

Endocrine Therapy for Transgender Adults in British Columbia: Suggested Guidelines

Physical Aspects of Transgender Endocrine Therapy

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Copies of these guidelines are available for download from the Transgender Health Information Program website. Updates and revisions will be made to the online version periodically. For more information or to contribute updates, please contact:

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Introductory Comments

Endocrine therapy is a strongly desired medical intervention for many transgender* individuals. The goal of transgender endocrine therapy is to change secondary sex characteristics to reduce gender dysphoria and/or facilitate gender presentation that is consistent with the felt sense of self. While there are risks associated with taking feminizing/masculinizing medications, when appropriately prescribed they can greatly improve mental health and quality of life for transgender people.^{1,2} In addition to inducing physical changes, the act of using hormones is itself an affirmation of gender identity.^{3,4}

In British Columbia, the care of transgender individuals is provided through a decentralized community-based model of care.² Clinicians with varying degrees of transgender training and experience are responsible for this care. This document provides updated protocols for the prescribing clinician relating to physical assessment, prescription planning, initiation of endocrine therapy, and ongoing maintenance. It is intended to assist endocrinologists, family physicians, and nurse practitioners whose patients may ask for feminizing/masculinizing medication. It is written for professionals who are already familiar with basic terms and concepts in transgender care and are seeking more advanced clinical guidance in work with transgender adults. Endocrine treatment of transgender adolescents is not discussed in this document.

Family physicians and nurse practitioners with training and experience in behavioural health, gender identity concerns, and sexual issues may choose to have sole responsibility for all aspects of transgender endocrine care, including assessment of eligibility and readiness. Alternatively, the primary psychological assessment may be performed by a mental health clinician, with the prescribing physician providing a briefer corroborating evaluation.

As discussed in the World Professional Association for Transgender Health (WPATH) *Standards of Care, (Version 7)*,⁵ transgender endocrine therapy is best undertaken in the context of a complete approach to health that includes comprehensive primary care and a coordinated approach to psychosocial issues. While the WPATH *Standards of Care, (Version 7)*,⁵ do not require psychotherapy prior to initiation of endocrine therapy, ideally a trans-experienced therapist will be available as needed to assist the patient in adjusting to the profound physical and psychosocial changes involved in endocrine therapy. Advocacy may also be required to assist with changes to legal name or identification.⁶

*WPATH Standards of Care (Version 7)*⁵ are intended as a flexible framework to guide the treatment of transgender people. Likewise, the recommendations made in this document should not be perceived as a rigid set of guidelines. In any clinical practice it is paramount that protocols be tailored to the specific needs of each patient, and clinicians are encouraged to adapt and modify our suggested protocols to address changing conditions and emerging issues. Research in transgender health is still in its early days, and there are widely diverging clinical (and consumer) opinions about “best” practice. In this document we offer suggestions based on an in-depth review of transgender health research, a review of protocols used in 16 clinics, interviews with expert clinicians, and the authors’ clinical experience. The updates are based in the new WPATH standards of care, guidelines from the European Endocrine Society, and a review of recent research. Ongoing research and collegial meetings are needed to further develop practice protocols.

* In this document, *transgender* includes any person who (a) has a gender identity that is different from their natal sex, and/or (b) who expresses their gender in ways that cross or transcend societal expectations of the range of possibilities for men and women. This umbrella term includes individuals who identify in many ways, including androgyne, agender, bigender, butch, cross-dresser, drag king, drag queen, femme, FTM, gender creative, gender fluid, gender non-conforming, genderqueer, gender variant, MTF, pangender, questioning, trans, trans man, trans woman, transfeminine, transgender, transmasculine, transsexual, and two-spirit.

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There is great variation in the extent to which hormonal changes are undertaken or desired. Some individuals seek maximum feminization/masculinization, while others experience relief with an androgynous presentation. Endocrine therapy must be individualized based on the patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues.

Most of the medications listed in this guide are considered eligible prescription drugs under the BC Fair PharmaCare program and other such formularies (although a Special Authority application may be needed in some instances). However, economic factors may still be a barrier for patients seeking medications. Approximate cost is included in our discussion of recommended regimens.

Responsibilities of the Prescribing Clinician

In British Columbia, feminizing/masculinizing medication is typically prescribed by a family physician, endocrinologist, or nurse practitioner.* With appropriate transgender health training, endocrinologic manipulation of secondary sex characteristics can usually be managed by the primary care provider. Medical visits relating to hormone maintenance provide an opportunity for broader care to a population that is often medically underserved, and many of the screening tasks involved in long-term hormone maintenance fall within the scope of primary care rather than specialist care*. For this reason we suggest that if hormones are prescribed by an endocrinologist, rather than the primary care provider, there be close communication between the two clinicians to ensure adequate care. A trans-experienced endocrinologist should be involved if the primary care provider has no experience with transgender health, or if the patient has a pre-existing metabolic or endocrine disorder that may be affected by endocrine therapy.

* In BC nurse practitioners can prescribe anti-androgens, estrogen, and progestins, but not testosterone.⁷

The World Professional Association for Transgender Health (WPATH) *Standards of Care (Version 7)*⁵ state that the prescribing clinician should:

1. Perform an initial evaluation that includes discussion of the patient's physical transition goals, health history, physical examination, risk assessment, and relevant laboratory tests.
2. Discuss with the patient the expected effects of feminizing/masculinizing medications and the possible adverse health effects. These effects can include a reduction in fertility. Therefore, reproductive options should be discussed with the patient before starting hormone therapy.
3. Confirm that the patient has the capacity to understand the risks and benefits of treatment and is capable of making an informed decision about medical care.
4. Provide ongoing medical monitoring, including regular physical and laboratory examination to monitor hormone effectiveness and side effects.
5. Communicate as needed with the patient's primary care provider, mental health professional, and surgeon.
6. If needed, provide the patient with a brief written statement indicating that they are under medical supervision and care that includes feminizing/masculinizing hormone therapy. Particularly during the early phases of hormone treatment, the patient may wish to carry this statement at all times to help prevent difficulties with the police and other authorities.

Feminizing Endocrine Therapy

Mechanisms of action

Endocrinologic feminization of patients on the Male-to-Female (MTF) spectrum is achieved by (a) direct or indirect suppression of the effects of androgens, and (b) induction of female physical characteristics.^{8,9,10} Androgen suppression can be achieved by:

- Suppressing the production of gonadotropin-releasing hormone (GnRH): e.g. GnRH analogues such as leuprolide acetate
- Suppressing the production of luteinizing hormone: e.g. progestational agents, cyproterone acetate

- Interfering with the production of testosterone or metabolism of testosterone to dihydrotestosterone (DHT): e.g. spironolactone, finasteride, cyproterone acetate
- Interfering with the binding of androgens to receptors in target tissues: e.g. spironolactone, cyproterone acetate, flutamide

Estrogen is the principal agent used to induce female characteristics, and works primarily by direct stimulation of estrogen receptors in target tissues.¹¹ Although estrogen also suppresses luteinizing hormone (LH), the estrogen dose required for effective LH suppression is high and may be associated with undesirable side-effects.¹⁰

Expected feminizing effects

Rapidity and degree of change from feminizing endocrine therapy depends on the agents used, dosage, and the patient's responsiveness to endocrine therapy. Typically, within the first 1–6 months there is gradual redistribution of body fat to more closely approximate a female body habitus, decreased muscle mass and decreased upper body strength. These changes can be affected by diet, as well as the type and amount of physical activity.⁸ Patients also experience softening of skin, decreased libido and possible difficulty reaching orgasm, reduction of ejaculate, and decreased spontaneous/morning erections.^{5,8–14} Testicular volume is reduced by up to 25% within the first year,^{8,9} with gradual reduction up to 50% of the original volume over a long period of time.¹⁵ The shrinkage of testes may make them feel softer on palpation.⁸ Testicular atrophy impacts sperm maturation and motility, and may be permanent.⁹ However, the patient may still be fertile and should be counselled accordingly.

Tender breast buds may start to form within 3–6 months, with gradual breast growth (highly variable) and nipple development taking two or more years.^{8,9,13,14,16} Typically breast growth is not as pronounced in people on the MTF spectrum as in non-transgender women, and it is rare for MTF-spectrum breasts to reach Tanner Stage 5 appearance.^{17,18} The greatest proportion of breast growth occurs within 18–24 months of feminizing endocrine therapy¹⁹. If by this time, breast growth is not sufficient for comfort, patients often consider surgical augmentation. In those patients utilizing feminizing hormones, WPATH recommends a minimum of a 12-months of hormone therapy before considering augmentation surgery.⁵ Weight increase may help promote breast development in thin MTF-spectrum patients.

Over a period of several years, body and facial hair becomes finer and growth is slowed,^{5,8,9,10,12,20} but typically cannot be eliminated by hormones alone. Electrolysis,

laser treatment, or other forms of hair removal may be desired.^{5,9,21–23} While feminizing endocrine therapy may gradually slow or stop the progression of male-pattern baldness, scalp hair does not completely re-grow in bald areas.^{5,8,9,12,24}

Most of these changes are reversible if treatment is discontinued. Breast growth and development of the nipple–areolar complex are permanent. It is not known if changes to fertility are completely reversible, and options for sperm banking should be discussed prior to initiation of endocrine therapy.^{5,25}

Research evidence to date does not demonstrate that any particular medically approved type or method of administering hormones is more effective than another in producing desired physical changes.⁵ Response to hormone therapy cannot be reliably predicted based on the patient’s age, body habitus, family appearance, or ethnicity.

Approach to patients across the feminine spectrum

Not every person on the MTF spectrum patient desires to maximally feminize their body, whether related to their gender expression or due to current life circumstances. Some patients may begin hormone therapy seeking minimal changes, and later pursue a full physical transition. The provider and patient need to establish which feminine and masculine characteristics (including fertility and sexual function) are important for the patient, and if that combination is medically achievable with hormone therapy. Anti-androgen therapy alone, low-dose estrogen, or even surgical intervention, with or without low doses of hormones, may be needed to achieve the patient’s goals.

Recommended feminizing regimen

Table 1 below summarizes our recommendations for a basic regimen for the MTF-spectrum patient who desires maximum feminization. A combination of estrogen + spironolactone (an androgen antagonist) is recommended, as spironolactone has a direct effect of reducing male-pattern hair growth and also minimizes the dosage of estrogen needed to suppress testosterone (thereby reducing risks associated with high-dose exogenous estrogen).^{5,8} Finasteride may be added to slow male-pattern balding.

Androgen antagonists (aka “anti-androgens”) may be prescribed alone for patients who wish to reduce masculine characteristics for a more androgynous appearance. As spironolactone can induce irreversible gynecomastia, 5 α -reductase inhibitors are preferred for those who do not want visible breast development.

With both estrogen and androgen antagonists, the starting dose for patients who are at low risk for adverse effects can be gradually increased to the recommended maximum if needed to achieve the desired changes and to bring bioavailable testosterone to the lower half of the female range. Following orchiectomy, the dosage should be adjusted as endogenous androgen production is significantly reduced. To preserve bone density following orchiectomy, estrogen supplementation should be maintained throughout life as long as the benefits outweigh the risks, given an individual's health status and life expectancy. Very low doses of estrogen are likely adequate for this purpose.²⁶⁻²⁸

Table 1: Basic feminizing regimen

Agent	Estrogen			Androgen antagonist				
	17 β -estradiol			spironolactone	<i>and/or</i>	finasteride	<i>and/or</i>	Cyproterone acetate
Administration	Transdermal	<i>or</i>	oral	oral		oral		oral
Brand name	Estradot®, Estraderm®, Oesclim®		Estrace®	Aldactone®		Proscar®		Androcur®
Pre-orchiectomy	Use transdermal if >40 yrs or at risk for DVT start at 0.1 mg/24 hrs, applied twice per week; gradually increase up to maximum of 0.4 mg/24 hrs, applied twice per week		Oral is an option if <40 yrs and low risk for DVT start with 1–2 mg qd; gradually increase up to maximum 6 mg qd	start with 50–100 mg qd; increase by 50–100 mg each month up to average 200–300 mg qd (maximum 500 mg qd) <i>modify if risks of adverse effects: see below§</i>		2.5–5.0 mg qd for systemic anti-androgen effect; 2.5 mg every other day if solely for androgenic alopecia		25-50 mg qd
Post-orchiectomy	0.025–0.1 mg/24 hrs, applied twice per week		1–2 mg qd	25–50 mg qd		2.5 mg qd		0 mg qd
Monthly cost	0.1 mg/24 hours, applied twice per week: ~\$25/month*		2 mg qd: ~\$14/month*	300 mg qd: ~\$22/month*		5.0 mg qd: ~\$58/month*		50 mg qd ~ \$50.00/month

§ If taking ACE-inhibitors or other potassium-sparing medication, spironolactone should not go above 25 mg qd, and serum potassium should be closely monitored. If the patient has low blood pressure or renal insufficiency, start at 50 mg and increase by up to 50 mg per week to a maximum of 300 mg qd, with a renal function test 1–2 weeks after each increase.

* Plus the dispensing fee set by each pharmacy and billed each time a prescription is refilled. In BC the average fee in 2013 was \$10.43, although compounding pharmacies may charge significantly more.

Spironolactone

In the mid-1980s, clinicians at the Vancouver Gender Dysphoria Program began using spironolactone as part of the feminizing regimen for people on the MTF

spectrum, based on its anti-androgenic properties and its use for treatment of hirsutism in non-transgender women.^{10,29,30} It has since been adopted for use by many other transgender centres.^{13,16,20,24,31,32} Possible adverse effects of spironolactone include hyperkalemia (particularly in conjunction with ACE-inhibitors, angiotensin receptor blockers, and Type IV renal tubular acidosis – found in some patients with diabetes), renal insufficiency, hypotension, and rash.^{5,8,33}

Estrogen-related effects and alternative regimens and agents

Estrogen

There is evidence that people on the MTF spectrum who take estrogen are at increased risk for venous thrombosis, pulmonary embolism, and stroke.^{8,34-36} These risks may be mitigated by the type of endocrine agent chosen, the route of administration (transdermal vs. oral), dosage, and by other factors (e.g. smoking cessation). Some centres taper or temporarily discontinue estrogen 2–4 weeks before any major surgery (including genital surgery) to minimize thrombosis risk, restarting after the patient has recovered sufficiently to be significantly mobile.^{8,13,16,24,37}

In the absence of empirical evidence that one type of estrogen (esterified vs. conjugated vs. estradiol) is a more effective feminizing agent than another, our recommendation to use 17 β -estradiol is based on concerns about thromboembolic risk. Evidence suggests the lowest thromboembolic risk with transdermal estradiol.^{35,37-39} This is particularly important for those with vascular or thrombotic risks (including smokers and people age 40+) and for people with co-morbid conditions. If an oral agent is desired, oral 17 β -estradiol is recommended rather than oral ethinyl estradiol or conjugated estrogens (e.g. Premarin®), since some studies suggest higher risks of blood clots with the latter forms.^{36,37,44,41}

Retrospective studies of long-term use of feminizing hormones suggest a possible increase in cardiovascular risk over time. MTF-spectrum patients in general had trends resembling worsening of metabolic syndrome with weight gain, increased body mass index, visceral fat and a slight decrease in insulin sensitivity, but no hyperglycemia. Lipid effects showed increased HDL and triglycerides, unchanged total cholesterol and decreased LDL cholesterol, albeit with smaller particle size. Studies have been mixed in terms of detecting any elevations in cardiovascular morbidity or mortality.^{8,42}

Other risks that have been associated with estrogen use include: cholelithiasis, hyperprolactinemia, hypertriglyceridemia, and abnormal liver enzymes. While cases of breast cancer have occurred, evidence regarding an increased risk is

inconclusive¹¹, and recent studies do not indicate an increase in cancer prevalence among patients taking feminizing hormones.^{43,44} Short and medium term studies indicate feminizing hormone therapy is acceptably safe, however large-scale, long-term data are not yet available.⁴⁵

The Drug and Poison Information Centre of BC's *Drug Information Reference* lists three clinically significant interactions between estrogen and other medications: anticonvulsants (decreased estrogen effect), rifampin (decreased estrogen effect), and corticosteroids (increased corticosteroid effect).

Progestins

The inclusion of progestins in feminizing therapy is controversial.^{8,33} Some clinicians believe progestins are necessary for full nipple development.⁸ However, a clinical comparison of feminization regimens with and without progestins found that the addition of progestins neither enhanced breast growth nor lowered serum levels of free testosterone.⁸ There are concerns regarding potential adverse effects of progestins (including weak androgen receptor stimulation, depression, weight gain, and lipid changes),^{8,16,31} As well, the findings of a Women's Health Initiative study (increased risk of coronary heart disease, stroke, pulmonary embolism, and invasive breast cancer in postmenopausal women taking combined estrogen and progestin HRT) are noteworthy.⁴⁶ Many of the clinical protocols reviewed for this guideline did not include progestins, and some clinicians explicitly recommended against their use.^{5,8,11,16,31,47} Others have included medroxyprogesterone acetate as part of their basic feminizing regimen.^{10,8,20}

We do not recommend progestin unless further androgen suppression effects are required after substantial estrogen doses have been used, or if the patient cannot tolerate an estrogen-based regimen.²⁸ Table 2 summarizes our recommended doses for progestin use in these circumstances.

Table 2: Progestin options in a feminizing regimen

	Progestin Options	Cost per month
Oral	Micronized progesterone (Prometrium®): 100–400 mg qd	300 mg qd: ~\$87/month*
	Medroxyprogesterone acetate (Provera®): 5–30 mg po qd (in divided doses at higher range)	30 mg qd: ~\$33/month*
Transdermal single patch	140 µg or 250 µg norethindrone acetate (progestin) with 50 µg 17β-estradiol§ twice per week (Estalis®)	140/50 patch: ~\$26/month*

§ If also taking estradiol alone, adjust the dosage of estradiol accordingly.

* Plus the dispensing fee set by each pharmacy and billed each time a prescription is refilled. In BC the average fee in 2013 was \$10.43, although compounding pharmacies may charge significantly more.

Alternative forms of estrogen

There is no empirical evidence that one form of estrogen brings about greater feminization than other forms of estrogen. However, it has been observed that IM estrogen tends to give slightly faster results compared to oral/transdermal estrogen, and patients may therefore request it. IM estrogen is typically not a first choice, as IM administration results in larger fluctuations in blood levels than transdermal/oral administration (with according greater risks of adverse effects and mood lability). We recommend that IM injection only be used if the clinician has high confidence in patient compliance and if the patient is at low risk for DVT.

If in the first two years of treatment there is minimal breast development or an early plateau in growth (no change in three months despite being on the maximum dose), some clinicians switch to IM estradiol valerate (Delestrogen®: 20–40 mg IM q 2 weeks) for 3–6 months to see if it is possible to boost breast development. Clinician-administered IM estrogen may be a safer or more convenient alternative for patients in supervised living arrangements (incarceration, group homes) and homeless individuals, or in conditions where the patient may be pressured to share or sell oral or transdermal medication. Delestrogen® and other commercial brands of injectable estrogen are not currently available in Canada; however, injectable forms of estrogen can be prepared by compounding pharmacies.

Transdermal gel (Estragel®) is a possible alternative to the transdermal patch for those who experience a skin reaction from the patch. Two pumps of gel applied daily is roughly equivalent to Estradot 50®. The amount of skin needed for absorption of this amount of gel is quite large (both legs) so Estragel® is not a first choice for most patients.

As IM and transdermal (patch and gel) estrogen both bypass first-pass hepatic metabolism, there is decreased risk of drug interactions in patients on multiple medications with hepatic metabolism. In addition, these preparations may be more effective in patients that do not absorb estrogen well through the GI tract.

There is no evidence that custom compounded bioidentical hormones are safer or more effective than government agency–approved bioidentical hormones.⁴⁸ Unless there are no other options, we do not support the use of compounded estrogens of any form, due to lack of evidence and lack of consistency of products.

Alternative androgen antagonists

Cyproterone acetate (Androcur®) is used by some transgender clinics as an alternative to spironolactone.^{5,8,9,27,35,49,50} Cyproterone acetate inhibits the production of luteinizing hormone, is a 5 α -reductase inhibitor, and interferes with the binding of testosterone at

receptor sites. Possible adverse effects include liver enzyme elevation and depression,^{5,8,9,12} and for this reason we do not recommend it unless spironolactone cannot be tolerated.

Flutamide (Euflex®) use was reported by two transgender clinics surveyed (750 mg po qd).^{13,20} Hepatotoxicity has been reported in non-transgender men receiving comparable doses of flutamide for treatment of prostate cancer,⁵¹ and for this reason we do not recommend flutamide as part of feminizing endocrine therapy. A clinical trial of flutamide, finasteride, and spironolactone in the treatment of hirsute non-transgender women found all agents equally effective in reducing facial hair.⁵²

Assessment prior to initiating feminizing endocrine therapy

1. Comprehensive primary care evaluation

A full primary care evaluation should be completed, with particular attention to risks/history of venous thrombosis, atherosclerotic vascular disease, cholelithiasis, glucose intolerance, dyslipidemia, estrogen-dependent cancer, migraine, and hepatic disease. If there are additional primary care concerns, these should be appropriately investigated. When possible, efforts should be made to stabilize and control co-morbid conditions (with medication, lifestyle changes, or other suitable interventions) prior to initiating hormones.

Cigarette smoking is associated with increased risk for venous thrombosis. We recommend a harm-reduction approach that strongly encourages patients to reduce or stop smoking along with a clear recommendation that their estrogen dosage must be kept low as long as they are smoking.

2. Baseline evaluation

To assist in monitoring of adverse effects, baseline values should be recorded for lipid profile, fasting blood glucose (and A1C if diabetes or suspected glucose intolerance), liver enzymes, electrolytes, and creatinine. If there are clinical concerns, there may be indications for additional tests, including complete blood count, creatinine/eGFR, and coagulation profile.

To assess feminizing effects, laboratory investigation should include baseline total testosterone* and baseline measurements of the breasts and hips should be recorded. Measure breasts in a standing position (a) vertically from the mid-clavicular line to the

* There are varying clinical opinions on the accuracy and reliability of testosterone assays. Total testosterone is now the standard available method of measurement in British Columbia after a laboratory assessment process de-emphasized the use of free and bioavailable testosterone except in the case of borderline total testosterone values.

infra-mammary fold, across the largest portion of the breast, and (b) from the anterior axillary line to the mid-sternum, across the largest portion of the breast.

3. *Written informed consent document*

The WPATH *Standards of Care (Version 7)*⁵ note that providers should document in the medical record that comprehensive information has been provided and understood about all relevant aspects of the hormone therapy, including both possible benefits and risks. Sample informed consent forms for feminizing endocrine therapy are included as Appendix C.

Monitoring recommendations following initiation of feminizing endocrine therapy

At minimum patients should be seen every 1–3 months after initiating treatment or while adjusting medication dosages, then every 3–6 months for the first year, then every 6 months thereafter. The primary focus of monitoring feminizing endocrine therapy use is to assess the degree of feminization and the possible presence of adverse effects of medication. However, as with monitoring of any long-term medication, monitoring should take place in the context of comprehensive care of all health concerns.

1. *Evaluation of feminization*

Feminization takes place gradually over a period of years. Observed changes to male-pattern hair growth, breast/nipple development, and testicular volume should be noted; breast and hip measurements recorded; and the patient asked about changes to male-pattern hair quality and growth (e.g., mechanical hair-removal frequency), mood changes, libido, and sexual function. Other changes should also be noted. Breast budding should be discussed in advance to reassure the patient that it is not a malignant process.

Testosterone level should be checked every 3–6 months until stable in the female range of <1.5 nmol/L. Total testosterone, followed by bioavailable testosterone levels, can be used if lab and clinical results do not correspond (i.e. total testosterone is suppressed, with an inadequate physical response).

Estradiol levels should be checked if the patient is not feminizing as expected, or if there are concerns about excessive estrogen levels.

2. Monitoring of adverse effects

All exams should include careful assessment of cardiovascular and thrombosis risk, including measurement of blood pressure and weight, lung exam, and examination of the extremities for peripheral edema, localized swelling, or pain.

At minimum, laboratory tests should include (see Table 3 for summary):

- Liver enzymes: 1–3 months after starting estrogen or changing dose, 3 months thereafter, and every 6 months once estrogen dose is stable. Investigate rises with abdominal ultrasound and hepatitis serology and/or consultation as indicated; discuss alcohol use.
- Lipid profile: 1–3 months after starting estrogen or changing dose, and every 6–12 months once estrogen dose is stable, unless concerned about triglycerides at baseline.
- Fasting glucose: 1–3 months after starting estrogen or changing dose, 3–6 months thereafter, and then every 6 months once estrogen dose is stable. Monitor more frequently and include evaluation of A1C if significant weight gain, increase in fasting glucose levels, or family history of diabetes mellitus.
- Prolactin: 3 months, 6 months, then annually to 3 years; stop if stable at that point. Mild hyperprolactinemia may be seen with estrogen administration and is typically reversible if estrogen is reduced or temporarily discontinued. Hyperprolactinemia may also result from antidepressants or other medication, antipsychotics, antidopaminergic gastrointestinal prokinetics, marked hypothyroidism, unrecognized supplementation with additional estrogen, or prolactin-secreting pituitary adenoma. Further investigation may be warranted if prolactin levels are unusually high or do not reverse with reduction of estrogen dosage.
- If taking spironolactone: monitor serum potassium and creatinine 1 month after starting spironolactone or changing dose, or after 1 week if there are risk factors for hyperkalemia (see above). Subsequently, monitor every 3 months in the first year, and every 6 months thereafter.

Table 3: Feminizing regime laboratory summary

Table 3 represents minimum timelines. Closer monitoring should be done for patients at risk for or with co-existing cardiovascular disease, diabetes, hepatic disease, etc.

Timeline for Laboratory Tests			
Baseline (before starting feminizing endocrine therapy)	<ul style="list-style-type: none"> • Total testosterone, lipid profile, fasting blood glucose (and A1C if diabetes or suspected glucose intolerance), liver enzymes, electrolytes, creatinine • Additional tests as clinically indicated (e.g. CBC, coagulation profile) 		
1 week after starting spironolactone (if risk factors for hyperkalemia)	<ul style="list-style-type: none"> • Serum potassium, creatinine 		
1 month after starting/changing dose of spironolactone	<ul style="list-style-type: none"> • Serum potassium, creatinine 		
1 month after starting/changing dose of estrogen	<ul style="list-style-type: none"> • Liver enzymes, lipid profile, fasting glucose • If taking spironolactone: serum potassium, creatinine 		
3 months after starting estrogen	<ul style="list-style-type: none"> • Testosterone: repeat every 3 months until testosterone is in target range of <1.5 nmol/L • Liver enzymes, lipid profile, fasting glucose, prolactin • If taking spironolactone: serum potassium, creatinine 		
6 months after starting estrogen and every 6 months thereafter if dose is stable	<ul style="list-style-type: none"> • Liver enzymes, fasting glucose • If taking spironolactone: serum potassium, creatinine • Add lipid profile every 6–12 months (once estrogen dose is stable) • Add prolactin at 6 months, 12 months, 24 months, and 36 months; cease prolactin thereafter if stable. 		
Testosterone Reference Ranges (goal: reduce to female range)			
	BC Bio Medical Labs	Life Labs	Vancouver Hospital
Total testosterone:	F >17 yrs: 0.5–2.6 nmol/L	F: <1.5 nmol/L	F >11 yrs: <0.5–2.4 nmol/L

3. Ongoing comprehensive primary care

Cardiovascular risk factors should be aggressively screened for and treated, osteoporosis assessment should be considered for MTF-spectrum patients who are at risk (e.g. thin and age 50+, particularly those who have taken hormones intermittently or have had orchiectomy), and breast cancer screening should be implemented as breast tissue develops. Primary care of the MTF-spectrum patient includes screening for other types of cancer (e.g. colorectal, anal) and regular prostate evaluation as for non-transgender males, as well as periodic screening for concerns relating to sexual health, mental health, and substance use.

Masculinizing Therapy

Mechanisms of action

Endocrinologic masculinization of patients on the Female-to-Male (FTM) spectrum is achieved by the use of testosterone to induce male physical characteristics. Testosterone works primarily by direct stimulation of androgen receptors in target tissues; clinical effects correlate to elevation of serum testosterone level to a male reference range, rather than a decrease in serum estradiol.¹¹ Testosterone also inhibits gonadotropin-c secretion in high doses.⁸

Expected masculinizing effects

Rapidity and degree of change from masculinizing endocrine therapy depends on the agents used, dosage, and the patient's responsiveness to endocrine therapy. Typically, within the first 1–3 months patients experience oilier skin/acne, increased muscle mass and upper body strength, and redistribution of fat to a more masculine pattern (shifting from the hips and buttocks to the abdomen).^{5,8,9,16,24,53–55} There are case reports of tendon rupture in both FTM-spectrum patients on testosterone and non-transgender men taking anabolic steroids,^{55,56} and FTM-spectrum people who are involved in strength training should be cautioned to increase weight load gradually, with an emphasis on repetitions rather than weight. Testosterone therapy tends to increase both sexual desire and arousal.⁵⁷ The voice often starts to crack and deepen within the first 3–6 months, but it can take a year or more for the voice pitch to fully drop.^{5,8,9} In 75% of FTM-spectrum people, testosterone will cause voice pitch to drop to a level sufficient for them to be understood to be male even on the telephone.⁵⁸

Clitoral growth begins within the first few months of testosterone initiation and typically plateaus within the first year.^{8,9} The degree of enlargement is variable, with studies reporting a range of 3.5–6 cm maximal stretched length.^{8,9} Clitoral growth does not appear to be enhanced by topical application of testosterone to the clitoris. Long-term testosterone use causes vaginal and cervical atrophy,^{8,50} with decreased vaginal secretions and difficult penetration reported by some patients.⁵⁵

In most cases, menses stop within 1–6 months.^{5,8,9,13,16,24,55} If after 3 months menses have not stopped, the dosage of testosterone may be increased (to the maximum recommended dose) until serum testosterone is within the upper quartile of the normal male range or menses stop. Despite endometrial atrophy, cessation of menses, and reduced fertility, there is evidence of ovulation even after several years of testosterone administration,⁵⁰ and testosterone should not be relied upon as a failsafe contraceptive.

There is gradual increased growth, coarseness, and thickness of hairs on the torso and extremities in the first year.^{5,8,9,16} Facial hair increases more slowly, typically taking 3–5 years to reach full growth.⁵ Some patients experience male-pattern baldness during this later stage of masculinization.^{5,8,9,16,24,32,54}

Most of these changes are reversible if treatment is discontinued. Voice changes and male-pattern baldness are not reversible. Growth of facial and body hair can be reversed through the use of electrolysis, laser treatment, or similar treatments. It is not known if changes to fertility and to clitoral growth are reversible. Reproductive counselling, including options for banking reproductive tissue, may be advised, particularly for young patients.⁹

Approach to patients across the masculine spectrum

Not every patient desires to maximally masculinize their body, whether as part of their gender expression or due to current life circumstances. Some patients may begin hormone therapy seeking minimal changes, and later pursue a full physical transition. The provider and patient need to establish which feminine and masculine characteristics (including fertility and sexual function) are important for the patient, and if that combination is medically achievable with hormone therapy. Interventions to stop menstruation, such as depot medroxyprogesterone or a progesterone-containing IUD with or without low doses of testosterone, may be needed to achieve the patient's goals.

Recommended masculinizing regimen

Table 4 below summarizes our recommendations for a basic regimen for the FTM-spectrum patient who desires maximum masculinization. The starting dose for patients who are at low risk for adverse effects can be gradually increased to the recommended maximum if needed to achieve the desired changes and to bring testosterone within the male range (Table 5). Once maximum masculinization has been reached (typically changes plateau after 2 years, although there may still be facial hair growth/male pattern baldness after that time), the dosage can often be reduced while maintaining amenorrhea and adequate masculinization (Table 5) even prior to oophorectomy. To preserve bone density following oophorectomy, testosterone supplementation should be maintained throughout life as long as the benefits outweigh the risks, given an individual's health status and life expectancy, and calcium/Vitamin D supplementation is recommended.

Table 4: Basic masculinizing regimen

	Intramuscular injection (esterified testosterone)		Transdermal gel	Transdermal patch
Agent	Testosterone cypionate	Testosterone enanthate	Testosterone crystals dissolved in gel	
Brand name	Depo-Testosterone®	Delatestryl®	AndroGel®	Androderm®
Pre- oophorectomy	40-50 mg every week; adjust after one month to ensure blood testosterone is in the middle of the normal male range. Thereafter, adjust as needed to suppress menses and achieve visible secondary masculine characteristics (voice change, and body/facial hair, upper body muscle mass). (typically 50–100 mg every week, or 100–200 mg every 2 weeks) <i>ensure patient knows how much to inject – there are 100 mg/mL (cypionate) and 200 mg/mL (enantate) preparations</i>		5–10 g qd; start with 2.5 g qd if there are comorbid conditions that may be exacerbated by testosterone (see discussion below)	5–10 mg/24 hours, applied daily; start with 2.5 mg patch if there are comorbid conditions that may be exacerbated by testosterone (see discussion below)
Maintenance (after 2 years)	Reduce to level needed to keep serum testosterone within the male reference interval (page 14). Monitor risk of osteoporosis.			
Monthly cost	150 mg every two weeks: ~\$10/month*		5 g qd: ~\$130/month*	5 mg qd: ~\$130/month*
* Plus the dispensing fee set by each pharmacy and billed each time a prescription is refilled. In BC the average fee in 2013 was \$10.43, although compounding pharmacies may charge significantly more. ** Compounded testosterone creams and gels may be significantly less expensive than AndroGel or Androderm.				

Testosterone-related effects and alternative regimens and agents

Testosterone

Increases in some cardiovascular risk factors have been observed in one long-term clinic experience, and several smaller studies. Weight gain and visceral fat were increased. A small decrease in insulin sensitivity occurred, and small increases in HDL cholesterol (0.1–0.3 mmol/L) and triglycerides (0–0.7 mmol/L) were noted. There is no reported increase in cardiovascular morbidity or mortality.^{8,42}

The largest transgender hormone studies done to date have found no increased mortality in androgen treatment for FTM-spectrum individuals; however, most patients started hormones at a younger age and thus were not followed into higher risk age groups.⁸ Most studies indicate that androgen use may worsen lipid abnormalities, obstructive sleep apnea, obesity, and acne.^{8,24,35,32,59} Erythrocytosis is also a concern with testosterone therapy, with an increased risk of thromboembolic events, aggravation of vascular disease, and clinical manifestation of hemochromatosis in at-risk patients.⁹ Overall, recent studies indicate that testosterone is relatively safe with regards to short

and medium term cardiovascular health (5-10 years average follow-up) with similar morbidity rates for individuals receiving masculinizing endocrine therapy and controls.^{43,44}

Increased visceral fat depot, particularly pronounced in FTM-spectrum individuals who gained weight after starting testosterone,⁸ is a concern as this is associated with increased risk for cardiovascular disease and non-insulin-dependent diabetes mellitus. The aromatization of testosterone to estrogen may increase risk of malignancy in patients with a strong family history of estrogen-dependent cancers.^{11,13,60} However, large cohort studies ($n=50$ and $n=138$) failed to document any increased cancer risk for FTM-spectrum patients (7.4 and 5 years average follow-up).^{43,44}

Parenteral androgen preparations (intramuscular and transdermal) minimize hepatic exposure to androgens so have the potential to reduce adverse hepatic effects. Because intramuscular androgen preparations are administered intermittently, some people may notice cyclic variation in effects (e.g. fatigue and irritability at the end of the injection cycle, aggression or expansive mood at the beginning of the injection cycle). This may be mitigated by using a more frequent dosage schedule (weekly rather than every two weeks) or by using a transdermal or oral preparation. Transdermal testosterone may be preferred by patients who have difficulty self-injecting, have significant adverse effects related to the injection cycle, or need a slow, even titration.⁵ AndroGel®, Androderm®, and Axiron®, are forms of commercially prepared transdermal testosterone available in Canada; AndroGel® may be applied to the upper arms, Androderm® is a patch applied to the torso and Axiron® is applied to the axillae. Unintentional transfer to others can be minimized by covering or washing the area before skin-to-skin contact.

Testosterone increases serum levels of anticoagulants and sulfonylureas, and may interact with corticosteroids.

Alternative forms of testosterone

Testosterone undecanoate (Andriol®) does not have the hepatotoxicity associated with older 17-alkylated forms of oral testosterone (e.g. methyltestosterone) and is considered safe for FTM-spectrum masculinization (160–240 mg po qd).⁸ It is generally not preferred, as it is less effective than IM or transdermal testosterone in suppressing menstruation, with only 50% of patients experiencing menstrual cessation after 6 months of taking oral testosterone.^{8,9,61} It is also much more expensive than testosterone esters (160 mg po qd: ~\$130/month + pharmacy fee).

Progestins

Progestins can be used in hormone therapy for people on the FTM spectrum, to assist with menstrual cessation and to provide contraception if needed. Depo-Provera® can be given by IM injection (150 mg every 3 months) to stop menses either before or concurrent with starting testosterone, stopping the injections after 3–6 months on testosterone.^{8,9} The Mirena IUD can serve this function as well.

Gonadotropin-releasing hormone (GnRH) analogues

GnRH analogues (e.g., leuprolide acetate, Lupron Depot®) have a longer half-life than natural GnRH and after a period of brief overstimulation down-regulate the pituitary, with consequent reduction of follicle-stimulating hormone and luteinizing hormone. This causes a decrease in estrogen levels similar to postmenopausal levels. GnRH analogues are often used with strongly dysphoric young adolescents to delay puberty, but are not commonly used in the treatment of transgender adults. They are expensive and tend to have stronger adverse effects than testosterone. However, they may be used if testosterone or progestins are not tolerated.⁸

Assessment prior to initiating masculinizing endocrine therapy

1. Comprehensive primary care evaluation

A full primary care evaluation should be completed, with particular attention to weight and risks/history of cardiovascular disease, diabetes/glucose intolerance, dyslipidemia, estrogen-dependent cancer, gynecologic disease (including polycystic ovarian disease), and hepatic disease. If there are additional primary care concerns these should be appropriately investigated (e.g. consider stress testing for patients at high risk for cardiovascular disease or with any cardiovascular symptoms). When possible, efforts should be made to stabilize and control co-morbid conditions (with medication, lifestyle changes, or other suitable interventions) prior to initiating hormones. Pregnancy and unstable coronary artery disease are absolute contraindications to androgen use. Patients at risk of becoming pregnant require adequate contraception.

Cigarette smoking is associated with increased risk for cardiovascular disease. We recommend a harm-reduction approach that strongly encourages patients to reduce or stop smoking, along with a clear recommendation that their testosterone dosage must be kept low as long as they are smoking.

2. Baseline evaluation

To assist in monitoring of adverse effects, baseline values should be recorded for lipid profile, fasting glucose (and A1C if high risk for diabetes/glucose intolerance), hemoglobin and/or hematocrit, and liver enzymes. Serum testosterone* may be evaluated

if there is clinical suspicion of hyperandrogenism or if the patient wants to be informed of changes to serum testosterone levels with androgen therapy.

3. *Written informed consent document*

The WPATH SOC 7 notes that providers should document in the medical record that comprehensive information has been provided and understood about all relevant aspects of the hormone therapy, including both possible benefits and risks. Sample informed consent forms for masculinizing endocrine therapy are included as Appendix D.

Monitoring recommendations following initiation of masculinizing endocrine therapy

At a minimum, patients should be seen every 1–3 months after initiating treatment or while adjusting medication dosages, then every 3–6 months for the first year, then every 6 months thereafter. The primary focus of monitoring masculinizing endocrine therapy is to assess the degree of masculinization and the possible presence of adverse effects of medication. However, as with monitoring of any long-term medication, monitoring should take place in the context of comprehensive care of all health concerns.

1. *Evaluation of masculinization*

Masculinization takes place gradually over a period of years. Observed changes to male-pattern hair growth and voice should be noted, and the patient should be asked about changes to menstrual pattern, mood, clitoral growth, libido, and sexual function. Other changes should also be noted.

To avoid a supraphysiological dose of testosterone, serum total testosterone should be checked 1–3 months after starting testosterone, or after a dose adjustment, and every 6–12 months thereafter.* The biochemical goal is to achieve levels within the male reference interval (Table 5). The Endocrine Society Guidelines⁹ suggest monitoring midcycle levels, although clinical practices differ in this regard. If the patient is using transdermal testosterone gel on the arms, the area near the blood draw should be washed prior to the draw, to prevent falsely elevated levels.

2. *Monitoring of adverse effects*

All exams should include assessment of weight, cardiovascular risk, diabetes risk, and blood pressure, as well as unexplained uterine bleeding. There are case reports of

* There are varying clinical opinions on the accuracy and reliability of testosterone assays. Total testosterone is now the standard available method of measurement in British Columbia after a laboratory assessment process de-emphasized the use of free and bioavailable testosterone, except in the case of borderline total testosterone values.

destabilization of bipolar disorder, schizophrenia, and schizoaffective disorder in non-transgender men with the use of testosterone, and clinicians have also found this in people on the FTM spectrum.⁶¹ Mental health should be monitored carefully in FTM-spectrum patients with these conditions for the duration of testosterone therapy.

At minimum, laboratory tests should include (see Table 5 for summary):

- Fasting blood glucose: 3 and 6 months after starting testosterone or after a dose adjustment, then annually. Increase frequency and monitor A1C if elevated lipids, significant weight gain, elevated fasting glucose levels, personal history of glucose intolerance, or family history of diabetes.
- Hemoglobin and/or hematocrit: 3 and 6 months after starting testosterone or after a dose adjustment, then annually.
- Lipid profile: 3 and 6 months after starting testosterone or after a dose adjustment, then annually; increase frequency if pre-existing high lipid levels or an increase in lipid levels, significant weight gain, personal history of glucose intolerance, or family history of diabetes
- Liver enzymes: 3 and 6 months after starting testosterone or after dose increase, then annually.

Table 5: Female-to-Male (FTM) laboratory summary

Table 5 represents minimum timelines. Closer monitoring should be done for patients at risk for or with co-existing cardiovascular disease, diabetes, hepatic disease, etc.

Timeline for Laboratory Tests			
Baseline (before starting masculinizing endocrine therapy)	<ul style="list-style-type: none"> • Lipid profile, fasting glucose (and A1C if high risk for diabetes/glucose intolerance), Hct or Hgb and liver enzymes • Testosterone if clinical suspicion of hyperandrogenism, or if patient wants to know of changes after starting testosterone 		
4–6 weeks after starting/changing dose	<ul style="list-style-type: none"> • Testosterone (trough or midcycle if IM) 		
3 months after starting testosterone	<ul style="list-style-type: none"> • Hgb and/or Hct, fasting blood glucose, lipid profile, liver enzymes 		
6 months after starting testosterone	<ul style="list-style-type: none"> • Hgb and/or Hct, fasting blood glucose, lipid profile, liver enzymes • Testosterone (trough or midcycle if IM) 		
12 months after starting testosterone and annually thereafter	<ul style="list-style-type: none"> • Hgb and/or Hct, fasting blood glucose, lipid profile, liver enzymes • Testosterone (trough or midcycle if IM) 		
Testosterone Reference Ranges (goal: elevate to within normal male range)			
	BC Bio Medical Labs	Life Labs	Vancouver Hospital
Total testosterone:	M >17 yrs: 8.4–28.8 nmol/L	M: 8.4–28.8 nmol/L	M >15 yrs: 10–38 nmol/L

3. Ongoing comprehensive primary care

Cardiovascular risk factors should be screened for and treated, and osteoporosis assessment should be considered for FTM-spectrum patients who are at risk (e.g. family history of osteoporosis, additional risk factors, oophorectomy with intermittent or inadequate doses of testosterone replacement). Primary care of the FTM-spectrum patient includes screening for all other types of cancer (e.g. colorectal, anal) as for non-transgender females, as well as periodic screening for concerns relating to sexual health, mental health, and substance use.

FTM-spectrum patients should receive regular monitoring by a primary care provider for breast cancer. If the patient undergoes chest surgery, monitoring should continue after surgery, as chest reconstruction typically does not involve the removal of all breast tissue. If the uterus and cervix are present, regular gynecologic screening is also recommended as part of basic primary care. After androgen-induced cessation of menses, vaginal bleeding should be evaluated as for post-menopausal women.

Concluding Remarks

Individual tailoring of endocrine regimens to fit the transgender patient's history, risk factors, desired outcomes, and administration preferences holds promise both for maximization of desired effects and minimization of adverse effects. We hope that the recommendations in this document help family physicians, endocrinologists, and nurse practitioners in BC feel more confident to determine when endocrine therapy may be appropriate, and to care for patients who are undergoing endocrinologic feminization/masculinization.

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Appendices

Appendix A: Resources

Appendix B: Summary of the World Professional Association for Transgender Health's *Standards of Care (Version 7)*

Appendix C: Informed Consent for Feminizing Hormones

Appendix D: Informed Consent for Masculinizing Hormones

Appendix A: Resources

Rapid Access to Consultative Expertise

www.RACEconnect.ca

Physicians and nurse practitioners in British Columbia can access consultation on transgender care by calling the provincial R.A.C.E. (Rapid Access to Consultative Expertise) Line from Monday to Friday, 0800-1700. Calls are generally returned within 2 hours.

Phone: 1-877-696-2131

Transgender Health Information Program

<http://transhealth.vch.ca>

The Transgender Health Information Program – THiP – is a BC-wide information service and resource hub. At the Transgender Health Information Program we provide:

- Telephone and email support
- Referrals to gender affirming care and supports
- Web and print resources
- Health care provider consultation services
- Support and information groups

Please visit THiP's website for more information, or contact:

Phone/TTY/TDD: 604-734-1514 or
Toll-free in BC: 1-866-999-1514
Email: transhealth@vch.ca

Canadian Professional Association for Transgender Health

www.cpath.ca

CPATH is an interdisciplinary professional organization which works to improve the lives of trans and gender diverse people. It is the largest national professional organization for transgender health in the world. CPATH's vision is "A Canada without barriers to the health, well-being and self-actualization of trans and gender diverse people". CPATH seeks to be both connected with and responsive to the needs emerging from trans people and communities.

World Professional Association for Transgender Health

www.wpath.org

The World Professional Association for Transgender Health (WPATH), formerly known as the (Harry Benjamin International Gender Dysphoria Association, HBGDA), is a professional organization devoted to the understanding and treatment of gender identity disorders. As an international multidisciplinary professional Association, the mission of WPATH is to promote evidence based care, education, research, advocacy, public policy and respect in transgender health. The vision of WPATH is to bring together diverse professionals dedicated to developing best practices and supportive policies worldwide that promote health, research, education, respect, dignity, and equality for transgender, transsexual, and gender-variant people in all cultural settings.

WPATH works to further the understanding and treatment of gender identity disorders by professionals in medicine, psychology, law, social work, counseling, psychotherapy, family studies, sociology, anthropology, sexology, speech and voice therapy, and other related fields. The association provides opportunities for professionals from various sub-specialties to communicate with each other in the context of research and treatment of gender identity disorder including sponsoring biennial scientific symposia.

WPATH publishes the Standards of Care and Ethical Guidelines, which articulate a professional consensus about the psychiatric, psychological, medical, and surgical management of gender identity disorders, and help professionals understand the parameters within which they may offer assistance to those with these conditions.

Appendix B: Summary of the World Professional Association for Transgender Health's *Standards of Care (Version 7)*⁵

The World Professional Association for Transgender Health's (WPATH) *Standards of Care* are an evolving set of guidelines based on international consensus. The standards are designed to provide clinical guidance for health professionals to assist transsexual, transgender, and gender nonconforming people with safe and effective pathways to achieving lasting personal comfort with their gendered selves, in order to maximize their own health, psychological well-being, and self-fulfillment.

This handout summarizes standards relating to hormone care. The complete WPATH *Standards of Care (Version 7)* are available from WPATH (<http://www.wpath.org>).

Criteria for feminizing / masculinizing hormone therapy

- Persistent, well-documented gender dysphoria
- Ability to make a fully informed decision and to consent for treatment
- Age of majority (if younger, follow guidelines for children and adolescents)
- If significant medical health concerns are present, they must be reasonably well-controlled

Psychological Assessment Prior to Prescribing Hormones

Prior to prescribing hormones, the WPATH standards suggest assessment by a clinician who has:

- at least a master's degree in a clinical behavioural science that has a credentialing process (e.g., psychology, psychiatry, social work, counselling, nursing)
- demonstrated competence in using the *DSM-5 / ICD-10* for diagnostic purposes
- the ability to recognize and diagnose co-existing mental health concerns and to distinguish these from gender dysphoria
- documented supervised training and competence in psychotherapy or counselling
- ongoing education in transgender care: supervision, workshops, seminars, research, etc.

In some cases the prescribing clinician may have the required training and expertise in transgender medicine to be an assessor. If so, they should document each of the points below. If not, referral to a mental health professional may be necessary. The WPATH

standards state the assessor should write a letter to the prescribing clinician that includes:

- the patient's general identifying characteristics
- results of psychosocial assessments, including any diagnoses
- duration of professional relationship, including type of evaluation/therapy
- eligibility criteria that the patient has met
- the rationale for hormones (why it is appropriate treatment)
- a statement that the assessor is available for the coordination of care, and welcomes contact to establish this

The WPATH Standards note that where the referring clinician is working within a multidisciplinary care team, a letter may not be necessary; rather, the assessment and recommendation can be documented in the patient's chart.

The WPATH Standards also note that psychotherapy is not an absolute requirement for hormone therapy or surgery, nor do the Standards recommend a minimum number of psychotherapy sessions prior to hormone therapy.

Responsibilities of the Prescribing Clinician

In general, clinicians who prescribe hormones should engage in the following tasks:

- doing an initial evaluation (transition goals, health history, physical examination, relevant risks, bloodwork, etc.)
- explaining what hormones do and possible side effects/health risks; also discussing reduction in fertility and reproductive options
- ensuring that the patient has the capacity to understand the risks and benefits, and can give informed consent
- providing ongoing medical monitoring (regular physical exams relating to hormone effects and side effects, measurement of vital signs before and during hormone therapy, weight measurement, laboratory assessment, etc.)
- communicating as needed with a patient's primary care provider, mental health professional, and surgeon
- if needed, providing patients with a brief written statement indicating that they are under medical supervision and care that includes feminizing / masculinizing hormone therapy

Depending on the clinical context, some of these responsibilities are less relevant and should be individualized to a patient's needs.

Appendix C: Informed Consent for Feminizing Hormones

The following consent document is adapted from the Catherine White Holman Wellness Centre (www.cwhwc.com).

Informed Consent

Estrogens and Testosterone Blockers for Trans* Clients

What is informed consent?

Before starting hormone treatment, it is important to understand the possible benefits, risks, warning signs, and alternatives. You and your healthcare provider will work together to make sure you have all the information you need to decide if hormone treatment is right for you. Agreeing to start hormone treatment once you know all of the benefits, risks, warning signs, and alternatives, and have had all of your questions answered, is called informed consent.

What are the different medications that can feminize my appearance?

Part of transition for many trans* people involves taking hormones. For hormone treatment to be most effective, most people who were assigned male at birth take not only estrogens (female hormones), but also androgen blockers to prevent their body from producing or utilizing testosterone (male hormones).

What is estrogen and how is it taken?

Different forms of the hormone estrogen are used to change your appearance and how you feel. Estrogen can be given as an injection (weekly or every other week), as a pill (daily or twice a day), or as a patch (which is changed every three or four days).

What are androgen blockers and how are they taken?

Medications that block the production or effects of testosterone are called androgen blockers. Androgen is another term for male sex hormones. Spironolactone is the androgen blocker that is most commonly used in Canada. It is a pill that you swallow once or twice a day. Other medicines are sometimes used, but because spironolactone is relatively safe, inexpensive, and effective, it is the primary androgen blocker.

Benefits, Risks, Warnings and Alternatives

Benefits (* means it is a permanent change)

Physical changes including:

- softer skin
- slower growth of body hair
- slowed hair loss on head
- change in body fat shape: more on hips, less on belly
- breast development*
- decreased muscle mass
- decreased spontaneous erections
- smaller testicles*

Risks

- blood clots including thrombophlebitis or pulmonary embolus (blood clot in the lung)
- more risk of stroke
- emotional changes
- headache
- high blood pressure (hypertension)
- infertility
- inflamed liver
- interaction with drugs for diabetes and blood thinning — for example Warfarin
- more risk of diabetes or cholesterol change
- more risk of heart disease
- less sex drive and spontaneous erection
- unknown risk of breast cancer and possible interference in assessing for prostate cancer
- risk of disturbance to body's potassium leading to dizziness or heart rhythm abnormality (spironolactone)

Warning: Who should not take estrogen?

Estrogen should not be used by anyone who has a history of:

- an estrogen-dependent cancer
- a disorder that makes them more likely to get blood clots that could travel to the lungs (unless they are also taking blood thinners and are followed by a specialist)

Estrogen should be used with caution and only after a full discussion of risks by anyone who:

- has a strong family history of breast cancer or other cancers that grow quicker when estrogens are present
- has uncontrolled diabetes
- has heart disease
- has chronic hepatitis or other liver disease
- has uncontrolled high cholesterol
- has migraines or seizures
- is obese
- smokes cigarettes

Alternatives

Not all trans* people choose to take hormones. It is up to you whether or not they want to take them, and it will not affect how you are treated at this clinic.

There are alternatives to using feminizing medications to help people change their physical gender. If you are interested in alternatives to hormone treatment, talk to your clinician about your options.

Please initial each statement to show you understand the benefits, risks, and changes that may occur from taking these medications.

Informed Consent: Physical Changes

_____ Estrogen or anti-androgens – or both – may be prescribed to cause changes in my appearance that are typically considered feminine.

_____ It can take several months or longer for the effects to become noticeable. No one can predict how fast or how much change will happen.

_____ If I am taking estrogen, I will develop breasts.

- It takes several years for breasts to get to their full size.
- The breasts will remain, even if I stop taking estrogen.
- I might have a milky discharge from my nipples — galactorrhea. If I do, I know I should check it out with my clinician because it could be caused by the estrogen or by something else.
- While we do not know the exact risk, my risk of breast cancer may be increased to as high as if I had been born female
- I should take care of my breasts. This includes breast exams from my health provider, and regular mammograms after a certain age.

_____ The following changes are usually not permanent — they are likely to go away if I stop taking the medicines.

- Body hair will become less noticeable and will grow more slowly, but it won't stop completely, even if I take the medicines for years.
- I will probably have less fat on my abdomen and more on my buttocks, hips, and thighs — changing from apple shape to pear shape.
- If I have the predisposition to have male pattern baldness it may start later than it would have, but may not stop completely.
- If I stop taking hormones I may lose my hair faster than if I hadn't taken hormones.
- I know I may lose muscle and strength in my upper body
- I know that my skin may become softer.

_____ My body will make less testosterone. This may affect my sex life in different ways and future ability to cause a pregnancy:

- My sperm may no longer get to mature. This could make me less able to cause a pregnancy. There is a small risk that I might never produce mature sperm again. It's also possible that my sperm could still mature even while I am taking hormones. I might get someone pregnant if we have vaginal intercourse and we don't use birth control.
- options for sperm banking have been explained to me.
- My testicles may shrink down to half their size. They are still part of my body and I need to take care of them unless I have surgery to remove them. This means that I will need regular checkups for them.
- I won't have as much semen when I ejaculate.
- It is likely that I won't be hard in the morning as often as before. And it is likely that I will have fewer spontaneous erections.
- I may not be able to get hard enough for penetrative sex.
- I may want to masturbate or have sex less and may find it harder to orgasm when I do.
- I know this treatment may (but is not assured to) make me permanently unable to make someone pregnant.

_____ Some parts of my body will not change much by using these medicines.

- I know the hair of my beard and mustache may grow more slowly than before. It may become less noticeable, but it will not go away unless I have treatments like electrolysis.
- I know the pitch of my voice will not rise, and my speech patterns will not change.
- I know my Adam's apple will not shrink.
- Although these medicines can't make these changes happen, there are other treatments that may be helpful.

_____ There may be mood changes with these medicines. My care providers will check in regularly about how my mood is. I know there are mental health resources available to me if I need them.

Informed Consent: Risks

Risks of Estrogens and Androgen-Blocking Medications

_____ The side effects and safety of these medicines are not completely known. There may be long-term risks that are not yet known.

_____ I know not to take more medicine than I am prescribed. This increases health risks. Taking more than I am prescribed won't make changes happen more quickly or more significantly.

_____ These medicines may damage the liver and may lead to liver disease. I will require regular blood tests for possible liver damage as long as I take them.

_____ These medicines cause changes that other people will notice. Some transgender people have experienced discrimination because of this. My clinician can help me find advocacy and support resources.

_____ I know that a minority of people (1-3%) will later regret their decision to take hormone therapy. I know that under these circumstances some physical changes that occurred while on hormone therapy will be irreversible.

Risks of Estrogen

_____ Taking estrogen increases the risk of blood clots or problems with blood vessels that can result in:

- chronic problems with veins in the legs
- heart attack
- pulmonary embolism – blood clot to the lungs – which may cause permanent lung damage or death
- stroke, which may cause permanent neurologic damage or death

_____ The risk of blood clots is much worse if I smoke cigarettes. The danger is so high that I should stop smoking completely if I start taking estrogen. I know that I can ask my clinician for advice about how to stop smoking.

_____ Taking estrogen can increase the deposits of fat around my internal organs. This can increase my risk for diabetes and heart disease.

_____ Taking estrogen can raise my blood pressure. If it goes up, my clinician can work with me to try to control it with diet, lifestyle changes, and/or medication.

_____ Taking estrogen increases my risk of getting gallstones. I should talk with my clinician if I get severe or long-lasting pain in my abdomen.

_____ Estrogen can cause nausea and vomiting. I should talk with my clinician if I have long-lasting nausea or vomiting.

_____ Estrogen can cause migraines or make them worse if I already have them. I should talk with my clinician if I have headaches or migraines often or if the pain is unusually severe.

_____ It is not yet known if taking estrogen increases the risk of prolactinomas. These are non-cancerous tumors of the pituitary gland. They are not usually life threatening, but they can damage vision and cause headaches if they are not treated properly. Changes in vision, headaches that are worse when I wake up in the morning, and milky discharge from my nipples can be signs of a prolactinoma, and I should talk to my health care provider if I develop these symptoms. There is a blood test that can check for this that will be ordered regularly.

_____ I am more likely to have dangerous side effects if:

- I smoke.
- I am overweight.
- I have a personal or family history of blood clots.
- I have a personal or family history of heart disease and stroke.
- My family has a history of breast cancer.

Risks of Androgen Antagonists

_____ Spironolactone affects the balance of water and salts in the kidneys. This may:

- Increase the amount of urine I produce, making it necessary to urinate more frequently.
- Increase thirst.
- Rarely, cause high levels of potassium in the blood, which can cause changes in heart rhythms that may be life-threatening.
- Reduce blood pressure.

_____ Cyproterone has the potential to damage my liver and my clinician will monitor my liver with blood tests.

_____ Some androgen antagonists make it more difficult to evaluate test results for cancer of the prostate. This can make it more difficult to check up on prostate problems. If I am over 50, I should discuss appropriate prostate cancer screening with my care provider. Even if I have genital sex reassignment surgery the prostate is not usually removed.

Informed Consent: Prevention

Prevention of Medical Complications

_____ I agree to take medications as prescribed. I agree to tell my care provider if I have any problems or am unhappy with the treatment.

_____ The dose and type of medication that's prescribed for me may not be the same as someone else's.

_____ I need periodic physical exams and blood tests to check for any side effects.

_____ In addition to periodic checks from my provider, I must also treat my body with respect. This means that paying attention and talking to my provider if I develop any symptoms that might be side effects from medicines.

_____ These medications can interact with other drugs and prescribed and over the counter medicines. These include alcohol, diet supplements, herbs, other hormones, and street drugs. This kind of interaction can cause complications. I need to prevent complications because they can be life-threatening. That's why I need to be keep my clinician informed about whatever else I take. I also know that I will continue to get medical care here no matter what I share about what I take.

_____ Even if I have to stop my estrogens, I may still be able to take the testosterone blockers that I am on, to help prevent the effects of my body producing testosterone again.

_____ Using these medicines to feminize is an off-label use. I know this means it is not approved by Health Canada. I know that the medicine and dose that is recommended for me is based on the judgment and experience of my health care provider and the best information that is currently available in the medical literature.

_____ I can choose to stop taking these medicines at any time. If I decide to do that, I should do it with the help of my clinician. This will help me make sure there are no negative reactions.

_____ My clinician may suggest that I reduce my dose or stop taking estrogens or blockers at all if certain conditions develop. This may happen if the side effects are severe or there are health risks that can't be controlled.

Informed Consent: Alternatives

_____ Not all trans* people choose to take hormones and my decision about whether to take them or not will not affect how I am treated at this clinic.

_____ There are alternatives to using feminizing medicines to help people change their physical gender. Some trans* people choose to not take hormones or have surgery and may only socially transition. If I am

interested in alternatives, I can talk with my health care provider about my options.

Signature

My signature below confirms that:

My clinician has talked with me about:

- the physical changes and risks of taking feminizing medication;
- warnings and prevention of medical complications; and
- potential alternative treatments

I understand the risks that may be involved.

I know the information in this form includes the known effects and risks.

I understand that there may be unknown long-term effects of risks.

I understand that counselling can be beneficial for some people who are considering hormone therapy (support through the decision-making process, support with coming out, adjusting to the physical and emotional changes that may come with hormone therapy, etc.) and my provider has let me know about counselling and support options that are available to me.

I have had enough opportunity to discuss treatment options with my clinician. All of my questions have been answered to my satisfaction.

I believe I know enough information to give informed consent to take, refuse, or postpone therapy with feminizing medications.

Based on all this information:

_____ I want to begin taking estrogen

_____ I want to begin taking androgen antagonists (e.g., spironolactone)

_____ I do not wish to begin taking feminizing medication at this time

Client Signature _____

Date: _____

Prescribing Clinician Signature _____

Date: _____

Appendix D: Informed Consent for Masculinizing Hormones

The following consent document is adapted from the Catherine White Holman Wellness Centre (www.cwhwc.com).

Informed Consent

TESTOSTERONE FOR TRANS* CLIENTS

What is informed consent?

Before starting hormone treatment, it is important to understand the possible benefits, risks, warning signs, and alternatives. You and your healthcare provider will work together to make sure you have all the information you need to decide if hormone treatment is right for you. Agreeing to start hormone treatment once you know all of the benefits, risks, warning signs, and alternatives, and have had all of your questions answered, is called informed consent.

What medication can masculinize my appearance?

Part of transition for many trans* people involves taking hormones. Testosterone is the medication given to people assigned female at birth, who want to appear more masculine. You may want to take testosterone to masculinize your body, to appear more androgynous, or to feel more comfortable in your lived gender.

What is testosterone?

It is a sex hormone that is found in almost all bodies. It is responsible for physical changes to the body that are typically considered more “masculine.” For example, it builds muscle and causes the development of facial hair and a deeper voice. Some trans* and gender diverse people choose to take extra testosterone and others do not. The choice is based on personal preference and the desired benefits of the hormone.

How is testosterone taken?

It is usually injected every one to four weeks. It is not used as a pill because the body may not absorb it properly and it may cause liver problems. Some people use skin creams and patches, but they tend to be more expensive. The doses used for injection differ from product to product and from person to person. The injections are made in a large muscle to slow the release of the hormone.

Benefits, Risks, Warnings and Alternatives

Benefits (* means it is a permanent change)

Physical changes including:

- bigger clitoris*
- coarser skin
- lower voice*
- more body hair*
- more facial hair*
- more muscle mass
- more strength
- no more menstrual periods
- more physical energy
- more sex drive
- protection against bone thinning (osteoporosis)

Risks

- acne (may permanently scar)
- blood clots (thrombophlebitis)
- emotional changes — for example, more aggression
- headache
- high blood pressure (hypertension)
- increased red-blood-cell count
- infertility
- inflamed liver
- interaction with drugs for diabetes and blood thinning — for example Warfarin
- male pattern baldness
- more abdominal fat and less in the hips (“apple” vs “pear” shape)*
- more risk of heart disease
- swelling of hands, feet, and legs
- weight gain
- thinning and atrophy of vaginal tissues

Warning: Who should not take testosterone?

It should not be used by anyone who is pregnant or has uncontrolled coronary artery disease.

It should be used with caution and only after a full discussion of risks by anyone who:

- has acne
- has a family history of heart disease or breast cancer
- has had a blood clot
- has high levels of cholesterol
- has liver disease
- has a high red-blood-cell count
- is obese
- smokes cigarettes

Periodic blood tests to check on the effects of the hormone will be needed. Routine breast/chest exams and internal exams with Pap tests should be continued, when applicable.

Alternatives

Not all trans* people choose to take hormones. It is up to you whether or not they want to take them, and it will not affect how you are treated at this clinic.

There are alternatives to using testosterone to help people change their physical gender. If you are interested in alternatives to testosterone treatment, talk to your clinician about your options.

Please initial each statement to show you understand the benefits, risks, and changes that may occur from taking these medications.

Informed Consent: Physical Changes

_____ Testosterone may be prescribed to change the way my physical gender appears to myself and others.

_____ It can take several months or longer for the effects to become noticeable. No one can predict how fast – or how much – change will happen. The changes may not be complete for two to five years.

_____ The following changes are likely and permanent even if I stop taking testosterone:

- bigger clitoris — typically half an inch to a little more than an inch
- deeper voice
- gradual growth of mustache and beard
- hair loss at the temples and crown of the head — possibility of being completely bald
- more, thicker, and coarser hairs on abdomen, arms, back, chest, legs

_____ I know that the following changes are usually not permanent — they are likely to go away if I stop taking testosterone:

- acne (many permanently scar)
- menstrual periods typically stop one to six months after starting
- more abdominal fat – decreased on buttocks, hips, and thighs; increased in abdomen – changing from “pear shape” to “apple shape”
- more muscle mass and strength
- more sex drive
- vaginal dryness

_____ The effects of testosterone on fertility are unknown. I may or may not be able to get pregnant even if I stop taking testosterone. I might still get pregnant even after testosterone stops my menstrual periods. I know about my birth control options (if applicable), and that I can't take testosterone if I am pregnant.

_____ Some aspects of my body will not be changed:

- Losing some fat may make my breasts appear slightly smaller, but they will not shrink very much.
- Although my voice will deepen, other aspects of my voice and the mannerisms with which I speak may not sound different.

_____ There are other methods that may be helpful to make my breast tissue less apparent or change my speech. My health care provider can give me referrals to help me explore treatment options.

Informed Consent: Risks

_____ The medical effects and the safety of testosterone are not completely known. There may be long-term risks that are not yet known.

_____ I know not to take more testosterone than prescribed. Doing so would increase health risks without making changes happen more quickly or more significantly. My body can convert extra testosterone into estrogen.

_____ Testosterone can cause changes that increase my risk of heart disease. These changes include having:

- less good cholesterol (HDL) that may protect against heart disease and more bad cholesterol (LDL) that may increase the risk of heart disease
- higher blood pressure
- more deposits of fat around my internal organs

_____ My risk of heart disease is higher if people in my family have had heart disease, if I am overweight, or if I smoke.

_____ I should have periodic heart-health checkups for as long as I take testosterone. That means I must watch my weight and cholesterol levels and have them checked by my health care provider.

_____ Testosterone can damage the liver and possibly lead to liver disease. I should be checked for possible liver damage for as long as I take testosterone.

_____ Testosterone can increase my red blood cells and hemoglobin. The increase is usually only to what is normal for a man and that has no health risks, but a higher increase can cause problems that can be life-threatening. These problems include stroke and heart attack. I need to have periodic blood checks for as long as I take testosterone.

_____ Taking testosterone can increase my risk for diabetes. It may decrease my body's response to insulin, cause weight gain, and increase deposits of fat around my internal organs. I should have periodic checks of my blood glucose for as long as I take testosterone.

_____ My body can turn testosterone into estrogen. No one knows if that could increase the risk of cancers of the breast, the ovaries, or the uterus.

_____ Taking testosterone can thin the tissue of my cervix and the walls of my vagina. This can lead to tears or abrasions during vaginal sex. This raises my risk of getting a sexually transmitted infection, including HIV. I should take precautions regardless of the gender(s) of my partner(s). I should speak frankly with my clinician about my sex life to learn the best ways to prevent and check for infections.

_____ Testosterone can give me headaches or migraines. It's best to talk with my clinician if I get them a lot or if the pain is unusually severe.

_____ Testosterone can cause mood changes. My clinician will check in regularly about my mood and mental health. Resources are available for my mental health.

_____ Testosterone causes changes that other people will notice. Some transgender people have experienced harassment, discrimination, and violence because of this. Others have lost the support of loved ones. I know my clinician can help me find advocacy and support resources.

_____ I know that a minority of people (1-3%) will later regret their decision to take hormone therapy. I know that under these circumstances some physical changes that occurred while on hormone therapy will be irreversible.

Informed Consent: Prevention

_____ I agree to take testosterone as prescribed. I will tell my clinician if I have any problems or am unhappy with the treatment.

_____ The dose and type of medication that's prescribed for me may not be the same as someone else's.

_____ I need periodic physical exams and blood tests to check for any side effects.

_____ Testosterone can interact with other drugs and medicines. These include alcohol, diet supplements, herbs, other hormones, and street drugs. This kind of interaction can cause complications. This kind of interaction can cause complications. I need to prevent complications because they can be life-threatening. That's why I need to be keep my clinician informed about whatever else I take. I will continue to get medical care here no matter what I share about what I take.

_____ It can be risky for anyone with certain conditions to take testosterone. I agree to be evaluated if my clinician thinks I may have one of these conditions. Then we will decide if it's a good idea to start or continue using testosterone.

_____ Using testosterone to change my appearance is an off-label use. This means it is not approved by the government for this use. The medicine and dose that is recommended for me is based on the judgment and experience of the health care provider.

_____ I can choose to stop taking testosterone at any time. If I decide to do that, I should do it with the help of my clinician. This will help me make sure there are no negative reactions.

_____ My clinician may suggest I lower the dose or stop taking testosterone if certain conditions develop. This may happen if the side effects are severe or there are health risks that can't be controlled.

Informed Consent: Alternatives

_____ Not all trans* people choose to take hormones. My decision about whether to take them or not will not affect how I am treated at this clinic.

_____ There are alternatives to using masculinizing medicines to help people change their physical gender. Some trans* people choose to not take hormones or have surgery and may only socially transition. If I am interested in alternatives, I can talk with my clinician about my options.

Signature

My signature below confirms that:

My clinician has talked with me about:

- the physical changes and risks of taking testosterone;
- warnings and prevention of medical complications; and
- potential alternative treatments

I understand the risks that may be involved.

I know the information in this form includes the known effects and risks.

I understand that there may be unknown long-term effects of risks.

I understand that counselling can be beneficial for some people who are considering hormone therapy (support through the decision-making process, support with coming out, adjusting to the physical and emotional changes that may come with hormone therapy, etc.) and my provider has let me know about counselling and support options that are available to me.

I have had enough opportunity to discuss treatment options with my clinician. All of my questions have been answered to my satisfaction.

I believe I know enough information to give informed consent to take, refuse, or postpone therapy with testosterone.

Based on all this information:

_____ I want to begin taking testosterone

_____ I do not wish to begin taking testosterone at this time

Client Signature _____

Date: _____

Prescribing Clinician Signature _____

Date: _____