SHARED CARE PRESCRIBING GUIDANCE FOR

Treatment of Gender Incongruence in Transgender women, Transfeminine and Non-binary People (Assigned Male at Birth)

Applicable to:	GPs referring clients to the adult Gender Identity Clinic, Tavistock and Portman NHS Foundation Trust
Date Approved:	January 2025
Principal Author(s):	Professor Leighton Seal, Consultant Endocrinologist Dr James Barrett, Clinical Director Dr Sofia Laura Yovou, Endocrinologist Dr Robert Stocker-Rodrigues Endocrine Clinical Nurse Specialist
Expiry date/ Review date:	January 2028
Version:	11.1
Updated on:	April 2025
Changes since last update in January 2025 (version 11)	• Minor updates to typographical errors

CONTENTS LIST

INTRODUCTION

This document has been prepared by Professor Leighton Seal, Consultant Endocrinologist, and the GIC's Clinical Team.

The information contained in this document has been compiled in order to support GPs and other medical practitioners in safe prescribing and monitoring arrangements. The document outlines the roles and responsibilities of the Gender Specialists, General Practitioners and Clients and contains both a **shared care agreement** and a client **letter of consent** for the initiation of hormones. It is imperative that clients who take the preparations, as listed, do so under medical supervision, and are monitored as recommended.

Please ensure that the latest updates on the medications and interactions, as listed, are obtained from the BNF.

Enduring validity of the principle of shared care:

If we have assessed a patient and on the basis of gender incongruence suggested hormone therapy, the principle of shared care remains valid for the duration of their time under active treatment with our service, and also after discharge. A new shared care document is not required each time we update the guidance, as the principle of shared care remains valid. Inevitably over time on hormone therapy, as with most medications, adjustments need to be made in relation to blood test results and clinical response to treatment and we give advice on this in clinic letters and

correspondence. We do not send a new shared care document each time a change to hormone therapy dosing or formulation is suggested, because the advice we provide is consistent with the shared care guidelines.

LETTER FROM CLINICAL DIRECTOR
and
CONSULTANT ENDOCRINOLOGIST

Dear Colleague

We have created this shared care protocol in order to ensure that clients who attend the Charing Cross Gender Identity Clinic receive a partnership of care from both their Gender Clinicians and their General Practitioners.

The medicine recommended by the GIC is usually an oestrogen (e.g. estradiol valerate) to cause feminisation, and which will be continued indefinitely after surgery. In some cases additional or alternative medicines are used, as outlined in the shared care protocol. Sometimes there is a need for a GnRH analogue (e.g. Decapeptyl or Zoladex) to suppress testosterone prior to surgery.

In view of the fact that clients will be having long-term maintenance treatment, it is in their best interests for their GP to prescribe and monitor their treatment, with support from our clinic as necessary.

Although not all these medicines are licensed for the treatment of gender dysphoria (nor are they likely to be), they are medicines with which, in our experience, GPs will be familiar. The doses of oestrogen are often slightly higher than would usually be prescribed, as a person assigned male at birth tends to have a larger frame and needs a bigger dose to reach the normal physiological range for a woman.

This devolvement of prescriptions to Primary Care is consistent with the GMC guidance on the provision of prescriptions for patients with gender dysphoria in Primary Care. The link for that is as follows: https://www.gmc-uk.org/ethical-guidance/ethical-hub/trans-healthcare---advice-based-on-gmc-guidance

There is a comprehensive programme for assessment and evaluation of clients referred to this clinic, into which GPs and any relevant secondary care clinicians are routinely copied. When all these assessments have been undertaken, the decision may be taken to recommend medication.

In the event that a written recommendation for hormone therapy is made, we would be grateful if arrangements can be made by the client's GP to see the client within two weeks in order to initiate the treatment.

We hope that this will give GPs enough information to feel confident to prescribe the maintenance medication as specified. If you have any questions, or would like more information, you are welcome to contact us.

Yours sincerely,

Dr James Barrett
Clinical Director, Gender Identity Clinic

Professor Leighton Seal
Consultant and Professor in Endocrinology

SUPPORTING CLINICAL INFORMATION

Indication(s):	Treatment of gender incongruence following psychiatric/psychological assessment at a Gender Identity Clinic. Binary gender identities (transgender women): The standard protocol is outlined in this shared care document. Non-binary gender identities: Though based on knowledge and experience of cross-sex hormonal therapies in transgender men and transgender women, our approach to hormone therapy for non-binary clients is multidisciplinary and individualised. An individualised assessment and treatment approach is consistent with WPATH (2022) SOC 8 guidance [1]. For clients with a non-binary gender identity, the aims of therapy may be different to the standard aims outlined in this document and as such an individualised care plan will be documented and may be updated over time.
Place in Therapy:	Hormonal therapy will usually be recommended after the initial assessments are complete. Commencement of hormonal therapy is recommended when a secure diagnosis of gender incongruence is made and the person is psychologically and socially stable. The person will be assessed as being capacitous to understand the pros and cons of treatment. Any psychological or physical health complications will be assessed and advice given on optimisation of the individual's psychological and physical health prior to starting on hormone treatment. Clinical practice in the GIC follows a modified version of the WPATH version 8 Standards of Care. The use of hormonal manipulation in the treatment of trans women is hampered by a lack of any randomised controlled trials to assist in our therapeutic decisions. There has, however, been a significant amount of experience in the treatment of this condition over the last 60 years, using several well-established hormonal protocols, and the totality of the available evidence demonstrates that, for carefully selected clients, hormone therapy is a safe and effective means of alleviating the potentially debilitating condition of gender dysphoria [2-5].
Dose & route of administration:	Baseline tests should be done, see below, prior to commencing hormone treatments. **Oestrogen to cause feminisation:** ***First Line:*** Transdermal/topical estradiol gels, patches or sprays are usually recommended as first line for patients who: • Are age 45 or higher • Have a BMI of 40 kg/m2 or higher • Smoke/use tobacco (if smoking, use cisgender HRT dosing) • Have a history of thromboembolism or risk factors for thromboembolism • Have a history of cardiovascular event or risk factors for cardiovascular disease • Have abnormal liver function tests that do not normalise on repeat • Have chronic headaches or migraine (and if there are focal/hemiplegic symptoms Neurology advice is also required regarding stroke risk and safety of oestrogen therapy). Topical oestrogen (estradiol) gel (Sandrena or Oestrogel 0.06% gel): **Sandrena gel (0.5-5mg once a day):**

Sandrena gel is initiated at a dose of 0.5 mg once a day, up to a maximum of 5 mg once a day. Dose adjusted by 0.5-1 mg every three months until there is a plasma oestradiol level of 400-600 pmol/l, 4-6 hours after the gel is applied to the skin of the body or legs (avoiding the arms).

Oestrogel Pump-Pack 0.06% gel (0.75–7.5 mg/day):

Oestrogel is initiated a dose of 1 pump actuation (0.75 mg) once a day, up to a maximum of 10 pumps (7.5 mg) once a day. Dose adjusted by 1 pump (0.75 mg) every three months until there is a plasma oestradiol level of 400-600 pmol/l, 4-6 hours after the gel is applied to the skin of the body or legs (avoiding the arms).

For estradiol gels, the first set of monitoring bloods is due 8 weeks after initiating therapy, as follows:

- Blood should be drawn for: **oestradiol (aim 400-600 pmol/L), testosterone, prolactin, liver function**
- The blood test should be taken 4-6 hours after the gel is applied to the skin making sure the gel is put on the body or legs, not the arms.
- **Blood pressure** and **BMI**

After any adjustment to the dose or brand of estradiol gel, repeat monitoring is due 8 weeks later, as per the above instructions.

Additionally, monitoring should be done every 3-6 months in the first year, every 6-12 months in the second year, and then annually thereafter if therapy is stable.

The GIC can advise on dose titration and adjustments to therapy, on receipt of blood test results and other monitoring information.

Topical oestrogen (estradiol) spray (Lenzetto):

Lenzetto 1.53 mg/dose transdermal spray

Lenzetto is initiated at 1 spray once a day, up to a maximum 6 sprays per day. Dose adjusted by 1 spray every three months until there is a plasma oestradiol level of 400-600 pmol/l, 4-6 hours after the spray is applied to the skin of the body or legs (avoiding the arms).

For Lenzetto spray, the first set of monitoring bloods is due 8 weeks after initiating therapy, as follows:

- Blood should be drawn for: **oestradiol (aim 400-600 pmol/L), testosterone, prolactin, liver function**
- The blood test should be taken 4-6 hours after the spray is applied to the skin making sure the spray is put on the body or legs, not the arms.
- **Blood pressure** and **BMI**

After any adjustment to the dose or Lenzetto spray, repeat monitoring is due 8 weeks later, as per the above instructions.

Additionally, monitoring should be done every 3-6 months in the first year, every 6-12 months in the second year, and then annually thereafter if therapy is stable.

The GIC can advise on dose titration and adjustments to therapy, on receipt of blood test results and other monitoring information.

Topical Oestrogen (estradiol) patches 50–250 micrograms/24hr, applied twice a week

(examples of estradiol patches include: Estradot, Evorel, Estraderm MX, Progynova TS)

Estradiol patches are initiated at a dose of 50 micrograms twice a week (patches changed after 3-4 days), up to a maximum of 250 micrograms twice per week (patches changed after 3-4 days). Dose adjusted by 50 micrograms every three months until there is a plasma oestradiol level of 400-600 pmol/l, 48-72 hours after the patch is applied to the skin.

For Estradiol patches, the first set of monitoring bloods is due 8 weeks after initiating therapy, as follows:

- Blood should be drawn for: **oestradiol (aim 400-600 pmol/L), testosterone, prolactin, liver function**
- The blood test should be taken 48-72 hours after patch application to the skin.
- **Blood pressure** and **BMI**

After any adjustment to the dose or brand of estradiol patches, repeat monitoring is due 8 weeks later, as per the above instructions.

Additionally, monitoring should be done every 3-6 months in the first year, every 6-12 months in the second year, and then annually thereafter if therapy is stable.

The GIC can advise on dose titration and adjustments to therapy, on receipt of blood test results and other monitoring information.

Oral oestrogen (estradiol) tablets):

Estradiol valerate or Estradiol hemihydrate tablets are initiated at a dose of 2 mg once a day orally, up to a maximum of 10 mg once a day. Dose adjusted by 2 mg every three months until there is a plasma oestradiol level of 400-600 pmol/l, 4-6 hours after taking the tablets.

Tablets should be swallowed whole, all at the same time, and not taken sublingually nor allowed to dissolve in the mouth.

For Estradiol tablets, the first set of monitoring bloods is due 8 weeks after initiating therapy, as follows:

- Blood should be drawn for: **oestradiol (aim 400-600 pmol/L), testosterone, prolactin, liver function**
- The blood should be taken at least 4 hours (ideally 4-6 hours) after the estradiol tablets are taken all together in the morning, swallowed whole with water.
- **Blood pressure** and **BMI**

After any adjustment to the dose or brand of estradiol tablets, repeat monitoring is due 8 weeks later, as per the above instructions.

Additionally, monitoring should be done every 3-6 months in the first year, every 6-12 months in the second year, and then annually thereafter if therapy is stable.

The GIC can advise on dose titration and adjustments to therapy, on receipt of blood test results and other monitoring information.

Perioperative management

The decision about whether oestrogen therapy is withdrawn at the time of surgery, especially genital surgery is a surgical decision. At the current time many genital surgeons ask for the patient to withdraw from oestrogen therapy prior to pelvic surgery.

The surgeon would advise when it is safe to restart hormone therapy and generally hormone therapy is restarted at the same dose the individual was taking prior to surgery, with repeat monitoring done 8 weeks later as above.

Testosterone suppression

Use of Gonadotrophin Releasing Hormone analogues (GnRH)

If oral oestrogen at 4 mg OD (or equivalent topical doses of Sandrena gel 2 mg OD or oestrogen patches 100 micrograms twice per week) does not suppress the plasma testosterone into the female range of 0-3 nmol/l, a GnRH analogue can be added, depending on patient goals, and testosterone suppression is required for at least 6 months in advance of genital reconstructive surgery or gonadectomy, as follows:

Decapeptyl (triptorelin) SR 11.25 mg (IM) every 12 weeks (most cost-effective option)
or
Zoladex (goserelin) 10.8 mg (sub cut) every 12 weeks

Alternatives:
Leuprorelin (Prostap) 11.25 mg (IM) every 3 months
Leuprorelin (Prostap) 3.75 mg (IM) monthly
Goserelin 3.75 mg (sub cut) monthly
Decapeptyl SR 3 mg (IM) monthly
Decapeptyl SR 22.5 mg (IM) every 6 months
Nafarelin (Synarel) nasal spray, 200-400 micrograms twice a day (see BNF)

To prevent the testosterone flare that can occur with GnRH analogues, Cyproterone Acetate 50 mg OD orally is co-administered *for two weeks with the first dose of a GnRH analogue, but* ***not*** *thereafter.* Cyproterone acetate is typically not recommended if the patient has significant liver disease or hyperprolactinaemia.

The usual side effect profile of accelerated cardiovascular disease and reduced bone mineralisation and menopausal symptoms do not occur because the patient has been given oestrogen treatment at the same time. GnRH analogues may prolong the QT interval and if the patient is taking medications that can prolong the QT interval such as antipsychotic medication they should have an ECG performed before commencing a GnRH analogue.

Additional treatments:

Antiandrogens may be used to counteract hirsutism.

Finasteride 5 mg OD

Dutasteride 0.5 mg OD

Cyproterone acetate 12.5 mg - 25 mg OD [27].

Cyproterone acetate is not used as first line medication because although it is an effective medication it has a side effect profile that can include abnormal liver function, negative effects on lipid profile, small prolactin elevations and an overall rare, but cumulative dose-dependent, increased risk of meningioma (single and multiple) and prolactinoma. There are occasionally patients that cannot tolerate GnRH analogues, in which case cyproterone acetate may be recommended. Recent

	studies have suggested that low-dose cyproterone acetate may be safer (at doses of 12.5 mg once a day). **Low dose testosterone gel** Low dose testosterone gel may be recommended for symptoms of hypoactive sexual desire disorder (HSDD). As per section below, this requires liaising with GIC team, who will advise what checks need to be done prior to starting low-dose testosterone gel, typically as Tostran 2% gel, half an actuation once a day (5 mg). **<u>Treatment of non-binary individuals</u>** For clients with a non-binary gender identity, the aims of therapy may be different to the standard aims outlined in this document and as such an individualised care plan will be documented and may be updated over time. After assessment (including general risks and benefits of hormone treatment) by gender specialists in the core side of the clinic, non-binary clients who opt for hormone therapy are routinely offered appointments in the endocrine department for an individualised discussion of their goals for hormone therapy, taking account of their desired degree of feminisation/masculinisation/androgyny. Based on knowledge and experience of cross-sex hormonal therapies in transgender men and transgender women undergoing a binary transition, our approach to hormone therapy for non-binary clients is multidisciplinary and individualised. An individualised assessment and treatment approach is consistent with WPATH (2022) guidance [1]. To manage expectations and explain limitations of hormone therapy, they are also counselled on what is likely or possible with regard to the usual expected timeframes and outcomes of hormone therapy and possible variations to this, as well as the more permanent or irreversible changes. The risks and benefits are discussed and an individualised care plan agreed. We often use low-dose oestrogen therapy to start with, but over time and depending on a client's goals and progress on treatment, standard-dose oestrogen therapy can be considered (in conjunction with the gender specialists in the core team). Additionally, anti-androgens or GnRH analogues may also be used depending on a client's individualised goals and progress on treatment [1].

Duration of treatment	Oestrogen treatment: lifelong GnRH analogues: until gender reassignment surgery or orchiectomy
Criteria for stopping treatment	**Preoperative:** Significant side effects / lack of response at adequate doses / client self-discharges from the GIC Review dosage if client starts smoking **Postoperative**: Development of significant contraindication to oestrogen use
Monitoring Requirements before Starting Treatment:	**Gender Clinicians:** Psychological / psychiatric assessment of client's suitability for treatment. Diagnosis of gender incongruence. Assessment of the individual's ability to consent to treatment. Screening for self-administered substances. Review of baseline screening blood tests and information once received from GP (as per below).

	GP: Organise **baseline tests, with blood tests taken as a 09:00am fasting sample**, as follows: • Blood tests: FSH, LH, Testosterone, Oestradiol, Prolactin, SHBG, Vitamin D, Liver function, Fasting glucose or Hba1c, Fasting lipids, U&Es (if taking Spironolactone or otherwise indicated). • Blood pressure and Height, Weight, BMI Please **send those results to** GIC.Endo@tavi-port.nhs.uk for review, along with a **general medical summary** and **medication list.** **Individuals over the age of 45 can be offered a PSA test but this should not be done without a discussion of the risks and benefits with the patients as per NICE guidance** [28]. PSA is an unreliable indicator for prostate cancer. Around 1 in 7 of those with prostate cancer have normal PSA levels. Occasionally, this test can give a false positive, indicating cancer where there is none. This is why it is recommended to confirm a tumour with an MRI scan before undergoing biopsies. The PSA test can find aggressive prostate cancer that needs treatment, but it can also find slow-growing cancer that may never cause symptoms or shorten life. Benefits of testing may be higher for high-risk groups, such as those with a family history or of Afro-Caribbean descent. For trans people, detecting a prostate cancer prior to hormone treatment may make it easier to characterise the cancer and plan ahead to coordinate appropriate treatment around gender affirming care. It also makes cancer easier to diagnose as hormone therapy lowers PSA. However, it can contribute to gender dysphoria, and delay commencement of hormone treatment. More information to help people make a decision can be found here: https://outpatients.org.uk/tnbgd-screening/https://prostatecanceruk.org/prostate-information-and-support/prostate-tests/psa-blood-test#advantages-and-disadvantages-of-the-psa-test
Monitoring requirements once stable, including frequency:	**Gender Clinicians:** To advise GP on dose alterations required based on hormone and other monitoring information provided. **GP:** Measure the following every 3–6 months until hormone levels are stable within target ranges (as above), annually thereafter: • Oestradiol (range 400-600 pmol/l), • Testosterone (range 0-3 nmol/l) • Prolactin • Liver function tests • BMI, blood pressure For non-binary patients, a DEXA scan 3 years after initiation of low-dose oestrogen treatment for bone assessment.
Follow up arrangements **and** **Prescribing Responsibilities:**	**Gender Clinicians:** • Clients will be reviewed by the GIC at regular intervals. • The specialist team will take responsibility for the recommendation of treatment, counselling about risks and benefits of therapy, and recommending alterations to GPs until client is stabilised on therapy • To oversee the whole programme of assessment and treatment, including dose adjustment as necessary to reach a maintenance level

	• To advise GP on any problems arising from treatment which may need a dose adjustment or a change in medication. **GP:** • The GP will take on prescribing as per the shared care agreement, with the support and guidance of the GIC • The GP will be responsible for the ongoing prescribing of oestrogens and anti-androgens and will continue to act as the primary contact for general healthcare. • The GP will refer to the specialist team if any significant developments or deteriorations occur, such as occurrence of side-effects, worsening of symptoms or complications of hormone therapy. • The GP to take advice of surgeons on pausing and restarting hormones in relation to gender reconstructive surgery. • Following discharge from the service the GP will follow the discharge guidance provided by the specialist service and maintain the prescription of the patient's hormone therapies. The GP will contact the specialist service if there are any complications that arise or if there are significant changes in the patient's gender situation and gain further advice from the specialist service. **Gender Nurse Specialist:** The Gender Nurse Specialist will provide support and advice for General Practitioners, Community Pharmacists, District Nurses, and the client on request.
Management of complications on hormone therapy	1. Testosterone suppression: If testes are still present, usual practice is to use medication to keep testosterone suppressed, i.e. under 3nmol/L. If total testosterone levels increase over 3 nmol/L, it may be worth checking compliance with recommended treatment. Seek advice from the GIC as required. 2. Thromboembolism: Stop oestrogen therapy until patient is anti-coagulated. Kindly alert the GIC team as soon as possible and forward relevant documentation on management and/or discharge letters. When haematology advises that it is safe to do so, oestrogen therapy with topical formulations (gel or patch) can be resumed. Anti-coagulation should be lifelong whilst on oestrogen therapy. 3. Prolactin: Transient mild hyperprolactinaemia is often seen with oestrogen therapy. If prolactin is higher than normal but less than 1000 then repeat the prolactin. If repeat prolactin levels remain elevated then discuss with the GIC. Review medications for those that can cause hyperprolactinaemia. If prolactin is higher than 1000 then please refer to local endocrine service for assessment and consider requesting a pituitary MRI scan. 4. Abnormal Liver Function Tests: For values less than 3x the upper limit of normal: check medicines and alcohol history and re-test in 4-6 weeks. If Liver function tests are abnormal on repeat, then perform further investigations to determine the cause: Hepatitis B and C serology, HIV serology, EBV, Ferritin, Copper, Caeruloplasmin, liver auto-immune screen, ultrasound of the liver.

	If the person is using oral oestrogen it may be appropriate to change to a topical oestrogen to reduce the strain on the liver; please discuss this with the GIC team. If values are greater than 3x the upper limit of normal: GP to temporarily suspend hormone therapy and refer to local hepatology. <u>5. New diagnosis of Cancer, Stroke or Myocardial Infarction:</u> Temporarily suspend hormone therapy until discussion with the GIC team.

Practical issues including other relevant advice/information: **Medication information, particularly in relation to potential interactions, can be found in the latest edition of the BNF**	The safety monitoring for this ongoing treatment has been outlined. This monitoring is designed to detect the major side effects of hormonal treatment. The risks of oestrogen exposure appear to be related to the duration of oestrogen treatment in genetic females. For this reason the long term monitoring of trans women should include health screening for breast cancer. **Monitoring of bone health** Monitoring of bone health is not routinely required unless the person has significant risk factors for osteoporosis or has had a significant break from sex steroid treatment (>24 months). The GIC clinician will make a recommendation about DEXA scanning but the performance of that scan would be deferred to primary care. **National Screening Programmes** The client should be advised that they will get an automatic call-up to female but not male screening if they have had their gender changed on the NHS computer system, and they will need to remember to access screening. There is a comprehensive document on the gov.uk website: https://www.gov.uk/government/publications/nhs-population-screening-information-for-transgender-people **Thromboembolic disease** The incidence of deep venous thrombosis (DVT) in trans women is approximately 2.6% (80% of reported cases are in the first 2 years of treatment but no increased risk with lifelong treatment); however in this young population this represents a risk that is 20 times that of the untreated population. The majority of these incidents occur during the first two years of treatment. There is, however, an ongoing risk of 0.4% per year which continues [6]. Using more modern oestrogen therapy the risk of thromboembolism has no decreased the risk is legible <37 years old and overall the prevalence is 2% [7]. The type of oestrogen may be important. It has been demonstrated that ethinylestradiol alters the levels of plasma protein S, C and prothrombin, which results in a procoagulant haemostatic profile in transgender subjects [8]. This is why ethinyl estradiol is not recommended as a first line treatment. We have demonstrated a DVT risk of 0.4% over 5 years in our clients [9]. **Breast cancer** The incidence of breast cancer with standard HRT in genetic females is estimated at an excess of 3.2/1000 aged 50–59 years and 4/1000 aged 60–69[10]. This is based on large population-based studies. We know from both the Heart and Estrogen/Progestin Replacement Study (HERS)[11] and Women's Health Initiative trial[12] that the inclusion of progesterone in the HRT regimen increases this risk. In the trans feminine population the risk of breast cancer appears to be reduced compared to cisgender females (incident ratio 0.3 [0.2–0.4]). This value is significantly higher than cisgender men (incident ratio 46.7 [27.2–75.4])[13]. **The risk of breast cancer secondary to feminising hormone therapy is very low when compared to cisgender females**. Which means that oestrogen use beyond 55 years of age in trans women appears safe from the point of view of breast health,

and indeed most trans women continue HRT lifelong. Breast screening should be offered however as per the national guidelines.

Hyperprolactinaemia

The lactotroph is sensitive to the ambient oestrogen levels in the serum. Oestrogen not only causes increased prolactin release from these cells, but also causes proliferation of them, which can result in hyperprolactinaemia and pituitary hypertrophy. The incidence of significant hyperprolactinaemia has been reported to be up to 15%[14]. There have only been rare case reports of prolactinomas in trans women and none have needed withdrawal of oestrogen treatment. This situation is complicated by the fact that many hormonal regimens in Europe co-prescribe cyproterone acetate with oestrogen. Cyproterone acetate has been shown to increase the risk of prolactinoma by 4.3 fold compared to cis gender females and 26.5 fold compared to cisgender males [15].

Abnormal liver function

Abnormalities of liver function are, rarely, associated with the use of oestrogen therapy.

The risk of abnormal liver function tests is approximately 3% in trans women.[16, 17]. In half of these, the abnormalities persist for more than 3 months. However the increases are mild and only rarely require discontinuation of treatment.

Prostate cancer

Prostate cancer is such a common malignancy among the male population, with an incidence of up to 50% by the eighth decade. As the majority of gender nonconforming women have treatment to reduce the testosterone they produce the risk of prostate cancer is consequently less in this population. The data in this field is scanty but one study suggests that the standardised incident ratio of prostate cancer in trans women who have been on estradiol either with cyproterone acetate or having undergone orchidectomy, is approximately 0.17 [0.05–0.44] the cisgender male population [18]. This may be even lower for those who access GnRHa.

Fertility

Oestrogen therapy leads to a suppression of gonadotrophin production and subsequent reduction in spermatogenesis. Clients are counselled that treatment will reduce their fertility. The effects of hormone treatment on fertility are usually reversible however there may be a permanent reduction in fertility potential Fertility preservation is discussed with client before they started on hormone treatment and if desired they should be referred for fertility preservation through local fertility services before commencing on hormone treatment.

With regards to contraception, hormone therapy cannot be relied upon as effective contraception. There are reports of active spermatozoa present in testicular samples taken at gender reassignment surgery. Clients should be advised that contraceptive measures need to be continued where appropriate whilst on hormone therapy until they undergo gonadectomy.

Myocardial Infarction.

The rate of myocardial infarction in the transgender female population is not increased in comparison to the cisgender male population. The incidence of myocardial infarction varies between 0.4-1 [16, 19, 20]. The risk seems to be limited to those using an oestradiol in some studies. The reason meta-analysis suggested that the pooled relative risk was 1 [CI, 0.8–1.2] [21].

Cerebrovascular Disease

The risk of stroke does not appear to be increased in transgender women compared to cisgender men. In the long-term study the incidence of stroke in transgender women taking oestrogen was strongly associated with smoking. The recent meta-

analysis has estimated the relative risk of stroke in trans men compared to cisgender men was 1.3 [95% CI, 1–1 0.8].

To attempt to minimise the cumulative exposure to oestrogen it is advisable to use the lowest oestrogen dose tolerated by the client, and when a preparation that can be monitored is used. The aim of treatment is to try and provide physiological oestrogen replacement aiming to have the oestradiol levels in the physiological range. On our local assay we aim for a plasma oestradiol level of 400 – 600 pmol/L. They should also be monitoring of the safety bloods as detailed above. Gonadotrophin level measurements are unhelpful.

GnRH analogues are used preoperatively to reduce testosterone production instead of increasing the dose of oestrogen therapy. In this situation these medicines are extremely effective and safe, as the majority of the side effects of GnRH analogues (ie hot flushes, depression and osteoporosis) do not occur as the client is co-administered oestrogen.

When the client reaches 45 years of age then consideration of transdermal oestrogen preparation has been recommended the international guidance of WPATH SOCS8. Large case studies in cisgender women suggest that topical oestrogen has lower impact of thromboembolism and stroke which is why topical oestrogen is used over the age of 45 [22, 23].

The increase in vascular disease appears to be associated with the use of Ethinyloestradiol, but not other oestrogen types, and so this oestrogen type should be avoided [1, 24].

The current data suggest that long-term treatment with oestrogen in trans women is associated with a slight increase in the standard mortality ratio. The increase in mortality appears to be associated with an increase in the risk of suicide in vulnerable individuals [HR 5.7[25] 19 [24] and also an increase in cardiovascular deaths RR1.46[25] 2.5 [24]. The increase in suicide deaths appears to be historical when comparing the cohort treated in 1972-1980 vs those treated 1983-2010. This may reflect improvements in the availability and quality of care or, alternatively, improvement in the status of transgender people in society, leading to a reduction in their psychological stress. It is important that the psychological health of people treated for gender dysphoria should be assessed.

Bone Health

We know that standard hormone therapy aimed at physiological replacement maintains bone mineralisation in transgender women. Routine monitoring of bone mineralisation is therefore not required unless there are specific risk factors for osteoporosis.

Monitoring of bone health is not routinely required unless the person has significant risk factors for osteoporosis or has had a significant break from sex steroid treatment (>24 months). The GIC clinician will make a recommendation about DEXA scanning but the performance of that scan would be deferred to primary care.

For non-binary people we do not have the same outcome data. We therefore suggest that in our monitoring of bone health by DEXA scanning is done 3 years after initiation of low-dose oestrogen therapy if testosterone production is suppressed.

Renal impairment

Estradiol replacement therapy has been shown to have several potential effects on renal function, including fluid retention, blood pressure changes, and possible increases in proteinuria [29, 30]. However, estradiol can also have beneficial effects on kidney function in some groups of patients such as postmenopausal women or those with pre-existing renal insufficiency. We don't routinely recommend adjustments to treatment in cases of mild renal impairment, but advise regular

	monitoring of kidney function and proteinuria in such patients to minimize associated risks. In cases of moderate to severe renal impairment, kindly consult the GIC. **Libido and energy issues** With regards to poor energy and libido disturbance, this patient group can suffer from hypoactive sexual desire disorder (HSSD), something which can respond well to adjustment in hormone therapy, including possible use of low-dose testosterone. If this seems to be the case then contacting the specialist team here or, a specialist endocrine service, for an assessment would be appropriate.
Information provided	Clients are given a copy of the clinic's Hormone Management Booklet which is also available for GPs on our website or GPs can request it by email at gic.endo@tavi-port.nhs.uk. It is based on it is based on The Transgender Handbook: A Guide for Transgender People, Their Families and Professionals [26]

COMMUNICATION AND SUPPORT

Gender Identity Clinic contacts:

GIC Clinic Web Site**: www.gic.nhs.uk** GIC phone number: 0208 938 7590

Email: hormone therapy related queries can be sent to gic.endo@tavi-port.nhs.uk (other queries will be forwarded to the most appropriate clinician or dealt with by the administrative team, as appropriate).

GP hormone advice line: 020 8938 7369 (this line is for GPs/healthcare professionals only with questions about hormone therapy).

REFERENCES

Evidence Base for treatment and Key references:

1. Coleman, E., et al., *Standards of Care for the Health of Transgender and Gender Diverse People, Version 8.* Int J Transgend Health, 2022. **23**(Suppl 1): p. S1-S259.
2. D'hoore, L. and G. T'Sjoen, *Gender-affirming hormone therapy: An updated literature review with an eye on the future.* J Intern Med, 2022. **291**(5): p. 574-592.
3. Seal, L.J., *Hormone treatment for transgender adults*, in *The transgender handbook : a guide for transgender people, their families and professionals*, W.P.A. Bouman, Jon, Editor. 2017, Nova Publishers: New York. p. 227-249.
4. Seal, L.J., *A review of the physical and metabolic effects of cross-sex hormonal therapy in the treatment of gender dysphoria.* Ann Clin Biochem, 2016. **53**(Pt 1): p. 10-20.
5. Nota, N.M., et al., *The Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy: Results from a Large Cohort Study.* Circulation, 2019.
6. van Kesteren, P., et al., *Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones.* Clin Endocrinol (Oxf), 1998. **48**(3): p. 347-54.
7. Totaro, M., et al., *Risk of Venous Thromboembolism in Transgender People Undergoing Hormone Feminizing Therapy: A Prevalence Meta-Analysis and Meta-Regression Study.* Front Endocrinol (Lausanne), 2021. **12**: p. 741866.
8. Toorians, A.W., et al., *Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people.* J Clin Endocrinol Metab, 2003. **88**(12): p. 5723-9.
9. Seal, L.J., et al., *Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens.* J Clin Endocrinol Metab, 2012. **97**(12): p. 4422-8.
10. Beral, V., E. Banks, and G. Reeves, *Evidence from randomised trials on the long-term effects of hormone replacement therapy.* Lancet, 2002. **360**(9337): p. 942-4.
11. Hulley, S., et al., *Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group.* JAMA, 1998. **280**(7): p. 605-13.
12. Rossouw, J.E., et al., *Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.* JAMA, 2002. **288**(3): p. 321-33.
13. de Blok, C.J.M., et al., *Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands.* BMJ, 2019. **365**: p. l1652.

14. Futterweit, W., *Endocrine therapy of transsexualism and potential complications of long-term treatment.* Arch Sex Behav, 1998. **27**(2): p. 209-26.
15. Nota, N.M., et al., *The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment.* Brain, 2018. **141**(7): p. 2047-2054.
16. van Kesteren, P.J., et al., *Mortality and morbidity in transsexual subjects treated with cross-sex hormones.* Clin Endocrinol (Oxf), 1997. **47**(3): p. 337-42.
17. Futterweit, W., *Endocrine therapy of transsexualism and potential complications of long-term treatment.* Arch Sex Behav, 1998. **27**(2): p. 209-26.
18. de Nie, I., et al., *Prostate Cancer Incidence under Androgen Deprivation: Nationwide Cohort Study in Trans Women Receiving Hormone Treatment.* J Clin Endocrinol Metab, 2020. **105**(9): p. e3293-9.
19. Getahun, D., et al., *Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study.* Ann Intern Med, 2018. **169**(4): p. 205-213.
20. Nota, N.M., et al., *Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy.* Circulation, 2019. **139**(11): p. 1461-1462.
21. van Zijverden, L.M., et al., *Cardiovascular disease in transgender people: a systematic review and meta-analysis.* Eur J Endocrinol, 2024. **190**(2): p. S13-S24.
22. Carrasquilla, G.D., et al., *Postmenopausal hormone therapy and risk of stroke: A pooled analysis of data from population-based cohort studies.* PLoS Med, 2017. **14**(11): p. e1002445.
23. Vinogradova, Y., C. Coupland, and J. Hippisley-Cox, *Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases.* BMJ, 2019. **364**: p. k4810.
24. Asscheman, H., et al., *A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones.* Eur J Endocrinol, 2011. **164**(4): p. 635-42.
25. Dhejne, C., et al., *Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden.* PLoS One, 2011. **6**(2): p. e16885.
26. Seal, L., J., *Hormone Treatment of Adults*, in *The Transgender Handbook: A Guide for Transgender People, Their Families and Professionals*, W.P. Bouman and J. Arcelus, Editors. 2017, Nova Science Publishers: New York.
27. Hembree, W.C., et al. (2017). *Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism*, 102(11), 3869–3903

28. NICE (2024) Guidelines on diagnosis and assessment of prostate cancer (September 2024 revision): http://https//cks.nice.org.uk/topics/prostate-cancer/diagnosis/assessment/#psa-testing

29. Gilsanz, P., et al. (2015). The Effects of Estrogen on the Kidney and Fluid Balance: Insights from Clinical Studies. Hypertension, 65(4), 823-829.

30. Dinesh, S. R., & Brown, R. W. (2018). Effect of Estrogen on Kidney Function and Disease. Journal of Clinical Endocrinology & Metabolism, 103(8), 3456-3463.

NB: for full details of adverse effects and drug interactions refer to latest Summary of Product Characteristics https://www.medicines.org.uk/emc/

SHARED CARE PRESCRIBING AGREEMENT

(Appendix ia)

CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- The GIC clinicians will establish that the person is suitable for hormone treatment when they are in a stable social and psychological circumstance.
- The GIC clinicians will establish that there is no significant medical or endocrinological contraindication to hormone therapy.
- The GIC clinicians will request that the GP commence prescribing when these conditions are met.
- The GIC clinicians will be available to give advice on further management.

AREAS OF RESPONSIBILITY

Specialist Gender Identity Clinician /Consultant Responsibilities

- Establish or confirm diagnosis and assess client suitability for treatment
- Assessment of baseline bloods and monitoring bloods until stable by GIC Endocrine Team
- Discuss treatment with client and ensure they have a clear understanding of benefits and side-effects of treatment, including dose adjustments and how to report any unexpected symptoms The specialist team provides the client with information and advice, supported by written information as required.
- Obtain signed consent for hormonal treatment
- Send a signed shared care guideline with client details completed together with relevant clinical information to GP.
- Contact GP directly if response to shared care request has not been received within two weeks
- Monitor treatment according to clinical guidance and advise client and GP on dose titration of medicines.

Ongoing Care Arrangements: Specialist team to

- Write to GP following clinic contacts and inform GP when client is stable on hormones.
- Inform GP of abnormal monitoring results and any recommended changes in therapy prescribed by the GP, including the need to discontinue if appropriate
- Evaluate adverse events reported by GP or client and communicate outcome to GP
- Make arrangements for ongoing monitoring and follow up accordingly to shared care guidelines, including continued need for therapy.

Gender Specialist Nurse:
The Gender Specialist Nurse will provide support and advice for General Practitioners, Community Pharmacists, District Nurses on request.

GP RESPONSIBILITIES
▪ Consider shared care proposal and if in agreement to respond within two weeks of receipt ▪ If do not agree to shared care, discuss with requesting consultant or local CCG medicines management team, within two weeks of receipt of shared care request ***After agreement to share care*** ▪ Prescribe and monitor treatment as advised by the specialist team and according to shared care guideline ▪ Monitor general health of client and check adverse effects as appropriate; ensure client is aware of warning symptoms and how to report them ▪ Inform specialist team of suspected adverse effects and also report via yellow card scheme if necessary ▪ Stop treatment on advice of specialist team or immediately if urgent need arises ▪ Check compatibility interactions when prescribing new or stopping existing medication ▪ Discuss any abnormal results with specialist consultant and agree any action required ▪ Take advice from surgical teams about pausing and restarting therapy in relation to genital reconstructive surgery. Only ask specialist to take back prescribing should unmanageable problems arise. Allow an adequate notice period.
CLIENT'S RESPONSIBILITIES
▪ Keep a copy of information provided by Gender Identity Clinic, including consent to treatment, to take along when seeing GP ▪ Take medicines as agreed and prescribed ▪ Report any adverse effects to GP or hospital doctor at the earliest opportunity ▪ Ensure that you attend for tests as requested by your Gender Clinician or GP ▪ Do not share medicines ▪ Attend appointments for review as necessary ▪ Always inform the specialist team and GP of all medication being taken, whether prescribed or bought

SHARED CARE PRESCRIBING AGREEMENT

(Appendix ib)

GENDER CLINICIAN

Client name:

Client ID:

Client NHS No:

Date of Birth:

☐ I confirm that I have assessed the above named individual and it is my clinical recommendation that the following treatment is prescribed:

☐ Furthermore, the "Areas of Responsibility" have been covered and I agree to the "follow-up arrangements".

Signature:

Print Name:

Date:

CLIENT CONSENT LETTER FOR INITIATION OF HORMONES

(Appendix ii)

I, …… (print name) met with the above named clinician.

☐ I can confirm that I am aware of the potential effects, side effects and expectations of hormone therapy. In addition I am also aware of the potential effects that this therapy will likely have on my fertility. I do not wish to discuss this further with another medical doctor.

☐ Furthermore I confirm that I will adhere to the "Client Responsibilities" as outlined in the shared care agreement.

…… (signature) Date: ……..

SHARED CARE PRESCRIBING AGREEMENT

(Appendix iii)

GP/Primary Care Provider

Client name:

Client ID:

Client NHS No:

Date of Birth:

☐ I confirm that I have read the shared care prescribing agreement and agree to the "Areas of Responsibility". As in shared care arrangements with other specialist services, and as is consistent with NHS England and GMC guidance, I understand that this includes prescribing and monitoring the recommended treatment as outlined in this shared care document, with the support and advice of the specialist gender service.

Signature:

Print Name:

Date: