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[Intervention Protocol]

Antiandrogens or estradiol treatments or both during hormone replacement therapy in transitioning transgender women

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objective of this proposed systematic review and meta-analysis is to assess the efficacy and safety of hormone replacement therapy with antiandrogens or estradiol or both in transitioning transgender women.

BACKGROUND

Description of the condition

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5, DSM-5 2013) describes gender dysphoria as a "marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or, in young adolescents, the anticipated secondary sex characteristics)
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or, in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
3. A strong desire for the primary and/or secondary sex characteristics of the other gender
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

The condition is associated with clinically significant distress or impairment in social, occupational or other important areas of functioning" (Zucker 2016).

There is a growing trend towards depsychopathologisation of transsexuality (Drescher 2014; ATME 2015). This means that worldwide, experts agree that transsexuality/gender dysphoria is not a psychiatric disorder (WPATH 2011). For instance, the new International Classification of Diseases (ICD, 11th Revision) no longer views transsexuality as a behavioural and personality disorder, but has instead drafted the term "gender incongruence" (Drescher 2014).

However, depsychopathologisation has made it increasingly difficult to select trial populations based on classic psychiatric diagnostic concepts (Drescher 2014; ATME 2015), and to make estimations of prevalence; only rough estimations are available (WPATH 2011; Garcia 2014; Hess 2014). In addition, the recent acceptance of gender variant phenomena, such as non-binary or genderqueer genders, makes an exact differentiation difficult. In parallel, there is ongoing development of terminology for possible spectral variability of the condition (Richards 2016). Thus, there are currently numerous labels applied to this group, such as gender identity disorder, transsexualism, transgenderism, gender dysphoria, transidentity, queer, bigender and non-binary genders. Due to the variation in self-labelling by the affected people themselves, as well as the lack of evidence-based studies and systematic diagnostic reviews (i.e. those fulfilling the criteria of Leeflang 2010), it is advantageous to adopt pragmatic differentiation criteria rather than to follow current diagnostic categories. These problems in differentiation and labelling, along with obstacles that transsexual people face in their lives, also make an estimation of prevalence difficult. However, studies and surveys suggest a prevalence of male-to-female (MTF) transsexuality of around 0.001% (Pauly 1968), to 0.6% (Joseph 2017), depending on time and location.

Transition from one gender to another is a critical phase with specific treatment, that differs fundamentally from later maintenance care, after the gender transition has been achieved. During the transition phase a balance between surgical and non-surgical interventions needs to be found. Currently there is uncertainty about the value of hormone therapy as a sole intervention or when combined with surgery. This proposed systematic review and meta-analysis focuses on 'transgender women in transition from male to female', a definition meant to include anyone starting with a sex that is commonly perceived as male with the goal to adapt their gender expression to something commonly and/or individually perceived as female. To meet these criteria, it is sufficient that the person undergoing a transition process be under appropriate medical and psychological care for monitoring outcomes.

Description of the intervention

Current guidelines suggest a combination of medical and surgical methods to treat gender dysphoria in transgender women. Hormone replacement therapy (HRT) aims to suppress the development of male attributes or reverse male attributes that have already developed. At the same time, the development of female attributes is supported. Where the HRT is not expected to be successful, which can be the case for facial bone structure, breast development and genitalia, surgical methods and techniques for permanent hair removal and hair transplantation may be used for further approximation of the body to a female body type (WPATH 2011).

The guidelines of the working group led by Wyley C Hembree suggest treatment with both oestrogens and antiandrogens. Oestrogens can be administered as either oral oestrogen, transdermal estradiol patches, or by injection of estradiol valerate or estradiol cypionate. The application frequency differs depending on the patient's reaction to the agent and the administration regimen; it could be multiple times per day or once every two weeks. Meanwhile, antiandrogens such as spironolactone or cyproterone acetate are commonly taken orally. Additionally, it is possible to block male puberty by treatment with gonadotropin-releasing hormone (GnRH) agonist injections. (Hembree 2017).

While not every transgender woman undergoes HRT in her transition, this intervention is still widely used (Hembree 2017). We know of no studies identifying the ratio of patients who undergo HRT, nor do we know of studies investigating how much time passes between the start of transition (respectively the decision to transition) and the start of HRT. We also know of no studies on how often androgens are being prescribed in addition to or instead of 17-beta-estradiol, how often they are being taken, or which kinds of androgens are in use besides cyproterone acetate (CPA) and spironolactone.

How the intervention might work

Several hormonal substances and combinations are used clinically for HRT in transitioning women. Cyproterone acetate is a progestin, steroidal anti-androgen and anti-gonadotropin that blocks the receptors for testosterone (T) and dihydrotestosterone (DHT), and thereby prevents these steroidal hormones from exerting their androgenic effects. Hence, it stops processes like body hair growth, hair loss on the head, male body fat distribution and others (Figg 2010; WPATH 2011). According to the World Professional Association for Transgender Health (WPATH) guidelines, it is possible to suppress puberty with GnRH analogues or progestins such as medroxyprogesterone (WPATH 2011).

Spironolactone acts as a weak androgen receptor antagonist (Wenqing 2005). It also causes an increase in oestradiol levels (Rose 1977), so that further virilisation is prevented and feminisation occurs (WPATH 2011).

17-beta-estradiol is used to feminise the external appearance (WPATH 2011). It binds to oestrogen receptors and thus ensures gene expression, which in turn feminises appearance (Hye-Rim 2012). In addition, estradiol suppresses gonadal testosterone production via the control systems of the hypothalamus (Hayes 2000).

For feminisation therapy, whose goal is to adapt the physical appearance and the experience of the body to a female model (by inducing breast growth, softening facial features, and inducing other physical changes commonly regarded with a feminine appearance) (WPATH 2011), the use of oral or transdermal oestrogen is recommended, and therapy with oestrogen in combination with antiandrogens is most common. Cotreatment with antiandrogens minimises the required dose of oestrogen, and thereby reduces the supposed risks of oestrogen identified in previous studies (Schürmeyer 1986; Prior 1989). Some antiandrogens are approved by WPATH - such as spironolactone, cyproterone acetate, GnRH analogists like goserelin, and 5alpha-reductase inhibitors like finasteride - but there is no mention of recommended dosages (WPATH 2011).

Why it is important to do this review

Antiandrogens like cyproterone acetate and spironolactone are prescribed to transgender women in transition by many gynaecologists and endocrinologists (Schneider 2006; Flütsch 2015), and they are commonly considered to be valuable drugs to support transition (WPATH 2011; Hembree 2017). However, clinical evidence suggests that this can result in adverse events; for example, CPA has significant potential for causing depression and for worsening depressive symptoms (Seal 2012). We cannot rule out that CPA contributes to the genesis of other conditions and negatively influences the course of illnesses, including psychiatric, neurological and metabolic disorders (Griard 1978; Ramsay 1990; Oberhammer 1996; Giltay 2000; Calderón 2009; Bessone 2015). The most common adverse events of spironolactone are hyperkalaemia, dehydration and hyponatraemia (Greenblatt 1973). Furthermore, spironolactone might have an influence on anxiety behavior (Fox 2016).

The adverse events of high estradiol doses described in studies from the 1980s and 1990s should be re-evaluated because those studies used ethinyl estradiol and premarin (equine estradiol) (Prior 1989), instead of bioidentical 17-beta-estradiol, and progestins instead of bioidentical progesterone. Unlike the bioidentical alternatives used today, substances administered in the past (e.g. equine oestrogens, ethinyl estradiol) were associated with diverse adverse effects like thrombophilia, cardiovascular problems, breast and prostate cancer, as well as liver, adrenal gland and neural dysfunction (Griard 1978; Calderón 2009; Asscheman 2011).

The health risks attributed to estradiol doses high enough to suppress androgens have not been found in the parenteral or transdermal application of bioidentical estradiol. Thus it is unclear why those estradiol doses should be kept low in order to make the addition of androgen antagonists like CPA or spironolactone necessary.

In light of the latest discussions among experts (Seal 2012; Wierckx 2014), and current recommendations for hormonal gender affirmation treatment (WPATH 2011) - which are strongly based on the values and preferences of health consumers - trials that show positive outcomes in the case of MTF, such as feminisation, satisfactory sexual function, reduced gender dysphoria, and high quality of life must be re-evaluated (e.g. Murad 2010).

In 2009, the overall quality of evidence relating to these outcomes was classified as low (Hembree 2017). In 2011, WPATH summarised: "There is a need for further research on the effects of hormone therapy without surgery, and without the goal of maximum physical feminisation or masculinisation" (WPATH 2011). It is necessary to determine whether subsequent trials have provided additional evidence for efficacy, or whether there is still a lack of evidence for these desired outcomes.

OBJECTIVES

The objective of this proposed systematic review and meta-analysis is to assess the efficacy and safety of hormone replacement therapy with antiandrogens or estradiol or both in transitioning transgender women.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), quasi-RCTs and cohort studies, with no restrictions based on language of publication, date of publication, or publication status.

We have chosen to include quasi-RCTs and cohort studies due to the low prevalence of the condition and the consequent current scarcity of RCTs (WPATH 2011).

Types of participants

We will include studies that enrol adult transgender women in transition from male to female. Transitioning is defined as the process of changing one's gender profile or sexual characteristics (or both) to accord with one's sense of gender identity (WPATH 2011). Transition as a concept thus encompasses several aspects, e.g. social, psychological, or physical aspects, or a combination of these. There is consistency in the literature on when the transition begins: namely, with the decision to change a person's gender assignment (Brown 1996). We will not differentiate between any supposed phases of the respective transitions. Depending on the personal situation, the process of transition (which may include the decision to transition, gathering of information, gathering of experience, medical treatment and change of social role), can take

very different periods of time, usually several months to years. Therefore, it is difficult to distinguish certain 'phases' of this process. However, when focusing on hormone therapy, the transition term can be more precisely defined: the transition process lasts as long as the patient is in the process of approaching the physiological adaptation goals (WPATH 2011).

We will include studies with participants aged 16 and older because, according to currently applied guidelines, this is the age where patients start being treated with hormone replacement therapy. Patients below this age are usually being treated with puberty blockers, which are outside the scope of this review (WPATH 2011).

For this review, we will only consider studies with a population using hormone-based interventions. Psychotherapeutic or surgical interventions (or both) may or may not be performed within the context of the studies.

Types of interventions

We will consider the following experimental interventions.

- Antiandrogens (cyproterone acetate or spironolactone) and estradiol
- Antiandrogens (cyproterone acetate or spironolactone) alone
- Estradiol alone

For the above interventions, we will consider all types of administration: oral, sublingual, transdermal, subdermal and intramuscular. For estradiol, we will also consider bioidentical 17-beta-estradiol, as well as synthetic derivatives.

We will consider the following comparator interventions.

- Any of the active interventions listed above
- Placebo (although we consider placebo-controlled studies to be unethical (Bostick 2008), we will include them in this review so that we can consider the evidence in its entirety)

We will not consider interventions consisting purely of psychological, spiritual, or similar treatment such as conversion therapy (Olson 2016).

Types of outcome measures

Primary outcomes

- Quality of life (QoL) as measured by validated generic instruments, e.g. Quality of Life Inventory (QOLI; Frisch 2005), or specific instruments, e.g. for body image the Body Image Quality of Life Inventory (BIQLI; Cash 2004), or for sexual life the Sexual Satisfaction Scale for Women (SSS-W; Meston 2005).
- Satisfaction with change of male to female body characteristics, as measured with validated instruments.
- Adverse events specific to hormone replacement therapy (HRT), including serious adverse events.

Secondary outcomes

- Severity of gender dysphoria/gender incongruence, e.g. as measured with the Utrecht Gender Dysphoria Scale (UGDS; Schneider 2016).
- Measures of specific body changes, including:
    - breast size, e.g. by measurement of bust girth;
    - skin thickness, e.g. by echographic measurement (Laurent 2007);
    - skin sebum production, e.g. as measured by three-hour sebum collection with absorbent paper (Downing 1981; Giltay 2008; Ezerskaia 2016); and
    - hair growth, including hair density, diameter, growth rate and anagen/telogen ratio (Giltay 2000; Hoffmann 2013).
- Incidence or severity of depression.

We will not include surrogate outcomes, such as serum hormone levels (e.g. 17-beta-estradiol or testosterone). While they can help with monitoring the progress of HRT, they are of little interest alone, especially since individuals require varying levels of these hormones to achieve a certain level of feminisation (Gooren 2017).

For studies with repeated follow-up (i.e. reporting of outcomes at multiple time points), we will regard follow-up at three to six months as short term, six months to two years as medium term, and more than two years as long term (WPATH 2011).

All studies that meet the criteria for type of study, participants, intervention and comparator will be included in the descriptive section of the review, regardless of outcomes reported or missing data.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases for relevant trials.

- MEDLINE via PubMed
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Embase
- Biosis Preview
- PsycINFO
- PSYNDEX

Our search strategy is outlined in Appendix 1. We have successfully tested the screening methods for abstracts and titles.

Searching other resources

We will also search the reference lists of included studies retrieved by the electronic search in order to find additional relevant studies. It is also possible that there are relevant studies that are yet to be published. To identify these, we will search the scientific abstracts of the last two meetings of each of the following organisations.

- American Association of Clinical Endocrinologists
- American Society of Andrology
- Berufsverband der deutschen Endokrinologen (Professional Association of the German Endocrinologists)
- Berufsverband der Frauenärzte e.V. (Professional Association of the Gynecologists)
- Dachverband Reproduktionsbiologie und Medizin e.V. (Federal Association Reproductive Biology and Medicine)
- Deutsche Gesellschaft für Endokrinologie (German Society for Endocrinology)
- Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (German Society for Gynecology and Obstretics)
- Endocrine Society
- European Society of Gynaecological Oncology
- European Thyroid Association
- Nordrhein-Westfälische Gesellschaft für Endokrinologie und Diabetologie (North Rhine-Westphalian Society for Endocrinology and Diabetology)
- Royal College of Obstetricians and Gynaecologists
- Society for Endocrinology
- Society for Gynecologic Investigation

We will also search the following grey literature databases.

- The New York Academy of Medicine Grey Literature Report (www.greylit.org/)
- OAIster (www.oclc.org/oaister.en.html)
- OpenGrey (www.opengrey.eu/)

Finally, in order to identify completed but unpublished or ongoing studies, we will search the following trial registries.

- ClinicalTrials.gov (www.clinicaltrials.gov/)
- metaRegister of Controlled Trials (mRCT; www.controlledtrials.com/mrct/)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (www.who.int/trialsearch/)
- Drugs@FDA (www.accessdata.fda.gov/scripts/cder/drugsatfda/)
- European Public Assessment Reports (EPAR; www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp)

We will seek to contact the manufacturers of hormonal agents and experts in the field to identify unpublished or ongoing trials.

Data collection and analysis

Selection of studies

We will use the reference management tool Covidence to identify and remove potential duplicate records of relevant studies (www.covidence.org). Two review authors (AKU and CHA) will independently scan titles and abstracts of the remaining records to compile a list of potential papers to be included in the final review. Then, the same review authors will investigate the references in detail (as full-text articles or map records to studies), and sort into 'included studies', 'excluded studies', 'studies awaiting classification' and 'ongoing studies.' This task will be executed in accordance with the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If there are discrepancies or if a consensus cannot be reached, a third review author will adjudicate (MHE). If the disagreement still cannot be resolved, we will designate the study as 'awaiting classification' and contact the study authors for clarification. We will list studies excluded during the full-text stage, and document the reasons in the excluded studies table. We will include an adapted PRISMA flow diagram outlining the study selection process (Moher 2009).

Data extraction and management

Two review authors (HHA and AKU) will independently extract data from all studies deemed eligible for inclusion, with the help of a standardised data extraction form that we will pilot test according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will use Google Spreadsheets to manage all data gathered.

We will collect data on the following items.

- General information on the study: first author, date of publication, study dates, publication type (full-text, abstract, unpublished), citation.
- Study methods: study design (e.g. parallel, factorial), number of study arms, study setting (single institution, multi-centre national, multi-centre international), study location, and length of follow-up.
- Participant characteristics: study inclusion/exclusion criteria, age (mean/median with range), ethnic distribution, number of participants randomised and included in analysis, participants lost to follow-up.
- Interventions: type of hormonal agents (for example cyproterone acetate (CPA), estradiol, progesterone, spironolactone), dose, administration route, dosing schedule and any other associated therapies. We will extract data on the sample size for each intervention group.
- Outcomes: definition and method of assessment for each outcome (including the adverse event classification system used in individual studies), as well as any relevant subgroups. We will extract the number of events and participants per treatment group for dichotomous outcomes. We will also extract the mean, standard deviation or median and range, and number of participants per treatment group for continuous outcomes.
- Study funding sources.
- Declarations of potential conflicts of interest reported by study authors.

For each included study, we will extract the outcome data relevant

for this review and required for the calculation of summary statistics and measures of variance. If there are disagreements, we will resolve them by discussion. If necessary, we will consult a third review author. We will provide key information about potentially relevant ongoing studies, including trial identifiers, in the table of 'Characteristics of ongoing studies'. We will attempt to contact authors of included studies to obtain missing key data if needed.

Assessment of risk of bias in included studies

Two review authors (MHE, HHA, or SBA) will independently examine all included studies to assess risk of bias (assessment of methodological quality). We will use the Cochrane tool for assessing risk of bias in randomised controlled trials, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will resolve disagreements by consensus or by consulting a third review author (AK). Our summary judgement will include a rating (low, high or unclear risk of bias) for each domain (Higgins 2011b). We will assess the risk of bias for the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other bias

We will evaluate the risks of performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment) separately for each outcome.
For any relevant cohort studies we identify, we will use the ROBINS-I tool to assess risk of bias (Sterne 2016).
We will assess each individual study as listed in the 'Risk of bias' tables and document the results using a spreadsheet. We will document the reasons of our judgements, and include relevant quotations from the full-text articles or from information about the study provided by authors in the notes section of the 'Risk of bias' tables. We will summarise the risk of bias across domains for each outcome in every included study, as well as across studies and domains for each outcome.

Measures of treatment effect

Dichotomous data

We will summarise dichotomous data using risk ratios (RRs), reported with 95% confidence intervals (CIs).

Continuous data

When standard measures are used for reporting continuous measures, we will summarise the obtained data as mean differences (MDs) with 95% CIs. For continuous outcomes without a standard measure, we will summarise data as standardised mean differences (SMDs) with 95% CIs. Alternatively, if the mean value and variance are missing, we will estimate them using the methods described in Hozo 2005, which allow estimations for mean value and variance of a sample when only the median, range and size of the sample are known. We will also consider the guidance in the *Cochrane Handbook* where appropriate (Higgins 2011c).

Unit of analysis issues

We will treat recurring events in individual participants as a single event occurring in one participant (i.e. three episodes of major depressive disorder in one participant will be recorded as one participant with major depressive disorder).
We do not expect to include studies with interventions given on the cluster level.

Dealing with missing data

For studies with missing data, we will follow the recommendations of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d). We will collect dropout rates for each study group and report these in the 'Risk of bias' table. Our preferred option will be to contact study authors in cases of missing data or statistics that are not due to participant dropout. (e.g. missing statistics such as standard deviation (SD)). If missing outcome data are not provided, then we will attempt to impute data where possible and appropriate, and conduct sensitivity analyses to assess the effect of this on the analysis. However, where imputation is not appropriate, we will not include the study in the respective meta-analysis, and will discuss the potential impact of this in the text of the review. In the case of participants lost to follow-up, we will perform meta-analyses on an intention-to-treat basis. We will perform sensitivity analyses, excluding studies with missing outcome data, to evaluate the impact of missing data.
We will discuss the potential impact of missing data on review findings in the 'Discussion' section of the full review, using a summary table if appropriate.

Assessment of heterogeneity

We will compare the characteristics of included studies to identify heterogeneity of content or methodology, and to determine the feasibility of performing a meta-analysis. We will deem meta-analysis as unsuitable in cases where there is substantial content-related or methodological heterogeneity across studies. Instead, we will use a narrative approach to data synthesis. Where meta-analysis is deemed appropriate, we will assess statistical heterogeneity by

visually inspecting the scatter of individual study effect estimates on forest plots and by calculating the I^2 statistic (Higgins 2011c), which gives the percentage of variability in effect estimations that can be attributed to heterogeneity rather than to chance. We will consider an I^2 of more than 50% to represent substantial heterogeneity. In the case of statistical heterogeneity, we will conduct the prespecified subgroup and sensitivity analyses described below to investigate the source.

Assessment of reporting biases

If we include 10 or more studies that investigate a particular outcome, we will use funnel plots to assess small-study effects and publication bias. Given that several explanations are possible for funnel plot asymmetry, we will interpret results carefully (Sterne 2011).

Data synthesis

We will provide a narrative summary of the included studies. We will also conduct a direct meta-analysis of all relevant outcomes from RCTs where possible, using data from studies that 1) compare the actual HRT-relevant agents or combinations of agents to placebo, and 2) compare the actual HRT-relevant agents or combinations of agents to other HRT-agents or combinations of agents. Studies comparing two variations on the intervention will be pooled separately to studies comparing the intervention to placebo. However, if there is significant variability in the definition of outcomes across trials, we may decide not to pool data at all. We will summarise outcome data from cohort studies (e.g. change scores) narratively.

Where meta-analysis is conducted, we will use the Mantel-Haenszel approach to combine dichotomous data and calculate RRs with 95% CIs (Higgins 2011c). For continuous outcomes (e.g. quality of life) we will calculate MDs or SMDs, with 95% CIs, using the inverse variance approach.

If studies report the same outcome measure but some report data for the change from baseline (e.g. mean values and standard deviations) and others for final measurements of outcomes, they will be placed in subgroups in the meta-analysis and pooled according to the *Cochrane Handbook* (Higgins 2011c).

For meta-analyses, we will use a random-effects model because we expect the true effects to be related, but not the same, across all studies. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual study (Riley 2011). In addition, we will perform statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook* (Higgins 2011c).

Subgroup analysis and investigation of heterogeneity

Wherever possible, we will consider subgroup analyses that are structured by the following characteristics.

- Type of application of intervention (oral, transdermal, intramuscular, subcutaneous)
- Orchiectomy before or during HRT

The justification for these analyses is as follows. It has been discussed that the intended outcomes of the intervention will be achieved less satisfactorily with increasing age at the beginning of transition (Leinung 2013). Accordingly, differentiation by age group could have an effect on outcomes. Secondly, pharmacokinetic mechanisms lead to significant differences in the absorption and metabolism of an active substance depending on the type of application. Therefore, we will, if possible, form appropriate subgroups based on the application method of the intervention. Finally, the endocrine system of patients who have undergone an orchiectomy could lead to different outcomes than those of patients with comparable HRT and testicles (Defreyne 2017).

Sensitivity analysis

We will conduct sensitivity analyses to investigate any potential effect of removing studies judged to be at high risk of bias from meta-analyses. We will classify studies as being at high risk of bias overall if one or more domains are judged to be at high risk. If appropriate, we will also conduct sensitivity analyses excluding studies with missing outcome data, or where missing data have been imputed by the review author team. We will also conduct a sensitivity analysis to compare a fixed-effect model to a random-effects model where the studies in a meta-analysis appear more homogeneous than expected.

'Summary of findings' table

Following standard Cochrane methodology, we will create a 'Summary of findings' table for all three Primary outcomes. Also following standard Cochrane methodology, we will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. OvidSP search strategy

Search	Query
#1	(transsexual* OR transgender OR "gender dysphoria" OR transident* OR "trans women" OR "trans woman").mp
#2	("cyproterone acetate" OR CPA OR androcur).mp. or cyproterone Acetate/
#3	(spironolactone OR Aldactone OR Jenaspiron OR Osyrol OR Spirobene OR Verospiron OR Xenalon).mp. or spironolactone/
#4	(estradiol* OR oestradiol* OR estrifam OR gynocadin OR neofollin OR lenzetto).mp. or Estradiol/
#5	2 OR 3 OR 4
#6	1 AND 5

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
Task	**Who has agreed to undertake the task?**

(*Continued*)

Draft the protocol	Claudia Haupt, Alexia Kutschmar, Miriam Henke, Birgit Hauser, Sandra Baldinger, Gerhard Schreiber
Develop a search strategy	Claudia Haupt, Alexia Kutschmar, Miriam Henke
Search for trials (usually 2 people)	Miriam Henke, Alexia Kutschmar, Sandra Baldinger
Obtain copies of trials	Miriam Henke, Birgit Hauser, Sandra Baldinger
Select which trials to include (2 people + 1 arbiter)	Claudia Haupt, Alexia Kutschmar, Birgit Hauser, Sandra Baldinger
Extract data from trials (2 people)	Claudia Haupt, Alexia Kutschmar
Enter data into Review Manager 5	Claudia Haupt, Miriam Henke, Alexia Kutschmar, Birgit Hauser, Gerhard Schreiber
Carry out the analysis	Claudia Haupt, Miriam Henke, Alexia Kutschmar, Birgit Hauser, Gerhard Schreiber
Interpret the analysis	Claudia Haupt, Miriam Henke, Alexia Kutschmar, Birgit Hauser, Sandra Baldinger, Gerhard Schreiber
Draft the final review	Claudia Haupt, Miriam Henke, Alexia Kutschmar, Birgit Hauser, Sandra Baldinger, Gerhard Schreiber
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DECLARATIONS OF INTEREST

Claudia Haupt declares no competing interest.

Miriam Henke declares no competing interest.

Alexia Kutschmar declares no competing interest.

Birgit Hauser (BH) declares no competing interest. BH is a clinical practitioner in private practice, who also prescribes hormone therapy.

Sandra Baldinger declares no competing interest.

Gerhard Schreiber declares no competing interest.

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