SHARED CARE PRESCRIBING GUIDANCE FOR

Treatment of Gender Dysphoria in People Assigned Male at Birth Transitioning to a Feminine Gender Identity

Applicable to:	GPs referring clients to the Charing Cross Gender Identity Clinic
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Changes since last update in April 2022 (version 10.2)	Updated section on monitoring requirements before starting treatment

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INTRODUCTION

This document has been prepared by Dr 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.

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. The standardised mortality rate for trans women is 1.0, demonstrating that longer term oestrogen therapy is not detrimental or harmful. That is to say, clients are no more likely to die as a result of taking this treatment than if the GP did not prescribe at all.

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 born male 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

Dr Leighton Seal
Consultant Endocrinologist

SUPPORTING CLINICAL INFORMATION

Indication(s):	Treatment of gender dysphoria following psychiatric/psychological assessment at a Gender Identity Clinic.
Place in Therapy:	Hormonal therapy will usually be recommended after two initial assessments are complete. Commencement of hormonal therapy should generally be recommended following commencement of a change of social gender role. Clinical practice in the GIC follows a modified version of the WPATH vers.7 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 30 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.[1.2]
Dose & route of administration:	**Oestrogen to cause feminisation:** ***First Line:*** Estradiol valerate or Estradiol hemihydrate initiated at a dose of 2 mg OD orally, and used in a range of 2-8 mg OD. 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 all at the same time, and not taken sublingually. **Alternatives (if estradiol tablets not tolerated or inadequate levels achieved)**: ***Second Line: Topical*** Gels often achieve better levels than patches: Topical oestrogen gel (Sandrena 0.5-5 mg/day): Initiated at a dose of 0.5 mg 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 Estradiol patches 50 –200 micrograms/24hr, applied twice a week dose adjusted by 50 micrograms every three months until there is a plasma oestradiol level of 400-600 pmol/l, 48 hours after the patch is applied to the skin ***Third line****:* Treatment *only used in exceptional circumstances* where levels have not been reached by alternatives above, or they have not been tolerated: Ethinyloestradiol 50-150 micrograms OD. (Note oestradiol levels cannot be used to monitor treatment with ethinyloestradiol) ****Post surgery oestrogen dose stays the same but wait for surgeon instruction to restart**** **Use of Gonadotrophin analogues (GnRH)** If oral oestrogen at 4 mg OD (or equivalent topical dose) does not suppress the plasma testosterone into the female range of 0-3 nmol/l, a GnRH analogue can be added: 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. **Rarely:** **Antiandrogens may be used to counteract hirsutism.** Finasteride 5 mg OD Cyproterone acetate 50 mg -150 mg OD

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. 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, PSA, U&Es (if taking Spironolactone or otherwise indicated) • Blood pressure and Height, Weight, BMI Please **send those results to** gic.endocrine@nhs.net for review, along with a **general medical summary** and **medication list.**
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 initially, annually thereafter: Oestradiol (unless taking ethinyloestradiol) (range 400-600 pmol/l), Testosterone (range 0-3 nmol/l) Prolactin LFTs

	BMI, blood pressure
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. **Gender Nurse Specialist:** The Gender Nurse Specialist will provide support and advice for General Practitioners, Community Pharmacists, District Nurses, and the client on request.

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[3]. The type of oestrogen may be important. It has been demonstrated that

ethinylestradiol alters the levels of plasma protein S, C and prothombin, which results in a procoagulant haemostatic profile in transgender subjects[4]. In our own clinic we have moved away from using ethinylestradiol to estrogen valerate; however we have demonstrated a **DVT risk of 0.4% over 5 years in our clients**.

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.[5] This is based on large population-based studies. We know from both the Heart and Estrogen/Progestin Replacement Study (HERS) [6]and Women's Health Initiative trial [,7] that the inclusion of progesterone in the HRT regimen increases this risk. There are no similar studies available in the trans female population. There have only been four case reports of breast tumours occurring in treated trans women in the world literature; this equates to the background breast cancer risk in males, suggesting that **the risk of breast cancer secondary to feminising hormone therapy is very low**. 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.

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%[8]. There have only been two case reports of prolactinomas in trans women and none have needed withdrawal of oestrogen treatment [9;10].

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. [3;8]. 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 has only been reported in two trans women in the world literature, despite many years of data collection.[11;12]. As prostate cancer is such a common malignancy among the male population, with an incidence of up to 50% by the eighth decade, this suggests that the incidence of prostate cancer is greatly reduced in trans women compared with the male population.

Fertility
Oestrogen therapy leads to a suppression of gonadotrophin production and subsequent reduction in spermatogenesis. Clients should be counselled that treatment will reduce their fertility, and offered the chance of sperm storage if desired.

Myocardial Infarction.
The rate of myocardial infarction in the trans female population is reduced by two thirds compared to a cisgender male population.

Cerebrovascular Disease
There does not appear to be an increased risk of stroke in the trans female population[3].
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, use plasma levels of oestrogen to guide replacement therapy (aiming 400 – 600 pmol/L), and monitor 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 40 years of age then consideration of transdermal oestrogen preparation has been recommended by one group in Europe; in our practice, however, there does not appear to be an increased risk of thromboembolic events after the age of 40, possibly reflecting the fact that we insist on clients stopping smoking (which is not the case in the Liège series). 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[15]. 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[14] 19 [15] and also an increase in cardiovascular deaths RR1.46[14] 2.5[15]]. 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. **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 via email FAO the gender nurse specialist at gic.noreply@nhs.net , or by writing to the clinic to request a copy. It is based on The Practical Management of Hormonal Treatment in Adults with Gender Dysphoria[13].

COMMUNICATION AND SUPPORT

Gender Identity Clinic contacts:

GIC Clinic Web Site: **www.gic.nhs.uk** GIC phone number: 0208 938 7590 Fax: 0208 181 4506

Email: gic.noreply@nhs.net (this is forwarded to either the Endocrine Team or the most appropriate clinician)

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

REFERENCES

Evidence Base for treatment and Key references:	(1) Gooren, L. J., van de Wall, H. A. D. (2007). Hormone treatment of adult and juvenile transsexual patients. In R. Ettner., S. Monstrey and A. E. Tyler (Eds.), Principles of Transgender Medicine and Surgery (pp 73-88). New York: The Haworth Press. (2) Seal, L.J. The practical management of hormonal treatment in adults with gender dysphoria. In: J Barrett, editor. Transsexual and Other Disorders of Gender Identity: a practical guide to management. Oxford: Radcliffe; 2007. 157-190. (3) van Kesteren P.J., Asscheman H., Megens J.A., Gooren L.J. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997; 47(3):337-342. (4) Toorians A.W., Thomassen M.C., Zweegman S., Magdeleyns E.J., Tans G., Gooren L.J., et al. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 2003; 88(12):5723-5729. (5) Beral V., Banks E., Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. Lancet 2002; 360(9337):942-944. (6) Hulley S., Grady D., Bush T., Furberg C., Herrington D., Riggs B., 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):605-613. (7) Rossouw J.E., Anderson G.L., Prentice R.L., LaCroix A.Z., Kooperberg C., Stefanick M.L., 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):321-333. (8) Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. Arch Sex Behav 1998; 27(2):209-226. (9) Gooren L.J., Assies J., Asscheman H., de Slegte R., van Kessel H. Estrogen-induced prolactinoma in a man. J Clin Endocrinol Metab 1988; 66(2):444-446. (10) Serri O., Noiseux D., Robert F., Hardy J. Lactotroph hyperplasia in an estrogen treated male-to-female transsexual patient. J Clin Endocrinol Metab 1996; 81(9):3177-3179. (11) Thurston A.V. Carcinoma of the prostate in a transsexual. Br J Urol 1994; 73(2):217. (12) Goodwin W.E., Cummings R.H. Squamous metaplasia of the verumontanum with obstruction due to hypertrophy: long-term effects of estrogen on the prostate in an aging male-to-female transsexual. J Urol 1984; 131(3):553-554. (13) Barrett, J. Transsexual and other disorders of Gender Identity a practical guide to management. 2007 Oxford Press (14) Cecilia Dhejne, Paul Lichtenstein, Marcus Boman, Anna L V Johansson, Niklas Lanstrom Mikael Landen Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 2011 22;6(2): (15) Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones Eur J Endocrinol. 2011 Apr;164(4):635-42

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: