



# City Research Online

## City St George's, University of London

**Citation:** Philippou, Y. A., Steggall, M. J., Treacy, C. L., Hirani, S. P., O'Driscoll, S., Bakker, C. J. & Dahm, P. (2016). Penile rehabilitation for post-prostatectomy erectile dysfunction. Cochrane Database of Systematic Reviews, 2016(11), :CD012414.. doi: 10.1002/14651858.cd012414

This is the published version of the paper.

This version of the publication may differ from the final published version. To cite this item please consult the publisher's version.

**Permanent repository link:** <https://city-ref-test.eprints-hosting.org/id/eprint/16651/>

**Link to published version:** <https://doi.org/10.1002/14651858.cd012414>

**Copyright and Reuse:** Copyright and Moral Rights remain with the author(s) and/or copyright holders. Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge, unless otherwise indicated, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way. For full details of reuse please refer to [City Research Online policy](#).



**Cochrane**  
**Library**

**Cochrane** Database of Systematic Reviews

## **Penile rehabilitation for post-prostatectomy erectile dysfunction (Protocol)**

Philippou YA, Steggall MJ, Treacy CL, Hirani S, O'Driscoll ST, Bakker CJ, Dahm P

Philippou YA, Steggall MJ, Treacy CL, Hirani S, O'Driscoll ST, Bakker CJ, Dahm P.

Penile rehabilitation for post-prostatectomy erectile dysfunction.

*Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD012414.

DOI: 10.1002/14651858.CD012414.

**[www.cochranelibrary.com](http://www.cochranelibrary.com)**

## TABLE OF CONTENTS

|                                    |    |
|------------------------------------|----|
| HEADER . . . . .                   | 1  |
| ABSTRACT . . . . .                 | 1  |
| BACKGROUND . . . . .               | 1  |
| OBJECTIVES . . . . .               | 3  |
| METHODS . . . . .                  | 3  |
| ACKNOWLEDGEMENTS . . . . .         | 7  |
| REFERENCES . . . . .               | 7  |
| APPENDICES . . . . .               | 9  |
| CONTRIBUTIONS OF AUTHORS . . . . . | 10 |
| DECLARATIONS OF INTEREST . . . . . | 11 |
| SOURCES OF SUPPORT . . . . .       | 11 |

# Penile rehabilitation for post-prostatectomy erectile dysfunction

Yiannis A Philippou<sup>1</sup>, Martin J Steggall<sup>2</sup>, Colm L Treacy<sup>3</sup>, Shashi Hirani<sup>4</sup>, Stephen T O'Driscoll<sup>5</sup>, Caitlin J Bakker<sup>6</sup>, Philipp Dahm<sup>7,8</sup>

<sup>1</sup>Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK. <sup>2</sup>Faculty of Life Sciences and Education, University of South Wales, Pontypridd, UK. <sup>3</sup>Faculty of Health, Social Care and Education, Kingston University and St George's University of London, London, UK. <sup>4</sup>School of Health Sciences, City University London, London, UK. <sup>5</sup>Information Services, City University London, London, UK. <sup>6</sup>Health Sciences Libraries, University of Minnesota, Minneapolis, Minnesota, USA. <sup>7</sup>Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA. <sup>8</sup>Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA

Contact address: Yiannis A Philippou, Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headington, Oxford, OX39DU, UK. [yp227@doctors.org.uk](mailto:yp227@doctors.org.uk).

**Editorial group:** Cochrane Urology Group.

**Publication status and date:** New, published in Issue 11, 2016.

**Citation:** Philippou YA, Steggall MJ, Treacy CL, Hirani S, O'Driscoll ST, Bakker CJ, Dahm P. Penile rehabilitation for post-prostatectomy erectile dysfunction. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD012414. DOI: 10.1002/14651858.CD012414.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

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

To assess the effects of penile rehabilitation interventions for post-prostatectomy erectile dysfunction.

## BACKGROUND

Prostate cancer is the most common non-skin cancer in men in the UK, accounting for about 23% of all new diagnoses and 13% of deaths (or about 35,000 new diagnoses and 10,000 deaths each year) in England and Wales (Bolland 2008). In the US, it accounts for 186,320 new diagnoses and 28,660 deaths each year and is the second leading cause of mortality in men (Jamal 2008; Goluboff 2013). Early stage prostate cancer is essentially a symptomless disease, particularly if the disease is confined to the prostate. For organ-confined prostate cancer, treatment options with curative intent include radical retropubic prostatectomy (RRP), robotic-assisted radical prostatectomy (RARP), brachytherapy, and external beam radiation therapy with or without concomitant hormone

treatment. Active surveillance of prostate cancer also falls into the category of treatments with curative intent. This treatment approach consists of an active decision not to treat the prostate cancer at the time of diagnosis but rather to monitor the patient closely to enable the proper timing of curative treatment, taking into account the patient's life expectancy. It is advocated by European and American urological guidelines in patients with low risk organ-confined prostate cancer (Heidenreich 2014). Radical prostatectomy (RP) has the potential to completely remove the tumour and remains a preferred and effective treatment modality utilised as a first option in approximately 33% of prostate cancer cases and in 52% of cases in men aged ≥ 62 years of age (Lalong-Muh 2012; American Cancer Society 2014). In 2010 in the US alone,

11,290 prostatectomies were performed, two-thirds of which were robotic-assisted. These figures compared to the data from 2004, when 6188 prostatectomies were performed, of which only eight per cent were robotic-assisted, suggests that RP rates have risen exponentially since the introduction of RARP (Lowrance 2012).

The common side-effects of RRP include erectile dysfunction (ED) and urinary incontinence (Bolland 2008). Despite attempts to preserve the neurovascular bundles with nerve-sparing surgery, ED remains common. Even with nerve-sparing surgery, there is a period of neuropraxia during which the man has no spontaneous erections, which can lead to penile hypoxia and long-lasting damage to the erectile tissue (Burnett 2005; Raina 2010). It is difficult to predict the length of time that neuropraxia will last, with some researchers suggesting it is between 9 and 24 months (Zippe 2001). A goal of ED management is therefore to restore blood flow (and oxygenation) to the penis at an early stage, with the hope of preventing irreversible neuropraxia and penile shortening, and hastening the recovery or preservation of pre-treatment erectile function.

Post-operative penile rehabilitation has now become an integral part of patient management after RP. First line strategies include the use of phosphodiesterase type 5 inhibitors (PDE5Is) alone or in combination at different strengths and dosing frequencies. Other modalities include injectable medications, medicated urethral systems for erections and vacuum pumps.

## Description of the condition

ED is defined as the inability of a man to achieve and maintain an erection of sufficient strength for satisfactory sexual activity (NIH Consensus Conference 1993). The incidence of ED reported in the literature after radical prostatectomy (RP) varies dramatically from 20% to 90% (Fowler 1993; Rabbani 2000; Stanford 2000; Kundu 2004; Rozet 2005; Penson 2008; Alemozaffar 2011). The discrepancy in the reported rates of erectile function after RP is due to many factors. These include variations in study population demographics, means of data acquisition, variability in questionnaire use, duration of postoperative follow up, variations in baseline erectile function status, inconsistency in defining adequate erectile function, surgical technique, and the definition of quality and consistency of erection (Mulhall 2009). ED can have a major impact on the individual's self-esteem, quality of life, confidence, and life satisfaction, causing depression in certain cases (Kubin 2003). Quantifying accurately the prevalence of ED after RP is of utmost importance in evaluating the burden of this treatment-related adverse effect, in order to set appropriate expectations and facilitate medical decision making. In a recent analysis, Mulhall 2009 identified 24 studies which originated from major cancer centres and reported ED recovery outcomes post RP, in large patient cohorts. In these studies, the mean overall rates of erectile function recovery were 48%  $\pm$  25% (range 12% to 96%). When

nerve sparing was accounted for, as it was in 14 (58%) of the 24 articles reviewed, mean erectile function recovery rates were 50%  $\pm$  24% for bilateral and 34%  $\pm$  16% for unilateral nerve-sparing surgery.

## Description of the intervention

Penile rehabilitation following RP revolves around the use of medications (alone or in combination) and/or devices to preserve erectile tissue health (Mulhall 2010). The treatment options include: phosphodiesterase type 5 inhibitors (sildenafil citrate; tadalafil; vardenafil) 'as required' or daily dosing (tadalafil); alprostadil preparations (prostaglandin E1, such as Viridal Duo or Caverject as injectables, or Medicated Urethral System for Erections (MUSE) as urethral pellets), and vacuum erection or vacuum constriction devices (VED/VCD) (Steggall 2011; Weyne 2015). These interventions have been used singly or in combination, either pre-surgery or following successful trial without catheter following surgery, and at different strengths, dosing frequencies and combinations, to attempt to identify the most suitable option to prevent or limit neuropraxia, recover erections and restore sexual activity.

## How the intervention might work

The main pathophysiological mechanism which underlies the development of ED after RP is damage to the cavernosal nerves. Damage to these nerves occurs either due to their complete transection during non-nerve-sparing procedures or due to neuropraxia which commonly occurs during nerve-sparing RP. Neuropraxia is defined by the transient block of nerve transmission despite an anatomically intact nerve, caused in this case by direct trauma, stretching, heating, ischaemia and local inflammation (Fode 2013). The direct effect of loss of cavernosal nerve function causes a reduction in the oxygenation of penile tissues. This results in loss of smooth muscle due to apoptosis (Kendirci 2006), impaired veno-occlusive function, collagen accumulation, and ultimately penile fibrosis (Hatzimouratidis 2009; Kacker 2013). Collectively these physiological changes result in ED and penile shortening.

Surgical intervention is known to induce hypoxia in a time-dependent manner, such that the potential for recovery of erectile function decreases with time. The goal of early intervention with penile rehabilitation strategies is to improve the oxygenation of cavernosal tissue during the period of neuropraxia, to prevent uninhibited deterioration of penile tissues and to minimise (if not abrogate) the adverse structural and physiological changes that occur in the penis following RP. Penile rehabilitation also ensures that the patient is well-placed to regain pre-surgery erectile function and not remain dependent on erectile aids following surgery (Burnett 2013; Segal 2013). Oral PDE5 inhibitors (PDE5Is), by virtue of

their ease of use, are often considered as the mainstay of ED management. They are generally well-tolerated, have proved to be relatively safe and are the preferred treatment post-prostatectomy in some centres. Nevertheless, there are a number of men with post surgery ED, who do not respond to PDE5Is, or who become less responsive and less satisfied as treatment progresses. In some men, PDE5Is are contraindicated by virtue of the use of nitrate medication and the risk of consequent hypotension. Apart from the oral PDE5Is, the other options for management of post-prostatectomy ED (including MUSE and intracavernosal injections (ICIs)) are invasive, uncomfortable, unappealing and sometimes ineffective for some patients. Whilst PDE5Is may be appealing as they appear 'easy' to use, there are limited data examining whether PDE5Is aid penile rehabilitation in a time dependent manner, which is critical as men often prefer to manage their incontinence before their erections, and if treatment is not introduced early, there is a risk of penile atrophy that will make the recovery of erections more problematic.

### Why it is important to do this review

ED is a common adverse event of RP and it significantly affects quality of life. Effective, convenient and well-tolerated penile rehabilitation interventions are important to minimise the incidence of ED after RP. Over the years a multitude of different penile rehabilitation strategies have been introduced which aim to improve the oxygenation of penile tissues during the period of neuropraxia that inevitably follows RP. Several randomised controlled trials have been published which address the question of whether these treatment modalities (alone or in combination) are of any benefit in reducing the incidence of ED after RP. The purpose of this review is to systematically evaluate these treatment options and combinations to identify whether these interventions can recover erections and restore sexual activity in addition to improving other important clinical outcomes such as quality of life (QOL). Our further aim is to compare, where evidence exists, different treatment modalities to determine which of these treatments may be most beneficial to patients suffering from post-prostatectomy ED. This may help in the creation of a step-wise management approach for patients with ED.

## OBJECTIVES

To assess the effects of penile rehabilitation interventions for post-prostatectomy erectile dysfunction.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomised controlled trials (RCTs) with a parallel or cross-over design, and quasi-randomised controlled trials. In the case of cross-over trials, only results from the first treatment arm (if available) will be utilised in order to exclude any carry-over effects (Elbourne 2002). Due to the nature of the review question, we will not consider cluster-RCTs.

#### Types of participants

Male participants (aged 18 years or over), receiving radical surgical intervention for clinically organ-confined prostate cancer (cT1 or T2, N0 and M0) irrespective of disease risk status. We will also consider patients with T3 disease who were treated by radical prostatectomy (RP) alone and received no other form of adjuvant or neoadjuvant therapy. We will consider all surgical approaches of RP such as radical retropubic prostatectomy (RRP), radical perineal prostatectomy, laparoscopic prostatectomy and RALP, irrespective of the nerve-sparing status. We will exclude patients who have had RP as a salvage procedure following failed primary therapy with another treatment modality.

We will also exclude patients who were administered androgen deprivation therapy (ADT) or salvage radiotherapy due to biochemical recurrence following RP. We will only include patients who had erectile function sufficient for intercourse prior to surgery, as documented by an International Index of Erectile Function (IIEF) score. We define these patients as those who have IIEF or IIEF-5 scores within the mild or no erectile dysfunction range (IIEF  $\geq 19$  and IIEF-5  $\geq 17$ ). We have chosen these baseline IIEF scores as they include patients with mild and no erectile function which we consider as having erectile function sufficient for intercourse. Patients also need to have a heterosexual partner and be sexually active. We will focus on men in heterosexual relationships since it has been reported that anal intercourse requires 33% greater penile rigidity (Gebert 2014). We will permit inclusion of studies in whom a small subset of patients (less than 10%) do not meet the IIEF or IIEF-5 score entry criterion as defined above, but we will consider the outcome data from these studies in a separate stratified analysis.

#### Types of interventions

We plan to investigate the following experimental versus comparison interventions.

#### Experimental interventions

1. Phosphodiesterase type 5 inhibitors (PDE5Is) - sildenafil, vardenafil and tadalafil 'as needed'

2. PDE5Is - tadalafil 2.5mg or 5mg daily
3. PDE5Is - sildenafil or vardenafil daily
4. Prostaglandin E1 (alprostadil) administered as intracavernosal injections (ICIs)
5. Prostaglandin E1 (alprostadil) administered intraurethrally - Medicated Urethral System for Erections (MUSE) and Vitaros (alprostadil topical cream)
6. Vacuum erection devices (VEDs) or vacuum constriction devices (VCDs)
7. Combination treatments (e.g. PDE5Is and VEDs)

### Comparator interventions

8. Placebo or no intervention/observation

### Primary comparisons

For the primary outcomes of interest we will compare interventions one to seven versus eight; where studies exist comparisons will be made between the different interventions listed from one to seven.

If appropriate studies are identified, we will report the secondary subgroup comparisons of interventions one to eight.

We will include studies of psychological interventions only if these are offered in combination with pharmacological interventions, or are received by patients in both the intervention and control groups.

### Types of outcome measures

We will only consider trials with a minimum follow-up of six weeks.

### Primary outcomes

1. Number or percentage of patients achieving self-reported potency after RP defined as an erection firm enough and of sufficient duration to have sexual intercourse at six, 12 and 24 months;
2. Number or percentage of patients achieving potency after RP according to IIEF and IIEF-5 scores at six, 12 and 24 months. For the IIEF-5 questionnaire, potency is defined as a score  $\geq 17$  (out of 25) points. For the standard formal IIEF questionnaire this is defined as a score of  $\geq 19$  (out of 30 points);
3. Rate of participants who suffered at least one serious adverse event using an erectile aid (using the NCI Common Terminology Criteria for Adverse Events (CTCAE) reporting; grades 3 to 5).

### Secondary outcomes

1. Acceptability of the intervention (whether acceptable/ convenient to use by the patient) evaluated by Treatment Acceptability Questionnaires (TAQ);

2. Rates of treatment discontinuation;
3. Quality of life and health-related quality of life using validated questionnaires such as EDITS (Erectile Dysfunction Inventory of Treatment Satisfaction) or QSF (Quality of Sexual Function);

To assess the efficacy of these agents to potentially improve the recovery of erectile function, patients of both groups being compared need to be receiving no additional treatment for erectile function or the same treatment (for example the same type and dosage of a PDE-5 inhibitor).

### Main outcomes for 'Summary of findings' table

We will present a 'Summary of findings' table reporting the following outcomes listed according to priority.

1. Patients achieving self-reported potency at six months
2. Patients achieving self-reported potency at 12 months
3. Patients achieving self-reported potency at 24 months
4. Patients achieving potency according to IIEF and IIEF-5 scores at six months
5. Patients achieving potency according to IIEF and IIEF-5 scores at 12 months
6. Patients achieving potency according to IIEF and IIEF-5 scores at 24 months
7. Participants who suffered at least one serious adverse event (grades 3-5)

### Search methods for identification of studies

#### Electronic searches

We will search for relevant references in:

- PubMed
- MEDLINE
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- CINAHL
- Embase
- PsycINFO

A list containing relevant search terms and search strategies (for each database) will be generated separately. An exemplar search strategy (MEDLINE via OvidSP) is provided in [Appendix 1](#). The search will be performed without language or data restrictions. The search will be re-run within 12 months after publication and include newly-identified studies in a further analysis.

The search terms used reflect the three components to our research question:

- A) interventions for ED;
- B) ED variants;
- C) RP for organ-confined prostate cancer.

The following search logic will be used:

- A) Interventions for ED: both controlled vocabulary and key-word searching related to drug interventions, including generic,

chemical and brand names for pharmaceuticals listed in [Types of interventions](#) section, as well as controlled vocabulary and keyword searching for vacuum therapy and alternative interventions, as described in the [Types of interventions](#) section. This will include variant terms and common abbreviations.

B) ED variants: both controlled vocabulary and keyword searching related to erectile dysfunction and impotency, as well as the converse (erectile function and potency) to avoid bias. Proximity searching for sexual and quality of life, satisfaction, function, dysfunction, and other like terms will be incorporated to account for all possible variations on ED.

C) RP for organ-confined prostate cancer: keyword and controlled vocabulary searching for prostatectomy will be combined with keyword and controlled vocabulary searching for prostatic neoplasms.

### Searching other resources

- We will examine the reference lists of relevant obtained articles, systematic reviews, and clinical practice guidelines, to check for additional related published and unpublished studies.
- The Conference Proceedings Citation Index (available through the Web of Science database) will be searched. Additionally, specific conference proceedings for the British Association of Urological Surgeons (BAUS); European Association of Urology (EAU); and American Urological Association (AUA) will also be searched (from 2008 onwards). We have selected 2008 as a cut-off as most conference proceedings are made available on international urological associations' websites from 2008 onwards.
- Consensus papers and proceedings from specialist meetings (e.g. Sexual Function Health Council of the American Foundation for Urologic Disease), will also be searched.
- We will contact experts in the field to enquire about any relevant clinical trials or journal articles that are not listed in other sources.
- We will also contact drug manufacturers, to enquire about any relevant trials or journal articles that are not listed in other sources.

Additionally, the following central registers of clinical trials will be searched to identify any unpublished, ongoing or proposed new trials:

- WHO International Clinical Trials Registry ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/))
- Current Controlled Trials ([www.controlled-trials.com/](http://www.controlled-trials.com/))
- UK Clinical Research Network Portfolio Database ([public.ukcrn.org.uk/search/](http://public.ukcrn.org.uk/search/))
- UK Clinical Trials Gateway ([www.ukctg.nihr.ac.uk/default.aspx](http://www.ukctg.nihr.ac.uk/default.aspx))
- ClinicalTrials.gov register ([www.clinicaltrials.gov/](http://www.clinicaltrials.gov/))
- Current Controlled Trials (ISRCTN Register) ([www.controlled-trials.com/mrct/](http://www.controlled-trials.com/mrct/))

- ClinicalStudyResults.org ([www.clinicalstudyresults.org](http://www.clinicalstudyresults.org))

## Data collection and analysis

### Selection of studies

We will use Covidence to identify and remove potential duplicate records. Two review authors (YP, MS) will independently scan the abstract, title, or both, of remaining records retrieved, to determine which records should be assessed further. Two review authors (YP, MS) will investigate all potentially-relevant records as full text, map records to studies, and classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will resolve any discrepancies through consensus or recourse to a third review author (CT or PD). If resolution of a disagreement is not possible, we will designate the study as 'awaiting classification' and we will contact study authors for clarification. We will document reasons for exclusion of studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. Studies will be included regardless of whether outcomes are reported in a useable way. We will present an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

### Data extraction and management

Data will be extracted independently and in duplicate for each trial/study by the authors (YP, MS). A data abstraction form based on the standardised Cochrane data extraction form will be used. We will also pilot test the data abstraction form in advance to confirm its usability.

For studies that fulfil inclusion criteria, two review authors (YP, MS) will independently abstract the following information, which we will provide in the 'Characteristics of included studies' table:

1. Study design;
2. Study dates (or report if these were not made available);
3. Participant details and baseline demographics;
4. Inclusion and exclusion criteria;
5. Number of participants by study/study arm;
6. Details of the intervention such as timing and dosage;
7. Definitions of outcomes, details of outcomes and how/when they were measured, as well as any relevant subgroups;
8. Study funding sources;
9. Declarations of interest by the investigators.

We will resolve any disagreements regarding study characteristics or outcome measures by discussion, or if required, by consultation with a third review author (CT or PD).

## Assessment of risk of bias in included studies

The Cochrane tool for assessing risk of bias (Jüni 2001; Higgins 2011b) will be used to objectively assess the included studies. We will judge the risk of bias on an outcome-specific basis as 'low risk', 'high risk' or 'unclear risk' for each of the following individual items:

1. Sequence generation (selection bias);
2. Allocation concealment (selection bias);
3. Blinding of participants and personnel (performance bias);
4. Blinding of outcome assessors (detection bias);
5. Incomplete outcome reporting (attrition bias);
6. Selective outcome reporting;
7. Other biases.

Each 'Risk of bias' determination will be made by three independent members of the investigative team who will reach consensus by discussion and if necessary, arbitration by an additional team member. We will summarise these findings in a 'Risk of bias' table with the justification for the findings made transparent, including information which is obtained outside of the publication, such as from direct contact with the authors.

## Measures of treatment effect

Where data are reported as dichotomous outcomes (e.g. achievement of potency), relative risk (RR) with 95% confidence interval (CI) will be generated to express effect size of recovery rate and ultimate recovery of erectile function, at various time points (three months, six months and 12 months following initiation of treatment regime) compared to no treatment or placebo, or between two different treatment modalities.

For outcome scales (e.g. 15-IEEF, 5-IEEF, EDITS scores), ordinal data will be assessed as continuous data. Mean differences will be calculated where a mean and a standard deviation are provided or can be generated. If different studies use different scales for the same outcome measure the standardised mean difference (SMD) will be calculated using Hedges' g.

## Unit of analysis issues

The unit of analysis will be the individual patient. In the case of multiple intervention groups in a single trial, we will combine groups to create a single pair-wise comparison; the approach recommended in the *Cochrane Handbook*.

## Dealing with missing data

To obtain additional/missing data not reported in the articles, we will contact the authors of papers. Where the data cannot be obtained from the authors, or if the data are conflicting or we are unable to pool the results, they will be discussed in view of the results obtained. For each included study, the number of drop-outs (including their characteristics and reasons for dropping out), exclusions from the analysis, or missing data, will be investigated and

reported. We plan to report an intention-to-treat analysis whenever possible. If the necessary data are not available, we will report an available case analysis, which we will label as such. We will not impute data.

## Assessment of heterogeneity

We will identify heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the  $I^2$  statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We will interpret  $I^2$  as follows.

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics. In the event of excessive heterogeneity unexplained by subgroup analyses, we will not report study results as the pooled effect estimate in a meta-analysis but will provide a narrative description of the results of each study.

## Assessment of reporting biases

Sources of publication bias will be investigated and graphically represented/summarised using standard methods (trial effect versus trial size), including funnel plots (after Egger 1997) if at least 10 studies report on a given outcome. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. We will therefore interpret results with caution (Sterne 2011).

## Data synthesis

Data from trials that are sufficiently similar and of sufficient quality will be combined to provide pooled effect estimates.

When meta-analysis would be considered inappropriate, only a narrative description of the study results will be provided.

Unless there is good evidence for homogeneous effects across studies, we will summarise data using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For dichotomous outcomes, we will use the Mantel-Haenszel method; for continuous outcomes, we will use the inverse variance method. We will use Review Manager (RevMan) software to perform analyses.

## Subgroup analysis and investigation of heterogeneity

We expect the following variables to be potential sources of heterogeneity and therefore plan to perform the following subgroup analyses to determine potential qualitative or quantitative interactions of the following subgroups with the effect estimate:

- Nerve-sparing approach (none versus unilateral or bilateral, partial or complete nerve-sparing) since it may affect the potential for recovery;
- Patient age (< 65 versus ≥65 years); older patients may have diminished recovery potential;
- Baseline erectile function scores (IIEF-5: 17 to 21 versus 22 to 25 or IIEF: 19 to 24 versus 25 to 30); patients with diminished baseline function may have diminished recovery potential.

Subgroup analyses of the nerve-sparing approach will be important to determine whether differences exist in effect estimate, if any, of penile rehabilitation strategies on erectile function recovery following RP between the subgroups. Age and baseline erectile function scores are important co-variables which can affect the degree of erectile function recovery offered by the penile rehabilitation strategies under investigation, and therefore it is important to evaluate these in separate subgroup analyses.

## Sensitivity analysis

We will perform a sensitivity analysis to assess the impact on the effect estimate of excluding studies rated to be of high or unclear risk of bias in terms of selection bias, performance bias or detection bias. In addition a sensitivity analyses will be performed if applicable to evaluate the impact on the effect estimate of excluding quasi-randomised controlled studies.

## 'Summary of findings' table

We will present the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Guyatt 2011). Two review authors (YP, PD) will independently rate the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low'; discrepancies will be resolved by consensus, or, if needed, by arbitration by a third review author (CT or PD). We will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Schünemann 2011). This will be accomplished in GRADEpro GDT. If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table. We plan to present all three primary outcomes in our 'Summary of findings' table.

## ACKNOWLEDGEMENTS

We are grateful to the editorial team of the Cochrane Urology Review Group for their help and support, especially Mrs. Molly Neuberger and Ms. Alea Miller.

## REFERENCES

### Additional references

#### Alemozaffar 2011

Alemozaffar M, Regan MM, Cooperberg MR, Wei JT, Michalski JM, Sandler HM, et al. Prediction of erectile function following treatment for prostate cancer. *JAMA* 2011;**306**(11):1205–14. [PUBMED: 21934053]

#### American Cancer Society 2014

American Cancer Society. Cancer treatment and survivorship facts and figures 2014-2015. Atlanta (GA) 2014.

#### Bolland 2008

Bolland W. Prostate cancer. *InnovAiT: The RCGP Journal for Associates in Training* 2008;**1**(9):642–50.

#### Burnett 2005

Burnett AL. Erectile dysfunction following radical prostatectomy. *JAMA* 2005;**293**(21):2648–53.

#### Burnett 2013

Burnett AL. Current rehabilitation strategy: clinical evidence for erection recovery after radical prostatectomy. *Translational Andrology and Urology* 2013;**2**(1):24–31.

#### Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629.

#### Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;**Feb**;**31**(1):140–149.

#### Fode 2013

Fode M, Ohl DA, Ralph D, Sonksen J. Penile rehabilitation after radical prostatectomy: what the evidence really says. *BJU international* 2013;**112**(7):998–1008. [PUBMED: 23826962]

**Fowler 1993**

Fowler FJ Jr, Barry MJ, Lu-Yao G, Roman A, Wasson J, Wennberg JE. Patient-reported complications and follow-up treatment after radical prostatectomy. The National Medicare Experience: 1988-1990 (updated June 1993). *Urology* 1993;**42**(6):622-9. [PUBMED: 8256394]

**Gebert 2014**

Gebert S. Are penile prostheses a viable option to recommend for gay men?. *International Journal of Urological Nursing* 2014;**8**(3):111-3.

**Goluboff 2013**

Goluboff ET, Wosnitzer M. Prostate cancer surveillance counterpoint: USA. In: Johnson, FE, Maehara Y, Browman GP, Margenthaler JA, Audisio RA, Thompson JF, et al. editor(s). *Patient Surveillance after Cancer Treatment*. New York: Springer, 2013:411-20.

**GRADEpro GDT [Computer program]**

GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 23 September 2016. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

**Guyatt 2011**

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [PUBMED: 21195583]

**Hatzimouratidis 2009**

Hatzimouratidis K, Burnett AL, Hatzichristou D, McCullough AR, Montorsi F, Mulhall JP. Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: a critical analysis of the basic science rationale and clinical application. *European Urology* 2009;**55**:334-47.

**Heidenreich 2014**

Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *European Urology* 2014;**65**(1):124-37. [PUBMED: 24207135]

**Higgins 2002**

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539-58.

**Higgins 2003**

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**:557-60.

**Higgins 2011a**

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

**Higgins 2011b**

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org) 2011.

**Jamal 2008**

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA: A Cancer Journal for Clinicians* 2008;**58**(2):71-96.

**Jüni 2001**

Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**(7303):42-6.

**Kacker 2013**

Kacker R, O'Leary MP. Penile rehabilitation after radical prostatectomy. *Trends in Urology & Men's Health* 2013; **September/October**:12-17.

**Kendirci 2006**

Kendirci M, Bejma J, Hellstrom WJG. Update on erectile dysfunction in prostate cancer patients. *Current Opinion in Urology* 2006;**16**(3):186-95.

**Kubin 2003**

Kubin M, Wagner G, Fugl-Meyer AR. Epidemiology of erectile dysfunction. *International Journal of Impotence Research* 2003;**15**(1):63-71.

**Kundu 2004**

Kundu SD, Roehl KA, Eggener SE, Antenor JA, Han M, Catalona WJ. Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. *Journal of Urology* 2004;**172**(6 Pt 1):2227-31. [PUBMED: 15538237]

**Lalong-Muh 2012**

Lalong-Muh J, Treacy C, Steggall M. Erectile dysfunction following retropubic prostatectomy. *British Journal of Nursing* 2012;**22**(4):S4-S9.

**Liberati 2009**

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):e1000100. [DOI: 10.1371/journal.pmed.1000100]

**Lowrance 2012**

Lowrance WT, Eastham JA, Savage C, Maschino AC, Laudone VP, Dechet CB, et al. Contemporary open and robotic radical prostatectomy practice patterns among urologists in the United States. *Journal of Urology* 2012;**187**(6):2087-92.

**Mulhall 2009**

Mulhall JP. Defining and reporting erectile function outcomes after radical prostatectomy: challenges and misconceptions. *Journal of Urology* 2009;**181**(2):462-71. [PUBMED: 19084865]

**Mulhall 2010**

Mulhall JP, Bella AJ, Briganti A, McCullough A, Brock G. Erectile function rehabilitation in the radical prostatectomy

- patient. *Journal of Sexual Medicine* 2010;7(4 (Pt 2)): 1687–98.
- NIH Consensus Conference 1993**  
NIH Consensus Conference. Impotence - Consensus Development Panel on Impotence. *Journal of the American Medical Association* 1993;270:83–90.
- Penson 2008**  
Penson DF, McLerran D, Feng Z, Li L, Albertsen PC, Gilliland FD, et al. 5-year urinary and sexual outcomes after radical prostatectomy: results from the Prostate Cancer Outcomes Study. *Journal of Urology* 2008;179(5 Suppl): S40–4. [PUBMED: 18405749]
- Rabbani 2000**  
Rabbani F, Stapleton AM, Kattan MW, Wheeler TM, Scardino PT. Factors predicting recovery of erections after radical prostatectomy. *Journal of Urology* 2000;164(6): 1929–34. [PUBMED: 11061884]
- Raina 2010**  
Raina R, Pahlajani G, Agarwal A, Jones S, Zippe C. Long-term potency after early use of a vacuum erection device following radical prostatectomy. *British Journal of Urology International* 2010;106(11):1719–22.
- Review Manager (RevMan) [Computer program]**  
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- Rozet 2005**  
Rozet F, Galiano M, Cathelineau X, Barret E, Cathala N, Vallancien G. Extraperitoneal laparoscopic radical prostatectomy: a prospective evaluation of 600 cases. *Journal of Urology* 2005;174(3):908–11. [PUBMED: 16093985]
- Schünemann 2011**  
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and ‘Summary of findings’ tables. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).
- Segal 2013**  
Segal RL, Bivalacqua TJ, Burnett AL. Current penile-rehabilitation strategies: clinical evidence. *Arab Journal of Urology* 2013;11:230–6.
- Stanford 2000**  
Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. *JAMA* 2000;283(3):354–60. [PUBMED: 10647798]
- Steggall 2011**  
Steggall MJ. Clinical management of erectile dysfunction. *International Journal of Urological Nursing* 2011;5(2):52–8.
- Sterne 2011**  
Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ (Clinical Research Ed.)* 2011;343:d4002. [DOI: 10.1136/bmj.d4002]
- Weyne 2015**  
Weyne E, Castiglione F, Van der Aa F, Bivalacqua TJ, Albersen M. Landmarks in erectile function recovery after radical prostatectomy. *Nature Reviews. Urology* 2015;12(5): 289–97. [PUBMED: 25868558]
- Wood 2008**  
Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;336(7644):601–5. [DOI: 10.1136/bmj.39465.451748.AD]
- Zippe 2001**  
Zippe CD, Raina R, Thukral M, Lakin MM, Klein EA, Agarwal A. Management of erectile dysfunction following radical prostatectomy. *Current Urology Reports* 2001;2(6): 495–503.
- \* Indicates the major publication for the study

## APPENDICES

### Appendix I. Exemplar search strategy - MEDLINE (via OvidSP)

1. Alprostadil/
2. "Prostaglandin E1".tw
3. alprostadil.tw
4. sildenafil.tw
5. viagra.tw
6. tadalafil.tw
7. cialis.tw
8. vardenafil.tw
9. levitra.tw
10. "penile rehabilitation".tw
11. "erect\$ rehabilitation".tw
12. "vacuum therapy".tw
13. "vacuum erection device\$.tw
14. VED.tw
15. "vacuum constriction device\$.tw
16. VCD.tw
17. exp Phosphodiesterase 5 Inhibitors/
18. (Phosphodiesterase adj1 "5 Inhibit\$").tw.
19. (Phosphodiesterase adj1 "V Inhibit\$").tw.
20. (PDE5 OR PDE-5 OR "PDE 5") adj1 inhibit\$.tw.
21. PDE5-I.tw
22. Muse\$.tw
23. ICI.tw
24. "intracavernosal injection\$.tw.
25. OR/1-24
26. exp Erectile Dysfunction/
27. "erectile dysfunction".tw
28. "erectile function".tw
29. ED.tw
30. impoten\$.tw
31. poten\$.tw
32. ((sex or sexual\$) adj3 (function\$ or dysfunc\$ or satisf\$ or problem\$ or symptom\$ or arous\$ or activ\$ or rehabilitation OR "quality of life\$)).tw.
33. OR/26-32
34. exp Prostatectomy/
35. Prostatectom\$.tw.
36. RP.tw
37. OR/34-36
38. exp Prostatic Neoplasms/
39. "prostate cancer".tw.
40. "prostat\$ neoplasm\$.tw.
41. CaP.tw.
42. OR/38-41
43. 37 AND 42
44. 25 AND 33 AND 43

## CONTRIBUTIONS OF AUTHORS

YP drafted the protocol.

MS conceptualised the review topic and drafted the protocol.

CT conceptualised the review topic and drafted the protocol.

SH provided methodological advice on statistical analyses and representation of summary data.

SO developed and ran the search strategy.

CB developed and ran the search strategy.

PD conceptualised the review topic, drafted the protocol and provided oversight.

## DECLARATIONS OF INTEREST

YP none.

MS none.

CT none.

SH none.

SO none.

CB none.

PD none.

## SOURCES OF SUPPORT

### Internal sources

- Minneapolis VAMC and UMN Department of Urology, USA.  
Protected research time

### External sources

- No sources of support supplied