Devon Partnership NHS
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Prescribing Guideline

PG12 Pharmacological Treatment of Gender Dysphoria

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Pharmacological Treatment of Gender Dysphoria

1. Background

A. The treatment of Gender Dyphoria by Specialised Gender Identity Services commissioned by NHS England

NHS England Specialised Commissioning commissions Specialist Gender Identity Services (SGIS) for persons aged 17 and older registered with a GP in England, SGIS provide assessment, care and treatment for people affected by concerns regarding gender identity (see Section 1b, below), role and/or expression that differs from the cultural norms for their birth-assigned sex; such concerns may result in gender dysphoria (see Section 1c, below). SGIS providers offer or facilitate a variety of therapeutic practical, physical, medical and surgical interventions for people affected by gender dysphoria. The service commissioned by NHS England is described in *NHS England Interim Gender Dysphoria Protocol and Service Guideline 2013/14*[1].

The Laurels Clinic for Gender and Sexual Medicine is a SGIS provider operated by Devon Partnership NHS Trust and is commissioned to accept referrals of patients registered with a GP anywhere in England; in practice, The Laurels offers a national service for the management of gender dysphoria.

Medical staff at The Laurels make recommendations to the GPs of patients referred to the service for endocrine and other pharmacological interventions to relieve gender dysphoria and facilitate changes in sex-specific characteristics, to include:

- Feminising and virilising hormone therapy (sex steroids, gonadotropin releasing hormone (GnRH) analogues, modifiers of sex steroid receptor function)
- Depilatory and hair growth-inhibiting agents

The drugs used in treatment of gender dysphoria are well-known and widely-prescribed in primary care. Apart from Sustanon®, there are no licensed products with an approved indication for the treatment of gender dysphoria. There is, however, extensive clinical experience of the use of these products in the treatment of gender dysphoria over decades, which provides evidence of tolerability and safety comparable with their use for approved indications.

Medical staff at The Laurels make recommendations for the prescription and monitoring of these therapies but do not directly prescribe them, or provide physical and laboratory monitoring procedures for patients. NHS England Specialised Services Circular SSC 1417 (published 26th March 2014) encourages GPs to collaborate with GICs in the initiation and on-going prescribing of hormone therapy, and for organising blood and other diagnostic tests as recommended by the GICs.

With regard to recommendations made to GPs for prescribing drugs for the treatment of gender dysphoria:

[1] http://www.england.nhs.uk/resources/spec-comm-resources/npc-crg/group-c/c05/; Retrieved 06/08/2014

i) Medical staff at The Laurels take responsibility to assess the capacity of patients to give meaningful informed consent to use such treatments, to explain their potential risks, benefits and limitations, to explain that some treatments are not approved for the indication of gender dysphoria and the implications thereof, and will obtain and document consent before making a recommendation to a GP to prescribe treatment for their patient;

ii) Medical staff at The Laurels take responsibility for overseeing patient care in collaboration with GPs, and for their recommendations to GPs that they prescribe and monitor drug treatments;

iii) Medical staff at The Laurels will provide the patient's GP with clear written guidance on prescribing and monitoring, be available to provide additional information on request, and answer GP questions regarding treatment and monitoring at reasonable notice;

iv) Prescribing of medicines for the unapproved application of treating gender dysphoria is supported by authoritative clinical guidance.

v) Once a patient has completed their episode of care with The Laurels, typically twelve months after completion of the last planned intervention, they will be discharged. As almost all patients will need to continue taking hormone therapy for the rest of their lives, medical staff at The Laurels will, at the time of discharge, provide GPs with written guidance for ongoing prescribing and monitoring of drug treatment.

The Laurels is not commissioned to prescribe any hormonal or other pharmacotherapy for patients under its care, although its medical staff may elect to do so in exceptional circumstances to protect patient safety.

B. Gender Identity

Gender Identity is the individual's personal sense of their own gender. It includes both binary and non-binary experiences of gender. Binary experience implies that an individual identifies either exclusively as a man or exclusively as a woman. However, there is growing recognition that many people do not regard themselves as conforming to the binary man/woman divide and that this will impact on their treatment. Self-descriptions include: *pan-gender*, *poly-gender*, *neutrois* and *gender queer*. A few people who reject the gender concept altogether, and see themselves as non-gendered (*agendered*), may require gender neutralising treatments from appropriate clinical services.

UK Intercollegiate Good Practice Guidelines for the Assessment and Treatment of Adults with Gender Dysphoria (UKGPG) recognise that there are gradations of gender experience between the binary 'man' or 'woman', some of which cause discomfort and may need some medical intervention; others may need little or none.

C. Gender Dysphoria

Gender dysphoria refers to psychological distress that is caused by a discrepancy between a person's gender identity, their sex assigned at birth (e.g. male or female) and their primary/secondary sex characteristics; it also includes the impact of that discrepancy on their gender role (the discrepancy between how they wish to live their lives and how society expects

them to live their lives) and the perceptions of others. Untreated, gender dysphoria can severely affect the individual's well-being and quality of life, and may lead to mental ill-health. People with untreated gender dysphoria are at much higher risk of self-harm and suicide than the general population. For the purposes of this document, the term gender dysphoria refers to both those who currently have gender dysphoria or who have had it in the past.

D. Epidemiology

A primary care population study of transsexual people conducted in Scotland reported of an incidence of 1:12,225 (0.00818%), and a prevalence of 1:7,500 in birth-assigned males and 1:31,000 in birth-assigned females. The trend in epidemiological research appears to be towards higher prevalence rates in the more recent studies.

In 2011, the Gender Identity Research and Education Society published a report[2] that suggested the gender balance of gender variant people was changing, as more people assigned as female at birth sought medical help. It also suggested that as much as 1% of the population may experience some degree of gender variance. Personal communications from Clinical Directors of GICs in England suggest that referral rates to their services have been increasing by around 20% per year for the past several years; in 2012/13, the referral rate to specialist gender clinics in England was around 2500 people a year. Not all of these people will be transsexual persons, nor will all be seeking to transition.

E. Evidence base

There is no NICE guidance with specific relevance to this service.

There are three current clinical guidance documents that are generally considered authoritative with respect to their guidance on clinical practice in general but not with respect to their guidance on prescribing.

i) *World Professional Association for Transgender Health Standards of Care (WPATH SoC) for the Health of Transsexual, Transgender and Gender Nonconforming People*, 7th version, 2011[3]

ii) *Good Practice Guidelines (UKGPG) for the Assessment & Treatment of Adults with Gender Dysphoria* (Royal College of Psychiatrists CR181; October 2013)[4].

iii) *Endocrine Treatment of Transsexual Persons (ETTP): An Endocrine Society Clinical Practice Guideline.* Journal of Clinical Endocrinology & Metabolism, September 2009, 94(9): 3132–3154[5]

The *WPATH SoC* provides only general advice on the use of hormone therapy in the treatment of gender dysphoria. The Royal College of Psychiatrists publication CR181, *UKGPG*, contains more specific guidance on the use of hormone therapy but is based upon the advice of a single

[2] http://www.gires.org.uk/assets/Research-Assets/Prevalence2011.pdf Retrieved 06/08/2014
[3] www.wpath.org/documents/IJT%20SOC,%20V7.pdf Retrieved on 06/08/2014
[4] http://www.rcpsych.ac.uk/files/pdfversion/CR181x.pdf Retrieved 06/08/2014
[5] https://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical%20Practice%20Guidelines/Endocrine-Treatment-of-Transsexual-Persons.pdf Retrieved on 06/08/2014

expert and, despite its relatively recent publication date, is quite dated and not consistent with current practice. The Endocrine Society's *ETTP* provides the best analysis of the level of supporting evidence but is primarily written for a North American audience, where there are major differences in the availability of specific endocrine drugs and in clinical practice. Articles on hormone therapy describing North American practice and those published before 2012 are of very limited value in guiding current prescribing practice. The reasons for this are: (i) there are major differences in drug and specific preparation availability between the US and Europe; (ii) patients in the US frequently seek the least costly treatment, sometimes compromising safety and efficacy to such as degree as to be unacceptable in NHS practice; (iii) prescribing practice in gender dysphoria has changed rapidly in the past three years, as traditional practices have begun to be been evaluated by clinical research. Overall, the three current clinical guidance documents are of limited value as a source of evidence, being primarily based upon expert opinion with little reference to outcomes data.

As part of the development process of the draft 2014/15 NHS England Gender Identity Service Policy document (approved by NHS England Mental Health Programme of Care Board on 31st July 2014; awaiting approval by NHS England Clinical Priorities Assessment Group at time of writing in August 2014), a literature review was undertaken by Dr John Dean (Chair, NHS England Clinical Reference Group for Gender Identity Services and Clinical Director, The Laurels, DPT) and Dr Syed Ahmed (Public Health Physician, NHS England) to identify evidence of clinical effectiveness and cost effectiveness of cross-sex hormone therapy and genital reconstructive surgery. It is difficult to determine the effectiveness of hormones alone in the relief of gender dysphoria because most studies have been conducted in patient populations who have also undergone surgery. 11 studies were found which met the inclusion criteria: two reviews (Murad et al. 2010 [LoE 1b] and Sutcliffe & Dixon 2002), one Health Technology Assessment (Day 2002), one survey and seven qualitative studies. The studies included the following outcomes: mortality, safety, psychological functioning, quality of life (QoL), personal experiences, relationships and satisfaction of treatment of transsexuals with cross-sex hormones. No studies were found on the impact of cross-sex hormone therapy and SRS on physical morbidity, physical functional status and cost-effectiveness.

Studies appear to suggest a positive impact of hormone treatment on gender dysphoria, psychological status, sexual functioning and quality of life. Mortality from suicides seems to be high despite treatment. However, the quality of evidence which these findings are based is low, and in some instances there are conflicting results.

Cross-sex hormone therapy appears to be safe, with mortality rates of those undergoing such treatment being similar to those found in the general population. A 2012 study by Asscheman *et al*[6] reported a three-fold increase in risk from cardiovascular death with current (but not previous) use of ethinylestradiol. The authors concluded that increased mortality in hormone-treated trans women was mainly due to non-hormone-related causes and that the use of testosterone in trans men at doses used for the treatment of male hypogonadism seemed safe [LoE 3b]. Also in 2012, Seal[7] et al reported that treatment with conjugated equine oestrogen was associated with a higher incidence of thromboembolism than treatment with other

[6] Asscheman H, et al (2011). *A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones.* European Journal of Endocrinology 164 635–642
[7] Seal LJ, et al (2012) *Predictive Markers for Mammoplasty and a Comparison of Side Effect Profiles in Transwomen Taking Various Hormonal Regimens* J Clin Endocrinol Metab, December 2012, 97(12):4422– 4428

oestrogen types, and that self-medication, particularly with spironolactone, was associated with increased subsequent requests for augmentation mammoplasty [LoE 4b].

John Dean subsequently reviewed all publications on gender dysphoria in English listed in the PubMed database by using Endnote x7 citation manager to interrogate the database, using the search term "gender dysphoria" and the English language filter; the search was performed on 9th August 2014. This identified 8 publications specifically related to hormone therapies[1-8], 4 general articles and reviews of treatment[9-12], including hormone therapy and seven related to hormone therapy treatment outcome (4 on outcome of gender dysphoria treatment[13-16], 1 on skin and hair outcome[17], 2 on bone health outcome[18, 19]). Also included in the review were all papers published in the *International Journal of Transgenderism* since 2004; this is the journal of the World Professional Association for Transgender Health. It is not indexed in PubMed and does not have an impact factor; papers in this journal are typically CEBM Level of Evidence 4. Two papers were identified that were of relevance to prescribing practice; references and abstracts are included in Appendix 3.

In a multicentre, 1-year prospective study in 53 trans men and 53 trans women receiving hormone therapy, Wierckx *et al*[2] examined a range of laboratory tests (sex steroids, prolactin, liver enzymes, lipids, haematocrit), blood pressure, anthropometrics, Ferriman and Gallwey score (a hirsutism assessment scale), and a global acne grading scale. Side effects, adverse events, and desired clinical changes were also recorded and evaluated. Trans men were treated with testosterone undeconate injection every three months (Nebido), trans women under 45 years with oral estradiol valerate 4mg daily and trans women 45 and over with transdermal patches; all rans women were additionally given cyproterone acetate 50mg daily. During the one-year follow-up period, no deaths or severe adverse events were observed. Two trans men developed erythrocytosis, and two had transient elevation of the liver enzymes. Trans men reported an increase in sexual desire, voice instability, and clitoral pain (all P </= 0.01). Testosterone therapy increased acne scores, facial and body hair, and prevalence of androgenic alopecia. Waist-hip ratio, muscle mass, triglycerides, total cholesterol (C), and LDL-C increased, whereas total body fat mass and HDL-C decreased. Three trans women experienced transient elevation of liver enzymes. A significant increase in breast tenderness, hot flashes, emotionality, and low sex drive was observed (all p≤0.02). Fasting insulin, total body fat mass, and prolactin levels increased, and waist-hip ratio, lean mass, total C, and LDL-C decreased. They concluded that treatment with hormone therapy was effective and carried a low risk for side effects and adverse events at short-time follow-up. In a second paper[17], the same authors concluded that treatment of trans men with testosterone increased facial and body hair in a time-dependent manner. The prevalence and severity of acne in the majority of trans men peaked 6 months after beginning treatment. Severe skin problems were absent after short- and long-term T treatment. [LoE 3b]

Heylens et al (2014) describe a prospective study that assessed 57 individuals with GID by using the Symptom Checklist-90 (SCL-90) at three different points of time: at presentation, after the start of hormonal treatment, and after sex reassignment surgery (SRS). Questionnaires on psychosocial variables were used to evaluate the evolution between the presentation and the postoperative period. A difference in SCL-90 overall psychoneurotic distress was observed at the different points of assessments (P = 0.003), with the most prominent decrease occurring after the initiation of hormone therapy (P < 0.001). Significant decreases were found in the subscales such as anxiety, depression, interpersonal sensitivity, and hostility. Furthermore, the

SCL-90 scores resembled those of a general population after hormone therapy was initiated. Analysis of the psychosocial variables showed no significant differences between pre- and postoperative assessments. They concluded that a marked reduction in psychopathology occurred during the process of sex reassignment therapy, especially after the initiation of hormone therapy. [LoE 3a]

Manieri et al (2014, Appendix 3.a) studied 83 subjects (56 male-to-female [MtF] and 27 female-to-male [FtM] trans people) with haematological and hormonal evaluations every 3 months during the first year of hormonal therapy. MtF persons were treated with 17βestradiol and antiandrogens (cyproterone acetate, spironolactone, dutasteride); FtM persons were treated with transdermal or intramuscular testosterone. The WHO Quality of Life questionnaire was administered at the beginning and 1 year later. Hormonal changes paralleled phenotype modifications with wide variability. Most of both MtF and FtM subjects reported a statistically significant improvement in body image ($p < 0.05$). In particular, MtF subjects reported a statistically significant improvement in the quality of their sexual life and in the general quality of life ($p < 0.05$) 1 year after treatment initiation. The authors concluded that cross-sex therapy seemed to be free of major risks in healthy subjects under clinical supervision during the first year, and that selected subjects showed an optimal adaptation to hormone-induced neuropsychological modifications and satisfaction regarding general and sexual life. [LoE 3b]

Overall, there is only limited evidence to demonstrate the efficacy of hormonal therapy with regard to, particularly, long-term complications or physical functional status.

There is no available evidence regarding cost-effectiveness of the treatment.

The following extract from WPATH SoC summarises evidence from studies of combined psychotherapeutic, endocrine and surgical interventions, as are offered through The Laurels service. “Favorable effects of therapies that included both hormones and surgery were reported in a comprehensive review of over 2000 patients in 79 studies (mostly observational) conducted between 1961 and 1991 (Eldh, Berg, & Gustafsson, 1997; Gijs & Brewaeys, 2007; Murad et al., 2010; Pfäfflin & Junge, 1998). Patients operated on after 1986 did better than those before 1986; this reflects significant improvement in surgical complications (Eldh et al., 1997). Most patients have reported improved psychosocial outcomes, ranging between 87% for MtF patients and 97% for FtM patients (Green & Fleming, 1990). Similar improvements were found in a Swedish study in which “almost all patients were satisfied with sex reassignment at 5 years, and 86% were assessed by clinicians at follow-up as stable or improved in global functioning” (Johansson, Sundbom, Höjerback, & Bodlund, 2010). Weaknesses of these earlier studies are their retrospective design and use of different criteria to evaluate outcomes.

A prospective study conducted in the Netherlands evaluated 325 consecutive adult and adolescent subjects seeking sex reassignment (Smith, Van Goozen, Kuiper, & Cohen-Kettenis, 2005). Patients who underwent sex reassignment therapy (both hormonal and surgical intervention) showed improvements in their mean gender dysphoria scores, measured by the Utrecht Gender Dysphoria Scale. Scores for body dissatisfaction and psychological function also improved in most categories. Fewer than 2% of patients expressed regret after therapy. This is the largest prospective study to affirm the results from retrospective studies that a combination of hormone therapy and surgery improves gender dysphoria and other areas of psychosocial functioning. There is a need for further research on the effects of hormone therapy without surgery, and without the goal of maximum physical feminization or masculinization.

Hair loss and gender dysphoria

Scalp hair loss (androgenetic alopecia, AGA, male pattern hair loss) is a common cause of gender dysphoria amongst trans women. Prevention and treatment may reduce gender dysphoria, reduce the likelihood of patients being misgendered by others, and reduce NHS cost of wig provision.

Everyone with scalp hair, regardless of their sex, experiences loss of scalp hair; all hair follicles are replaced at different rates by the normal process of hair cycling. Hair growth alternates between phases of activity and rest. The growth period, called the anagen phase, lasts for two to six years. During this time, the follicle is long and deep, and produces thick, well-pigmented hair. About 90% of all scalp hairs are in the anagen phase at a given time. Anagen is followed by a brief transition known as the catagen phase, which lasts a few weeks. During this time, the base of the follicle shrivels. The resting period, or telogen phase, lasts for two to four months. In this phase, the follicle withers even further. Following the telogen phase, the next anagen phase begins, and the old hair is dislodged and falls out to make room for a new hair to begin growing in its place.

AGA is an inherited condition, caused by a genetically-determined sensitivity to the effects of dihydrotestosterone (DHT) in some areas of the scalp. DHT is believed to shorten the growth (anagen) phase of the hair cycle, from a usual duration of 3-6 years to just weeks or months. This causes miniaturisation of the follicles, and producing progressively fewer and finer anagen hairs. The production of DHT is regulated by 5-alpha reductase. The typical pattern of hair loss is thinning or loss of hair at the vertex, frontal and temporal scalp. Several genes are involved, accounting for differing age of onset, progression, pattern and severity of hair loss in family members. The susceptibility genes are inherited from both mother and father. At this time, genetic testing for prediction of balding is unreliable.

A few women present with male pattern hair loss because they have excessive levels of androgens as well as genetic predisposition; this is the typical endocrine profile of a trans woman before suppression of exogenous testosterone by feminising hormone therapy for gender dysphoria. These women tend also to suffer from acne, irregular menses and excessive facial and body hair. Some women that lose their hair with age do not have elevated androgen levels; they are described as having female pattern hair loss; thinning of scalp hair at the vertex is typical, with sparing of frontal and temporal scalp hair.

AGA is a common dermatological condition affecting both men and women. In the case of men, up to 30% over the age of 30 and more than 50% over the age of 50 are affected. AGA also affects women although clinical signs are usually milder and associated with diffuse thinning of the scalp hair. AGA invariably causes serious psychological problems, especially in women. By far the most promising approaches to the treatment of baldness in men are drug therapies, such as topical minoxidil and finasteride administered systemically. Mild to moderate AGA in women can be treated with antiandrogens and/or topical minoxidil with good results in many cases[8].

[8] Bienova, M., et al. (2005). "Androgenetic alopecia and current methods of treatment." Acta Dermatovenerol Alp Pannonica Adriat 14(1): 5-8.

[LoE 4c] The results of efficacy studies are mixed; available studies are small, uncontrolled and of generally poor quality. No research has been conducted amongst trans women.

Facial hair growth and gender dysphoria

Facial hair growth is a common cause of gender dysphoria amongst trans women. Before entering the NHS care pathway, most trans women will manage this through frequent shaving, sometimes several times daily. This often results in skin irritation, inflammation and, occasionally, infection; too frequent shaving is undesirable. Physical epilation treatments (photoepilation and electroepilation) are funded as part of the NHS care pathway. However, such treatments are not effective for all patients, particularly those with white, fair or red hair, and do not provide permanent hair removal; they might best be considered as hair reduction treatments. Many patients will continue to shave from time to time; for some patients, the frequency of shaving may be reduced by the use of a topical epilatory drug, eflornithine. This irreversibly inhibits ornithine decarboxylase, an enzyme involved in the production of the hair shaft by the hair follicle.

General comments on evidence

Overall, studies have been reporting a steady improvement in outcomes as the field becomes more advanced. Outcome research has mainly focused on the outcome of sex reassignment surgery. In current practice there is a range of identity, role, and physical adaptations that could use additional follow-up or outcome research (Institute of Medicine, 2011)."

Treatment involving a combination of hormone administration and usually some combination of gender-confirming surgical procedures, following psychological assessment and accompanied by psychological support, is deemed to lead to good outcomes. A study using the post-genital-surgery end-point showed only a 3.8% regret rate and indicates that regrets are few (Landén *et al*, 1998). The study revealed that regrets were more likely where there was a lack of family support.

It is apparent that there is only limited outcome evidence for the treatment of gender dysphoria. In addition, such evidence of efficacy and treatment satisfaction that is available is generally of a low level. There are several reasons for this:

- There is no generally accepted and validated clinical outcome measure for "gender dysphoria"; two have been developed in the past twenty years but none has been widely used
- Outcome research for individual interventions, such as facial hair epilation, is largely derived from their use in other populations; expert opinion is that this cannot always be generalised and applied to a trans population. For example, a woman with facial hirsutism may be distressed by her facial hair growth, a response which she shares with a trans woman, but she does not usually fear misidentification as a man; the impact of hirsutism on well-being may be different between trans and non-trans populations. Simple scales that count hairs per cm^2 may be a valid assessment of the efficacy of a hair reduction treatment but will not measure its efficacy in modifying the trans woman's experience of gender dysphoria, The same may be said of other interventions used in the treatment of gender dysphoria that

were originally developed for other applications. Manufacturers of drugs are unlikely to apply to regulatory agencies for a new indication for the treatment of gender dysphoria because of the relatively high cost of such applications and the small volume of sales that will result.

- It is near-impossible to evaluate the impact of any single intervention in isolation, as they are often given concurrently and may have accessed directly by service users. Authoritative clinical guidelines on the treatment of gender dysphoria recommend concurrent use of several interventions; the delay to completion of treatment and the resulting increase burden of dysphoria upon patients renders sequential use of interventions impractical and ethically dubious.
- With respect to drug therapy, there are substantial variations in current UK prescribing practice and inadequate evidence or even consensus to agree what constitutes "best practice"
- Past prescribing practice has involved the use of hormone regimens that would, in the UK at least, be considered unacceptably high-risk in the general population. In other countries, self-funding drives patients to use the cheaper rather than optimal interventions. Consequently, older studies and international studies may not be relevant to contemporary UK practice.
- Worldwide, most people have been treated for gender dysphoria in private practice settings; people paying for their own treatment are not usually willing to participate in clinical trials.

Central to the commissioning of gender dysphoria services by NHS England is a parallel process of "evaluation of interventions" by providers, such as The Laurels, that will run concurrently with the process of "provision of interventions". The proposed policy for 2014/15 requires providers to undertake outcomes research, as well as to provide the services themselves. For the present, prescribing must be based upon the limited available evidence; in the future, it will be possible to base it more upon robust outcomes data.

F. Outcome

The over-arching outcome intended for the treatment of gender dysphoria is to assist transsexual, transgender, and gender nonconforming people in achieving lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment.

2. Recommended Prescribing Practice for the Treatment of Gender Dysphoria

Current prescribing practice for people with gender dysphoria at The Laurels is influenced by the published clinical guidance and evidence cited in Section 1.e, above. Having assessed that feminising or virilising therapy is clinically necessary for the treatment of gender dysphoria, having established the patient's capacity to give meaningful informed consent to treatment recommend and having discussed the product license status for any treatment recommended and the implications thereof, medical staff will complete a *pro forma* safety and risk assessment, described in Appendix 1, before recommending prescription of such treatment. Monitoring recommendations are described in Appendix 2.

For transgender people seeking physical feminisation:

Clinical treatment goal: relief of gender dysphoria; cognitive change; physical feminisation (skin and hair changes, breast growth, redistribution of body fat, reduction in body hair growth, cessation of erections, shrinkage of testes)

Biochemical treatment goal: serum total testosterone less than 3.0nmol/L and serum estradiol within the range 200-600pmol/L; prolactin, liver function, and fasting glucose and lipids within reference ranges.

Brief summary of intervention: Around two-thirds of patients will achieve treatment goals with estradiol therapy alone; over 80% are content to use transdermal estradiol preparations. Around one-third of patients will not achieve adequate suppression of endogenous testosterone with estradiol alone and will require additional treatment with a GnRH analogue. Progestogens are not prescribed for the treatment of gender dysphoria.

First line intervention: Transdermal estradiol (as patch or gel; Evorel® patches[9]; Sandrena® gel[10]; Oestrogel® 0.06% gel[11]); typical staring dose Evorel 100 (6.4mg estradiol/patch) patch twice weekly (range 1.6 to 9.6mg/patch or concurrently applied patches) or 2mg, as gel, daily (range 0.5 to 4mg). Risk of thrombosis is not dose-related with transdermal preparations.

a. Patients may be offered an oral estradiol preparation, if this is their preference.
b. Patients aged over 40 and those who may be at increased risk of thrombosis, are strongly recommended to use transdermal estradiol preparations as first-line therapy.
c. Some patients find patches and gel cause bothersome skin irritation; this may be severe enough to warrant changing to an oral preparation.
d. A minority of patients do not achieve adequate or reliable serum estradiol levels with transdermal preparations; they may be offered oral preparations as an alternative.

Second line intervention: For patients who are intolerant of, fail to achieve adequate serum estradiol levels with, or who refuse transdermal preparations, oral estradiol preparations may be offered as an alternative; typical starting dose: 4mg daily; range: 2mg to 12mg. Risk of thrombosis increases with dose and is greater in over-40s.

a. Micronized estradiol preparations (Zumenon®[12]) may reduce the metabolic and thrombogenic effects of estradiol
b. Estradiol implants are not recommended because of their association with supra-physiological serum estradiol levels.

[9] SPC Evorel®, 50, 75 and 100: https://www.medicines.org.uk/emc/medicine/7235 Retrieved 06/08/2014
[10] SPC Sandrena® 1.0mg gel: https://www.medicines.org.uk/emc/medicine/1392 Retrieved 06/08/2014
[11] SPC Oestrogel® 0.06% gel: https://www.medicines.org.uk/emc/medicine/19898 Retrieved 06/08/2014
[12] SPC Zumenon® 2mg tablets: https://www.medicines.org.uk/emc/medicine/2090 Retrieved 06/08/2014

Third line intervention: Addition of GnRH analogue may be required if endogenous testosterone is not adequately supressed by estradiol alone. The typical intervention is addition of triptorelin (Decapeptyl SR®[13]) 11.25 mg by intramuscular injection, given every three months, in addition to estradiol. Triptorelin is the preferred preparation; goserelin is administered as an implant, involving a more complex administration procedure that may cause abdominal scarring and persistent subcutaneous nodules; leuprorelin is less cost-effective. Treatment continues until gonadectomy or indefinitely, if gonadectomy is not performed. GnRH analogues are preferred to cyproterone acetate[14], because the former are very well tolerated and have a low rate of adverse effects, whereas the latter is associated with hepatotoxicity, and increased risk of thrombosis. In addition, unlike cyproterone acetate, GnRH analogues do not have to be discontinued during a peri-operative period.

Cyproterone acetate 50mg twice daily may be used for up to two weeks to block increased testosterone action consequent upon the initial administration of a GnRH analogue.

Following gonadectomy, GnRH analogue therapy is discontinued. estradiol doses should be reviewed in the sixth decade and, with the patient's agreement, may be reduced to the lowest effective dose for the prevention of oestrogen deficiency symptoms. Authoritative clinical guidelines recommend that treatment is continued lifelong, unless the patient desires otherwise.

Prevention and treatment of scalp hair loss

Finasteride may be recommended to *prevent* androgenic hair loss, frontal, temporal and vertex, which is a cause of gender dysphoria in trans women. Only the Proscar®[15] (finasteride 5mg daily) presentation is available on NHS prescription; 2.5mg daily is recommended for this indication.

Topical minoxidil may be recommended for the *treatment* of androgenic hair loss at the scalp vertex, which is a cause of gender dysphoria in trans women. It has little effect on frontal and temporal hair loss. Topical minoxidil is not available on NHS prescription. It is available from pharmacists, without prescription under the brand name Regaine®. There are two presentations: Regaine for Men Extra Strength®[16] (Minoxidil 50 mg/ml (5% w/v)) and Regaine for Women Regular Strength®[17] (Minoxidil 20 mg/ml (2% w/v)). The manufacturer offers no guidance as to which presentation to use in trans women; adverse reactions are dose-related but usually mild. In placebo controlled trials, the overall frequency of adverse events in females in all body system categories was approximately five times that of males. Several thousand patients have used topical minoxidil in clinical trials where a comparison with an inactive solution was made. Dermatological reactions (e.g. irritation, itching) occurred in patients using both solutions. This has been explained by the presence of propylene glycol in both the active and inactive solution. Side effects include headache, skin reactions and temporary hair loss; hypotension, palpitations and dyspnoea are uncommon.

[13] SPC Decapeptyl SR® 11.25mg: https://www.medicines.org.uk/emc/medicine/13851 Retrieved 06/08/2014
[14] SPC Cyproterone acetate 50mg tablets: https://www.medicines.org.uk/emc/medicine/28433 Retrieved 06/08/2014
[15] SPC Proscar® 5mg http://www.medicines.org.uk/emc/medicine/1190/SPC/
[16] SPC Regaine for Men Extra Strength® http://www.medicines.org.uk/emc/medicine/16535
[17] SPC Regaine for Women Regular Strength® http://www.medicines.org.uk/emc/medicine/16532

Facial epilation

Topical eflornithine may be recommended to reduce facial hair growth; it is available on NHS prescription as Vaniqa® 11.5% cream[18]. It should be applied to the face and chin only, twice daily, at least eight hours apart; she should not use more than 30g per month.

Treatments that are not recommended

Progestogens are endorsed by some clinicians, particularly in the US, and by several trans issue-focussed Websites, as promoting breast development. Progestogens play no role in physiological sex characteristic development in the pre- or post-natal period, or around puberty, and there is inadequate clinical evidence that they enhance breast growth in either the general or transgender populations. However, there is unequivocal evidence that they increase the risk of thrombosis. Progestogens are not recommended or prescribed by The Laurels service.

Spironolactone is endorsed by some clinicians, particularly in the US, and by several trans-issue Websites as suitable for use as an androgen receptor blocker in the treatment of gender dysphoria. It is approved as a potassium-sparing diuretic and its action as a competitive androgen receptor antagonist is considered an unwanted effect by most users. There are far more effective drugs than spironolactone that will reduce androgen action. For almost all patients with gender dysphoria, its potassium-sparing diuretic effect is unwanted and potentially dangerous. There is also evidence of an association between its use and inadequate breast growth in trans women; the authors of this research have speculated that this may be a specific effect on breast tissue or sex steroid receptors in breast tissue. Spironolactone is not recommended or prescribed by The Laurels service.

<u>For transgender people seeking physical virilisation:</u>

Clinical treatment goal: relief of gender dysphoria; cognitive change; amenorrhoea; physical virilisation (skin and hair changes; facial and body hair growth; deepening of voice; increased upper body muscle development; redistribution of body fat; breast atrophy)

Biochemical treatment goal: serum total testosterone around the midpoint of the laboratory reference range (18nmol/L), within the range 14-28nmol/L. Haematocrit, liver function, and fasting glucose and lipids within reference ranges. Suppression of cyclical changes in estradiol and gonadotropins is a treatment goal but is not included in routine laboratory monitoring unless the patients fails to become amenorrhoeic within 3 months of commencing testosterone therapy.

Brief summary of intervention: Around 80% of patients will use long-acting depot testosterone injections and around 20% will use transdermal preparations. Additional treatment with GnRH analogues is rarely necessary.

First-line intervention: Long-acting testosterone depot injection or transdermal testosterone gel, according to patient preference; transdermal testosterone may be recommended for patients with high haematocrit at baseline assessment (>0.50).

[18] SPC Vaniqa® cream http://www.medicines.org.uk/emc/medicine/21243

a. Testosterone undecanoate 1000mg depot injection (Nebido®[19]), given intramuscularly and initiated in accordance with the manufacturer's summary of product characteristics for the treatment of hypogonadal males (initial injection followed by second injection after six weeks, and subsequent injections at twelve week intervals; biochemical response assessed immediately before fourth injection; frequency of injection, rather than dose, may be adjusted to achieve treatment target range). Advantages: predictability and reliability of biochemical response (serum testosterone), lower incidence of polycythaemia than with short-acting testosterone injection and implants; patient convenience and reduced requirement for consultations in comparison to short-acting testosterone injection.

b. Testosterone 2% gel (Tostran®[20]) 10mg per metered dose from pump applicator. Typical starting dose is 5 pump actuations (50mg) daily as a single dose; range 1 to 8 pump actuations (10 to 80mg) daily as a single dose. Tostran® is the preparation preferred by The Laurels, as a pump dispenser allows more cost-effective dose adjustment than the use of 50mcg sachets, and the higher concentration of testosterone (Tostran® 2%; other gels 1%) improves patient convenience by reducing the volume of gel required for daily administration.

Only testosterone and testosterone esters are recommended, as they do not have the hepatotoxic effects associated with 17-alpha alkylated testosterone preparations.

Oral testosterone preparations are not recommended because of the high intra- and inter-patient variability in absorption and testosterone levels.

Testosterone implants are not recommended because of their association with supra-physiological serum testosterone levels, the lifelong requirement for 3- to 4-monthly minor surgical procedures to insert them (and the progressive accumulation of associated abdominal scarring) and the increased risk of polycythaemia associated with their use.

Second line intervention: Addition of a GnRH analogue may be necessary if amenorrhoea is not achieved within three months of commencing testosterone therapy, or is urgently required for other clinical reasons. The typical intervention is addition of triptorelin (Decapeptyl SR®) 11.25 mg by intramuscular injection, given every three months, in addition to estradiol. Triptorelin is the preferred preparation; goserelin is administered as an implant, involving a more complex administration procedure that may cause abdominal scarring and persistent subcutaneous nodules; leuprorelin is less cost-effective. Treatment continues until gonadectomy or indefinitely, if gonadectomy is not performed. GnRH analogues are preferred to cyproterone acetate, because the former are very well tolerated and have a low rate of adverse effects, whereas the latter is associated with hepatotoxicity, and increased risk of thrombosis. In addition, unlike cyproterone acetate, GnRH analogues do not have to be discontinued during a peri-operative period.

[19] SPC Nebido® 1000mg injection: https://www.medicines.org.uk/emc/medicine/15661 Retrieved 06/08/2014
[20] SPC Tostran® 2% gel: https://www.medicines.org.uk/emc/medicine/19702 Retrieved 06/08/2014

For transgender people seeking a reduction in sex steroid action

Some patients require a reduction in sex steroid action without concurrent administration of add-back cross-sex steroids; these include:

- People aged under 18 years of age with gender dysphoria, who do not meet the eligibility criteria for sex steroid therapy set out in authoritative clinical guidelines; for most patients, this is a temporary measure, as they will commence sex steroid therapy when they are 18 years old.
- People previously receiving oestrogen who are anticipating pelvic surgery or other procedures that confer an increased risk of thrombosis; for most patients, this is a temporary measure, until the period of increased risk has passed.
- People previously receiving oestrogen who have developed a thrombosis; for most patients, this is a temporary measure, which continues until the period of increased risk has passed. The decision to reintroduce estradiol therapy should be made in consultation with a haematologist.
- Non-binary gender, poly-gender, neutrois, gender queer and agendered people sometimes seek permanent castrate sex steroid levels; this is sometimes clinically necessary for relief of their gender dysphoria. A patient with capacity to give informed consent to medical interventions of this nature must be provided with information that enables them to balance the risks from long-term sex steroid deficiency against the risks of inadequately treated gender dysphoria when making a decision about treatment.

Expert opinion is that castrate sex steroid levels may be maintained for up to two years without significant risk to health. If maintenance of castrate sex steroid levels is likely to long-term or permanent, the following interventions are recommended and require close cooperation and collaboration with the patient's GP:

- Annual assessment of overall cardiovascular risk, with interventions to reduce modifiable risks, as necessary
- Six-monthly assessment of blood pressure, BMI and waist circumference, with intervention as necessary
- Annual assessment of fasting glucose and lipids (increased risk of diabetes and dyslipidaemia, with provision of specific treatment as necessary)
- Annual assessment of full blood count (increased risk of normocytic, normochromic anaemia)
- Baseline assessment of bone mineral density by DEXA scan (increased risk of osteoporosis), with ongoing regular reassessments in accordance with guidelines for the management of patients at high risk of osteoporosis. Consideration should be given to offering lifelong calcium and vitamin D supplements; the role of bisphosphonates in prevention of osteoporosis in this patient group has not been established.

Depression is more common amongst hypogonadal people than in the general population; patients should be warned of this and clinicians should be alert to their patients developing major depressive disorder.

Intervention: Treatment with a GnRH analgogue may be recommended. The typical intervention is addition of triptorelin (Decapeptyl SR®) 11.25 mg by intramuscular injection, given every three months, in addition to estradiol. Triptorelin is the preferred preparation; goserelin is administered as an implant, involving a more complex administration procedure that may cause abdominal scarring and persistent subcutaneous nodules; leuprorelin is less cost-effective. Treatment continues until gonadectomy or indefinitely, if gonadectomy is not performed.

Interventions for the prevention and treatment of AGA may also be recommended, according to clinical need.

Appendix 1

Pre-oestrogen treatment medical assessment

Conditions that might be exacerbated by oestrogen therapy

Very high risk of serious adverse outcomes

Thromboembolic disease: Y ☐; N ☐

Moderate to high risk of adverse outcomes

Macroprolactinoma: Y ☐; N ☐
Severe liver dysfunction (transaminases >3 times upper limit of normal): Y ☐; N ☐
Breast cancer: Y ☐; N ☐
Coronary artery disease: Y ☐; N ☐
Cerebrovascular disease: Y ☐; N ☐
Severe migraine headaches: Y ☐; N ☐

Future fertility considerations and implications of treatment discussed: Y ☐; N ☐

Medical History:
Smoking history: Y ☐; N ☐
Alcohol/substance history: Y ☐; N ☐
Personal or family history of thrombosis and thromboembolism: Y ☐; N ☐
Provoked, unprovoked or recurrent
Consider thrombophilia risk: Y ☐; N ☐
obesity, prolonged immobility, genetic, autoimmune disease, antiphospholipid syndrome
Arterial disease: Y ☐; N ☐
Angina, MI, stroke, peripheral vascular disease
Diabetes or glucose intolerance: Y ☐; N ☐
Migraine: Y ☐; N ☐
Classical or focal
Personal or family history of breast or other oestrogen-sensitive cancer: Y ☐; N ☐
Active liver disease: Y ☐; N ☐
Porphyria cutanea tarda: Y ☐; N ☐

Standard pre-treatment laboratory work-up:
Estradiol, testosterone, prolactin, FSH, LH, liver function, full blood count, and fasting glucose and lipid profile requested: Y ☐; N ☐; N/A ☐

Physical examination:
BP: ……
Weight/BMI: ……
Body habitus: ……
Mobility: ……

Prevention:
Requires smoking and substance use cessation advice: Y ☐; N ☐
Requires obesity management (target BMI ≤31 for genital surgery): Y ☐; N ☐
Requires cardiovascular risk assessment: Y ☐; N ☐
(Include recommendations in report to GP)

Consent:
Patient has capacity to give meaningful informed consent to treatment: Y ☐; N ☐

Consent form completed; by doctor: Y ☐; N ☐; by patient: Y ☐; N ☐

Pre-androgen treatment medical assessment

Conditions that might be exacerbated by androgen therapy

Very high risk of serious adverse outcomes

Breast or uterine cancer: Y ☐; N ☐

Polycythaemia/erythrocytosis (haematocrit ≥0.52): Y ☐; N ☐

Moderate to high risk of adverse outcomes

Severe liver dysfunction (transaminases >3 times upper limit of normal): Y ☐; N ☐

Future fertility considerations and implications of treatment discussed: Y ☐; N ☐

Medical History:

Exclude pregnancy by clinical history (by IPT only if clinically indicated): Y ☐; N ☐; N/A ☐
Smoking history: Y ☐; N ☐
Alcohol/substance history: Y ☐; N ☐
Undiagnosed vaginal bleeding: Y ☐; N ☐
Arterial disease: Y ☐; N ☐

Angina, MI, stroke, peripheral vascular disease

Diabetes or glucose intolerance: Y ☐; N ☐
Personal or family history of breast or other hormone-sensitive cancer: Y ☐; N ☐
Active liver disease: Y ☐; N ☐
Uterine cervix present: Y ☐; N ☐

Standard pre-treatment laboratory work-up:

Estradiol, prolactin, FSH, LH, liver function, full blood count and a fasting glucose and lipid profile requested: Y ☐; N ☐; N/A ☐

Physical examination:

BP: ……
Weight/BMI: ……
Body habitus: ……
Mobility: …….

Prevention:

Requires smoking and substance use cessation advice: Y ☐; N ☐
Requires obesity management (target BMI ≤31 for genital surgery): Y ☐; N ☐
Requires cardiovascular risk assessment: Y ☐; N ☐
Requires cervical cytology or HPV screening: Y ☐; N ☐; N/A ☐
(Include recommendations in report to GP)

Consent:

Patient has capacity to give meaningful informed consent to treatment: Y ☐; N ☐
Consent form completed; by doctor: Y ☐; N ☐; by patient: Y ☐; N ☐

Appendix 2

Guidance for physical and laboratory monitoring of persons receiving feminising hormone therapy

The following information is provided in leaflet form to both GPs and patients.

Before initiating treatment: Please perform assays of estradiol, testosterone, prolactin, FSH, LH, liver function, full blood count and a fasting glucose and lipid profile.

After commencing treatment with gel preparations: Please perform the same assays after use of treatment for at least two weeks. The blood sample should be drawn 2-4 hours after gel application; on the day of the blood draw, gel should only be applied to thighs, not arms, as it might otherwise contaminate the skin at the venepuncture site and give inaccurate results.

After commencing treatment with tablet and patch preparations: Please perform the same assays after use of treatment for at least two weeks. The timing of blood tests is not important.

Subsequently:

a. Please adjust the dose of estradiol in order to achieve a level within the ranges recommended below

b. The target range for testosterone is 3.0nmol/L or less; once this is achieved, an estradiol in the range 200-600pmol/L is acceptable

c. If, despite achieving an estradiol level within the range 400-600pmol/L, testosterone level remains greater than 3.0nmol/L, we usually recommend the addition of a gonadotrophin releasing hormone analogue (Decapeptyl SR 11.25mg injection every three months) to the treatment regimen, in order to suppress testosterone production

d. Please recheck estradiol , testosterone, LH and prolactin about four weeks after a dose adjustment

e. If prolactin rises above the laboratory reference range, please repeat and send us both reports

Longer-term monitoring: once testosterone and estradiol are stable within the reference range, please check estradiol, testosterone, prolactin, liver function, and fasting glucose and lipid profile every six months for next two years and then annually thereafter; omit testosterone if the patient is receiving a GnRH analogue or has had bilateral orchidectomy

In addition:

- Please check weight and blood pressure measured every six months
- Please ensure that trans women receiving estradiol are included in NHS mammography screening for breast cancer from the appropriate age and are offered breast awareness advice
- There is no requirement for prostate screening or routine assessment of bone mineral density in the absence of specific risk factors

Please inform us of any out-of-range, unexpected or unusual findings.

Guidance for physical and laboratory monitoring of persons receiving virilising hormone therapy

The following information is provided in leaflet form to both GPs and patients.

Before initiating treatment: Please perform assays of estradiol, prolactin, FSH, LH, liver function, full blood count and a fasting glucose and lipid profile.

After commencing treatment with gel preparations: Please check testosterone and haematocrit four weeks and three months after initiation of treatment. Once target is achieved, please recheck testosterone, haematocrit, liver function tests, and fasting blood sugar and lipid profile every three months for the first year, every six months for two years and annually thereafter. The blood sample should be drawn 2-4 hours after gel application; on the day of the blood draw, gel should only be applied to thighs, not arms, as it might otherwise contaminate the skin at the blood draw site, producing inaccurate results.

After commencing treatment with Nebido injection: Please check haematocrit four weeks and three months after initiation of treatment. Then, please check testosterone, haematocrit, liver function tests, and fasting blood sugar and lipid profile immediately before giving the fourth Nebido injection, and then annually thereafter, immediately prior to administration of a scheduled injection.

If menstruation does not cease within 3 months of treatment initiation, please check FSH, LH and estradiol, inform us of the continued menstruation and send the assay results to The Laurels.

Long-term monitoring: once testosterone is established within the treatment target range of 14 to 28nmol/L, please check testosterone, haematocrit, liver function tests, and fasting blood sugar and lipid profile every year for next two years and then annually thereafter; with Nebido, please take the blood sample immediately prior to administration of a scheduled injection

In addition:

- Please check weight and blood pressure measured every six months
- There is a risk of developing polycythaemia (haematocrit >0.52) with testosterone therapy. Switching to gel and/or modification of dosage may reduce this risk. If haematocrit exceeds 0.56, seek prompt advice from The Laurels and from a haematologist; venesection may be required
- Once menstruation has ceased for six months, an unexplained recurrence of vaginal bleeding requires investigation; please seek guidance from The Laurels if you become aware of this
- Patients with a uterine cervix should be offered cytology or HPV screening, or advised to discuss it with the medical staff at The Laurels
- There is no requirement for routine assessment of bone mineral density

Please inform us of any out-of-range, unexpected or unusual findings.

Appendix 3

a) Manieri C, et al (2014). **Medical Treatment of Subjects with Gender Identity Disorder: The Experience in an Italian Public Health Center.** International Journal of Transgenderism, 15:53–65, 2014

ABSTRACT. Hormonal treatment is the main element during the transition program for transpeople. The aim of this paper is to describe the care and treatment of subjects, highlighting both the endocrine/metabolic effects of the hormonal therapy and the quality of life during the first year of cross-sex therapy in an Italian gender team. We studied 83 subjects (56 male-to-female [MtF], 27 female-to-male [FtM]) with hematological and hormonal evaluations every 3 months during the first year of hormonal therapy. MtF persons were treated with 17βestradiol and antiandrogens (cyproterone acetate, spironolactone, dutasteride); FtM persons were treated with transdermal or intramuscular testosterone. The WHO Quality of Life questionnaire was administered at the beginning and 1 year later. Hormonal changes paralleled phenotype modifications with wide variability. Most of both MtF and FtM subjects reported a statistically significant improvement in body image ($p < 0.05$). In particular, MtF subjects reported a statistically significant improvement in the quality of their sexual life and in the general quality of life ($p < 0.05$) 1 year after treatment initiation. Cross-sex therapy seems to be free of major risks in healthy subjects under clinical supervision during the first year. Selected subjects show an optimal adaptation to hormone-induced neuropsychological modifications and satisfaction regarding general and sexual life. [LoE/SR: 3b]

b) Pimenoff V and Pfafflin F (2011). **Transsexualism: Treatment Outcome of Compliant and Noncompliant Patients.** International Journal of Transgenderism, 13:37–44, 2011

ABSTRACT. The objective of the study was a follow-up of the treatment outcome of Finnish transsexuals who sought sex reassignment during the period 1970–2002 and a comparison of the results and duration of treatment of compliant and noncompliant patients. Fifteen male-to-female transsexuals and 17 female-to-male transsexuals who had undergone hormone and surgical treatment and legal sex reassignment in Finland completed a questionnaire on psychosocial data and on their experience with the different phases of clinical assessment and treatment. The changes in their vocational functioning and social and psychic adjustment were used as outcome indicators. The results and duration of the treatment of compliant and noncompliant patients were compared. The patients benefited significantly from treatment. The noncompliant patients achieved equally good results as the compliant ones, and did so in a shorter time. A good treatment outcome could be achieved even when the patient had told the assessing psychiatrist a falsified story of his life and sought hormone therapy, genital surgery, or legal sex reassignment on his own initiative without a recommendation from the psychiatrist. Based on these findings, it is recommended that the doctor-patient relationship be reconsidered and founded on frank cooperation. [LoE/SR: 4c]

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Note on level of evidence and strength of recommendation annotation

Level of evidence and strength of recommendation were assessed by John Dean.

Level of evidence was graded using the *Centre for Evidence-Based Medicine LOE 2* (March 2011) system.

Strength of recommendation was graded using the *Strength of Recommendation Taxonomy* (SORT) system