort study of TMNB adolescents and young adults demonstrate that, in the context of a gender center where a multidisciplinary team is available to provide wrap around assessment and support, gender-affirming chest reconstruction is an effective way to improve gender and appearance congruence and reduce chest dysphoria in both nonbinary and binary populations across this age range."* *"Limitations include the fact that all individuals accessed gender-affirming surgery at a single center, by a single surgeon, the lack of racial diversity, the relatively low number of nonbinary individuals in our analytical sample, and the fact that it was not possible to have a control group as well as it would be unethical to withhold medically necessary care."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Becker-Hebly 2021[58] To describe mental health needs of adolescents diagnosed with GD prior to treatment. Score on quality criteria = 5 / 10.	Germany Pre-post University Medical Center Hamburg-Eppendorf.	**Psychosocial only (n=21); GnRHa (11) + GAHT (32) + GAS (11)** n=75 adolescents and young adults with GD. • PS: 8 trans males (72.7%), 3 trans females • PS+GAHT: 28 trans males, 4 trans females Surgery: 10 trans males, 1 trans female.	Emotional and behavioural problems, quality of life.	Adolescents in the gender-affirming hormone (GAH) and surgery (GAS) group reported emotional and behavioural problems and physical quality of life scores similar to the German norm mean. Improved mental health outcomes, cognitive functioning and quality of life observed in GAC group.	No evaluation of physical side effects due to the ethical research protocol.	*"Adolescents who underwent puberty suppression or GA (hormonal and surgical) interventions showed better scores in some of the psychosocial health dimensions, although we did not test whether this difference was statistically significant."* Study limitations: *"Due to the descriptive nature of the present analyses, the findings cannot be generalized to other samples. Because of the small sample size caused by the high drop-out rates during data collection, this study does not provide sufficient power for hypothesis testing … This study did not focus on the physical side effects of interventions because the ethical research protocol did not allow direct comparison with medical charts from the endocrinological department."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Tang 2022[88] To evaluate the prevalence of gender-affirming mastectomy and surgical results. Score on quality criteria = 4 / 9.	US Pre-post Integrated healthcare system (Kaiser Permanente Northern California).	Mastectomy N=209 adolescents Median age 16 years (range 12–17).	Incidence of gender-affirming mastectomy, prevalence of entailed complications.	Generally low prevalence of surgical complications.	10 patients (7.3%) had at least one surgical complication: haematoma (3.6%), infection (2.9%), hypertrophic scars requiring steroid injection (2.9%), seroma (0.7%), and suture granuloma (0.7%); 15 patients (10.9 %) underwent revision.	*"Between 2013–2020, we observed a marked increase in gender-affirming mastectomies in adolescents. The prevalence of surgical complications was low and of over 200 adolescents who underwent surgery, only two expressed regret, neither of which underwent a reversal operation."* Study limitations: *"First, its retrospective design meant we were unable to measure patient satisfaction and quality-of-life outcomes … Next, our study was conducted at KPNC in an insured cohort of individuals with access to gender-affirming medical and surgical care. Therefore, our outcomes may not be representative of the general population, many of whom lack similar access to care. Finally, the time to develop postoperative regret and/or dissatisfaction remains unknown and*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
					Two expressed regret.	*may be difficult to discern given that regret is quite rare."*

Fertility preservation

Context

Puberty suppression treatment and GAHT have a range of impacts on fertility. In transgender women, puberty suppression and GAHT can inhibit or prevent spermatogenesis. When puberty suppression and GAHT are ceased, spermatogenesis may return but the time course is uncertain. For transgender males, testosterone can inhibit the maturation of oocytes and follicle-stimulating hormone. They are not completely inhibited, however, and therefore ovulations and pregnancies can still occur in the setting of testosterone treatment. The effect of puberty suppression has also been shown to be reversible based on data from testosterone treatment given to people experiencing precocious puberty.[29] However, gender-affirming genital surgery to remove the testicles (orchiectomy / orchidectomy) or ovaries (oophorectomy) causes permanent fertility loss.[30]

For these reasons, transgender people who want children can require access to assisted reproductive technology. To facilitate this, consideration needs to be given to fertility preservation options prior to beginning pharmaceutical and / or surgical gender-affirming care, so that transgender people can access assisted reproduction later in life.[29,30] Preservation generally involves harvesting and cryopreservation (freezing) of semen (for transgender women) or oocytes (for transgender men).[29] Less frequently, testicular sperm extraction (TESE, also referred to as testicular sperm aspiration, TESA) may be used. This involves a small surgical procedure to harvest viable sperm from testicular tissue, and is used for transgender females unable to ejaculate for biological reasons or because of gender dysphoria.[29,30]

This Evidence Check update identified six studies focusing on fertility preservation, comprising two systematic reviews (Level I); one comparative study without concurrent control (Level III-2); and three case series / cross-sectional studies (Level IV).

The additional information on the benefits of fertility preservation provided by this update is summarised below (Table 10). It covers the effectiveness of semen and oocyte cryopreservation, pregnancy in transgender males, and the effectiveness of TESE.

Table 10a—Benefits of fertility preservation

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
Compromised fertility is a likely consequence of GAHT and fertility discussion is recommended with transgender adolescents before commencing GAHT. Expert statements warn testosterone therapy for trans boys may lead to sterility (two references) although it does not necessarily protect against unwanted pregnancy (one	**Effectiveness of semen cryopreservation** One Level I study[30] reported that semen cryopreservation was simple and reliable, with lower semen parameters offset by multiple sample collection. Two Level I studies[29,30] reported that banked sperm is of a lower quality compared with cis male samples. Stolk (2023)[29] reported

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
reference). Ovarian reserve and fertility preservation should be discussed with trans boys starting GAHT (one reference). Fertility may be compromised if GnRHa is started early and followed by GAHT. The only feasible option for fertility preservation among prepubertal trans girls is testicular tissue cryopreservation, or harvesting of oocytes for trans boys, both of which are still experimental and invasive. Clinical guidelines are unanimous in recommending that fertility preservation counselling is conducted with the young person and their family before initiating puberty suppression.	lowered sperm quality even prior to gender-affirming hormone treatment, with uncertain recovery of spermatogenesis after discontinuing treatment. One Level IV study[62] of 35 trans girls, included in both Level I reviews and identified in this Evidence Check update, reported that one third of patients were unable to produce a semen sample due to early stage of puberty and an additional 17% were uncomfortable with masturbation. A Level IV study by Dilday (2022)[67] compared semen quality in trans girls with adolescents with cancer (n = 45, mean age 15.8) finding semen parameters within the normal range for healthy adults. None were undergoing PS or GAHT. **Effectiveness of oocyte cryopreservation** One Level I study[29] reported that oocyte vitrification showed successful outcomes across 17 studies, even after testosterone cessation, with similar outcomes to both cisgender individuals and TGD individuals who have not yet initiated GAHT. The Stolk review[29] included a Level IV study by Barrett (2022)[57], also identified in this Evidence Check update. This study reported successful oocyte cryopreservation in 19 out of 20 patients with no significant adverse events. **Pregnancy in transgender males** One Level I study[29] reported 169 live births (39%), 142 miscarriages (33%) and 92 abortions (21%) in a cohort of 203 transgender males reporting ever being pregnant. Evidence from a smaller cohort of 41 reported that pregnancy, delivery and birth outcomes did not differ in relation to prior testosterone use.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	Note that sections on GnRHa and GAHT also update relevant findings pertaining to the fertility implications of these interventions.
For prepubertal transgender youth, the only feasible option of fertility preservation is testicular tissue cryopreservation, which is still experimental and not yet proven successful in humans (one reference, Level B–C).	**Effectiveness of testicular sperm extraction (TESE)** One Level I study[29] reported that there is evidence from a small number of primary studies in the setting of gender dysphoria that TESE can be successful. One of the studies in this review was a Level III-3 study by Peri (2021)[50], also identified in this Evidence Check update. This study examined cryopreservation outcomes in 25 transgender females with a median age of 13.4 (Tanner stage 2–5). Outcomes were successful in 17 patients; no sperm was detected in patients with testicular volume under 10ml and this was therefore advised as a threshold.

Table 10b—Risks of fertility preservation

The additional information on the risks of fertility preservation provided by this Evidence Check is summarised below. It covers adverse effects.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
No specific information on risk and harms reported.	**Adverse effects** Two Level I studies[29,30] reported that oocyte cryopreservation procedures were invasive and psychologically challenging and could worsen gender dysphoria. Other risk descriptions focused on risks associated with hormone therapy and lower semen quality.

Table 10c—Variation in the effectiveness and risks of fertility preservation

The information on variation in the effectiveness, risks and costs of fertility preservation are summarised in the table below. It covers desire for biological children and uptake of fertility preservation treatment.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
Fertility preservation is an issue for adolescents undergoing GAHT (one reference). A recent Australian study reported that no trans boys opted for fertility preservation and suggested this population were electing to delay this procedure until they were older. However, 62% of trans girls underwent fertility preservation. The rate of trans girls undergoing fertility preservation was higher than that reported in studies from the US (one reference) or the Netherlands (one reference). Pang et al. (see Pang et al.[69] in Watson et al. 2020[2]) suggested timely fertility preservation that did not substantially delay gender-affirming treatment explained the higher uptake. These authors suggested that being co-located with an onco-fertility centre and being publicly funded might explain the uptake rates. It is strongly recommended by expert consensus that fertility counselling be provided for all adolescents embarking on GAHT.	**Desire for biological children** One Level I study[29] reported that while more than 50% of adolescents reported a desire to have children, biological offspring was not the preferred option for most. **Uptake of fertility preservation treatment** One Level I study[30] reported fertility preservation is underused, potentially due to cost barriers, late referral and low awareness. A further Level I study[29] reinforced this finding, especially in countries with no insurance and in transgender men. One Level IV study[62] of 35 trans girls with a mean age of 14.8 reported a 38% uptake of fertility preservation in those counselled. This study was included in both Level I reviews and identified in this Evidence Check update.

Strengths and limitations of the evidence—fertility preservation

Consistent with previous interventions, the Level I study of Stolk et al. (2023)[29] identified limitations in study design (cross-sectional, case series, no control groups), small sample sizes and limited follow-up time. The Level I study of Yan et al. (2021)[30] also identified lack of information about dosages of hormone therapy or sperm / ovarian stimulation medication.

Acknowledged limitations in the primary studies included small sample sizes, single institution recruitment, retrospective design and lack of information on desire to have children.

It is also important to note that three of the four primary studies identified in this Evidence Check update were also included in at least one of the two Level I reviews. This has been taken into account in the conclusions for this intervention.

Conclusions of Evidence Check update—fertility preservation

This update has added two systematic reviews and a further four primary studies to the evidence base pertaining to cryopreservation (noting that three of the four primary studies were included in the two Level I reviews). Desire to have children among transgender adolescents is relatively high. Uptake of fertility preservation treatment remains low, however, owing to cost barriers, late referral and low awareness. Another factor contributing to low uptake of fertility preservation is evidence from one Level I review that having biological offspring was not the preferred option for most people who expressed an interest in having children. Although the newly identified evidence generally reports favourable **benefits and effectiveness** outcomes for both semen and oocyte cryopreservation, some **risks or potential harms** warrant mention**.** Studies consistently reported that semen was of lower quality if patients had received puberty suppression and / or GAHT. Furthermore, harvesting semen can be challenging in early puberty and / or due to discomfort with masturbation. There is emerging evidence that testicular sperm extraction can mitigate these limitations; however, this research is in its infancy and semen cryopreservation remains the dominant approach. Oocyte preservation was reported as generally effective with no adverse events; however, cryopreservation procedures are invasive and psychologically challenging and can worsen gender dysphoria.

In summary, while we identified additional evidence supporting fertility preservation, both reviews and primary studies remain limited by small sample sizes, single centre recruitment, study design limitations and variation in use of hormones in participant cohorts. Notwithstanding this, outcomes reported are predominantly positive and very few adverse effects were described in identified studies.

Table 11 below summarises the main features of each of the reports on fertility preservation included in this Evidence Check.

Included studies in this Evidence Check update—fertility preservation

Table 11a—NHMRC Level I. Systematic reviews—fertility preservation (n = 2)

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage	Benefits	Risks	Key conclusions and limitations reported by study authors
Stolk 2023[29] To examine the literature that discusses the desire for children and parenthood, available options for fertility preservation (FP), and the resulting outcomes for transgender and gender diverse (TGD) people. Score on quality criteria = 7.5 / 13.	76 studies: 19 studies on the desire for children and parenthood; 22 on fertility counselling and use; and 36 on options and outcomes.	AFAB (assigned female at birth): Oocyte and embryo cryopreservation, ovarian tissue cryopreservation and in vitro maturation. AMAP (assigned male at birth): Semen cryopreservation, testicular sperm extraction and testicular tissue cryopreservation.	> 50% of adolescents and adults expressed a desire for (future) parenthood; biological offspring was not the preferred option for most. Overall low FP use rate, with the lowest rate in countries with no insurance and in people AFAB. Oocyte vitrification in TGD individuals	TGD people AMAB prior to GAHT showed lower semen parameters compared with cisgender controls. High financial costs associated with FP.	*"This review showed that the majority of TGD adults and adolescents have a desire for children, but biological relatedness is less important."* *"Even though we included many studies, most were cross-sectional questionnaires, case series, or small sample size cohort studies with limited follow-up time and lack of control groups. Furthermore, the quality assessment of the included studies was low to moderate. Interpretation of this evidence requires caution."*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage	Benefits	Risks	Key conclusions and limitations reported by study authors
			AFAB, whether conducted during or after testosterone cessation, demonstrated similar outcomes to both cisgender individuals and TGD individuals who have not yet initiated GAHT.		
Yan 2021[30] To review evidence for the outcomes of FP options in transgender people. Score on quality criteria = 6.5 / 13.	15 articles. 8 articles describing FP options for transgender men, 7 for transgender women and one for both.	GAHT, gender-affirming surgery.	Semen cryopreservation is simple and reliable. If the sperm quality is low, multiple samples can be collected; additional methods such as intrauterine insemination (IUI)	Semen parameters are lower in transgender women in comparison with cisgender men. For transgender men, FP can involve invasive procedures, which	*"Several fertility preservation methods have shown to be effective in the transgender population. Our review shows that fertility preservation should be discussed early during gender transition and if possible, before any exogenous hormonal therapy is started, as the timeline for these interventions is important in order to preserve their reproductive potential as much as possible."*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage	Benefits	Risks	Key conclusions and limitations reported by study authors
			and in vitro fertilisation (IVF) can also be used. Testicular sperm extraction is an option for patients who are unable to ejaculate or for those with severe oligospermia or obstructive azoospermia. The most common method for fertility preservation in transgender men is oocyte cryopreservation.	can be a physically and psychologically challenging experience and may worsen gender dysphoria. Early oocyte retrieval could prevent patients having to temporarily stop their hormonal therapy. Discontinuing testosterone could worsen gender dysphoria. In patients undergoing hormonal therapy where spermatogenesis can be affected	Study limitations: *"… several studies did not provide the dose of the hormone therapy or sperm/ ovarian stimulation medication."*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage	Benefits	Risks	Key conclusions and limitations reported by study authors
				testicular sperm harvesting at the time of GAS can be contemplated. Immature testicular tissue cryopreservation is another experimental method.	

Table 11b—NHMRC Level III-3. Comparative studies without concurrent control—fertility preservation (n = 1)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Peri 2021[50] To identify factors that contribute to the success rate of sperm retrieval for cryo-preservation via testicular biopsy. Score on quality criteria = 7 / 10.	Australia Retrospective cohort study The Royal Children's Hospital Gender Service (RCHGS).	Testicular biopsy. N=25 transgender feminine adolescents. Median age 13.4, Tanner stage 2–5.	Successful sperm retrieval and potential predictors (i.e. age, testicular volume and serum testosterone, serum LH and FSH levels).	17/25 patients had successful sperm retrieval, with one case undergoing puberty suppression for more than 2 years.	No sperm was detected in anyone with less than 10 mL testicular volume. Adolescent patients should wait until their testicular volumes are ⩾ 10 mL before attempting FP via testicular biopsy.	*"… testicular volume was significantly higher in those with successful sperm retrieval …[and] is most useful in predicting successful sperm retrieval following testicular biopsy in transgender adolescents."* Study limitations: small number of participants; *"… our threshold might overpredict the likelihood of sperm being present … [and we were] missing data on testicular volume, Tanner stage, and serum hormone levels for a small number of patients, and we are unsure how these might have affected our results."*

Table 11c—NHMRC Level IV. Case series / cross-sectional—fertility preservation (n = 3)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Barrett 2022[57] To review authors' oocyte cryopreservation outcomes and best practices to guide treatment. Score on quality criteria = 8 / 9.	US Pre-post New York University Langone Fertility Center (NYULFC).	Transvaginal oocyte aspiration. N=44 adolescent and young adult trans men. Median age: 16 (12–23) at consultation.	Oocyte cryopreservation outcomes.	95% per cent (19/20) underwent successful transvaginal oocyte aspiration.	No significant adverse events.	*"Oocyte cryopreservation is a safe fertility preservation option in AYA trans men and is an important aspect of providing comprehensive transgender care."* Study limitations: *"… limited in its generalizability as it was completed at a single institution"*, and *"retrospective design and reliance on chart documentation"*.
Dilday 2022[67] To describe outcomes of sperm cryopreservation in trans girls and	US Pre-post The Fertility and Advanced Reproductive Medicine clinic	Sperm cryopreservation N=45 Trans girls (n=18) at Tanner stages	Successful rate of sperm cryo-preservation.	Semen parameters on GAHT were within normal range for healthy adults.	Information about side effects not reported.	*"This study supports the feasibility of sperm cryopreservation in the adolescent population, and assures that sperm cryopreservation does not*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
compare their semen parameters with adolescents with cancer. Score on quality criteria = 5 / 7.	of the University of Texas (UT).	of IV or V; mean (SD) age: 15.8 (1.6).		Sperm cryopreservation for transgender youth is feasible and cost-effective, with the added benefit of not causing significant treatment delays.		*significantly delay initiation of GAHT."* *"The limitations of this retrospective analysis include its small study population ... Given the retrospective design, demographic factors that could be confounders also impacting semen parameters were not available for evaluation."*
Brik 2019[62] To examine the prevalence of fertility preservation (FP) attempts among transgender girls.	Netherlands Pre-post Curium-Leiden University Medical Centre.	GnRHa N=35 trans girls Mean age (SD): 14.8 ±1.9.	Rate of FP attempts.	Out of those counselled about FP, 38% actually attempted it, which is higher than reported in prior studies in the US.	32% were unable to produce a semen sample due to early puberty, and an additional 17% felt uncomfortable	*"In conclusion, one third of the trans girls attempted FP, and most were able to store sperm suitable for future intrauterine insemination or ICSI."* *"Limitations of this study are its retrospective design and the small study population. Information on*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Score on quality criteria = 4 / 6.					with masturbation.	*sexual orientation or desire to have children was not documented for all individuals. The influence of these factors could be further explored in a prospective study using standardized questionnaires or interviews about reasons for declining FP."*

Question 2—Effective psychosocial interventions for trans and gender diverse young people under 18 years old with gender dysphoria

Psychosocial interventions

Context

Review-level evidence has demonstrated that transgender individuals experience an elevated prevalence of mental health problems, which negatively impact wellbeing and quality of life.[11] For example, suicidal ideation and suicide rates in the transgender population are higher than in the general population.[12] Based on gender-minority theory, this is driven in part by a combination of external stressors, for example events of prejudice such as rejection, discrimination and victimisation combined with internalised reactions such as anticipated stigma and gender-identity concealment. These influences are mediated by individual-level cognitive and emotional characteristics.[11]

In addition to whole-of-population statistics, elevated levels of mental illness have been demonstrated in adolescents, who experience gender-minority stressors in settings such as schools and through other peer interactions, for example teen dating violence.[12]

Gender-affirming psychological interventions are designed to support individuals experiencing gender dysphoria by providing respectful, aware and supportive interventions such as psychotherapy, family therapy and crisis support for those experiencing extreme distress such as suicidal ideation.[11,12,23] Psychosocial therapies are provided in parallel with the pharmaceutical, surgical and fertility preservation interventions described in previous sections of this Evidence Check update. This section focuses on studies that have a stated primary aim of evaluating the effectiveness of psychosocial interventions for transgender individuals.

This Evidence Check update identified seven studies focusing on psychosocial interventions, comprising three systematic reviews (Level I); one randomised controlled trial (II); one comparative study without concurrent control (III-3); and two case series / cross-sectional studies (IV).

The additional information about the benefits of psychosocial interventions provided by this Evidence Check is summarised below (Table 12). It covers suicidal ideation or attempt, psychological distress, depression, anxiety, social support, gender minority stress, belief in coping abilities and coping skills and access to care.

Table 12a—Benefits of psychosocial interventions

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
There is a lack of evidence from which to draw any conclusions regarding the effectiveness of psychosocial interventions for treating children and young people with gender dysphoria. Only one paper empirically examined the effect of psychological support for a cohort of transgender adolescents (Level D). This study compared the effect of psychological support and GnRHa with psychological support alone. It found all participants reported an improvement in psychological functioning at six months. However, only participants who received both GnRHa and psychological support continued to improve over the next 12 months. Another paper described a pilot program of group work for parents and carers of transgender adolescents (Level C–D) and one paper reported a single subject case study in which a trans girl in a youth justice facility received intensive voice feminisation therapy (Level D).	**Suicidal ideation or attempt** One Level I study[12] focused on transgender and gender diverse youth reported that gender-affirming crisis hotlines, gender-affirming medical care such as GnRHa and GAH, online media-based outreach, safety and connectedness, and family system-based interventions may influence suicide-related thoughts and behaviours. The importance of safety and connectedness was emphasised, with acceptance of gender identity in family, school and other settings reported as protective—for example by promoting help-seeking behaviours when having suicidal thoughts. **Psychological distress** One Level I study[11] reported that Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in psychological distress. **Depression** One Level I study[11] reported that Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in depression. One Level III-3 study of 142 transgender youth compared with a historical control group[48] reported that a First Assessment Single-Session Triage (FASST) clinic decreased depression.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	One Level IV study of 41 transgender and gender diverse adolescents[59] reported that an online self-compassion intervention had positive effects on depression. **Anxiety** One Level I study[11] reported that Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in anxiety. One Level III-3 study of 142 transgender youth compared with a historical control group[48] reported that a First Assessment Single-Session Triage (FASST) clinic decreased anxiety. One Level IV study of 41 transgender and gender diverse adolescents[59] reported that an online self-compassion intervention had positive effects on anxiety. **Social support** One Level I study[11] reported that Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in social support. One Level IV study of 41 transgender and gender diverse adolescents[59] reported that an online self-compassion intervention had no effect on sense of belongingness. **Gender minority stress** One Level I study[11] reported that Transgender Affirmative Psychotherapy +

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
	Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant improvements in some aspects of gender minority stress. One Level IV study of 684 participants aged 13–24[96] examining chest binding practices reported that people who undertook binding reported less 'misgendering'. **Belief in coping abilities and coping skills** One Level I study comparing 135 sexual and gender minority youth with 134 controls[32] reported that a web-based application designed to facilitate LGBTQ+ identity affirmation, promote a feeling of connectedness to the LGBTQ+ community and encourage cognitive and behavioural coping skill practice had significant positive effects on belief in coping abilities and coping skills. **Access to care** One Level IV study of 684 participants aged 13–24[96] examining chest binding practices reported that most people sought advice on binding online rather through gender care clinics.

Table 12b—Risks of psychosocial interventions

The additional information on the risks of psychosocial interventions provided by this Evidence Check is summarised below. It covers safety.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
There was no evidence of risk or potential harms from the psychosocial interventions identified in this Evidence Check. Of note, we did not identify any studies that met inclusion criteria whose aim was to change an individual's gender identity.	**Safety** One Level I study comparing 135 sexual and gender-minority youth with 134 controls[32] reported that a web-based application designed to facilitate LGBTQ+ identity affirmation promoted a feeling of connectedness to the LGBTQ+ community and encouraged cognitive and behavioural coping skills. The practice reported no adverse events. One Level IV study of 684 participants aged 13–24[96] examining chest binding practices found more than 95% of participants reported physical side effects such as back pain and overheating.

Table 12c—Variation in the effectiveness and risks of psychosocial interventions

The information on variation in the effectiveness and risks of psychological interventions is summarised in the table below. It covers acceptability.

Conclusions from previous Evidence Check (studies from 2000–2019)	What this Evidence Check update adds (studies from 2019–2023)
There was no evidence of effectiveness or risks associated with psychosocial interventions identified in this Evidence Check.	Most newly identified studies reported that there was good acceptability and / or no adverse impacts of the therapies studied.

Strengths and limitations of the evidence of psychosocial interventions

In addition to reinforcing previous conclusions pertaining to other gender dysphoria interventions, the confounding influence of factors such as family support, concomitant pharmaceutical and other gender-affirming interventions and the influence of puberty on mental health independent of gender identity were described in Level I studies.

Additionally, a broad array of psychosocial interventions was explored in review-level studies including psycho-education, transgender affirmative psychotherapy, cognitive behavioural therapy and family therapy. Furthermore, delivery modes varied from in-person to online. The differential effect of these therapy approaches and how they are delivered is therefore difficult to discern given the relatively low volume and quality of identified studies.

It is also important to note that not all review studies focused exclusively on transgender *adolescents* or transgender *individuals*. For example, in the review of Expósito-Campos (2023)[11], nine of the 22

studies explicitly referenced that some participants were aged under 18; of these, five had cohorts entirely aged 20 or under. The authors also noted that only eight of the 22 studies had exclusively transgender / nonbinary participants; two had mixed populations with subgroup transgender / nonbinary analysis; the remaining studies had mixed populations with no subgroup analysis. This review reported that studies focusing on this population were first conducted in 2014, *"while the most methodologically rigorous date from 2018 onwards"*.[11(p16)] Furthermore, the review of family-based therapies by Malpas et al. (2022)[23] encompassed *"transgender and gender expansive (TGE) youth"*.

Further limitations described in Level I studies included inadequate description of interventions, attrition, and lack of sustainment of outcomes at follow-up and lack of representation of participants of colour.[23]

Acknowledged limitations in primary studies included small sample sizes, use of historical controls, short follow-up periods, lack of validated outcome measures specific to adolescent populations, lack of control group and dependence on supportive parents / guardians to facilitate participation of adolescents in research.

Conclusions of Evidence Check update—psychosocial therapies

This Evidence Check update has added considerably to the volume of evidence evaluating psychosocial interventions such as such as psychotherapy, family therapy and mental health / crisis support. The previous Evidence Check identified only three studies, with one a single case study; this Evidence Check has identified three systematic reviews and four primary studies including a randomised controlled trial. The newly identified studies report **benefits and effectiveness** across numerous outcome domains including suicidal ideation, psychological distress, depression, anxiety and gender minority stress. Furthermore, most studies report that interventions are both acceptable and safe, with no **risks or potential harms** reported.

Although the existence of an RCT is unique to this intervention category, it should be noted that this was of a mixed population of sexual and gender-minority youth—the number of people experiencing gender dysphoria is not reported and there is no subgroup analysis of this group. Furthermore, considerable limitations in this body of literature were identified. In addition to the previously observed limitations of small sample sizes and lack of diversity in participant cohorts, these include a large number of psychological interventions with additional variability in delivery mode; and studies of mixed populations with no subgroup analysis of adolescents and / or transgender participants. Therefore, although study designs are stronger relative to other intervention areas in this Evidence Check update, a number of limitations that are applicable to studies of psychological therapies should be borne in mind when interpreting findings of studies of psychological interventions.

Table 13 below summarises the main features of each of the reports on psychosocial interventions included in this Evidence Check.

Included studies in this Evidence Check update—psychosocial interventions

Table 13a—NHMRC Level I. Systematic reviews—psychosocial interventions (n = 3)

Author, date, aims, quality criteria	Target population / included studies Age or stage	Intervention	Benefits	Risks	Key conclusions and limitations reported by study authors
Expósito-Campos 2023[11] To investigate the effect of psychological interventions on transgender and nonbinary (TGNB) individuals. Score on quality criteria = 8 / 12.	N=22 articles 8 with TGNB only; 2 mixed samples with separate outcome data for TGNB [3 RCTs, 7 pre-post no control]. 12 mixed samples without disaggregated data [4 RCTs, 2 quasi-experimental, 6 pre-post no control].	Psycho-education, transgender affirmative psychotherapy, online programs for stigma combating and stress management, online cognitive behavioural therapy (CBT), school-based counselling programs. The studies did not specify whether	Participants in Transgender Affirmative Psychotherapy + Building Awareness of Minority-Related Stressors [TA + BAMS], group transgender affirmative cognitive-behavioural therapy [AFFIRM], and Transgender Empowerment by Text [TExT] showed significant	Interventions for TGNB individuals were heterogeneous and not very well described. Further experimental testing is due, given that the improvements were not generally sustained at follow-up and only TA + BAMS was an RCT.	TA + BAMS, AFFIRM and TExT *"seem to be the most promising interventions"* for TGNB individuals … conclusions *"are limited by moderate-to-high risk of bias". "… the results of the psychological interventions analyzed are encouraging but also limited and, at times, difficult to interpret".* Limitations of included studies: *"… various studies presented very high attrition rates and did not analyze whether dropouts differed from completers, which poses a threat to the validity of their results ... only 40.9% of the 22 studies included in the review had a follow-up measurement, making it*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage	Benefits	Risks	Key conclusions and limitations reported by study authors
	2 dissertations.	their participants experienced gender dysphoria (GD) nor the type of gender transition (social, medical, or both) they were embarked on. 9 studies contained participants under 18.	improvements in psychological distress, depression, anxiety, social support, and some aspects of gender-minority stress. Results overall also suggest improvements in suicidality, substance-related risk behaviours, coping skills / emotion regulation, stress appraisal, self-esteem, self-acceptance, social support, resilience, hope, positive identity and		*difficult to ascertain if the interventions had long-lasting effects."*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage	Benefits	Risks	Key conclusions and limitations reported by study authors
			identity acceptance.		
Christensen 2023[12] To review interventions for preventing suicide among transgender children and adolescents. Score on quality criteria = 7 / 13.	17 articles Case-control or cohort studies published 2017–2023, mainly in the US. Participants aged 24 years and under.	Crisis interventions; gender-affirming crisis hotline, medical care via interdisciplinary gender clinics, online media-based outreach, safety and connectedness in schools, and family system-based.	Acceptance of gender identity in multiple domains—from family system, school, peers, and in legal documentation—has been found to be protective; for instance, perceived school safety and acceptance promote help-seeking behaviours when having suicidal thoughts. Evidence that gender-affirming	No clear perceivable risks reported for participating in ***psychological*** interventions in the review.	*"Interventions that may influence suicide-related thoughts and behaviours include gender-affirming crisis hotlines; gender-affirming medical care such as GnRHa and GAH; online media-based outreach, safety and connectedness, and family system-based interventions."* Limitations of the included studies: *"… the overall quality of evidence was low and the risk of bias high …* *… Common flaws that created high risk of bias included self-reporting, lack of controls for comparability, small sample sizes, and lack of generalizability."* Studies inconsistently used validated rating scales for depression, anxiety, gender dysphoria and suicide, making it

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage	Benefits	Risks	Key conclusions and limitations reported by study authors
			care reduced suicidal thoughts or behaviours compared with those not receiving treatment.		difficult to compare efficacy of intervention methods.
Malpas 2022[23] To review research literature that provide outcomes for family-based interventions with transgender and gender expansive (TGE) youth. Score on quality criteria = 5 / 12.	34 studies 32 studies examining family-based interventions with TGE youth and their families; 2 examining family-based interventions with sexual minority youth.	Family-based interventions and family therapy (e.g. family guidance sessions, offering parents TGE resources, collaborating with schools).	One study found Attachment-Based Family Therapy (ABFT) leads to a significant decrease in suicidal ideation and depressive symptoms in lesbian, gay and bisexual youth and a moderate (but nonsignificant) decrease in attachment-related	Principles of family-based therapy were articulated including provision of psycho-education; enabling caregivers their own supportive spaces; and framing family acceptance and engagement as a protective factor.	*"This systematic review of English-speaking peer-reviewed articles confirms the absence of youth and family outcome data as well as empirical research on the specific mechanisms of effectiveness of family therapy and family-based services for TGE youth."* Limitations of the included studies: *"… there are no quantitative outcome studies on family therapy or family-based interventions with TGE youth, [but] there are: (1) a small number of qualitative studies (n= 6) based on small samples of caregivers, (2) case studies (n= 9) arguing for the effectiveness of*

Author, date, aims, quality criteria	Target population / included studies	Intervention Age or stage	Benefits	Risks	Key conclusions and limitations reported by study authors
			anxiety and avoidance.		*family-based interventions for TGE youth and their families … there is a glaring absence of quantitative outcome data on family therapy and family-based interventions with LGBT youth in general and with TGE youth in particular … this review yielded no published quantitative outcome studies demonstrating the efficacy of family therapy interventions with TGE youth."*

Table 13b—NHMRC Level II. Randomised controlled trial—psychosocial interventions (n = 1)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Bauermeister 2022[32] To examine the effect of a web-based application on supporting mental health of sexual and gender minority youth. Score on quality criteria = 9 / 13.	US RCT Participants were recruited on Instagram.	Web-based application with materials, resources and peer stories. N=270 sexual and gender minority youth (SGM). Mean age 16.5, SD 1.5) • Treatment group (n=135): 29 AMAB and 106 AFAB • Control group (n=134): 32 AMAB and 103 AFAB.	Stress, mental health symptoms, coping skills	Significantly greater improvement in challenge appraisals (i.e. belief in one's coping abilities) compared with control; no differences for threat or resource appraisals. Greater increases in coping skills vs. control. Mental health symptoms improved across both the	No adverse events were reported during the intervention.	*"This study demonstrated that a brief web-based intervention can provide self-guided, asynchronous and confidential support that improves the ability of SGM youth to cope with minority stress."* Study limitations: *"… our ability to detect these effects with statistical precision was limited by our small sample size and short follow-up period … Second, some of the indicators used to measure our outcomes (e.g. authenticity and LGBTQ+ community connectedness) were originally developed with adult populations. Given the unique needs of SGM youth, it is possible that the measures used in our study were not optimal for use with SGM youth populations."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
				treatment and control arms; however, there were no differences between arms.		

Table 13c—NHMRC Level III-3. Comparative studies without concurrent control—psychosocial interventions (n = 1)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Allen 2021[48] To examine the clinical impact of an innovative mental health support clinic.	Australia A convergent, parallel mixed methods study Royal Children's	90-minute single session consultation provided in the First Assessment Single-Session	Anxiety, depression, quality of life.	Decreased anxiety and depression with enhanced family functioning and sense of agency.	Information on adverse effects or events not reported.	*"The results of this study are nonetheless encouraging and suggest that FASST may help to improve the lives of children and adolescents who are TGD awaiting care."* *"There are several limitations to this study. For the quantitative analysis,*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Score on quality criteria = 8 / 10.	Hospital Gender Service (RCHGS).	Triage (FASST) clinic. • Transgender youth in treatment group (n=142), median age was 15.0 years • Control group (n=120), median age was 15.0 years.				*only limited outcome measures (CBCL [Parent-rated Child Behavior Checklist] and YSR [Youth Self-Report]) were available from the historical control group. Additionally, our use of historical controls may have introduced confounders that contributed to the observed differences in mental health between those who did and did not attend FASST."*

Table 13d—NHMRC Level IV. Case series / cross-sectional—psychosocial interventions (n = 2)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
Julian 2021[96] To understand binding trends in adolescents and young adults. Score on quality criteria = 7 / 8.	US Cross-sectional Online survey distributed through social networks, social media, and community agencies.	Chest binding N=684 transgender adolescents and young adults (AYA): • Binding group (n=608): 16.49 ±2.69 • Non-binding (n=76): 15.89 ± 2.89.	Chest dysphoria, life satisfaction.	More gender congruence reported in the group practising chest binding, which is associated with an enhanced life satisfaction.	95.6% reported to have experienced physical side effect from chest binding, ranging from back pain to overheating. Both commercial binders and convenient items such as tape, bandages, plastic wrap, tarps, pantyhose and girdles were reportedly used	*"Most youth in this study reported binding every day more than 8 hours to provide protection against being misgendered and achieve psychological comfort, underscoring the importance of this practice. When young people are not given appropriate information about binding practices, they are left to find resources that may not be safe and inhibit help seeking behaviors."* *"To maintain institutional review board waiver of parental consent, all questions related to the mental health implications of chest binding were omitted … Another limitation to the study was that participants needed to have access to the Internet and be connected to some*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Benefits	Risks	Key conclusions and limitations reported by study authors
					for chest binding.	*form of social media or agency to receive the link."*
Bluth 2023[59] To investigate the impact of an online self-compassion intervention for transgender adolescents. Score on quality criteria = 7 / 10.	US & Canada Pre-post Online program delivered via Zoom platform.	A self-compassion program, delivered in eight 1.5h sessions. N=41 transgender and gender diverse adolescents, mean age (SD) 14.5 (1.49) years.	Feasibility of the program (attendance and retention), mental health outcomes.	Increased self-compassion and improved anxiety, depression, resilience and life satisfaction. The program demonstrated its feasibility, with 100% of participants attending more than 6 out of 8 classes.	No significant improvement in sense of belongingness.	*"Results suggest that self-compassion interventions can be incorporated into therapy programs to support and improve mental health for transgender adolescents."* Study limitations: *"First, the sample was relatively small. Second, there was no control group, which makes it impossible to conclude causality. Third, parents or guardians were required to consent to have their adolescent participate in the study, which meant that only those adolescents with parents or guardians who supported their gender transition could be involved."*

Discussion

This Evidence Check update identified a comparatively large volume of new research pertaining to interventions for children and young people with gender dysphoria. This is encouraging, especially considering the smaller span of years (four) covered by the update (2019–2023) compared with the time span (19 years) covered by the original review (2000–2019). The identified papers were published across a broad array of journals. While this was challenging with respect to defining key words to identify papers for the purpose of this Evidence Check, as they were not used consistently (e.g. in abstract indexing), the tailoring to different audiences does suggest a range of disciplines are involved in trans and gender diverse research. This may have positive implications for future work by NSW Health in deciding which groups and representatives can or should be consulted to develop holistic and inclusive models of care.

As shown in Table 13, the distribution of research study designs also showed some shifts relative to the original Evidence Check. There were comparatively more Level IV studies (57% of total research volume in this Evidence Check vs. 30% in the previous review), as well as review papers (20% vs. 13%) and fewer comparative studies. It is likely these differences in part reflect dedicated efforts to report outcomes or 'snapshots' of clinical interest for cohorts over time as they progress through management at specialist gender dysphoria clinics. Examples include the programs led by the Royal Children's Hospital in Melbourne[5,6] and in Amsterdam.[7,8] These studies have followed relatively large patient cohorts—the Melbourne-based studies had cohorts of 158 (2022)[5] and 131 (2023)[6] and the Amsterdam cohorts were 720 (2022)[8] and 1766 (2023).[7] While there has not been a rapid growth in the conventionally accepted gold standard designs of RCTs, this Evidence Check offers important insights into the effectiveness and risks associated with gender dysphoria interventions. The combined total of 128 studies (of varying quality, see below) provides a platform for engaging patients and carers in dialogue on key issues, including defining directions for future research investment.

Table 14—Comparison of volume and type of evidence in the original Evidence Check and this update

Level and study design	n (original review) (% of total)	n (this update) (% of total)
I. A systematic review (of level II studies*)	6 (13%)	16 (20%)
II. A randomised controlled trial	0	1 (1%)
III-1. A pseudo-nonrandomised controlled trial	0	0

Level and study design	n (original review) (% of total)	n (this update) (% of total)
III-2. A comparative study with concurrent controls	14 (30%)	12 (15%)
III-3. A comparative study without concurrent controls	7 (15%)	6 (7%)
IV. Case series or cross-sectional study	14 (30%)	47 (57%)
Other (committee opinion/recommendations, qualitative)	5 (11%)	Not in scope
TOTAL	**46**	**82**

* While level I evidence is strictly classified as systematic reviews of RCTs, almost no RCTs have been conducted in this area to date.

Confidence in research findings is highest when research studies compare those receiving treatment with a well-matched control group or a group receiving usual care so that the effect of the treatment can be ascertained. Research using control groups can be challenging in the field of research into interventions for gender dysphoria for several reasons. Ethical concerns arise regarding potential withholding of treatment to people experiencing gender dysphoria, which can cause distress to individuals. This was highlighted in the original Evidence Check of this topic, which forecast that RCTs were unlikely to increase in volume for this reason—a prediction borne out by this update, which identified only one RCT examining an online intervention to support mental health of sexual and gender minority youth.[32]

In addition, the nature of some gender dysphoria treatments themselves can make the selection of appropriate control groups difficult. For example, the one Level III-3 study examining puberty suppression treatment compared outcomes in transgender adolescents with those receiving therapy for central precocious puberty (CPP) who are, by definition, a younger cohort.[49] Another comparative study (Level III-2) of puberty suppression treatment examined the effect of later vs. earlier treatment, again creating inherently different groups with respect to age.[43]

Another key inherent limitation of research into interventions for gender dysphoria, independent of study design, is that gender dysphoria management is undertaken over a long period in which various interventions overlap. This makes it difficult to isolate the differential effect of individual interventions, even where a control group may be present. In this sense, gender dysphoria management can therefore be considered a complex intervention, defined as an intervention comprising numerous interacting components; a corresponding number and variability of outcomes; and flexibility and tailoring in delivery of the intervention.[4]

For example, puberty suppression treatment and gender-affirming hormone therapy, two interventions representing the majority (70%) of all included studies in this Evidence Check update, often overlap. Of the 57 primary studies examining these therapies, 40 contained cohorts that had received both therapies during the period of the study, including 21 of the 23 Level IV studies examining GAHT. The complex nature of gender dysphoria treatment, in addition to the above factors, should be considered when interpreting the findings of this

Evidence Check. Although RCTs are rarely ethically possible in the field of research into interventions for gender dysphoria, it is important to note that RCTs are not considered an optimal approach to evaluating complex interventions, independent of ethical considerations.[100]

Furthermore, other confounding effects, for example the influence of smoking and lifestyle factors on cardiovascular risk, socioeconomic status, geography and race, are generally not controlled for in the studies identified in this Evidence Check update.

Notwithstanding the above considerations, the consistency of findings across included studies are worthy of mention. Several newly identified studies in this update, including reviews and controlled empirical studies, supported the conclusion from the previous Evidence Check that gonadotropin-releasing hormone agonists are the most effective treatment for puberty suppression. Similarly, a relatively large number of studies reported positive impacts of gender-affirming hormone therapy on a range of psychosocial outcomes including gender dysphoria, depression, anxiety and suicide risk. Reviews and primary evidence identified in this update also reported that both semen and oocyte cryopreservation were successful approaches to fertility preservation.

This update had several strengths and limitations. Strengths were the use of a comprehensive search strategy across seven databases; independent screening of citations and full text studies by two researchers; quality appraisal of all included studies and mapping of the updated review outputs and findings against the original review of this topic. Although this update identified a high volume of relevant studies published since the original Evidence Check, some relevant studies may not have been identified for a range of reasons. First, the short time frame of the update mitigated against use of some techniques to ensure comprehensiveness, for example contacting authors of relevant studies to clarify understanding or identify additional papers. Second, given the increase in the volume of research in the period since the original Evidence Check, more relevant studies may have been published since the search was undertaken. Regular updates of the searches are therefore recommended as well as ongoing monitoring of research underway in large gender dysphoria clinics.

Finally, it is important to emphasise that this Evidence Check provides a synthesis of reported findings of eligible studies, the strength of the study design and how each study has been conducted. This Evidence Check is not designed to guide policy or clinical practice. Although knowledge of the state of the research evidence is an important input into policy and clinical practice guideline development, these activities involve considerable additional processes, consultations and inputs. Therefore, this update should not be used in isolation to guide policy or practice.

Gaps in evidence

Table 15 provides an overview of key gaps in the evidence identified in the previous Evidence Check and the extent to which these gaps have been addressed by newly identified studies in this update.

Table 15—Update on key gaps in the evidence identified in the previous Evidence Check

Identified gap in evidence from previous Evidence Check	Newly identified evidence pertaining to gap	Conclusion
Understanding the characteristics of trans and gender diverse (TGD) youth in Australia.	As in the previous Evidence Check, examination of the characteristics of trans and gender diverse (TGD) youth in Australia outside the context of interventions was out of scope. Notwithstanding this, we identified several Australian studies that provided some description of Australian cohorts. The two Melbourne-based studies of Moussaoui (2022, 2023)[5,6] focused on pelvic pain in a cohort of 158 patients (2022) and menstrual suppression in a cohort of 131 patients compared with 399 controls (2023). Both studies therefore provided descriptive information or relatively large cohorts. Another Melbourne-based study[48] evaluating the effectiveness of a single-session triage and support service also described a large cohort of 142 participants. A smaller Melbourne study examined fertility preservation in 25 participants.[50] The NSW study by Elkadi (2023)[68] examined treatment pathways in 79 people with less focus on describing the cohort.	Although not a focus of this Evidence Check, large cohort studies provide description of Melbourne-based cohorts of youth seeking gender-affirming care. Knowledge of characteristics of cohorts in other Australian jurisdictions remains poor.

Identified gap in evidence from previous Evidence Check	Newly identified evidence pertaining to gap	Conclusion
Timing of gender-affirming medical interventions / long-term evaluations of medical intervention.	The previous Evidence Check reported a lack of studies examining short- and long-term effects of initiating GAHT. This update identified several longer-term follow-up studies including from large centres such as those in the Netherlands[7,8] and Melbourne[5,6] (as described earlier). Other examples of longer-term follow-up included a large systematic review examining cardiovascular outcomes over 10 years[21] and studies of chest surgery, which generally had follow-up periods of years.[3] However, many reviews and primary studies were limited in the extent and length of follow-up with resultant impacts on interpretation.[21,22,63] Those with longer follow-up periods were limited in other ways, for example lack of a control group.[65] One review of 22 studies noted lack of sustainment of outcomes in psychological interventions at follow-up.[11]	Newly identified studies in this Evidence Check update include those that follow up cohorts over longer time periods, including studies of the Dutch cohort focusing on GAHT.[7,8] There are also examples of longer-term follow-up studies examining cardiovascular risk and surgical outcomes. However, gaps remain with regards to long-term follow-up studies, as noted across several reviews. Additionally, some longer-term studies have methodological limitations.
Social isolation during puberty suppression.	We found no newly identified evidence pertaining to social isolation.	This gap in the evidence remains unchanged.

Identified gap in evidence from previous Evidence Check	Newly identified evidence pertaining to gap	Conclusion
The role of pubertal suppression and GAHT on the outcomes of surgery.	This Evidence Check identified one study exploring the relationship between pubertal suppression, GAHT and surgical outcomes. The findings of this study were mixed. The study found that while puberty suppression treatment reduces the need for mastectomy in trans men, it can create complications for trans women as penile inversion may not be possible (noting that genital surgery was out of scope of this Evidence Check).[46]	This gap in the evidence remains largely unchanged, with only one study explicitly examining the relationship between pubertal suppression and surgical outcomes.
The effect of exercise and diet on bone density.	We found no newly identified evidence pertaining to the influence of exercise and diet on bone density.	This gap in the evidence remains unchanged. The confounding effect of these influences on bone density is also inadequately controlled for in studies examining bone density outcomes.
A wide range of outcomes measured using validated instruments.	Although a wide range of outcomes have been encompassed by the included studies, use of validated instruments remains sparse (Rowniak 2019[28], Bauermeister 2022[32]—validated in adults but not youth). Lack of validated instruments is noted as a shortcoming across included studies.[12,83]	Despite increases in the volume of studies and breadth of outcomes measured, used of validated instruments remains low.

Identified gap in evidence from previous Evidence Check	Newly identified evidence pertaining to gap	Conclusion
The independent effect of medical interventions on psychological outcomes.	Lack of a control group remains a key limitation, with 46 of the 82 newly identified studies not having a control group and a further five having no concurrent control group. This is compounded by the complex nature of gender-affirming interventions, which makes evaluation of the isolated effects of individual therapies challenging.	Despite increases in the volume of evidence identified, research remains limited by lack of control groups and the multifaceted nature of gender-affirming interventions.
Type and effect of psychosocial interventions.	Newly identified evidence in this update has added to the evidence base for psychosocial interventions. Three reviews and four primary studies were identified, compared with three studies including one single case study in the previous Evidence Check. Studies report generally positive findings across multiple domains and few risks or potential harms. However, confidence in findings remains low despite one RCT being identified.	This gap in the evidence has been partially addressed by newly identified studies; however; further research is required to explore specific effects of therapies at different ages and build confidence in reported findings.

Recommendations for research

Based on these findings and the volume and nature of the evidence identified in this Evidence Check update, we make the following research recommendations:

1. **Existing identified cohorts from longitudinal studies should continue to be followed up periodically to continue filling persistent gaps in understanding of longer-term outcomes.** This harnesses the considerable research effort already expended in the studies described above on an ongoing basis. In the Australian context, this involves exploring research plans for the study conducted in Melbourne and other jurisdictions. For international studies, periodic searches should be undertaken regularly (e.g. every six months) with a particular focus on the Dutch cohort and other studies conducted in large centres. Longitudinal studies can provide detailed information about patient experiences and outcomes over the life course. While this information may not result in cause and effect information, in the absence of a comparison group descriptive studies remain important as a source of data, particularly if linked to sources of administrative data.

2. **Newly established research studies in Australia should collaborate as much as practicable to build multicentre cohorts.** Research strategies for relatively small clinical populations such as spinal cord injury emphasise the need to conduct multicentre studies.[101,102,103] Similar recommendations have flowed from the experience of COVID-19 research, which was characterised by research waste owing to numerous small and underpowered studies examining the same intervention rather than large multicentre trials.[104] Multicentre cohorts boost statistical power and enable variations in outcome across different contexts to be explored. Likewise, collaborative data sets might potentially harness the power of data linkage, to explore other topics such as service use, including care-seeking for services outside the specialised clinics.

3. **More controlled studies are needed where feasible and ethically acceptable.** In addition to larger cohorts, research should use control groups to better understand the effect of treatment compared with non-treated groups. This is especially important given that the adolescent years, within and outside the context of gender dysphoria, are characterised by significant hormonal, physical and emotional disruptions. Despite the acknowledged limitation of undertaking RCTs in people with gender dysphoria, several studies used innovative approaches to generating control cohorts. For example, the high-quality retrospective cohort (case-control) study by Hisle-Gorman et al. (2021)[73] examined mental health care use in a cohort of 3754 TGD adolescents with 6603 sibling controls. All participants were in military-connected families with equal access to healthcare. While this is a distinctive setting, 18 other studies included in this Evidence Check update used some form of control group, including one RCT and 12 studies with concurrent controls. These included use of cisgender controls[45]; a population-wide cross-sectional study that examined cardiovascular risk in large numbers of participants with gender dysphoria (4172) compared with controls (16,648)[44]; use of population datasets as reference controls[41]; and use of historical control groups.[48] While all these

approaches have limitations, study designs that have a control group of any type are inherently more robust than those that do not, as reflected by the NHMRC hierarchy of evidence.[14]

Conclusion

This Evidence Check aimed to update a 2020 review of evidence pertaining to the effectiveness of interventions for children and young people with gender dysphoria. A comprehensive search strategy identified 82 studies published since the previous review comprising 16 systematic reviews (Level I—however, reviews did not contain RCTs), one randomised controlled trial (Level II), 12 comparative studies with concurrent controls (III-2), six comparative studies without a concurrent control (III-3) and 47 Level IV case series / cross-sectional studies. The most frequently studied interventions were gender-affirming hormone therapy (38 studies, including 23 Level IV) and puberty suppression treatment (18, including 11 Level IV). We identified fewer than 10 studies for other intervention areas of gender-affirming surgery (eight), psychosocial interventions (seven) and fertility preservation (six). Key conclusions by intervention were:

- *Puberty suppression treatment:* This Evidence Check update predominantly reinforces findings of the previous review, with research reporting that puberty suppression treatment is safe, effective and reversible. However, the strength of this evidence remains low.
- *Gender-affirming hormone therapy:* Conclusions from included studies are consistent with the previous review that GAHT is associated with more positive than neutral / negative psychosocial outcomes and carries few cardiovascular side effects, although meningioma risk associated with cumulative dose exposures of cyproterone acetate greater than 3g was noted in one Level I study. Some physiological parameters such as creatinine were altered, with no serious clinical implications. The large research volume in this area was offset by generally poor study designs.
- *Gender-affirming chest surgery:* Updated evidence reported generally positive findings for chest surgery across satisfaction, dysphoria and psychosocial domains. Although this update provides some additional evidence that supports chest surgery, methodological flaws, particularly the confounding effect of concurrent gender dysphoria interventions, were reported.
- *Fertility preservation:* This update added two systematic reviews and four primary studies. These reported that both semen and oocyte cryopreservation remain the mainstays of treatment and have favourable outcomes and very few adverse effects.
- *Psychosocial therapies:* This Evidence Check added considerably to the evidence base from the original review. Newly identified studies reported a range of benefits across suicidal ideation, depression and anxiety. Furthermore, most studies reported that interventions are both acceptable and safe, with no risks or potential harms reported. Although we identified one RCT, it was not specific to gender dysphoria. Furthermore, the considerable variation in the psychological therapies and delivery modes evaluated should be borne in mind when interpreting findings of studies of psychological interventions.

Analysis of gaps in research when compared against the previous Evidence Check resulted in three research recommendations:

1. Existing identified cohorts from longitudinal studies should continue to be followed up periodically to continue filling persistent gaps in understanding of longer-term outcomes.
2. Newly established research studies in Australia should collaborate as much as practicable with established research teams to build multicentre cohorts.
3. More controlled studies are needed where feasible and ethically acceptable.

Appendix 1—Care use

NOTE: Care use was not a primary focus of this Evidence Check, which focused on intervention effectiveness. Where studies included in this update also reported on care use, that information has been extracted, but it does not represent all the available evidence on this topic.

Few intervention studies included in this Evidence Check reported on the proportion of participants who discontinued gender-affirming medical treatment. One moderate-quality Level I study (NICE 2020a) systematic review of nine observational studies of people aged ⩽ 18 reported rates of people ceasing GnRHa treatment were 9/143 (6.2%) in one study (five no longer wanted therapy, four had side effects) and 11/26 (42%) in another study. However, there was low confidence in the overall findings of this review owing to methodological limitations in the identified studies.

Five Level IV studies focused on care use.

- Elkadi et al. (2023)[68] reported that 9% of patients in a case series of 66 people with confirmed gender dysphoria had desisted, where desistance was defined as *"resolution/disappearance of the gender-related distress that was the foundation for the young person to present to the service"*.[68(p2)]
- A study by Gupta et al. (2023)[72] of 385 mixed age (paediatric 121; adult 264) transgender individuals attending specialised academic centres reported that six participants (1.6%) had discontinued GAHT, with the predominant reasons being external (e.g. insurance, pregnancy, complications) rather than due to change in gender identity. Only two participants discontinued GAHT permanently.[72]
- A study by Nieder et al. (2021)[80] focused on satisfaction with gender-affirming care in 75 trans adolescents and young adults with gender dysphoria attending the Hamburg Gender Identity Service (mean age 17.4). Overall high satisfaction was reported. Nine people suspended or terminated treatment prior to receiving medical interventions; three people receiving GAHT and one person receiving surgical care suspended or terminated treatment. Reasons for terminating or suspending treatment were mental health issues; long distance to service; and other ('did not feel understood'). No adolescents regretted undergoing treatment at follow-up.[80]
- A large longitudinal study by van der Loos (2023)[7] of 1766 children and adolescents in the Amsterdam Cohort of Gender Dysphoria reported that the majority of adolescents (93%) using GnRHa went on to start GAH and only a few individuals (1.6%) discontinued GnRHa, mainly due to remission of GD.[7]
- Another study by van der Loos (2022)[8] examined treatment continuation rates for 715 people who started medical treatment in adolescence with a gonadotropin-releasing hormone agonist (GnRHa) to suppress puberty before the age of 18 years and used GnRHa for a minimum duration of three months before addition of gender-affirming

hormones. The rate of identified prescriptions for gender-affirming hormones, identified through a nationwide prescription registry, was 98%. Twelve of the 16 people for whom no prescription was found had undergone gonadectomy. For these individuals, no prescriptions were found for sex hormones of the sex assigned at birth either (this was suggested to indicate regret by the authors). Reasons postulated for discontinuation included medication side effects and lack of knowledge of the need to continue hormone therapy following gonadectomy.[8]

A key limitation in the identified studies is that because the concept of gender transition is still evolving, comparison of findings between studies is hampered by variability in outcome definition. A 2021 overview of gender detransition by Expósito-Campos (2023)[11] concluded that:

> *"Gender detransition is an emerging yet poorly understood phenomenon in our society, which poses significant professional and bioethical challenges for clinicians working in the field of GD. The absence of systematic research around detransition has given rise to inconsistencies in its conceptual use and application, adding to the unclarity and confusion. A typology of gender detransition based on the cessation or the continuation of a transgender identity could address these issues, while offering clinicians a framework to reflect on their therapeutic endeavour when treating patients with GD".*[11(276–77)]

In addition to this lack of conceptual clarity, there is variability between studies in treatment setting and specifics of care; a range of reasons for discontinuing treatment are reported; and the data identified is from Level IV studies with cohorts ranging in size (66–1766) and age.

For these reasons, no conclusions about care use can be made from the identified evidence.

Table 16 below summarises the main features of each of the reports on care use included in this Evidence Check.

Table 16—Included studies in this Evidence Check update—care use

NHMRC Level IV—Case series / cross-sectional—care use (n = 5)

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Key outcomes	Key conclusions and limitations reported by study authors
Gupta 2023[72] To investigate the discontinuation rate after 4 years receiving GAHT and reasons. Score on quality criteria = 7 / 10.	US Pre-post Academic centres providing care to TGD adolescents and adults.	**GnRHa + GAHT (GAHT focus)** Transgender and gender diverse (TGD) N=385 Paediatric cohorts (n=121): 67 trans male, 54 trans female; **mean age** 15 years. Adults (n=264): 87 trans male, 177 trans female.	Discontinuation rate, reasons.	GAHT discontinuation is uncommon (1.6%), with reasons being external rather than change in gender identity (i.e. insurance issue, pregnancy and medical complications).	*"Our study indicates that the majority of TGD individuals who start GAHT adhere to prescribed therapy."* Study limitations: *"An important limitation of our study is the relatively limited success of contacting all study subjects, especially those who disenrolled prior to the end of follow-up. The sensitivity analyses demonstrated the results may change if all participants were followed for the entire study period."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Key outcomes	Key conclusions and limitations reported by study authors
Nieder 2021[80] To investigate satisfaction with TRC, regret, and reasons for (dis) satisfaction with transition-related medical interventions. Score on quality criteria = 7 / 10.	Germany Pre-post Hamburg Gender Identity Service for children and adolescents (Hamburg GIS).	**Diagnostic / psychosocial only (21), GnRHa (11), GAH (32), GAH + surgery (11)** N=75 trans adolescents and young adults (n=64 AFAB & n=11 AMAB). Mean age at 17.4 years.	GAC satisfaction, desistance rate, reasons.	Overall high satisfaction with GAC services and no regret recorded. *"In total, 13 participants (of which 4 were AMAB) indicated at follow-up that they had either suspended or terminated their TRC [transition-related care] at the Hamburg GIS. Nine participants did so while in the no-TRMI group, while three individuals did so*	*"Overall, satisfaction with TRC was high in this population of trans youth, and no participants regretted treatment, reflecting high quality of care at the Hamburg GIS. Participants' focus on physical results of treatment as reason for (dis) satisfaction with TRMI adds to the literature supporting the use of TRMI on adolescent populations."* *"In sum, sampling limitations imply that the results cannot be transferable to all other trans populations, particularly non-Western countries or people of color, or youth identifying with nonbinary genders, but also to AMAB youth or those undergoing other types of TRMI, such as genital surgeries."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Key outcomes	Key conclusions and limitations reported by study authors
				at the GAH stage."	
van der Loos 2023[7] To explore the trends in diagnostic and treatment trajectories of children and adolescents referred for GD evaluation. Score on quality criteria = 7 / 10.	Netherlands Pre-post Center of Expertise on Gender Dysphoria of the Amsterdam UMC.	**GnRHa + GAHT** N = 1766 children and adolescents. GnRHa initiation: trans girls at a median age of 14 years, and trans boys at 15.5 years. GAHT: trans girls at a median age of 16 years, and trans boys at 16.7 years.	Admission rate, age at admission and initiating GnRHa and GAHT, proportion of individuals assigned a specific sex at birth, puberty stages, reasons for not using GnRHa and rate of individuals undergoing	The majority of adolescents (93%) using GnRHa go on to start with GAH. Only a few individuals (1.6%) discontinued GnRHa. The main reason for discontinuing GnRHa was remission of GD.	*"Risk for retransitioning was very low, providing ongoing support for medical interventions in comprehensively assessed gender diverse adolescents."* Study limitations: *"… the results may be different for centers following a different treatment approach … Due to the retrospective design, data might be lacking … calculated proportions in the most recent years are likely an underestimation".*
van der Loos 2022[8] To investigate the continuation rate of adolescents	Netherlands Pre-post Amsterdam UMC.	**GnRHa + GAHT** GnRHa for a minimum of three	Continuation of GAHT (based on prescription of	High rate of continuation from PS with GnRH to GAHT (98%).	*"Overall, 98% of people who had started gender-affirming medical treatment with puberty suppression in adolescence in this study continued gender-affirming hormones."*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Key outcomes	Key conclusions and limitations reported by study authors
starting PS and GAHT. Score on quality criteria = 8 / 10.		months and then GAHT. N = 720 (n=220 trans girls, n=500 trans boys). Median age GnRHa started in trans females 14.1 years, trans males 16 years.	gender-affirming hormones).		*"A limitation of our study is that gender-affirming hormones being prescribed does not necessarily mean that people are using the medication, possibly overestimating the number of people still using gender-affirming hormones."*
Elkadi 2023[68] To explore the developmental pathway choices of youth presenting to a tertiary Gender Service.	Australia Pre-post Tertiary care hospital.	**Social transition only (1) + GnRHa (49) + GAHT (51) + Surgery (6)** N=68 with GD (of 79 referrals; 2 lost to follow-up).	Persistence and desistance rate—where persistence was defined as *"continuation of the journey to transition to the other gender"* and desistance was defined as *"resolution / disappearance of*	Within the GD subgroup (n=68) (with two lost to follow-up), six had desisted (desistance rate of 9.1%; 6/66), and 60 had persisted on a GD (transgender)	*"The data from this study show that when young people with gender distress present to health services seeking medical interventions, they end up following a diverse range of developmental pathways …* *… the evidence-base pertaining to the gender-affirming medical pathway is sparse and, for the young people who may regret their choice of pathway at a future point in time, the risks for potential harm are significant".*

Author, date, aims, quality criteria	Country, design, setting	Intervention Sample N = age, gender identity	Main outcomes	Key outcomes	Key conclusions and limitations reported by study authors
Score on quality criteria = 6 / 9.		Young people (13.25–23.75 years old).	*the gender-related distress that was the foundation for the young person to present to the service".*	pathway (persistence rate of 90.9%; 60/66).	Study limitations: *"It did not have a control group …* *the current study does not provide information about possible side effects experienced in relation to cross-sex hormones …* *It is possible that therapists' own perspectives affected the patients' decisions to choose to persist or desist …* *… a substantial percentage of young people who had exited the service could not be contacted at this final follow-up time point …* *our data pertaining to current mental health concerns are limited …* *… this study is unable to examine issues pertaining to any placebo effects that accompany medication use".*

Appendix 2—Evidence Check protocol

Evidence Check questions

Question 1—Effective clinical medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria

- Question 1a—What have been shown to be the most effective medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?
- Question 1b—What have been shown to be the risks or potential harms from medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?
- Question 1c—Is there variation in the effectiveness and risks associated with medical interventions for trans and gender diverse young people under 18 years old with gender dysphoria?

Question 2—Effective psychosocial interventions for trans and gender diverse young people under 18 years old with gender dysphoria

- Question 2a—What have been shown to be the most effective psychosocial interventions for treating trans and gender diverse young people under 18 years old with gender dysphoria?
- Question 2b—What have been shown to be the risks or potential harms from psychosocial interventions for treating trans and gender diverse young people under 18 years old with gender dysphoria?
- Question 2c—Is there variation in the effectiveness or risks associated with psychosocial interventions for treating trans and gender diverse young people under 18 years old with gender dysphoria?

The agreed final search strategies and yields are contained overleaf:

- Figures in brackets are the yields from the previous Evidence Check
- TOTAL YIELD for screening after deduplication = 2766.

Database: Embase Classic+Embase <1947 – 2023 August 25>
Search date: 19 Sep 2023
Yield: 1923

#	Query	Results
1	(Transgender or gender dysphoria or trans or gender diverse or "trans or gender diverse" or TGD or gender incongruent or gender incongruence or gender identity or gender identity disorders or non-binary or nonbinary).ti,ab.	202,123 [200,946]
2	(Treatment* or management or intervention* or hormone blocker* or hormone therap* or puberty suppress* or puberty blocker* or pubertal suppress* or anti-androgen or antiandrogen* or androgen antagonist* or oestradiol or estradiol or gender-affirming hormone or gonadotropin releasing hormone agonist or gender reassignment or clinical psychology or counselling or psychotherapy or gender-affirming or gender-affirming or oestrogen or estrogen or testosterone or fertility preservation or social transitioning or voice training).ti,ab.	10,637,013 [10,390,339]
3	(Adolescen* or youth* or young person* or young people* or teen* or young adult* or pediatric* or paediatric* or child*).ti,ab.	2,998,133 [2,987,776]
4	(Safety or benefit* or Side-effect* or risk* or harm* or significant adverse drug reaction* or ADRs or effect* or impact* or outcome*).ti,ab.	17,068,501 [6,417,445]
5	1 and 2 and 3 and 4	3762 [1979]
6	limit 5 to yr="2019 - 2023"	1946 [1008]
7	**limit 6 to english language**	**1923 [991]**

Database: Ovid MEDLINE(R) <1946 – September 15, 2023>

Search date: 19 Sep 2023

Yield: 830

#	Query	Results
1	(Transgender or gender dysphoria or trans or gender diverse or "trans or gender diverse" or TGD or gender incongruent or gender identity or gender identity disorders or gender incongruence or non binary or non-binary).ti,ab.	**128,751** [128,172]
2	(Treatment* or management or intervention* or hormone blocker* or hormone therap* or puberty suppress* or puberty blocker* or pubertal suppress* or anti-androgen or antiandrogen* or androgen antagonist* or oestradiol or estradiol or gender-affirming hormone or gonadotropin releasing hormone agonist or gender reassignment or clinical psychology or counselling or psychotherapy or gender-affirming or gender-affirming or oestrogen or estrogen or testosterone or fertility preservation or social transitioning or voice training).ti,ab.	**6,399,657** [6,241,959]
3	(Adolescen* or youth* or young person* or young people* or teen* or young adult* or pediatric* or paediatric* or child*).ti,ab.	**1,905,666** [1,900,880]
4	(Safety or benefit* or Side-effect* or risk* or harm* or significant adverse drug reaction* or ADRs or effect* or impact* or outcome*).ti,ab.	**10,758,706** [3,758,912]
5	1 and 2 and 3 and 4	**1602** [780]
6	limit 5 to yr="2019 - 2023"	**847** [403]
7	**limit 6 to english language**	**830 [393]**

Database: SCOPUS

Search date: 19 Sep 2023

Yield: 1433

(TITLE-ABS (transgender OR "gender dysphoria" OR trans OR "gender diverse" OR "trans or gender diverse" OR tgd OR "gender incongruent" OR "gender identity" OR "gender identity disorders" OR “gender incongruence” OR “non-binary” OR “non binary”)) AND (TITLE-ABS (treatment* OR management OR intervention* OR "hormone blocker*" OR "hormone therap*" OR "puberty suppress*" OR "puberty blocker*" OR "pubertal suppress*" OR anti-androgen OR antiandrogen* OR "androgen antagonist*" OR oestradiol OR estradiol OR "gender-affirming hormone" OR "gonadotropin releasing hormone agonist" OR "gender reassignment" OR “clinical psychology” OR counselling OR psychotherapy OR “gender affirming” OR “gender-affirming” OR oestrogen OR estrogen OR testosterone OR “fertility preservation” OR “social transitioning” OR “voice training”)) AND (TITLE-ABS (adolescen* OR youth* OR "young person*" OR "young people*" OR teen* OR "young adult*" OR pediatric* OR paediatric* OR child*)) AND (TITLE-ABS (safety OR benefit* OR side-effect* OR risk* OR harm* OR "significant adverse drug reaction*" OR adrs OR effect* OR impact* OR outcome*)) AND PUBYEAR > 2018 AND (LIMIT-TO (LANGUAGE , "English"))

Database: APA PsycInfo <1806 – September Week 1 2023>

Search Date: 19 Sep 2023

Yield: 582

#	Query	Results
1	(Transgender or gender dysphoria or trans or gender diverse or "trans or gender diverse" or TGD or gender incongruent or gender identity or gender identity disorders or gender incongruence or non-binary or non binary).ti,ab.	**23,090** [22,735]
2	(Treatment* or management or intervention* or hormone blocker* or hormone therap* or puberty suppress* or puberty blocker* or pubertal suppress* or anti-androgen or antiandrogen* or androgen antagonist* or oestradiol or estradiol or gender-affirming hormone or gonadotropin releasing hormone agonist or gender reassignment or clinical psychology or counselling or psychotherapy or gender-affirming or gender-affirming or oestrogen or estrogen or testosterone or fertility preservation or social transitioning or voice training).ti,ab.	**1,275,707** [1,200,881]
3	(Adolescen* or youth* or young person* or young people* or teen* or young adult* or pediatric* or paediatric* or child*).ti,ab.	**1,044,595** [1,042,962]
4	(Safety or benefit* or Side-effect* or risk* or harm* or significant adverse drug reaction* or ADRs or effect* or impact* or outcome*).ti,ab.	**2,459,235** [794,681]
5	1 and 2 and 3 and 4	**1220** [605]
6	limit 5 to yr="2019 - 2023"	**674** [335]
7	**limit 6 to english language**	**582 [289]**

Database: Joanna Briggs Institute: JBI EBP Database <Current to August 23, 2023>
Search Date: 19 Sep 2023
Yield: 0

#	Query	Results
1	(Transgender or gender dysphoria or trans or gender diverse or "trans or gender diverse" or TGD or gender incongruent or gender identity or gender identity disorders or gender incongruence or non-binary or non binary).ti,ab.	**11** [10]
2	(Treatment* or management or intervention* or hormone blocker* or hormone therap* or puberty suppress* or puberty blocker* or pubertal suppress* or anti-androgen or antiandrogen* or androgen antagonist* or oestradiol or estradiol or gender-affirming hormone dose or gonadotropin releasing hormone agonist or gender reassignment or clinical psychology or counselling or psychotherapy or gender-affirming or gender-affirming or oestrogen or estrogen or testosterone or fertility preservation or social transitioning or voice training).ti,ab.	**1389** [1378]
3	(Adolescen* or youth* or young person* or young people* or teen* or young adult* or pediatric* or paediatric* or child*).ti,ab.	**451** [454]
4	(Safety or benefit* or Side-effect* or risk* or harm* or significant adverse drug reaction* or ADRs or effect* or impact* or outcome*).ti,ab.	**801** [426]
5	1 and 2 and 3 and 4	0 [0]
6	limit 5 to yr="2019 - 2023"	0 [0]
7	**limit 6 to english language [Limit not valid; records were retained]**	**0 [0]**

Database: Cochrane
Search Date: 19 Sep 2023
Yield: 295

Query	Results
(Transgender:ti,ab OR "gender dysphoria":ti,ab OR trans:ti,ab OR "gender diverse":ti,ab OR "trans or gender diverse":ti,ab OR TGD:ti,ab OR "gender incongruent":ti,ab OR "gender identity":ti,ab OR "gender identity disorders":ti,ab OR “gender incongruence”:ti,ab OR “non-binary”:ti,ab OR “non binary”:ti,ab)	**5749** [5699]
(Treatment*:ti,ab OR management:ti,ab OR intervention*:ti,ab OR ("hormone" NEXT blocker*):ti,ab OR ("hormone" NEXT therap*):ti,ab OR ("puberty" NEXT suppress*):ti,ab OR ("puberty" NEXT blocker*):ti,ab OR ("pubertal" NEXT suppress*):ti,ab OR anti-androgen:ti,ab OR antiandrogen*:ti,ab OR ("androgen" NEXT antagonist*):ti,ab OR oestradiol:ti,ab OR estradiol:ti,ab OR "gender-affirming hormone":ti,ab OR "gonadotropin releasing hormone agonist":ti,ab OR "gender reassignment":ti,ab OR “clinical psychology”:ti,ab OR counselling:ti,ab OR psychotherapy:ti,ab OR “gender affirming”:ti,ab OR “gender-affirming”:ti,ab OR oestrogen:ti,ab OR estrogen:ti,ab OR testosterone:ti,ab OR “fertility preservation”:ti,ab OR “social transitioning”:ti,ab OR “voice training”:ti,ab)	**1,215,913** [1,201,199]
(Adolescen*:ti,ab OR youth*:ti,ab OR ("young" NEXT person*):ti,ab OR ("young" NEXT people*):ti,ab OR teen*:ti,ab OR ("young" NEXT adult*):ti,ab OR pediatric*:ti,ab OR paediatric*:ti,ab OR child*:ti,ab)	**203,311** [202,361]
(Safety:ti,ab OR benefit*:ti,ab OR Side-effect*:ti,ab OR risk*:ti,ab OR harm*:ti,ab OR ("significant adverse drug" NEXT reaction*):ti,ab OR ADRs:ti,ab OR effect*:ti,ab OR impact*:ti,ab OR outcome*:ti,ab)	**1,532,955** [649,385]
#1 AND #2 AND #3 AND #4	**399**
Limit to Jan 2019 to Dec 2023	**295 [164]**

Database: CINAHL

Search Date: 19 Sep 2023

Yield: 504

Query	Results
((TI Transgender OR AB Transgender) OR (TI "gender dysphoria" OR AB "gender dysphoria") OR (TI trans OR AB trans) OR (TI "gender diverse" OR AB "gender diverse") OR (TI "trans or gender diverse" OR AB "trans or gender diverse") OR (TI TGD OR AB TGD) OR (TI "gender incongruent" OR AB "gender incongruent") OR (TI "gender identity" OR AB "gender identity")OR (TI "gender identity disorders" OR AB "gender identity disorders") OR (TI "gender incongruence" OR AB "gender incongruence") OR (TI "non-binary" OR AB "non-binary") OR (TI "non binary" OR AB "non binary"))	**19,872** [19,619]
((TI Treatment* OR AB Treatment*) OR (TI management OR AB management) OR (TI intervention* OR AB intervention*) OR (TI "hormone blocker*" OR AB "hormone blocker*") OR (TI "hormone therap*" OR AB "hormone therap*") OR (TI "puberty suppress*" OR AB "puberty suppress*") OR (TI "puberty blocker*" OR AB "puberty blocker*") OR (TI "pubertal suppress*" OR AB "pubertal suppress*") OR (TI anti-androgen OR AB anti-androgen) OR (TI antiandrogen* OR AB antiandrogen*) OR (TI "androgen antagonist*" OR AB "androgen antagonist*") OR (TI oestradiol OR AB oestradiol) OR (TI estradiol OR AB estradiol) OR (TI "gender-affirming hormone dose" OR AB "gender-affirming hormone") OR (TI "gonadotropin releasing hormone agonist" OR AB "gonadotropin releasing hormone agonist") OR (TI "gender reassignment" OR AB "gender reassignment") OR (TI "clinical psychology" OR AB "clinical psychology") OR (TI counselling OR AB counselling) OR (TI psychotherapy OR AB psychotherapy) OR (TI "gender affirming" OR AB "gender affirming") OR (TI "gender-affirming" OR AB "gender-affirming") OR (TI oestrogen OR AB oestrogen) OR (TI estrogen OR AB estrogen) OR (TI testosterone OR AB testosterone) OR (TI "fertility preservation" OR AB "fertility preservation") OR (TI "social transitioning" OR AB “social transitioning”) OR TI "voice training" OR AB “voice training”))	**1,842,601** [1,802,740]
((TI adolescen* OR AB adolescen*) OR (TI youth* OR AB youth*) OR (TI "young person*" OR AB "young person*") OR (TI "young people*" OR AB "young people*") OR (TI teen* OR AB teen*) OR (TI "young adult*" OR AB "young adult*") OR (TI pediatric* OR AB pediatric*) OR (TI paediatric* OR AB paediatric*) OR (TI child* OR AB child*))	**854,420**
((TI Safety OR AB Safety) OR (TI benefit* OR AB benefit*) OR (TI Side-effect* OR AB Side-effect*) OR (TI risk* OR AB risk*) OR (TI harm* OR AB harm*) OR (TI "significant adverse drug reaction*" OR AB "significant adverse drug reaction*") OR (TI ADRs OR AB ADRs) OR (TI effect* OR AB effect*) OR (TI impact* OR AB impact*) OR (TI outcome* OR AB outcome*))	**2,919,809** [1,802,740]

1 and 2 and 3 and 4	936
Limit to 2019 – 2023	**582**
Limit to English	**581**

Reference list checking of supplied guidelines

Telfer MM, Tollit MA, Pace CC Pang KC. (2020) Australian Standards of Care and Treatment Guidelines for Trans and Gender Diverse Children and Adolescents. Melbourne: The Royal Children's Hospital: **No citations from 2019 were identified.**

AusPATH (2022) Australian Informed Consent Standards of Care for Gender-affirming Hormone Therapy. Australia: Australian Professional Association for Trans Health:

- **One relevant citation was identified, which was already included in the Evidence Check (**Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to Gender-Affirming Hormones during Adolescence and Mental Health Outcomes among Transgender Adults. PLOS ONE. 2022;17(1): e0261039. https://doi.org/10.1371/journal.pone.0261039).
- **One relevant additional study was added:** Scheim AI, Perez-Brumer AG, Bauer GR. Gender-Concordant Identity Documents and Mental Health among Transgender Adults in the USA: A Cross-Sectional Study. Lancet Pub Health. 2020;5(4): e196–203. https://doi.org/10.1016/S2468-2667(20)30032-3.

Cheung AS, Wynne K, Erasmus J, Murray S, Zajac JD. Position statement on the hormonal management of adult transgender and gender diverse individuals. Med J Aust. 2019;211(3): 127–33. https://doi.org/10.5694/mja2.50259: **No relevant citations were identified.**

Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema, SE, Meyer WJ, Murad MH et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102(11): 3869–3903. https://doi.org/10.1210/jc.2017-01658. **The reference list was not scanned as this guideline was written in 2017.**

Coleman E, Radix AE, Bouman WP, Brown GR, de Vries ALC, Deutsch MB et al. Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, Int J Transgend Health. 2022;23(sup1): S1–S259. https://doi.org/10.1080/26895269.2022.2100644.

We reviewed 29 potentially relevant citations in full text and added an additional nine relevant studies.

References

1. NSW Government 2023. Framework for the Specialist Trans and Gender Diverse Health Service for People Under 25 Years. NSW Ministry of Health. https://www.health.nsw.gov.au/lgbtiq-health/Pages/tgd-framework.aspx.

2. Watson C, Davidson S, Bourke S, Bourchier L, Temple-Smith M, Sanci L. Evidence for Effective Interventions for Children and Young People with Gender Dysphoria: An Evidence Check Rapid Review Brokered by the Sax Institute (www.saxinstitute.org.au) for the NSW Ministry of Health, 2020. The Sax Institute.

3. Javier C, Crimston CR, Barlow FK. Surgical Satisfaction and Quality of Life Outcomes Reported by Transgender Men and Women at Least One Year Post Gender-Affirming Surgery: A Systematic Literature Review. Int J Transgend Health 2022;23(3):255–73. https://doi.org/10.1080/26895269.2022.2038334.

4. Craig P, Gunnell D, Ogilvie D, Sutton M, Thompson S. Using Natural Experiments to Evaluate Population Health Interventions: Guidance for Producers and Users of Evidence Prepared on Behalf of the Medical Research Council, 2012. www.mrc.ac.uk/naturalexperimentsguidance.

5. Moussaoui D, Elder CV, O'Connell MA, Mclean A, Grover SR, Pang KC. Pelvic Pain in Transmasculine Adolescents Receiving Testosterone Therapy. Int J Transgend Health 2022 Nov;25(1):10–18. https://doi.org/10.1080/26895269.2022.2147118.

6. Moussaoui D, O'Connell MA, Elder CV, Grover SR, Pang KC. Characteristics of Menstrual Suppression and Its Association With Mental Health in Transgender Adolescents. Obstet Gynecol 2023;142(5):1096–1104. https://doi.org/10.1097/AOG.0000000000005317.

7. van der Loos MATC, Klink DT, Hannema SE, Bruinsma S, Steensma TD, Kreukels BPC, Cohen-Kettenis PT, de Vries ALC, den Heijer M, Wiepjes CM. Children and Adolescents in the Amsterdam Cohort of Gender Dysphoria: Trends in Diagnostic- and Treatment Trajectories during the First 20 Years of the Dutch Protocol. J Sex Med 2023;20(3):398–409. https://doi.org/10.1093/jsxmed/qdac029.

8. van der Loos MATC, Hannema SE, Klink DT, den Heijer M, Wiepjes CM. Continuation of Gender-Affirming Hormones in Transgender People Starting Puberty Suppression in Adolescence: A Cohort Study in the Netherlands. Lancet Child Adolesc Health 2022;6(12):869–75. https://doi.org/10.1016/S2352-4642(22)00254-1.

9. Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty Suppression in Transgender Children and Adolescents. Lancet Diabetes Endocrinol 2017;5(10):816–26. https://doi.org/10.1016/S2213-8587(17)30099-2.

10. Telfer MM, Tollit MA, Pace CC, Pang KC. Australian Standards of Care and Treatment Guidelines for Transgender and Gender Diverse Children and Adolescents. Med J Aust 2018;209(3):132–36. https://doi.org/10.5694/mja17.01044.

11. Expósito-Campos, P, Pérez-Fernández JI, Salaberria K. Empirically Supported Affirmative Psychological Interventions for Transgender and Non-Binary Youth and Adults: A Systematic Review. Clin Psychol Rev 2023(Mar);100:102229. https://doi.org/10.1016/j.cpr.2022.102229.

12. Christensen JA, Oh J, Linder K, Imhof RL, Croarkin PE, Bostwick JM, McKean AJS. Systematic Review of Interventions to Reduce Suicide Risk in Transgender and Gender Diverse Youth. Child Psychiatry Hum Dev 2023; Epub ahead of print 2023 May 10. https://doi.org/10.1007/s10578-023-01541-w.

13. NSW Government 2022. NSW LGBTQI+ Health Strategy 2022–2027. NSW Ministry of Health. https://www.health.nsw.gov.au/lgbtiq-health/Pages/lgbtiq-health-strategy.aspx.

14. Coleman K, Norris S, Middleton P, Tooher R, Salisbury J. NHMRC Additional Levels of Evidence and Grades for Recommendations for Developers of Guidelines STAGE 2 CONSULTATION. Early 2008 – end June 2009.

15. Merlin T, Weston A, Tooher R. Extending an Evidence Hierarchy to Include Topics Other than Treatment: Revising the Australian 'Levels of Evidence.' BMC Med Res Methodol 2009;9(1):34. https://doi.org/10.1186/1471-2288-9-34.

16. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J et al. "AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews That Include Randomised or Non-Randomised Studies of Healthcare Interventions, or Both." BMJ 2017 Sep 21;358:j4008. https://doi.org/10.1136/bmj.j4008.

17. Expósito-Campos P. A Typology of Gender Detransition and Its Implications for Healthcare Providers. J Sex Marital Ther 2021;47(3):270–80. https://doi.org/10.1080/0092623X.2020.1869126.

18. Angus LM, Nolan BJ, Jeffrey D. Zajac JD, Cheung AS. A Systematic Review of Antiandrogens and Feminization in Transgender Women. Clin Endocrinol (Oxf) 2021; 94(5):743–52. https://doi.org/10.1111/cen.14329.

19. Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review. J Endocr Soc 2021 Feb 2;(4): bvab011. doi: 10.1210/jendso/bvab011.

20. D'hoore L, T'Sjoen Guy. Gender-affirming Hormone Therapy: An Updated Literature Review with an Eye on the Future. J Intern Med 2022;291(5):574–92. https://doi.org/10.1111/joim.13441.

21. Defreyne J, van de Bruaene LDL, Rietzschel E, van Schuylenbergh J, T'Sjoen GGR. Effects of Gender-Affirming Hormones on Lipid, Metabolic, and Cardiac Surrogate Blood Markers in Transgender Persons. Clin Chem 2019;65(1):119–34. https://doi.org/10.1373/clinchem.2018.288241.

22. Ludvigsson JF, Adolfsson J, Höistad M, Rydelius P-A, Kriström B, Landén M. A Systematic Review of Hormone Treatment for Children with Gender Dysphoria and Recommendations for Research. Acta Paediatr 2023;112(11):2279–92. https://doi.org/10.1111/apa.16791.

23. Malpas J, Pellicane MJ, Glaeser E. Family-Based Interventions with Transgender and Gender Expansive Youth: Systematic Review and Best Practice Recommendations. Transgend Health 2022;7(1):7–29. https://doi.org/10.1089/trgh.2020.0165.

24. National Institute for Health and Care Excellence (NICE). Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria. NICE 2020a. https://cass.independent-review.uk/nice-evidence-reviews/.

25. National Institute for Health and Care Excellence (NICE). Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria. NICE 2020b. https://cass.independent-review.uk/nice-evidence-reviews/.

26. Ramos GGF, Mengai ACS, Daltro CAT, Cutrim PT, Zlotnik E, Beck APA. Systematic Review: Puberty Suppression with GnRH Analogues in Adolescents with Gender Incongruity. J Endocrinol Invest 2021;44(6):1151–58. https://doi.org/10.1007/s40618-020-01449-5.

27. Rew L, Young CC, Monge M, Bogucka R. Review: Puberty blockers for transgender and gender diverse youth—a critical review of the literature. Child Adolesc Ment Health 2021;26(1):3–14. https://doi.org/10.1111/camh.12437.

28. Rowniak S, Bolt L, Sharifi C. Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: A quantitative systematic review. JBI Database System Rev Implement Rep 2019;17(9):1826–54. https://doi.org/10.11124/JBISRIR-2017-003869.

29. Stolk THR, Asseler JD, Huirne JAF, van den Boogaard E, van Mello NM. Desire for Children and Fertility Preservation in Transgender and Gender-Diverse People: A Systematic Review. Best Pract Res Clin Obstet Gynaecol 2023 Mar;87:102312. https://doi.org/10.1016/j.bpobgyn.2023.102312.

30. Yan M, Bustos SS, Kuruoglu D, Ciudad P, Forte AJ, Kim EA et al. “Systematic Review of Fertility Preservation Options in Transgender Patients: A Guide for Plastic Surgeons.” Ann Transl Med 2021;9(7):613. https://doi.org/10.21037/atm-20-4523.

31. Aromataris E, Munn Z (eds). JBI Manual for Evidence Synthesis. JBI. 2020. https://doi.org/10.46658/JBIMES-20-01.

32. Bauermeister J, Choi SK, Bruehlman-Senecal E, Golinkoff J, Taboada A, Lavra J, Ramazzini L, Dillon F, Haritatos J. An Identity-Affirming Web Application to Help Sexual and Gender Minority Youth Cope With Minority Stress: Pilot Randomized Controlled Trial. J Med Internet Res 2022;24(8):e39094. https://doi.org/10.2196/39094.

33. Barker TH, Stone JC, Sears K, Klugar M, Tufanaru C, Leonardi-Bee J, Aromataris E, Munn Z. The Revised JBI Critical Appraisal Tool for the Assessment of Risk of Bias for Randomized Controlled Trials. JBI Evid Synth 2023.21(3):494–506. https://doi.org/10.11124/JBIES-22-00430.

34. Rochlin DH, Brazio P, Wapnir I, Nguyen D. Immediate Targeted Nipple–Areolar Complex Reinnervation: Improving Outcomes in Gender-Affirming Mastectomy. Plast Reconstr Surg Glob Open 2020 Mar 25;8(3):e2719. https://doi.org/10.1097/GOX.0000000000002719.

35. Tufanaru C, Munn Z, Aromatis E, Campbell J, Hopp L. Checklist for Quasi-Experimental Studies (Non-Randomized Experimental Studies). In Chapter 3: Systematic Reviews of Effectiveness. In JBI Manual for Evidence Synthesis. Adelaide, Australia: JBI 2020. https://synthesismanual.jbi.global.

36. Ascha M, Sasson DC, Sood R, Cornelius JW, Schauer JM, Runge A et al. Top Surgery and Chest Dysphoria Among Transmasculine and Nonbinary Adolescents and Young Adults. JAMA Pediatr 2022;176(11):1115–22. https://doi.org/10.1001/jamapediatrics.2022.3424.

37. Boogers LS, Wiepjes CM, Klink DT, Hellinga I, van Trotsenburg ASP, den Heijer M et al. Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment. J Clin Endocrinol Metab 2022;107(9):e3805–15. https://doi.org/10.1210/clinem/dgac349.

38. Bungener SL, de Vries ALC, Popma A, Thomas D. Steensma TD. Sexual Experiences of Young Transgender Persons During and After Gender-Affirmative Treatment. Pediatrics 2020.146(6):e20191411. https://doi.org/10.1542/peds.2019-1411.

39. Eitel KB, Hodax JK, DiVall S, Kidd KM, Salehi P, Sequeira GM. Leuprolide Acetate for Puberty Suppression in Transgender and Gender Diverse Youth: A Comparison of Subcutaneous Eligard Versus Intramuscular Lupron. J Adolesc Health 2023;72(2):307–11. https://doi.org/10.1016/j.jadohealth.2022.09.017.

40. Hranilovich JA, Millington K. Headache Prevalence in Transgender and Gender Diverse Youth: A Single-center Case–Control Study. Headache 2023;63(4):517–22. https://doi.org/10.1111/head.14493.

41. Millington K, Barrera E, Daga A, Mann N, Olson-Kennedy J, Garofalo R, Rosenthal SM, Chan Y-M. The Effect of Gender-Affirming Hormone Treatment on Serum Creatinine in Transgender and Gender-Diverse Youth: Implications for Estimating GFR. Pediatr Nephrol 2022;37(9):2141–50.

42. Olson-Kennedy J, Streeter LH, Garofalo R, Chan Y-M, Rosenthal SM. Histrelin Implants for Suppression of Puberty in Youth with Gender Dysphoria: A Comparison of 50 Mcg/Day (Vantas) and 65 Mcg/Day (SupprelinLA). Transgend Health 2021;6(1): 36–42. https://doi.org/10.1089/trgh.2020.0055.

43. Schulmeister C, Millington K, Kaufman M, Finlayson C, Olson-Kennedy J, Garofalo R et al. Growth in Transgender/Gender-Diverse Youth in the First Year of Treatment With Gonadotropin-Releasing Hormone Agonists. J Adolesc Health 2022;70(1):108–13. https://doi.org/10.1016/j.jadohealth.2021.06.022.

44. Valentine A, Davis S, Furniss A, Dowshen N, Kazak AE, Lewis C et al. Multicenter Analysis of Cardiometabolic-Related Diagnoses in Transgender and Gender-Diverse Youth: A PEDSnet Study. J Clin Endocrinol Metab 2022;107(10):e4004–14. https://doi.org/10.1210/clinem/dgac469.

45. Valentine A, Nokoff N, Bonny A, Chelvakumar G, Indyk J, Leibowitz S et al. Cardiometabolic Parameters Among Transgender Adolescent Males on Testosterone Therapy and Body Mass Index-Matched Cisgender Females. Transgend Health 2021;6(6):369–73. https://doi.org/10.1089/trgh.2020.0052.

46. van de Grift TC, van Gelder ZJ, Mullender MG, Steensma TD, de Vries ALC, Bouman M-B. Timing of Puberty Suppression and Surgical Options for Transgender Youth. Pediatrics 2020;146 (5): e20193653. https://doi.org/10.1542/peds.2019-3653.

47. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R et al. Checklist for Cohort Studies. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (eds) JBI Manual for Evidence Synthesis. JBI, 2020c. Available from https://synthesismanual.jbi.global.

48. Allen SD, Tollit MA, McDougall R, Eade D, Hoq M, Pang KC. A Waitlist Intervention for Transgender Young People and Psychosocial Outcomes. Pediatrics 2021;148(2):e2020042762. doi: 10.1542/peds.2020-042762.

49. Mejia-Otero JD, White P, Lopez X. Effectiveness of Puberty Suppression with Gonadotropin-Releasing Hormone Agonists in Transgender Youth. Transgend Health 2021;6(1):31–35. https://doi.org/10.1089/trgh.2020.0007.

50. Peri A, Ahler A, Gook D, O'Connell MA, Bourne H, Nightingale M et al. Predicting Successful Sperm Retrieval in Transfeminine Adolescents after Testicular Biopsy. J Assist Reprod Genet 2021;38(10):2735–43. https://doi.org/10.1007/s10815-021-02293-z.

51. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R et al. Checklist for Case Control Studies. Chapter 7: Systematic Reviews of Etiology and Risk. In Aromataris E, Munn Z (eds) JBI Manual for Evidence Synthesis. JBI, 2020b. Available from https://synthesismanual.jbi.global.

52. Lavender R, Shaw S, Maninger J-K, Butler G, Carruthers P, Carmichael P, Masic U. Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. LGBT Health 2023;10(5):382–90. https://doi.org/10.1089/lgbt.2022.0201.

53. Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. J Clin Endocrinol Metab 2020 Dec 1;105(12):e4252–63. https://doi.org/10.1210/clinem/dgaa604.

54. Alaniz VI, Sheeder JL, Whitmore GT, Wilde MD, Hutchens KJ, Nokoff NJ et al. Menstrual Suppression in Adolescent and Young Adult Transgender Males. J Pediatr Adolesc Gynecol 2023;36(2):116–21. https://doi.org/10.1016/j.jpag.2022.10.007.

55. Allen LR, Watson LB, Egan AM, Moser CN. Well-Being and Suicidality among Transgender Youth after Gender-Affirming Hormones. Clin Pract Pediatr Psychol 2019;7(3):302–11. https://doi.org/10.1037/cpp0000288.

56. Arnoldussen M, Evelien C Hooijman EC, Kreukels BPC, de Vries ALC. Association between Pre-Treatment IQ and Educational Achievement after Gender-Affirming Treatment Including Puberty Suppression in Transgender Adolescents. Clin Child Psychol Psychiatry 2022;27(4):1069–76. https://doi.org/10.1177/13591045221091652.

57. Barrett F, Shaw J, Blakemore JK, Fino ME. Fertility Preservation for Adolescent and Young Adult Transmen: A Case Series and Insights on Oocyte Cryopreservation. Front Endocrinol (Lausanne) 2022 May 24;13:873508. https://doi.org/10.3389/fendo.2022.873508.

58. Becker-Hebly I Fahrenkrug S, Campion F, Richter-Appelt H, Schulte-Markwort M, Barkmann C. Psychosocial Health in Adolescents and Young Adults with Gender Dysphoria before and after Gender-Affirming Medical Interventions: A Descriptive Study from the Hamburg Gender Identity Service. Eur Child Adolesc Psychiatry. 2021;30(11)1755–67.

59. Bluth K, Lathren C, Clepper-Faith M, Larson LM, Ogunbamowo DO, Pflum S. Improving Mental Health Among Transgender Adolescents: Implementing Mindful Self-Compassion for Teens. J Adolesc Res 2023;38(2):271–302. https://doi.org/10.1177/07435584211062126.

60. Boogers LS, van der Loos MATC, Wiepjes CM, van Trotsenburg ASP, den Heijer M, Hannema SE. 2023. The Dose-Dependent Effect of Estrogen on Bone Mineral Density in Trans Girls. Eur J Endocrinol 2023;189(2):290–96. https://doi.org/10.1093/ejendo/lvad116.

61. Boskey ER, Jolly D, Kant JD, Ganor O. Prospective Evaluation of Psychosocial Changes After Chest Reconstruction in Transmasculine and Non-Binary Youth. J Adolesc Health 2023;73(3):503–09. https://doi.org/10.1016/j.jadohealth.2023.04.029.

62. Brik T, Vrouenraets LJJJ, Schagen SEE, Meissner A, de Vries MC, Hannema SE. Use of Fertility Preservation Among a Cohort of Transgirls in the Netherlands. J Adolesc Health 2019;64(5):589–93. https://doi.org/10.1016/j.jadohealth.2018.11.008.

63. Cantu AL, Moyer DN, Connelly KJ, Holley AL. Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic. Transgend Health 2020;5(3):196–200. https://doi.org/10.1089/trgh.2019.0077.

64. Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S et al. Short-Term Outcomes of Pubertal Suppression in a Selected Cohort of 12 to 15 Year Old Young People with Persistent Gender Dysphoria in the UK. PLoS ONE 2021 Feb 2;16(2):0243894. doi: 10.1371/journal.pone.0243894.

65. Chen D, Berona J, Chan Y-M, Ehrensaft D, Garofalo R, Hidalgo MA et al. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. N Engl J Med. 2023;388(3):240–50.

66. de Nie I, Mulder CL, Meißner A, Schut Y, Holleman EM, van der Sluis WB et al. Histological Study on the Influence of Puberty Suppression and Hormonal Treatment on Developing Germ Cells in Transgender Women. Hum Reprod 2022;37(2):297–308. https://doi.org/10.1093/humrep/deab240.

67. Dilday EA, Bukulmez O, Saner K, Lopez X, Jarin J. Sperm Cryopreservation Outcomes in Transgender Adolescents Compared with Adolescents Receiving Gonadotoxic Therapy. Transgend Health 2022;7(6):528–32. https://doi.org/10.1089/trgh.2021.0037.

68. Elkadi J, Chudleigh C, Maguire AM, Ambler GR, Scher S, Kozlowska K. Developmental Pathway Choices of Young People Presenting to a Gender Service with Gender Distress: A Prospective Follow-Up Study. Children 2023;10(2):314. https://doi.org/10.3390/children10020314.

69. Ghelani R, Lim C, Brain C, Fewtrell M, Butler G. Sudden Sex Hormone Withdrawal and the Effects on Body Composition in Late Pubertal Adolescents with Gender Dysphoria. J Pediatr Endocrinol Metab 2020;33(1):107–12. https://doi.org/10.1515/jpem-2019-0045.

70. Grimstad F, Kremen J, Shim J, Charlton BM, Boskey ER. Breakthrough Bleeding in Transgender and Gender Diverse Adolescents and Young Adults on Long-Term Testosterone. J Pediatr Adolesc Gynecol 2021b;34(5):706–16. https://doi.org/10.1016/j.jpag.2021.04.004.

71. Grimstad FW, Knoll MM, Jacobson JD. Oxandrolone Use in Trans-Masculine Youth Appears to Increase Adult Height: Preliminary Evidence. LGBT Health 2021;8(4):300–306. https://doi.org/10.1089/lgbt.2020.0355.

72. Gupta P, Patterson BC, Chu L, Gold S, Amos S, Yeung H et al. Adherence to Gender Affirming Hormone Therapy in Transgender Adolescents and Adults: A Retrospective Cohort Study. J Clin Endocrinol 2023 Oct 18;108(11):e1236–44. doi: 10.1210/clinem/dgad306.

73. Hisle-Gorman E, Schvey NA, Adirim TA, Rayne AK, Susi Apryl, Roberts TA et al. Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment. J Sex Med 2021;18 (8):1444–54. https://doi.org/10.1016/j.jsxm.2021.05.014.

74. Joseph T, Ting J, Butler G. The Effect of GnRH Analogue Treatment on Bone Mineral Density in Young Adolescents with Gender Dysphoria: Findings from a Large National Cohort. J Pediatr Endocrinol Metab 2019;32(10):1077–81. https://doi.org/10.1515/jpem-2019-0046.

75. Kaltiala R, Heino E, Työläjärvi M, Suomalainen L. Adolescent Development and Psychosocial Functioning after Starting Cross-Sex Hormones for Gender Dysphoria. Nord J Psychiatry 2020;74(3):213–19. https://doi.org/10.1080/08039488.2019.1691260.

76. Laurenzano SE, Newfield RS, Lee E, and Marinkovic M. Subcutaneous Testosterone Is Effective and Safe as Gender-Affirming Hormone Therapy in Transmasculine and Gender-Diverse Adolescents and Young Adults: A Single Center's 8-Year Experience. Transgend Health 2021 Dec 2;6(6):343–52. https://doi.org/10.1089/trgh.2020.0103.

77. Millington K, Liu E, Chan Y-M. The Utility of Potassium Monitoring in Gender-Diverse Adolescents Taking Spironolactone. J Endoc Soc 2019;3(5):1031–38. https://doi.org/10.1210/js.2019-00030.

78. Mullins ES, Geer R, Metcalf M, Piccola J, Lane A, Conard LAE et al.. Thrombosis Risk in Transgender Adolescents Receiving Gender-Affirming Hormone Therapy Pediatrics 2021 Apr;147(4)e2020023549. doi:10.1542/peds.2020-023549.

79. Navabi B, Tang K, Khatchadourian K, Lawson ML. Pubertal Suppression, Bone Mass, and Body Composition in Youth With Gender Dysphoria. Pediatrics 2021;148(4):e2020039339. https://doi.org/10.1542/peds.2020-039339.

80. Nieder TO, Mayer TK, Hinz S, Fahrenkrug S, Herrmann L, Becker-Hebly I. Individual Treatment Progress Predicts Satisfaction with Transition-Related Care for Youth with Gender Dysphoria: A Prospective Clinical Cohort Study. J Sex Med 2021;18(3):632–45. https://doi.org/10.1016/j.jsxm.2020.12.010.

81. Nos AL, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E, Susi A et al. Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming

Hormones Among Transgender Adolescents. JAMA Netw Open 2022;5(11):e2239758. https://doi.org/10.1001/jamanetworkopen.2022.39758.

82. Olsavsky AL, Grannis C, Bricker J, Chelvakumar G, Indyk JA, Leibowitz SF et al. Associations Among Gender-Affirming Hormonal Interventions, Social Support, and Transgender Adolescents' Mental Health. J Adolesc Health 2023;72(6):860–68. https://doi.org/10.1016/j.jadohealth.2023.01.031.

83. Pham AH, Eadeh H-M, Garrison MM, Ahrens KR. A Longitudinal Study on Disordered Eating in Transgender and Nonbinary Adolescents. Acad Pediatr 2023;23(6):1247–51. https://doi.org/10.1016/j.acap.2022.12.013.

84. Pine-Twaddell E, Newfield RS, Marinkovic M. Extended Use of Histrelin Implant in Pediatric Patients. Transgend Health 2023;8(3):264–72. https://doi.org/10.1089/trgh.2021.0130.

85. Schwartz BI, Bear B, Short VL, Kazak AE. Outcomes of Menstrual Management Use in Transgender and Gender-Diverse Adolescents. Obstet Gynecol 2023;141(4):748–55. https://doi.org/10.1097/AOG.0000000000005123.

86. Sequeira GM, Kidd K, El Nokali NE, Rothenberger SD, Levine MD, Montano GT et al. Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. J Adolesc Health 2019;65 (6):818–20. https://doi.org/10.1016/j.jadohealth.2019.06.009.

87. Strang JF, Chen D, Nelson E, Leibowitz SF, Nahata L, Anthony LG et al. Transgender Youth Executive Functioning: Relationships with Anxiety Symptoms, Autism Spectrum Disorder, and Gender-Affirming Medical Treatment Status. Child Psychiatry Hum Dev 2022 Dec;53(6):1252–65. https://doi.org/10.1007/s10578-021-01195-6.

88. Tang A, Hojilla JC, Jackson JE, Rothenberg KA, Gologorsky RC, Stram DA et al. Gender-Affirming Mastectomy Trends and Surgical Outcomes in Adolescents. Ann Plast Surg 2022;88(4):S325–31. https://doi.org/10.1097/SAP.0000000000003135.

89. Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. JAMA Netw Open 2022 Feb 1;5(2):e220978. https://doi.org/10.1001/jamanetworkopen.2022.0978.

90. Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to Gender-Affirming Hormones during Adolescence and Mental Health Outcomes among Transgender Adults. Edited by Radix AE. *PLoS ONE* 2022.17 (1): e0261039. https://doi.org/10.1371/journal.pone.0261039.Erratum in: PLoS One. 2023 Jun 12;18(6):e0287283. doi: 10.1371/journal.pone.0287283. PMID: 35020719; PMCID: PMC8754307.

91. Waldner RC, Doulla M, Atallah J, Rathwell S, Grimbly C. Leuprolide Acetate and QTc Interval in Gender-Diverse Youth. Transgend Health 2023;8(1):84–88. https://doi.org/10.1089/trgh.2021.0102.

92. National Institutes of Health. The National Institutes of Health (NIH) Quality Assessment Tool for before-after (Pre-Post) Study with No Control Group. 2021. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

93. Grannis C, Leibowitz SF, Gahn S, Nahata L, Morningstar M, Mattson WI et al. Testosterone Treatment, Internalizing Symptoms, and Body Image Dissatisfaction in Transgender Boys. Psychoneuroendocrinology 2021 Oct;132:105358. Epub 2021 Jul 17. https://doi.org/10.1016/j.psyneuen.2021.105358.

94. Grannis C, Mattson WI, Leibowitz SF, Nahata L, Chen D, Strang JF et al. Expanding upon the Relationship between Gender-Affirming Hormone Therapy, Neural Connectivity, Mental Health, and Body Image Dissatisfaction. Psychoneuroendocrinology 2023 Oct;156:106319. Epub 2023 Jun 8. https://doi.org/10.1016/j.psyneuen.2023.106319.

95. Hughto JMW, Gunn HA, Rood BA, Pantalone DavidW. Social and Medical Gender Affirmation Experiences Are Inversely Associated with Mental Health Problems in a U.S. Non-Probability Sample of Transgender Adults. Arch Sex Behav 2020;49(7):2635–47. https://doi.org/10.1007/s10508-020-01655-5.

96. Julian JM, Salvetti B, Held JI, Murray PM, Lara-Rojas L, Olson-Kennedy J. The Impact of Chest Binding in Transgender and Gender Diverse Youth and Young Adults. J Adolesc Health 2021 Jun;68(6):1129–34. https://doi.org/10.1016/j.jadohealth.2020.09.029.

97. Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics 2020 Feb;145(2):e20191725. https://doi.org/10.1542/peds.2019-1725.

98. van der Miesen AIR, Steensma TD, de Vries ALC, Bos H, Popma A. Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. J Adolesc Health 2020 Jun;66(6):699-704. Epub 2020 Apr 6. doi:10.1016/j.jadohealth.2019.12.018.

99. Moola S, Munn Z, Aromataris E, Sears K, Sfetcu R, Currie M et al. Checklist for Analytical Cross Sectional Studies. In Chapter 7: Systematic Reviews of Etiology and Risk. In JBI Manual for Evidence Synthesis. JBI. 2020a. Available from https://synthesismanual.jbi.global.

100. Frieden TR. Evidence for Health Decision Making — Beyond Randomized, Controlled Trials. *N Eng J Med* 2017;377(5):465–75. https://doi.org/10.1056/NEJMra1614394.

101. Bragge P, Piccenna L, Middleton JW, Williams S, Creasey G, Dunlop S et al. Developing a Spinal Cord Injury Research Strategy Using a Structured Process of Evidence Review and Stakeholder Dialogue. Part I: Rapid Review of SCI Prioritisation Literature. Spinal Cord 2015a;53(10):714–20. https://doi.org/10.1038/sc.2015.85.

102. Bragge P, Piccenna L, Middleton J, Williams S, Creasey G, Dunlop S et al. Developing a Spinal Cord Injury Research Strategy Using a Structured Process of Evidence Review and Stakeholder Dialogue. Part II: Background to a Research Strategy. Spinal Cord 2015b;53(10):721–28. https://doi.org/10.1038/sc.2015.86.

103. Middleton JW, Piccenna L, Lindsay Gruen R, Williams S, Creasey G et al. Developing a Spinal Cord Injury Research Strategy Using a Structured Process of Evidence Review and Stakeholder Dialogue. Part III: Outcomes. Spinal Cord 2015c;53 (10):729–37. https://doi.org/10.1038/sc.2015.87.

104. Pearson H. How COVID Broke the Evidence Pipeline. Nature 2021 May 12; 593(7858): 182–85. https://doi.org/10.1038/d41586-021-01246-x.

From: CLANCY, Trish
To: s47F ; MARTIN, Nick; s47F
Cc: s47F ; DEVELIN, Liz; ANDREWS, Tracey; s47E(c), s47F
Subject: RE: Puberty blocker medication for under 18s information brief [SEC=OFFICIAL]
Date: Thursday, 19 December 2024 5:54:48 PM
Attachments: image001.png
Attachment C - Sax Institute - Evidence for effective interventions for children and young people with gender dyspho.pdf
Attachment B - Sax Institute - 2024 Evidence Brief Summary - Understanding interventions for children and young peop.pdf
Attachment A - Summary of State and Territory gender-affirming care.pdf
MB24-003236.docx

Hello s47F

Please find attached the requested brief and some supporting materials.

We will also progress it through the official PDMS system tomorrow morning.

Let us know if you have any additional questions.

Trish

From: s47F @Health.gov.au>
Sent: Wednesday, 18 December 2024 10:36 AM
To: CLANCY, Trish <s47E(c), s47F @Health.gov.au>; MARTIN, Nick <s47F @Health.gov.au>; s47F @Health.gov.au>
Cc: s47E(c), s47F @Health.gov.au>; DEVELIN, Liz <s47E(c), s47F @Health.gov.au>; ANDREWS, Tracey s47E(c), s47F @health.gov.au>; s47E(c), s47F @Health.gov.au>
Subject: RE: Puberty blocker medication for under 18s information brief [SEC=OFFICIAL]

Hi Trish

Thanks again for the info brief provided on Monday.

Minister Butler has considered the brief and has requested further advice please. Can you please provide this to the office via a further info brief, **due by end of day tomorrow (Thur, 19 Dec)**.

The Minister has requested information please on:

- The prevalence of people seeking gender-affirming care in Australia, and how that has changed over time
- The model of care in Australia, including referral pathways and the treatment journey, and the occurrence and role of puberty blocker medications in the treatment journey
- More detail on how the above differs or aligns with the situation in the UK
- More details on the scope, conduct, findings, and any limitations of the Sax Institute review

Thanks in advance.

Cheers
s47F

From: CLANCY, Trish <s47E(c), s47F @Health.gov.au>
Sent: Monday, 16 December 2024 6:43 PM
To: s47F @Health.gov.au>
Cc: s47F @Health.gov.au>; DEVELIN, Liz <s47E(c), s47F @Health.gov.au>; ANDREWS, Tracey s47E(c), s47F @health.gov.au>; s47E(c), s47F @Health.gov.au>
Subject: Puberty blocker medication for under 18s information brief [SEC=OFFICIAL]

Hello s47F

Thanks for your time today.

I've approved the **Puberty blocker medication for under 18s** information brief in PDMS. I assume that it won't get through the system to you until the morning and so am also attaching it here.

You asked about the long-term impacts that the NSW Sax review outlined. The only impact (see the original text below) that was called out in any depth was the potential reduction in bone density.

I hope this helps,

Trish

Puberty suppression treatment (PS) (Number of studies by level of evidence: 3x Level I, 4x Level III-2, 1x Level III-3, 9x Level IV; total 17 studies)

We identified 17 studies pertaining to puberty suppression treatment (PS) in this Evidence Check update. Broadly, the newly identified evidence reinforced the finding of the previous Evidence Check regarding benefits and effectiveness. That is, PS agents (generally referred to as GnRHa) were reported to be safe, effective and reversible. As a counterpoint, this update identified one study describing differential implications of PS for later surgery, with reduced need for mastectomy in trans men but potential complications for genital surgery in trans women as penile inversion may be compromised. Psychological effects of PS on conditions such as depression and anxiety appear modest in comparison with GAHT, with the primary impact being reduction of distress associated with unwanted secondary sexual characteristics; two Level IV studies reflected positive impacts on gender dysphoria.

With regard to risks and potential harms, reductions in bone density remain the primary concern with PS and monitoring of bone mineral density is recommended. However, some newly identified studies suggest maintenance of bone mineral density during PS treatment. Studies reported no indications to monitor liver or renal function in the PS setting. Other reported side effects of PS were also relatively minor. Instances of insufficient suppression of puberty (known as 'pubertal escape') were reported, but satisfaction with PS treatment was reported as good overall. In summary, this Evidence Check update predominantly reinforces the findings of the previous review and adds to the evidence base underpinning these findings; with the qualification that the strength of the evidence remains low.

Evidence for effective interventions for children and young people with gender dysphoria—update (page 10)

Trish Clancy
First Assistant Secretary

Population Health Division | Primary & Community Care Group
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PO Box 9848, Canberra ACT 2601, Australia
The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present

From: CLANCY, Trish
To: DEVELIN, Liz
Cc: s47E(c), s47F ; ANDREWS, Tracey; s47E(c), s47F ; s47E(c), s47F
Subject: for info/ input: Information Brief – Additional Advice – Puberty blocker medication for under 18s [SEC=OFFICIAL]
Date: Thursday, 19 December 2024 2:51:05 PM
Attachments: MB24-003236 offline.docx
image001.png

Hi Liz,

We've been asked by the MO to provide additional information on Puberty blocker medication for under 18s:

a. Prevalence of people seeking gender-affirming care in Australia, and how that has changed over time
b. The model of care in Australia, including referral pathways and the treatment journey, and the occurrence and role of puberty blocker medications in the treatment journey
c. More detail on how the above differs or aligns with the situation in the UK
d. More details on the scope, conduct, findings, and any limitations of the Sax Institute review.

Given it's a brief you do not have a formal role in the PDMS chain, but I wanted you to have an opportunity to review. Please let us know if you have comments.

Note this is due CoB today.

Thanks to s47E(c), s47F for taking the lead here.

Cheers,

Trish

Trish Clancy
First Assistant Secretary

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The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present