Feminising Endocrine Treatment: Treatment of gender dysphoria following assessment at the Gender Identity Clinic in adults >17 years old.

The Lothian GP Sub-Committee's advice can be viewed here: intranet.lothian.scot.nhs.uk.

THE FOLLOWING ARRANGEMENTS HAVE BEEN AGREED IN PRINCIPLE – but are not yet operating, whilst resource discussions are ongoing. However, in the interim, it was felt to be useful to have prescribing and clinical guidance available on the intranet section of RefHelp.

Chalmers GIC (GIC) will undertake initial assessment and establishment of treatment for all those seeking feminising endocrine treatment. Following that, GPs will be asked to be responsible for prescribing, and reporting any issues to the GIC. ***However, monitoring arrangements (including phlebotomy) are not yet in place and a Shared Care Agreement is still being negotiated.***

This document uses the term **trans women** to include trans women and non-binary people (assigned male at birth) using feminising hormones in connection with gender dysphoria or incongruence.

New Patients

All patients requesting gender dysphoria assessment or treatment should first be referred to Chalmers Gender Identity Clinic via SCI Gateway.

Some people will have been assessed, or had treatment, by a recognised NHS gender clinic elsewhere and are new to Borders, Lothian or Fife (the areas served by the Chalmers GIC). If they have been assessed by an NHS GIC (or equivalent overseas), then Chalmers GIC can provide email advice on ongoing treatment or see patients where that is necessary. The clinic is unable to prioritise patients who have accessed private treatment and recommends continued engagement with their existing provider until they have completed the Chalmers specialist assessment.

For those moving into Scotland, please see the advice about the process for changing CHI numbers (which are gender-specific) and enrolling in the relevant national screening programmes.

INITIAL SPECIALIST ASSESSMENT - Chalmers Gender Identity Clinic:

- Baseline assessment, treatment counselling, gaining informed consent and recommending initiation of treatment (communicated to GP to prescribe). This will include consent for the unlicensed use of medications; and that clinical risks are higher if a treating clinician is unaware of the patient's transgender status.
- Provide leaflet both to the GP and the patient outlining risks of treatment – to follow
- Monitoring for the first year (or until patient is on a stable medication regimen)
- Communication with the GP about any changes in treatment
- Referral for specialist interventions relating to gender reassignment and transitioning
- Referral for non-specialist interventions suggested by the GIC (e.g. CMHT, weight management etc)
- Advise about changes in CHI, breast cancer screening, prostate awareness and over-65 Abdominal Aortic Aneurysm screening – details available from national screening programmes
- Assess cardiovascular risk status (ASSIGN score) and advise appropriately. The literature suggests that the cardiovascular risks are those of untreated men, so the CGIC recommendation is to use male gender in the risk calculation
- Assess thrombo-embolic risk and advise appropriately
- There should be no need for additional bone protection, except in the rare situation of someone having had gonadal removal who is not also taking hormonal therapy. Please note the advice about Vitamin D in Scotland and on standard osteoporosis management.

ONGOING CARE (shared):

Much of the longer-term prescribing work may be undertaken by practices, but please note that currently there is no contractual requirement for GPs to undertake monitoring or annual checks. A Shared Care Agreement is currently being developed.

The following model is likely to apply, with checks organised by Chalmers GIC as part of an annual recall system, to monitor ongoing hormonal therapy treatments:

- Maintain awareness of prostatic disease and institute appropriate investigations if lower urinary tract symptoms occur. PSA monitoring is not required.
- Advise when BP measurement or blood tests are required: the long-term aim is for this work to be resourced by the specialist service and undertaken in CTACS. Please see 'Monitoring' below for more detail.

GPs to:

- Be aware of the potential for prostatic disease and institute appropriate investigations if lower urinary tract symptoms occur. PSA monitoring is not required.
- Institute changes in treatment as per Chalmers GIC advice following annual review. If the patient does not attend necessary reviews, the GP will be informed to ensure prescribing ceases.
- Inform the Chalmers GIC (Lothian patients) or local endocrine or other appropriate local service (non-Lothian patients):
    - for risk re-evaluation for new diagnoses of cerebrovascular disease, coronary heart disease or venous thrombo-embolism
    - if new diagnosis of active liver disease or liver tumours.

There will be a very small number of high-risk patients whose care should be solely undertaken by the specialist service.

THERE IS A SUMMARY OF MONITORING REQUIREMENTS AT THE END OF THIS DOCUMENT.

Please note that for patients aged under 40 (the vast majority), unless there is a significant new diagnosis, the only monitoring requirement is for annual BP and smoking advice. The only exception is the (very rare) patient on spironolactone or cyproterone.

Support and Advice for the GP.

Health professionals can contact the Chalmers Gender Identity Clinic on:
gic@nhslothian.scot.nhs.uk. Enquiries are forwarded directly to the GIC team, who aim to respond within two working days.

Background and use of feminising endocrine treatment for gender dysphoria.

Hormone therapies are recommended under the Endocrine Management of Adult Transgender Patients 2018, based on the Scottish Government Gender Reassignment Protocol 2012. This advice is regularly updated by the clinical network (NCGICNS) and the latest available at Endocrinology Guidance (scot.nhs.uk). Hormonal therapy is usually recommended after the initial assessment is completed.

Oestrogen evidence base in cis women

The risks of exogenous oestrogen have been investigated in large studies of HRT in cisgender women, although this remains a debated area. The impact of age is however very important: for younger patients, the equivalent patient group would be women with premature ovarian insufficiency, but the evidence regarding risk in this group is very limited[i].

The oestrogen doses used for feminising treatment for gender dysphoria are generally higher than those used for HRT, but some of the evidence relating to HRT is likely to have relevance. It is important to note that some HRT risks only relate to, or are magnified by, combined preparations (ie progestogen-containing) which are not used in trans women. These progestogen-related risks include

VTE and breast cancer. Current understanding is that starting oestrogen-only HRT in a healthy 50-year-old woman increases life expectancy, largely related to **reduced** risk of cardiovascular disease.

It is however clear that exogenous oestrogen:

- *increases the incidence of venous thrombo-embolism (VTE), particularly with oral preparations, and this risk is dose-dependent*
- *also increases the risk of ischaemic stroke, particularly in older women. The CHD risk is reduced with oestrogen-only HRT in healthy peri/postmenopausal women but rises if combined HRT is started >10 years after the natural menopause*
- *increases the risk of breast cancer.*

For further information on the risks in cis women please see the relevant MHRA advice.

Oestrogen evidence base in trans women

The evidence base in trans women is very limited. A retrospective case-controlled study has shown that trans women on hormone therapy had a higher incidence of both VTE and ischaemic stroke[ii]. The risk differences for VTE at 2 and 8 years were 3.4 and 13.7 relative to cis women on no oestrogen. In contrast to HRT where the VTE risk rises soon after starting treatment, *the risks in the trans women study continued to rise over time.*

There may be an increased risk of MI, and the evidence suggests this, though the estimated risks are the same as those for cis men. Whilst this is a relatively large study in this patient population, very few events were detected, and it was not possible to explore the effects of age or oestrogen dose. Thus, the precision of these risks, and their relevance to younger trans women, particularly with physiological levels of estradiol replacement, remain very unclear.

Older studies are generally poor, because of compounding factors, and that a variety of doses and preparations have been used historically.

Taking the available evidence together:

- *it is very clear that transdermal, rather than oral preparations have the lowest risk of VTE, and that the risk particularly with oral preparations is dose-dependent*
- *That VTE risk is likely raised, and it is also likely that it continues to rise with duration of use (unlike HRT)*
- *There may be an increased risk of MI (likely similar to cis men).*

Monitoring.

There is some internationally recognised guidance for monitoring, but it too has limitations and this guidance reflects a Lothian pragmatic multi-disciplinary consensus view. Many of the recommendations for monitoring come from American practice, often over-interventional in relation to the available evidence. There is limited data on the long-term health risks of hormone treatment and patients should be made aware that this is the case and the importance of long-term monitoring. However, overall, the evidence strongly supports the use of interventions in gender dysphoria for better clinical outcomes in consideration of the emotional and psychological risk versus benefit to the patient. Additionally, for patients who have had surgical orchidectomy, exogenous treatment is their only source of sex steroids, which also bring benefits, for bone health for example.

Risks may change over the course of a lifetime and need to be reassessed where new morbidities become apparent. Trans women need to understand that they are at increased risk of the following complications. We recommend use of the risk leaflet: to follow.

1. **Breast cancer.**

   Trans women taking oestrogen may be at risk of developing breast cancer because of the development of breast tissue. They should be made aware of this, and encouraged to participate in the national breast screening programme.

2. **Venous thrombo-embolism.**

   Trans women taking oestrogen, and their clinicians, should remain vigilant about the increased risk of VTE, a complication which can happen several years after starting hormone treatment: risks may

rise over time. The risk is minimised by taking transdermal oestrogen preparations, and the lowest effective dose.

If someone suffers a venous thromboembolism, oestrogen therapy should be stopped until further assessments are made.

All will be risk-assessed by the Chalmers GIC at the commencement of treatment, but advice should be sought from the Chalmers GIC, or other relevant specialties, should high-risk situations develop such as:

- Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
- The presence of multiple risk factors including family history or conditions with a strong association with VTE.

Those undergoing major surgery with prolonged immobilisation may need additional prophylaxis.

3. Cardiovascular disease.

- **Risk Assessment.** All women will have an initial cardiovascular risk assessment (ASSIGN score, using male gender for the risk calculation) at commencement of therapy and be advised accordingly.
- **Risk Minimisation.** All should be encouraged to minimise risk through a healthy lifestyle. The standard advice is for: smoking cessation, maintaining a healthy weight, drinking alcohol according to national guidance (maximum 14 units per week), exercising regularly and eating well. Further advice is available at: https://www.nhs.uk/live-well/
- **BP and smoking advice**
- annually
- ASSIGN score 5 yearly (age 40-55) and 3 yearly after that to optimise adverse lipid and blood pressure management, using male gender in the risk calculation.

We suggest that:

- Hypertension be treated at the threshold for diabetes or target organ damage. This means active management for those with Stage 1 hypertension and blood pressure readings of: clinic BP≥140/90 (multiple readings) and confirmed by subsequent ABPM daytime average ≥135/85 in keeping with the Lothian Hypertension Guidelines
- Advice should be sought for those with ASSIGN scores over 20, or hypertension or hyperlipidaemia less than optimally controlled.

4. Cardiovascular High-risk situations - Presence or risk of arterial thromboembolism (ATE)

In the following situations, patients will need immediate specialist care or advice:

- Arterial thromboembolism - current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
- Cerebrovascular disease - current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack)
- Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and anti-phospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant)
- New onset of migraine with focal neurological symptoms.

Urgent advice sought for those with a high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:

- Diabetes mellitus with vascular symptoms
- Severe hypertension
- Severe dyslipoproteinaemia.

The following are NOT required:

- Osteoporosis screening (bone loss only happens with prolonged GnRH treatment without added-in oestrogen, which should not happen)
- Routine measurement of estradiol levels
- Prolactin measurement
- PSA screens
- Screening for meningiomas and prolactinomas (which may be linked to cyproterone acetate usage) as these are exceptionally rare.

Also note that the reference range for some tests will differ from the standard range for that gender. Please see: Laboratory tests with gender-specific reference ranges (excluding hormones).

Dosage and administration

- Transdermal preparations, which avoid first pass metabolism in the liver, are strongly recommended for all patients especially those aged > 40 years and those with higher cardiovascular risk, a high BMI or liver disease. They are associated with reduced VTE risk compared with oral preparations.
- Transdermal estradiol patches up to 200 micrograms, changed once or twice weekly according to manufacturer instructions (initial dose titration at CGIC).
- Estradiol gel 0.5mg to 3mg, applied daily.
- Oral estradiol 1mg to 6mg daily.

Androgen Suppression

- Leuprorelin/Triptorelin 3/3.75mg 4 weekly or 11.25mg 3 monthly or 22.5mg (triptorelin) 6 monthly by IM injection **OR** Goserelin 3.6mg implant subcutaneously 4 weekly or 10.8 mg implant 3 monthly

OR

- Cyproterone Acetate (25-100 mg daily: 6 monthly checks of LFTs are necessary as serious hepatotoxicity has been reported). This is likely to be used only when patients are already taking it eg prior to moving to Lothian, and is rarely prescribed.

Patients may require re-titration of estradiol following gonadectomy, when androgen suppression therapy can be stopped. All should re-engage with the GIC during this period, and the GIC will carry out this titration if indicated.

Estradiol levels up to 600 pmol/L are appropriate though regular screening of estradiol levels is not recommended. The Chalmers GIC will base its advice regarding changing dose primarily according to clinical response.

Monitoring summary

Cautions, contraindications, adverse effects, or drug interactions – please refer to the current Summary of Product Characteristics (SPC): www.medicines.org.uk

Test	Frequency	Abnormal Result	Action if Abnormal Result
Creatinine and electrolytes	Annual – ONLY if taking spironolactone		Stop medication and seek advice

LFTs	6 monthly – ONLY if on cyproterone		Seek advice
BP and smoking advice	Annually	If hypertensive, treat at threshold for diabetes or target organ damage	Seek advice if severe / poorly controlled hypertension
Cardiovascular risk assessment	See comments above: ASSIGN score 5 yearly (age 40-55) and 3 yearly after that. *Use male gender for risk calculation.*	Treat stage 1 hypertension and provide lifestyle advice. Advise of increased risk.	Chalmers GIC will advise practices if ASSIGN score >20.
VTE	Risk assessment at commencement of treatment and if new diagnosis or high-risk situation develops throughout treatment (see section 2 above).		Stop oestrogen and seek immediate advice. Note that VTE is especially associated with oral preparations.
New onset active liver disease or malignancy	Throughout duration of treatment.	This includes: 1. Presence or history of severe hepatic disease, e.g. active viral hepatitis and severe cirrhosis, as long as liver function values have not returned to normal. 2. Presence or history of liver tumours (benign or malignant).	Refer back to Chalmers GIC (Lothian patients or major complications) or appropriate local endocrine or other relevant service for non-Lothian patients. Please note that different blood reference ranges may apply and please see Lothian laboratory recommendations
Screening	Advise: breast and abdominal aortic aneurism screening and prostate awareness.		NHS Inform provides transgender screening advice.

[i] ESHRE Guideline Group on POI, Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, de Muinck Keizer-Schrama S, Hogervorst E, Janse F, Liao L, Vlaisavljevic V, Zillikens C, Vermeulen N. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod 2016; 31:926-937.

[ii] Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons A Cohort Study. Getahun, D. et al. Ann Intern Med. 2018;169:205-213. doi:10.7326/M17-2785.