Masculinising 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 Gender Identity Clinic (GIC) will undertake initial assessment and establishment of treatment for all those seeking masculinising endocrine treatment.

Following that, GPs will be asked to be responsible for prescribing, and reporting any issues to the Chalmers GIC. ***However, monitoring arrangements (including phlebotomy) are not yet in place and a Shared Care Agreement is still being developed.***

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

New Patients

Some people will have been assessed by, or had treatment from, a recognised NHS gender identity clinic 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), the Chalmers GIC can provide email advice on ongoing treatment or see patients where that is necessary. The Chalmers Clinic is unable to prioritise patients who have accessed private treatment and recommends that they are advised to continue their engagement with their existing provider until the GIC has completed its assessment.

For those moving into Scotland, please advise about the procedures for changing CHI numbers and enrolling in the relevant national screening programmes.

INITIAL SPECIALIST ASSESSMENT - Chalmers Gender Identity Clinic:

- Baseline assessment, treatment counselling, gaining informed consent, and recommendation of initiation of treatment (communicated to GP to be prescribed). 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
- Patient - signed agreement with the specialist about use of unlicensed medications, copied to the GP
- Assess contraceptive needs – all those of reproductive age
- 3 monthly monitoring for the first year (or until patient on a stable medication regimen)
- Communication with GP about any changes in treatment
- Referral for specialist interventions relating to gender reassignment and transitioning
- Referral for non-specialist interventions as suggested by the Chalmers GIC (e.g. CMHT, weight management etc)
- Advise about changes in CHI.
- Discussion of relevant screening programmes (breast – may not be required if mastectomy has been performed; cervical for those with an intact uterus) details available from national screening programmes
- Cardiovascular risk assessment: ASSIGN.
- 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)

This will require a recall system and will likely be organised by the Chalmers GIC. The aim is for tests to be resourced by the specialist service and provided by CTACS:

- 12 monthly monitoring: FBC (Hb & haematocrit) for all on testosterone treatment.
- Testosterone levels:
    - Trough sampling immediately before dose for parenteral treatment
    - 2-4 hours after dosing for transdermal treatment
- From age of 50, 5 yearly BP measurement and full lipid profile for ASSIGN

CHALMERS GIC ANNUAL REVIEW:

The patient will be offered a virtual review with the option of Patient-Initiated Followup (PIFU) with the Chalmers GIC if there are interim clinical issues, thereby retaining specialist clinical oversight

- Review of response to treatment, as indicated
- Review of all the blood results as above, and 5 yearly ASSIGN score in those aged over 50
- Discuss and encourage healthy lifestyle in line with standard advice – 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/
- Communicate outcome to GP, including any changes in medication, or non-attendance for required checks when prescribing would stop.

GENERAL PRACTITIONER RESPONSIBILITIES:

- Cervical screening as for assigned female guidelines (requires sensitive discussion, taking into account the patient's dysphoria)
- Consider contraceptive needs, where indicated (reproductive age) – see here
- Prescribing of treatment as per Chalmers GIC advice
- Inform the Lothian Chalmers GIC (or local appropriate specialties in Borders or Fife) if there is a new diagnosis of liver, breast or other hormone-dependent cancers
- Inform the Chalmers GIC if there is a diagnosis of severe liver, renal or cardiac insufficiency, or new onset IHD (or other new cardiovascular diagnosis), diabetes or rheumatoid arthritis

Opportunistically encourage healthy lifestyle in line with standard advice – smoking cessation, maintaining a healthy weight, drinking alcohol according to national guidance (maximum 14 units per week), exercising regularly and eating well.

Support and Advice for the GP

Chalmers Gender Identity Clinic can be contacted by health professionals only for advice on: gic@nhslothian.scot.nhs.uk Enquiries are forwarded directly to the GIC team, and they aim to respond within two working days.

Key Information on the Medicine

Please refer to the current edition of the British National Formulary (BNF), available at www.bnf.org, and Summary of Product Characteristics (SPC), available at www.medicines.org.uk for detailed product and prescribing information and specific guidance.

Background and use of drug for the given indication.

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 and

the Lothian approach to prescribing and monitoring is recommended which has been agreed by a multidisciplinary expert team.

BACKGROUND - TESTOSTERONE.

The literature for use of masculinising hormones is limited, but continues to evolve, and this guidance will be amended as new evidence emerges. The research is hampered by confounding factors, and that historically a variety of hormone doses and preparations have been used. Many of the recommendations for monitoring come from American practice, often over-cautious in relation to the available evidence. There is some internationally recognised guidance for monitoring, but it too has limitations and the recommendations in this document reflect a pragmatic multi-disciplinary consensus view.

There is now a growing - and reassuring - evidence base around the safety of testosterone used for gender reassignment. This now demonstrates that generally the risks are those of (physiological) replacement therapy in men with hypogonadism, as are the monitoring requirements. There are no prospective trials assessing risk, but retrospective cohort studies indicate a probable small rise in some cardiovascular markers (such as non-calcified plaque) but not in cardiovascular events. The largest of these was well-validated, but involved a young population[i], so we suggest vigilance remains necessary in older groups and those with other cardiovascular risk factors until prospective evidence becomes clearer. However, any additional risks are small, particularly when compared with the baseline prevalence. We therefore recommend standard healthy lifestyle approaches, and ASSIGN scores in older age groups to optimise blood pressure and lipid management in lines with standard care. But this is not a clinical indication to limit or stop testosterone use. There is no evidence of raised VTE risk.

There are 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, evidence strongly supports the use of interventions in gender dysphoria for better clinical outcomes when the emotional and psychological risk versus benefit to the patient is accounted for. Risks may change over the course of a lifetime and need to be reassessed where new morbidities become apparent. The majority of people currently using masculinising treatment are young.

This is an unlicensed use of testosterone (except for Sustanon®), so the Summary of Product Characteristics relates to use in the cis male only, in whom breast cancer, and current or previous liver tumours are listed as contraindications.

Most trans men will not require GnRH analogues with masculinising hormones. If this does happen, please refer to the feminising treatment guidance for further detail.

In particular there is NO indication for the following checks or screening:

- Cardiovascular risk assessment in those aged under 50
- Routine liver function testing
- Osteoporosis screening
- Pituitary tumours (there seems to be a small rise in somatotrophinomas, but these are excessively rare)
- Change of dose in older age.

There needs to be caution about prescribing with cardiovascular co-morbidity, but there will be an initial assessment of this made at therapy initiation. However, it is thought that overall, the additional risks brought by testosterone are very low in healthy individuals and that there only needs to be a further assessment made if the person acquires a significant new cardiovascular diagnosis or risk factor such as diabetes or rheumatoid arthritis. Currently, most people receiving testosterone therapy for gender transition are low risk because they are young.

Please note that Chalmers Gender Identity Clinic can also provide email advice, available to professionals only.

Please note that NEITHER TESTOSTERONE NOR GnRH analogue treatments PROVIDE CONTRACEPTION.

Contraception is recommended where appropriate to prevent unintended pregnancy unless bilateral oophorectomy or hysterectomy has been undertaken. Neither testosterone therapy nor gonadotrophin releasing hormone (GnRH) analogues are contraceptive.

Suitable contraception:

- All progestogen only methods (Implant, injectable, progesterone-only pill)
- LNG IUS
- Copper IUD

All methods of emergency contraception (CU-IUD, ulipristal, levonorgestrel) can also be used.

NB Combined hormonal methods should not be used as estrogen counteracts masculinising effects of testosterone.

The Faculty of Sexual and Reproductive Healthcare (RCOG) provides further guidance.

Exogenous testosterone:

- The most common side effect is polycythaemia with raised haematocrit (risk is related to peak testosterone levels, so more common with short-acting injectable preparations, less common with transdermal administration).
- Administration of any oily depot preparation can very rarely cause Pulmonary Oil Microembolism – POME. This can be avoided by injecting very slowly over two minutes.
- The manufacturers advice is that it is contraindicated in those with severe cardiac, renal or hepatic insufficiency, or IHD
- May increase coumarin anticoagulant activity – *increased INR monitoring is recommended at times of dose changes.*

Indication - Treatment of gender dysphoria following assessment at the Chalmers GIC.

Dosage and administration

Androgens are introduced gradually and slowly titrated to avoid adverse reactions (e.g. headache, affective changes etc).

Introduction & titration: - undertaken by the GIC, with advice to GPs about prescribing

- Tostran® 2%, 20mg (2 'presses')/day may be titrated to 40-60mg (4-6 'presses')/day
- **OR**
- Transdermal testosterone: Testogel® 16.2mg/g, 20.25mg/day (1 press) may be titrated to 40.5-60.75mg/day (2-3 presses)

  OR
- Testavan® 2% gel 23mg (1 press) may be titrated to 46-69 mg/day (2-3 presses).

  OR
- Sustanon® by injection, 125mg every 2-4 weeks for 2-3 months, increase to 250mg every 2-4 weeks if tolerated and testosterone levels sub-therapeutic. This should be injected slowly over 2 minutes.

Gels have a longer half-life than other preparations so can help stabilise the small number of people who are chaotic with their treatment.

After 6 months, or once stable, patients either continue on the treatment they are on or offered the following maintenance treatments.

Maintenance:

- Testosterone undecanoate 1000mg deep intramuscular injection over at least 2 minutes every 10-14 weeks according to GIC recommendations **OR**

- Transdermal testosterone (Testogel® 16.2mg/g or Tostran® 2% or Testavan® 2%) 40mg-60mg daily **OR**
- Sustanon® intramuscular injection 125-250mg (NOT in the deltoid) every 2-3 weeks according to Chalmers GIC recommendations.

Oral testosterone preparations are **not** recommended.

Non-binary patients may be maintained at lower doses.

Decisions to adjust doses should be undertaken by the Chalmers GIC.

Monitoring

Counsel patients not to apply gels to arm/shoulders where bloods will be taken from otherwise testosterone results will be falsely high.

Test	Frequency	Normal / abnormal ranges	Action if Abnormal Result
Testosterone ***(if transdermal treatment)***	Annually	Normal: 10-39nmol/L	Chalmers GIC will action: standard advice is to recheck to for persistent elevation.
Testosterone trough levels ***(if parenteral treatment)***	Annually	Abnormal: < 9nmol/L or >15nmol/L	Chalmers GIC will action: standard advice is to defer next injection by 2 weeks; if persistently above 20nmol/L, dose review is required.
FBC and haematocrit	Annually	Abnormal: Haematocrit > 0.52	Chalmers GIC will action. The following is standard advice: there are often minor rises in haematocrit which can be ignored. Increasing injection interval or changing to transdermal preparation can be effective. Consider referral to haematology for assessment and rarely venesection. *PLEASE ENSURE THE MALE REFERENCE RANGE IS BEING USED -* Gender-specific reference ranges for blood tests.pdf (nhslothian.scot)

INR	Increased monitoring at time of dose change if coumarin anticoagulants used		Adjust warfarin dose accordingly
Cardiovascular health	Age <50, maximise opportunities to give healthy lifestyle advice. Age >50, 5 yearly ASSIGN score.		Chalmers GIC will advise treating blood pressure and adverse lipid profiles in line with standard national guidance. GPs are reminded to seek Chalmers advice if new onset cardiovascular disease, diabetes or other concern about significant new risk.
Screening	Consider that breast and cervical screening may still be needed.		For specific transgender advice, please see: national screening programmes

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

Please contact the Chalmers GIC advice if concerns or queries.

[i] 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.