M E M O R A N D U M

DATE: August 14, 2001

TO: Interested Parties

FROM: Tom Waddell Health Center Transgender Team

We are happy to give you the most recent revision of our protocols. We are currently practicing under these protocols and have found them useful. Please review them. We would greatly appreciate your feedback as they are under regular review and revision. Please pass this memo and the protocols on to others who are interested. Feel free to contact us if you have questions or comments. The following people contributed to these protocols

Chenit Flaherty, RN
Jim Franicevich, FNP
Mark Freeman, FNP
Pam Klein, RN
Lori Kohler, MD
Clara Lusardi, HW
Linette Martinez, MD
Mary Monihan, RN
Jody Vormohr, MD
Barry Zevin, MD

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Tom Waddell Health Center
Protocols for Hormonal Reassignment of Gender (7/24/01)

Introduction
Patients presenting with gender identity disorders may be appropriate for hormonal reassignment of gender. Standards for who is appropriate for treatment are outside of the scope of this document but are available (see Harry Benjamin International Gender Dysphoria Association Standards of Care, Transgender Care Recommended Guidelines). Our clinic's protocols cover issues related to hormonal reassignment of gender for male-to-female (MTF) and female-to-male (FTM) patients. The purpose for writing these protocols is to share our experience with providers and their patients with the goals on expected results, and risks of therapy.

As medical providers, we are concerned first and foremost with the safety and health of our patients. No medical treatment is entirely harmless, but we aim to minimize harm to our patients. Hormonal reassignment of gender has undergone some scientific study and where scientific knowledge is present, it guides these protocols. Unfortunately, a great deal has not been studied, and this allows for some uncertainty in our medical practice. It is therefore of utmost importance that we inform our patients of the risks and benefits of treatment and of the aspects of treatment in which uncertainty exists. All patients are required to give informed consent to the procedure of hormonal reassignment of gender. A patient's ability to understand and consent to the process, its risks and expected results, is an absolute requirement prior to starting treatment. In our practice, hormonal reassignment of gender is provided as a component of comprehensive primary health care.

Background
November of 1994 marked the initiation of Transgender Tuesdays. It was perhaps the first time a public health department had created a clinic specifically dedicated to reaching patients who self-identified as transgender. The Health Department acted in response to a felicitous combination of eagerness on the part of Tom Waddell Health Center's busy, multi-disciplinary HIV team, and the concurrent urging of several community organizations which already had working relationships with the HIV clinic. These organizations included: the Tenderloin AIDS Resource Center, Brothers' Network, Asian AIDS Project (now API Wellness Center), and Proyecto Contra-SIDA Por Vida, FTM International. Assorted transgender activists and other community providers also helped make the clinic a reality.

The rationale that eventually won the Health Department over was fairly simple. There exists a large group of individuals who are at risk for HIV transmission, and who are also in need of general primary care services. This group is known to be averse to accessing medical services for a number of reasons, including: prior negative experience in clinic settings, expectation of discriminatory treatment, the requirement of psychiatric treatment and approval for traditional gender-reassignment treatment, and, in some cases, reticence to reveal illegal occupational activities to authorities. Yet many in this group actively pursue pharmaceuticals on a regular basis, most notably hormones or "silicone" injections purchased on the street. A few unscrupulous medical practitioners also provide hormones, yet they do not bother to monitor their patients health via physical and laboratory exams.

It was argued that by offering a range of services that included the possibility of hormonal therapy, members of this group might be brought in to access primary medical care. The clinic was scheduled for a weekday evening so as to be especially accessible to commercial sex workers. In the subsequent six and a half years since its inception, this targeted primary care clinic at Tom Waddell Health Center in San Francisco's famed Tenderloin District has seen nearly 700 patients.

Our clinic's target population is self-defined transgender people; we do not require clients to present any documentation attesting to their transgender status. All prospective patients meet first with a nurse who completes a preliminary assessment of the person's appropriateness for the clinic. The nurse also identifies highly at-risk patients (those with immediate illness or homelessness for instance) and expedites their intake process. The nurse schedules a psychosocial intake interview and a first time provider visit. The team meets regularly to discuss issues and plans of action for individual patients.

We tell patients that we are not a surgery clinic, nor do we provide psychiatric approval for surgery. Rather, we are a Primary Care clinic available to meet all of their general medical needs. We also clarify that we discourage outside hormone purchase or use, and we will prescribe based on protocols designed to have the desired effect with a minimum of undesirable side effects. However, we do not turn patients away due to their use of street hormones or other drugs. Our standard for prescribing hormones is one of informed consent, which includes mental capacity to understand possible risks as well as limits to benefits. Our rationale is one of harm reduction.

In addition to regular visits with a Primary Care provider, clients may take advantage of on-site auxiliary services including: urgent care, a licensed nutritionist, acupuncture, a smoking-cessation group, and an ongoing peer support group with supervision by our social worker. At times, researchers are on-site providing an opportunity for patients to participate in research studies.

I. Treatment Principles

A. Patient's desired outcomes

Each patient has his or her own specific idea or definition of what it is to be transgender or what a transgender person needs. It is essential to explore these ideas and definitions, as patients often have specific goals and expectations in mind when they are in the process of transitioning from one gender to another. Some common desires include:

1. For MTF

Decreased facial/body hair
Increased breast size/breast growth
Change in body fat distribution to gynoid "pear"
Weight loss/weight gain
Softening of facial skin and other features
Decreased or elimination of erection/ejaculation
Maintain a strong transgender identity
Maintain a strong feminine identity
Change in voice tone or quality
Decreased or reverse male pattern baldness
Vaginoplasty and/or other surgeries
No surgery

2. For FTM

Facial hair with or without body hair
Increased body musculature
Maintain a strong transgender identity
Maintain a strong male identity
Mastectomy
Phalloplasty
No surgery
Masculine body

Treatment should be individualized for each patient. Patients often have unrealistic expectations and education about what to expect from treatment is imperative in the first visits. The use of estrogen has potentially serious and life-threatening adverse effects. The medical provider should obtain a signed consent indicating agreement and understanding of treatment from the patient. The process of hormonal reassignment is slow; maximum effects may be achieved after 2-3 years of therapy.

B. Health care provider's desired outcome

Increased overall health and well-being
Increased trust and ability to overcome previous negative experiences in medical systems
Adherence to advice regarding lab tests, office visits etc.
Discussion of harm reduction regarding substance use, sexual practices, occupational sex work
Discussion of HIV risk and testing
Patient benefits by supportive comprehensive primary care.
Serve as a link between the patient and social, medical, psychological and educational opportunities of main society

C. Healthcare upon initiating care

- Psychosocial intake
- Baseline labs: CBC with differential, liver panel, renal panel, glucose, hepatitis B total core ab, Hepatitis C ab, VDRL (or RPR), lipid profile, prolactin level, Urine GC and Chlamydia.
- Review health care maintenance including: immunizations, TB screening, safety and safer sex counseling, and HIV testing if appropriate
- Address medical problems as needed
- Discuss patients goals and expectations for therapy
- Review side effects, risks and benefits of hormone therapy and obtain informed consent
- Prescribe medications and follow patients per protocols

D. At every visit

- Assess for desired and adverse effects of medication
- Check weight, blood pressure
- Review health maintenance
- Directed physical exam as needed

E. HIV Disease and transgender people

HIV infection is unfortunately prevalent among the transgender population. There is no evidence in the medical literature or in our experience that the natural history of HIV disease differs in transgender people. HIV is not a contraindication or precaution for any of our protocols. While drug-drug interactions may occur, we know of no specific dangerous interactions or likely causes of drug failure. Treatment with hormones is frequently an incentive for patients to address their HIV disease and providers of care for transgender people should enhance their HIV expertise.

F. Consent

The use of medications for gender reassignment is off-label. There are potentially life-threatening complications. The medical provider should obtain a signed consent indicating agreement to and understanding of treatment from the patient.

IV. MTF Hormonal Therapy

Male to female hormonal reassignment of gender is based on the ability of medications to effect de-masculinization by blocking production and action of Androgens (testosterone) and to effect feminization by responsive but latent tissue.

A. Anti-Androgen Therapy

Several classes of medications will specifically or nonspecifically decrease testosterone to normal or lower than normal female levels: GnRH analogues, cyproterone, testosterone uptake inhibitors, high dose estrogens, progesterone, and spironolactone. Due to safety and cost considerations we use spironoloctone as our anti-androgen of choice. It appears to act both in blocking testosterone production and blocking androgen receptors. It may be used alone but is usually used in combination with estrogens.

1. Dosing

- Typical spironolactone starting dose: 25mg-50mg twice a day
- Typical spironolactone dose: 50mg twice a day
- Maximum dose spironolactone: 200mg twice a day

2. Contraindications

- Renal insufficiency
- Serum potassium greater than 5.5 meq/L

3. Expected desirable effects:

- Suppression of testosterone production/activity
- Decreased facial and body hair growth
- Decreased progression of male pattern baldness
- Decrease libido
- Decrease erections
- Mild breast growth
- Decrease BPH

4. Adverse effects - adverse effects have been very rare in our experience.

- Mild diuretic
- Hyperkalemia
- Increased excretion of sodium, calcium, chloride
- Hypertension
- Impotence/decreased libido

5. Drug interactions

Avoid using concomitantly with digoxin, ACE inhibitors, potassium-sparing diuretics, AT II receptor antagonists.

6. Monitoring Labs

Electrolytes, BUN, and creatinine at baseline, 2 months after starting or increasing dose, and every 6 months after establishing stable dose

B. Estrogen therapy

Estrogens are the primary hormones used for feminization. Adverse effects from Estrogen therapy including increased risk of death are well-documented, and patients should be fully informed of possible risk. Nevertheless, these drugs are extremely useful and have been used with relative safety. Despite our high-risk population, we have rarely seen adverse effects. Numerous classes of estrogens have been used for gender reassignment. There is a thriving illicit market for these drugs and many patients have been taking them on the streets without medical monitoring. Patients frequently take estrogens from several classes and have a misconception that "more is better." Education is essential to avoid adverse outcomes and optimize effect.

Common Prescribed estrogens used for reassignment of gender include:
Conjugated estrogens (Premarin)
Ethinyl estradiol (Estinyl)
17 Beta Estradiol (Estradiol)
Estrogen transdermal (Estroderm, Climara)
Estradiol valerate injection

Premarin is our typical starting medication, mostly due to our patients' positive experience with it and the widespread availability of the drug. Transdermal estradiol, by avoiding a hepatic first pass effect, may cause less thromboembolism and may be appropriate for high risk (cigarette smokers, greater than age 40, sedentary) patients. It is more expensive. Ethinyl Estradiol may cause more birth control pill-like side effects (nausea, HA, edema) and may be more susceptible to drug-drug interactions. We prescribe injectable estrogen as a second line alternative because of the variation in plasma concentration between injections, and the difficulty in titration.

Many patients prefer a combination of estrogens, and doses should be calculated to not exceed the bio-equivalent maximum (see below). Estrogens can be combined with any dose of an anti-androgen. Add Aspirin 81mg to 325mg for all patients at increased risk of thrombo-embolism (cigarette smoker, age greater than 40, obese, cardiac risk factors) and consider aspirin for all patients without contraindication.

1. Principles of estrogen therapy

- All estrogens increase the risk of thrombo-embolism and prolactinoma. This risk is dose-dependent, controlling for other risk factors.
- All estrogens work on the same receptors and should have similar effects at equi-potent doses. Nevertheless, there are patient-specific variations and preferences in response to dose and type of estrogen.
- Oral preparations have the advantage of being easy to titrate or stop in case of adverse effects, as injectable forms may stay present in the body for four weeks or longer.
- Response to treatment is extremely variable. In our experience, younger age and less body hair are predictable factors of a more satisfactory outcome.
- Estrogen doses can be reduced to a minimum dose after Gender Reassignment Surgery (GRS) or after maximum feminization is evident, which is usually after two years of high dose treatment.
- Stop all estrogens two weeks prior to any major surgery or other immobilizing event, and resume one week after or upon resumption of mobility.

2. Dosing

Approximate Estrogen Bio-Equivalencies

Medication	Post-menopausal replacement dose	Gender reassignment dose
Conjugated Estrogens (Premarin)	0.625mg po QD	Starting: 1.25-2.5mg/d Average: 5mg/d Maximum: 10mg/d
Ethinyl Estradiol (Estinyl)	0.05mg po QD	Starting: 0.1-0.2mg/d Average: 0.4mg/d Maximum: 0.5mg/d
Estradiol (Estrace)	0.5mg po QD	Starting: 1-2mg/d Average: 4mg/d Maximum: 5mg/d
Estradiol Valerate inj (Delestrogen)	10mg q2wks IM	Starting: 20-40mg IM q2wks Average: 40mg IM q2wks Maximum: 40-60 mg IM q2wks
Estradiol patch	0.05mg/d dermal (0.5-1.0mg patches to be changed once-twice/wk)	Starting: 0.1-0.2mg/d Average: 0.2-0.3mg/d Maximum: 0.3mg/d

Note: The Equivalent maximum dose of the injectable estradiol valerate in the table is less than calculated more for safety reasons and lack of information using the higher doses. Also, the maximum dose of the Estradiol patch is less than calculated due to the impractical number of patches and prohibitive cost.

3. Contraindications

Presence of estrogen-dependent cancer, history of thromboembolism or severe thrombophlebitis.

4. Precautions

Hyperlipidemia, diabetes, cigarette smoking, hepatitis, alcoholic liver disease, renal insufficiency, migraine, seizure disorder, retinopathy, obesity, coronary artery disease, valvular heart disease, congestive heart failure or other cardiac dysfunction, any condition causing tendency to thrombosis, strong family history of breast cancer or other estrogen dependent tumor.

Note: Attempt to control all above conditions prior to starting estrogen therapy. Inform patient risk status. Consider lower threshold maximum dose for these patients.

5. Expected desirable effects

- Breast development
- Redistribution of body fat
- Softening of skin
- Suppression of testosterone production

6. Possible or theoretical desirable effects

- Improved lipid profile/decreased CAD risk
- Improved mood/improved impulse control

7. Adverse effects

Definite: Deep venous thrombosis, Pulmonary embolism, Other thromboembolism, Thrombophlebitis, Hypertension, Prolactinoma, Diabetes, Nausea/vomiting, Migraine/headache, Decreased libido/impotence, Gallbladder disease, Abnormal liver function tests, Mood disorder/depression, Melasma (skin darkening), Acne, Lipid abnormalities, Hypertriglyceridemia

Possible or theoretical adverse effects: Increased risk of breast cancer, Hepatitis, Increased risk of heart attack, Stroke, Increased risk of other cancers

8. Adverse drug interactions (See Attachment: Drug Interactions)

- Nicotine/cigarettes increased degradation of estrogens and increase DVT risks
- HIV Protease inhibitors increase metabolism of Ethinyl Estradiol.
- Many other drugs increase or decrease metabolism of Ethinyl estradiol.

9. Lab monitoring

- Baseline: liver panel, renal panel, lipid profile, prolactin level, glucose.
- Recheck 1-2 months after starting, 3 months after changing dose, and every 6 months after establishing stable dose.

10. Other clinical monitoring

- Breast symptoms and breast exam every 6 months, BSE education
- Prostate exam as in the general population
- Extremity exam for varicose veins, edema, signs of DVT every visit.
- Review history and teach warning signs of DVT/PE
- Cardiac/respiratory exam
- Focused neurological exam and mental status

11. Other tests

- Mammogram for any patient with breast tissue with suspicious findings on manual exam. Consider annually for all patients over age 50.
- Testosterone level: used selectively and rarely but may be appropriate for patient not showing expected demasculinization after 6-12 months on maximum anti-androgen therapy or for a patient requiring reassurance that regimen is working.
- Prolactin levels: serum prolactin level correlates well with pituitary activity and prolactin is likely to be significantly increased for a long period (greater than 1 year) prior to an adenoma becoming autonomous and enlarging. Elevated prolactin levels frequently decrease spontaneously. Therefore:

    - If prolactin is less than 25, continue to monitor per protocol.
    - If prolactin is 25-40, confront patient about outside sources of extra estrogen (usually injections) and encourage patient to cease these. Continue to monitor per protocol.
    - If prolactin is greater than 40, decrease estrogen dose by 1/2 or ask patient to stop estrogens, recheck 6-8 weeks.
    - If prolactin is greater than 100, stop all estrogens and retest in 6-8 weeks. If continues very high consider MRI of pituitary. If prolactin level is falling, restart estrogen at lower dose and monitor every 6-8 weeks.
- Estrogen levels are not useful.

C. Progesterone therapy

Medroxyprogesterone has a demonstrated anti-androgen effect at high doses but has no advantage over spironolactone. Its physiological effect is primarily on the uterus and effects on feminization are unclear. Some patients report a potentiating effect on breast growth or fat redistribution. There are also reports of androgenic effect in some patients and an adverse effect on mood (PMS-like effect) in some patients. Medroxyprogesterone is not a routine part of our hormonal reassignment regimen but may be used in the following situations:

- As adjunct for patients on maximum estrogen doses with unsatisfactory effects.
- In patients intolerant of other drugs.

1. Dosing
- Typical Medroxyprogesterone starting doses: 2.5mg qday
- Typical Medroxyprogesterone dose: 5mg/day
- Maximum dose Medroxyprogesterone: 10mg qday

2. Contraindications
Same as estrogens.

3. Precautions
Same as estrogens. Carefully review use in any patient with underlying psychiatric disorders.

4. Expected desirable effects
Enhanced estrogen feminization effects.

5. Adverse effects
Lipid abnormalities, weight gain, edema, mood disorders (depression/irritability), facial and body hair growth and coarsening.

6. Adverse drug interactions
Unknown

7. Lab monitoring
Same as estrogens

V. FTM Treatment Protocol

The main available treatment for hormonal reassignment for FTM patients are androgens which usually produce satisfactory virilizing results. The entire process of virilization can take years to complete. However, in many patients, changes in voice pitch, muscle mass, and hair growth become apparent after just a few months of a regular hormonal treatment regimen.

A. Testosterone

1. Available forms of testosterone and dosing

a) Intramuscular Route

- Testosterone Cypionate 100 - 400 mg IM Q 2-4wks
- Testosterone Enanthate 100-400 mg IM Q 2 -4 wks
- Testosterone Propionate 100-200 mg IM 1-2 times/wk.

IM testosterone is released slowly from the muscle. There are variations in the plasma concentration through injection cycles, causing symptoms that may require dose or frequency changes.

b) Transdermal System

- Androderm patch (2.5mg/patch), 1-2 patches/day. This is a non-scrotal patch. It has the advantage of avoiding peak ups and downs in testosterone levels, thus delivering a constant dose of hormone. This form can be an effective alternative in patients who are more sensitive to variable testosterone levels.
- Testosterone ointment in petrolatum base 2-4%. Used as an adjuvant to increase concentration in local areas (face, clitoral area). Mixed results in terms of effectiveness.
- Androgel (testosterone gel 1%). Avoid the use of the patch . Need to be used with caution at the possibility of exposing partners and loss of absorption.

c) Oral preparations (Methyl/testosterone; Oxandrolone)
These are not used in our clinic. PO preparations undergo extensive liver metabolism, increasing the possibility of liver complications.

2. Contraindications

Hx of coronary uncontrolled artery disease, pregnancy.

3. Precautions

Hyperlipidemia, liver disease, cigarette smoking, obesity, family history of coronary artery disease, family history of breast cancer, acne, history of deep venous thrombosis, erythrocytosis.

4. Masculinizing effects

- Cessation of menses
- Voice change to a male range
- Increased hair growth on face, chest, and extremities
- Increased muscular mass and strength
- Clitoral enlargement

Note: Changes in voice range, hair follicles, and clitoral size are permanent. Other effects are reversible at the cessation of hormonal therapy.

5. Other Effects

- Protection against osteoporosis
- Increased libido
- Increased physical energy

6. Possible adverse effects

- Increased weight
- Peripheral edema
- Acne
- Erythrocitosis
- Liver enzyme elevations
- Decrease in the HDL fraction of cholesterol
- Increased risk of cardiovascular disease
- Coarsening of skin
- Headache
- Emotional changes, increased aggressiveness
- Redistribution of body fat to an android (apple) shape
- Male pattern baldness
- Increased risk of breast cancer
- Hypertension
- Thrombophlebitis

7. Drug Interactions (See Attachment: Drug Interactions)

- Potentiation of warfarins.
- In diabetic patients, blood sugar decreases, requiring adjustments in dose of hypoglycemic agents.

8. Special Considerations

- Smoking cessation should be strongly encouraged to decrease cardiac risk factors
- Any vaginal bleeding after cessation of menses should be evaluated as post menopausal bleeding.
- Circulating testosterone has been associated with breast cancer. Breast exams and mammograms are essential. Any post-surgical residual axillary breast tissue requires regular examination as well.
- Pap smears are still important follow-up.
- Assess for hypersexual behavior and safe sex practices.

VI. Other considerations

A. Surgical options

About 10% of our patients undergo surgical gender modification, including breast augmentation, vaginoplasty, castration, neck shaving, vocal cord surgery, etc. We encourage our patients to wait until their breasts grow to a maximum with the use of medications before deciding upon breast augmentation surgery, as breasts growth without surgical intervention can achieve a very satisfactory result. We assist our patients in their surgical decisions by offering education about the procedures and their effects, providing a directory of different surgical groups within the country and abroad, and facilitating pre-op requirements. Usually, our clinic follows the medical care after surgery. After castration, exogenous hormonal requirements drop significantly.

B. Adolescents

We take care of a few adolescents in our practice. We require psychiatric evaluation and diagnosis, ongoing psychotherapy, and family support and involvement in the process. .Emancipated teenagers are not required to have parental input. Initiating hormones at a younger age has a better outcome than starting them later, but this also creates physical and physiological changes that are irreversible in case of future regret.

C. Psychosocial

Adequate treatment of gender dysphoria requires available psychosocial support. Diagnosed mental disease is more prevalent in our transgender clinic than in our general clinic. Some studies find a correlation between schizophrenia and gender dysphoria. Other medical research mention changes in spatial, verbal, and memory abilities after hormonal treatment in both MTF and FTM patients. Not all of our patients have the need for ongoing psychological therapy, but we facilitate access to this with in-house support and outside referrals.

DRUG INTERACTIONS

Levels of Estradiol, Ethinyl Estradiol

Increased by:	**Decreased by:**
Astemizole	Benzoflavone
Cimetidine	Carbamazepine
Clarithromycin	Dexamethasone
Diltiazem	Napthoflavone
Erythromycin	Phenobarbital
Fluconazole	Phenylbutazone
Fluoxetine	Phenytoin
Fluvoxamine	Progesterone
Grapefruit	Rifampin
Isoniazid	Sulfamidine
Itrakonazole	Sulfinpyrazone
Ketoconazole	
Miconazole	
Nefazadone	
Paroxetine	
Sertraline	
Triacetyloleandomycin	
Verapamil	

Levels of Estrogen

Increased by:	**Decreased by:**
Efavirenz	Nelfinavir
Indinavir	Nevirapine
Vitamin C	Ritonavir
	Smoking

Testosterone increases the hypoglycemic effect of Sulfonylureas and the anticoagulant effect of Warfarin