psu
Priorities
Support Unit

NHS

Committee name:	South Central Priorities Committee: MOBBB
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Evaluation of treatments for erectile dysfunction

QUESTION FOR PRIORITIES COMMITTEES TO CONSIDER:
What is the evidence for clinical and cost effectiveness for treatments (oral medications, locally injectable drugs, vacuum erection devices and penile implants) for the treatment of adult males with erectile dysfunction (primary or secondary to underlying pathology / previous surgery)?

OPTIONS:

Phosphodiesterase type 5 inhibitors:
Funding for treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors is RECOMMENDED in view of the evidence of effectiveness and cost effectiveness.

Funding for treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors is RECOMMENDED for the groups identified in HSC 1999/177 with a maximum frequency of dosing of three times per month.

Funding for treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors is LOW PRIORITY.

Psychosexual interventions:
Funding for treatment of erectile dysfunction with psychosexual interventions is RECOMMENDED.

Funding for treatment of erectile dysfunction with psychosexual interventions is LOW PRIORITY in view of limited evidence for effectiveness and cost effectiveness.

Vacuum erection devices:
Funding for treatment of erectile dysfunction with vacuum erection devices is RECOMMENDED.

Funding for treatment of erectile dysfunction with vacuum erection devices is LOW PRIORITY in view of limited evidence for effectiveness and cost effectiveness.

Intracavernosal injections of prostaglandin E1:

Funding for treatment of erectile dysfunction with intracavernosal injections of prostaglandin E1is RECOMMENDED.

Funding for treatment of erectile dysfunction with intracavernosal injections of prostaglandin E1 is RECOMMENDED for the groups identified in HSC 1999/177 and those not responding to treatment with oral medications.

Funding for treatment of erectile dysfunction with intracavernosal injections of prostaglandin E1is LOW PRIORITY in view of limited evidence for effectiveness and cost effectiveness.

Penile implants:
Funding for treatment of erectile dysfunction with penile implants is RECOMMENDED.

Funding for treatment of erectile dysfunction with penile implants is RECOMMENDED for the groups identified in HSC 1999/177 and those not responding to treatment with oral medications and intracavernosal injections of prostaglandin E1.

Funding for treatment of erectile dysfunction with penile implants is LOW PRIORITY in view of limited evidence for effectiveness and cost effectiveness.

SUMMARY:

- Health service circulars from 1998 and 1999 restrict the NHS provision of treatments for ED to defined subgroups and set out a mechanism for the treatment to be prescribed and reimbursed on the NHS.
- NICE guidance on prostate cancer (CG 58) recommends that men and their partners have early and ongoing access to specialist services for erectile dysfunction.
- It is estimated that 33,000 men across South Central may need treatment for ED
- Evidence from Cochrane reviews and meta-analysis suggest that PDE-5 inhibitors (sildenafil, tadalafil and vardenafil) are effective in the treatment of ED, with a NNT of 2 for successful intercourse at 60% of attempts with sildenafil.
- The most common adverse events with sildenafil comprised vasodilatation (NNH 9), headache (NNH 10) and dyspepsia (NNH 31). The adverse event profile for all three PDE-5 inhibitors considered was similar.
- Evidence for the effectiveness of psychosexual interventions was weak, from systematic review of small trials of 16-70 patients. There was a wide variation in the type of therapy considered and the comparators used in the trials.
- The evidence for the intracavernosal injection of prostaglandin E1 comprised a systematic review in a population of men with spinal cord injury and from RCTs suggesting that this is as effective as PDE-5 inhibitors and effective in men unresponsive to PDE-5 inhibitors.
- Evidence for the effectiveness of vacuum erection devices comprised RCTs in patients who had undergone treatments for prostate cancer. This provided weak evidence for effectiveness in this population.
- Evidence for the effectiveness of penile prosthesis comprised case series that suggest this is an effective intervention but with high rates of complications. The literature suggests that about 10% of those undergoing penile implants need

removal or replacement of the implant, and published audit data suggests that this is much higher in UK clinical practice.
- Evidence of cost effectiveness is only available for sildenafil and suggests that this is a cost effective intervention.
- The current spend on oral drug treatments across South Central amounts to about £4.4 million and for penile implants about £82,000 excluding the cost of the implant.

1 Context

1.1 Introduction

Erectile dysfunction (ED) has been defined as an inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse. This is measured using the International Index of Erectile Function (IIEF) score, a self-administered patient questionnaire measuring all domains of sexual function with six of fifteen questions specifically measuring the domain of erectile function.
ED can be of psychogenic or organic cause. There are many conditions causing ED of organic origin, ranging from diseases of the vascular system (heart disease, arteriosclerosis, hypertension and diabetes); neurogenic diseases (multiple sclerosis, Parkinson's disease, spinal cord injury or tumours); and hormonal abnormalities. In addition some commonly used medications such as anti depressants, antihypertensives, diuretics and anticonvulsants; and surgical treatments notably surgery for prostate cancer and abdominal aneurysm repair, obesity, smoking and alcohol and substance misuse can also cause ED. ED secondary to other medications is usually reversible upon stopping the drugs responsible. In many cases however, the cause for ED cannot be determined and treatment is aimed towards addressing symptoms.

ED of psychological origin is treated with psychosexual counselling. Treatments of erectile dysfunction of any organic cause comprise oral medications (phosphodiesterase type 5 inhibitors), medications injectable into the penis, vacuum devices and surgery for penile implants. There has been a proliferation of treatments with the development of PD-5 inhibitor drugs and advancements in the design of penile prostheses. This has led to greater case finding and the development of treatment pathways. In addition iatrogenic causes of ED have also risen, particularly with increase in the diagnosis of prostate cancer and the use of radical treatments for this in men who are in otherwise good health.

1.2 Existing national and local policies and guidance

Following the introduction of sildenafil in 1998 a health circular issued by the secretary of state specified that drug treatments for ED (including intrapenile injections) would be available on the NHS only for specified conditions and suggested that frequency of dosing should be once a week. A further health circular in 1999 (1) restricted prescription of these drugs to patients not eligible for NHS treatment to specialist services in secondary care and added the criterion of 'significant distress'. This second health circular states that it is for guidance only and aims to share good practice. However, it established a mechanism so that prescriptions for treatments for ED secondary to conditions described in the health circular (as determined by the

prescribing doctor) are marked "SLS" allowing them to be dispensed on the NHS. This makes the health circular guidance a standard that is implemented. This has been implemented in Oxfordshire with a policy statement for drug treatment for erectile dysfunction (including vacuum erection devices).

NICE guidance on prostate cancer (CG 58) recommends that "Healthcare professionals should ensure that men and their partners have early and ongoing access to specialist erectile dysfunction services." There is no further detail in this document on the treatments or indications for treatment of ED.

2 Epidemiology

Although erectile dysfunction is a hidden condition, it is recognised as a common problem with an overall prevalence of around 10% throughout all ages.(2) The prevalence increases with age as well as with comorbid conditions such as cardiovascular diseases, diabetes, neurological diseases, and depression.(2,3)

A community-based observational study, the Massachusetts Male Aging Study (MMAS) reported prevalence of ED as 52% in men aged between 40-70 years old. In the same study, ED was strongly associated with treated heart disease and diabetes, with prevalences four and three times higher than in the general male population respectively.(4)

A recent study (5) reported that 50% of sufferers had not discussed it with anyone and of those who did discuss it with their general practitioner, no treatment was offered in 40% of cases. This suggests that about 60,000 men across the South Central PCTs might require treatment.

Data on incidence of ED in the general population is very limited. However the figure of about 26 cases per 1,000 men annually is quoted in one study(6) equating to about 33,000 men across the South Central PCTs.

3 The intervention

Assessment of ED: The International Index of Erectile Function (IIEF) is a self-administered patient questionnaire comprising 15 questions relating to all phases of sexual function. Six questions relate directly to ED comprising the erectile function domain (IIEF EF domain) while the others relate to other phases of sexual activity. Each question is scored from 0-5 with a higher score indicating better function. A score of 0 indicates no sexual activity. Questions 3 (patients' subjective assessment of probability of successful penetration) and 4 (patients' subjective assessment of the probability maintaining an erection during intercourse) of the IIEF questionnaire, a part of the IIEF EF domain are also used as primary outcome measures in studies.

Treatments for ED: ED is currently treated with oral medications, local injections of drugs into the penis, vacuum pump devices and surgery for penile implants.

Oral medications: These are phosphodiesterase type 5 inhibitors that increase relaxation of the vasculature of the blood vessels in the penis, leading to increased blood flow and an erection with sexual stimulation. Sildenafil (Viagra) was the first drug of this type, launched in 1998 and was followed by two other drugs tadalafil

and vardenafil. These are administered on an as required basis (not greater than once in 24 hours). Sildenafil needs to be taken 1 hour prior to sexual activity and requires some planning of sexual activity as a result. Vardenafil and tadalafil have different pharmaco-kinetics with a longer duration of action requiring less planning.

Local injections: Alprostadil is a prostaglandin that induces a dilatation of the blood vessels when injected into the penis, producing an erection.
Papaverine and phentolamine are unlicensed for use in ED and will not be considered in this paper.

Vacuum erection devices: These devices consist of a cylinder within which a negative pressure is created to induce blood flow into the penis and the erection obtained as a result is maintained by placing a constricting band around the base of the penis.

Surgical implantation of penile prosthesis: Surgery for erectile dysfunction entails the placement of an implant into the penis. There are several kinds of implants with the commonest being semi-rigid implants made of a malleable material and inflatable implants which require a reservoir of fluid that can be pumped into the penile implant to produce a rigid penis when required. Placement of both types of implants requires an incision into the tissues of the penis and the creation of a space into which the implant can be inserted. This then makes any other therapy for erectile dysfunction difficult.

4 Findings

4.1 Evidence of effectiveness

A standard PSU literature search was conducted, initially restricted to meta-analysis and systematic reviews and further expanded to include observational studies for psychosexual interventions, vacuum erection devices, intracavernosal injections and penile implants. Details of the search are presented in the appendix.

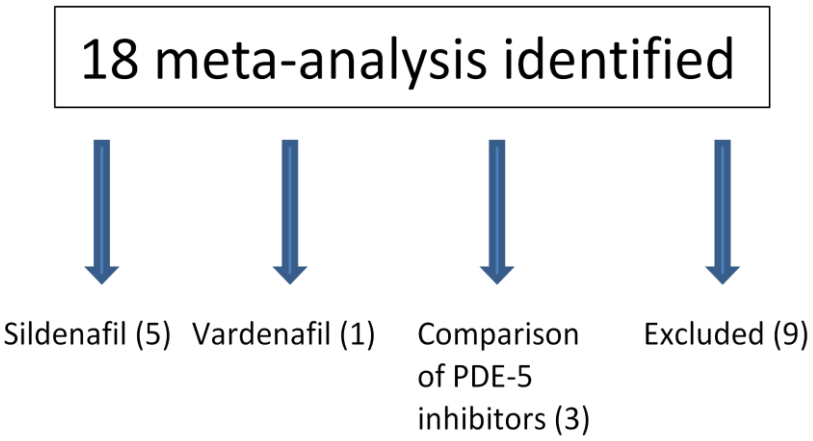
Phosphodiesterase type 5 (PDE-5) inhibitors:
Two Cochrane reviews of treatments for ED in population subgroups (in ED following treatments for cancer and in diabetes) were identified in the literature search. The Cochrane review of treatments for ED following treatments for cancer examined all treatments for the condition from a literature search extending to January 2007.(7) For PDE-5 inhibitors 6 trials were identified with all reporting an improvement of IIEF score with treatment. All trials assessed the global efficacy question (GEQ) and two trials could be combined to give a combined OR of 10.09 (6.20 – 16.43). A comparison of PDE-5 inhibitors was not possible in the studies identified in this review. The review concluded that despite the poor quality of evidence there is sufficient evidence for the use of PDE-5 inhibitors in the treatment of ED following treatments for cancer.

The second Cochrane review examined the use of PDE-5 inhibitors for the treatment of ED in men with diabetes.(8) The literature search extended to October 2005 (publication date 2009) for electronic databases and 2006 for the Cochrane library. Eight studies were included in this review with 1759 participants (976 receiving PDE-5

inhibitors). All trials compared PDE-5 inhibitors with placebo with no head to head trials. Only 3 trials described the randomisation method and only one described blinding. The weighted mean difference (WMD) for IIEF Q3 and Q4, available in five of eight studies was 0.9 (0.8-1.1) and 1.1 (1.0-1.2). The RR for the GEQ was 3.75 (3.12-4.51), indicating that patients were 3.75 times more likely to report that treatment improved their erections. A sensitivity analysis was conducted and the results were found to be significant. Based on two studies included in the review sildenafil was found to significantly improve the scores for sexual life but not for other domains of overall quality of life. The review concludes that PDE-5 inhibitors are clinically beneficial for the treatment of diabetic men with ED. This was a high quality Cochrane review, though restricted to the literature to 2005.

The literature search identified 6 meta-analyses of single PDE-5 inhibitors. Five of these compared sildenafil with placebo and one vardenafil with placebo. A further three meta-analyses of good quality were identified comparing sildenafil, vardenafil and tadalafil individually with placebo and comparing them (indirectly or directly) with each other. A further 9 meta-analyses were identified but were not included in the paper as they had methodological weaknesses such as pooled analysis, no documented search strategy, no documented selection criteria for the primary studies, no assessment of quality of primary studies, poor or no referencing of primary studies and no assessment of heterogeneity.

Figure 1: Selection of meta-analysis for effectiveness of PDE-5 inhibitors



For sildenafil alone compared with placebo Moore et al, found that sildenafil was significantly better than placebo in the percentage of men achieving successful intercourse at 40% and 60% of attempts with a number needed to treat (NNT) at 3 and 2 respectively.(9) The response showed a dose response relationship with best results with dose optimisation. For adverse events numbers needed to harm (NNH) were also estimated at 9 for vasodilatation, 10 for headache and 31 for dyspepsia. This was a well conducted meta-analysis but end points were different from most other studies which relied on the IIEF score (EF domain), IIEF Q3 and 4, and the GEQ. Fink et al also found a significant difference with sildenafil in the proportion of men with 40% and 60% successful attempts at intercourse and in the IIEF scores for Q3 and Q4.(10) This study also examined the effect in older age groups (>65) and found significant benefit with sildenafil though absolute IIEF scores were lower than in younger men.

For vardenafil, a single high quality meta-analysis by Markou et al was identified.(11) This showed that vardenafil in 10 and 20 mg doses was significantly better than placebo in IIEF-EF domain score and GEQ. There was no significant difference between the 10 mg and 20 mg doses.

For tadalafil, four meta-analysis were identified, all sponsored by the manufacturer and two of them reported by employees of the manufacturer and based on the same dataset, comprising a pooled analysis. All four of these had methodological weaknesses; unclear trial selection, no quality assessment of included studies, no assessment of heterogeneity or publication biases and an enriched enrolment (excluding those known to be unresponsive to other PDE-5 inhibitors), and were not considered further.

A further three meta-analyses of good quality evaluated the three PDE-5 inhibitors with placebo and compared the PDE-5 inhibitors for efficacy and adverse events. Moore et al, in an indirect comparison of PDE-5 inhibitors found all three drugs to be largely similar.(12) Berner et al also found no significant differences between the drugs on indirect comparison. Tsertvadze et al identified four direct comparisons, three of which were of poor quality and differences were either small or insignificant between drugs.(13)

Tsertvadze et al also conducted a meta-analysis of harms of sildenafil and identified headache, flushing, dyspepsia and visual disturbance as common but mild adverse events without a significant increase in severe adverse events.(14)

Table 1: Meta-analysis of effectiveness of sildenafil, vardenafil and tadalafil, compared with placebo and with active treatment with PDE-5 inhibitors.

Study	Patients	Intervention	Comparator	Outcomes	Comments
Tsertsvadze, 2009	Meta-analysis of harms including 49 RCTs with 12 – 586 participants and >70% of trials conducted in North America and Europe.	Sildenafil alone (fixed or flexible dose) and placebo.	Placebo	MA of harms only. Most frequent AEs were headache (RR=2.57), flushing (RR=4.99), dyspepsia (RR=3.00) and visual disturbance (RR=3.51). Overall AEs higher in Sildenafil group (RR=1.56, 95% CI 1.38-1.76). No significant difference in risks for serious AEs. Specific clinical sub-groups: Diabetes: single trial with non significant differences in AEs. Depression: 4 trials, significantly increased risk of flushing (RR=10.16, CI 1.93-53.35) and dyspepsia (RR=2.62, CI1.14-34.41) CVD: 4 trials showing higher risk of any AE (RR=1.34, CI 1.05-1.72, headache (RR=6.60, CI 2.32-18.74) and flushing (RR=9.21, CI 2.88-29.42). No significant difference in SAEs.	Well conducted SR and MA, though total patients in each arm for all outcomes not specified.
Moore, 2002	10 RCTs with 2123 men on sildenafil and 1131 on placebo. All trials sponsored by manufacturer.	Sildenafil 25-100 mg.	Placebo	% of men with 60% and 40% of attempts at intercourse successful: All doses significantly more effective than placebo, NNT for 60% of attempts successful was 2.7 (CI 2.3-3.2). NNT for 40% of attempts successful was 2.4 (CI 2.1-2.9) with dose optimisation. AEs: No significant difference in serious AEs at any dose. NNH for dyspepsia 31 (19-82), headache 9.8 (7.5-14) and vasodilatation 8.5 (6.7-11). Both efficacy and AEs showed a dose response relationship.	
Fink, 2002	27 RCTs with 4240 men in the sildenafil group and 2707 men in the placebo group. Only 2	Sildenafil	Placebo	Mean % of sexual intercourse attempts that were successful was significantly higher at 57% for sildenafil group compared with 21% for the placebo group.	

	trials adequately described randomisation and blinding.			Significantly higher proportion (83%) in the sildenafil group reported at least 1successful attempt compared with placebo group (45%) in the last 4 weeks of treatment. IIEF Q3: weighted mean for sildenafil group 3.8 vs 2.3 for placebo group (WMD 1.4, CI 1.3-1.5) IIEF Q4: weighted mean for sildenafil group 3.6 vs 2.1 for placebo group (WMD 1.5, CI 1.4-1.6). Subgroups by age and severity of ED showed significant improvement with sildenafil for those over 65 and with severe ED though absolute scores were lower. Adverse events: At least 1 AE: RR 1.4 (CI 1.3-1.6), 48% (sildenafil) vs 36% (placebo). Significantly higher risk of headache (11% vs 4%), flushing (12% vs 2%), dyspepsia (5% vs 1%) and visual disturbance (3% vs 0.8%) with treatment.	
Burls, 2001	21 trials identified from the literature search for SR, 16 included in MA.	Sildenafil in fixed or flexible dosage ranging from 5 mg to 200mg.	Placebo	Primary outcomes: IIEF Q3 and Q4 – Significant improvement with sildenafil with dose response relationship. GEQ showed significant improvement with sildenafil treatment, NNT=2. Sub-groups: Diabetes – two studies showed a significant improvement with sildenafil but magnitude of improvement was smaller than in those with ED of broad etiology. Spinal cord injury – two studies with a total of 205 men with reflex activity showed significant benefit comparable to those with broad spectrum etiology for ED.	
Montorsi, 2005	SR of efficacy of sildenafil for ED following radical prostatectomy. Limited literature search of	Sildenafil	Placebo	Pre-operative ED present in 25% of those undergoing non nerve sparing surgery compared with <15% in those undergoing nerve sparing surgery (2 studies). Significant heterogeneity present between	

	MEDLINE and CANCERLIT identified 11 suitable articles.			studies. Response rate to sildenafil following radical prostatectomy ranged from 14% to 53%	

Study	Patients	Intervention	Comparator	Outcomes	Comments
Markou, 2004	Comprehensive literature search with selection criteria identified 10 RCTs for inclusion. All identified papers were financially supported or had authors affiliated with commercial bodies. History of unresponsiveness was an exclusion criterion in 5 trials.	Vardenafil 5, 10 and 20 mg.	Placebo	Vardenafil in all doses was significantly better than placebo in the IIEF-EF domain score. Difference between 20 mg and 10 mg doses was not statistically significant. General assessment question showed a significant improvement for all vardenafil groups. AEs that occurred at least twice as often on vardenafil than on placebo were headache, flushing, rhinitis–sinusitis, and dyspepsia.	Overall a well conducted and good quality meta-analysis.
Study	**Patients**	**Intervention**	**Comparator**	**Outcomes**	**Comments**
Moore, 2005	50 RCTs (sildenafil 35, tadalafil 8 and vardenafil 7) with n=7077 for sildenafil, 2036 for tadalafil and 3274 for vardenafil). Five of the tadalafil and six of vardenafil studies excluded men previously unresponsive to PDE-5 inhibitors.	Sildenafil, tadalafil and vardenafil.	Sildenafil, tadalafil, vardenafil and placebo	Individual analysis: Sildenafil - Improved erections in 76% of men on sildenafil as compared with 23% on placebo, NNT 2 (1.8-2.0). NNH for adverse event withdrawals was 120 (67-560), NNH 4.9 for men reporting at least one adverse event. Vardenafil – NNT for improved erections 2.0 (1.9-2.2). NNH of 65 (37-250) for adverse event withdrawals and 8.0 (6.9-9.6) for flushing. Tadalafil – improved erections NNT 1.9 (1.8-2.1), NNH for adverse event withdrawals of 52 (29-260). Indirect comparison of PDE-5 inhibitors: All three PDE-5 inhibitors were largely similar.	Inadequate presentation of individual trial assessment. No measures of heterogeneity presented.
Berner, 2006	A total of 14 RCTs with a total of 4836 patients were selected based on	Sildenafil, tadalafil, vardenafil	Sildenafil, tadalafil, vardenafil, or	IIEF-EF domain score (weighted mean difference): Sildenafil – 9.65 (8.50 – 10.79), tadalafil – 8.52	Study assessment well presented with

	defined selection criteria. 3 for sildenafil, 8 for tadalafil and 3 for vardenafil.		placebo. Heterogeneity assessed.	(7.61 – 9.42) and vardenafil 7.50 (6.50 – 8.50). Indirect comparison: No significant difference between sildenafil and tadalafil and tadalafil and vardenafil but sildenafil was significantly better than vardenafil (p=0.132). Moderate evidence of publication bias.	tests for heterogeneity and publication bias.
Tsertsvadze, 2009	130 RCTs (sildenafil 72, vardenafil 27 and tadalafil 28) included in the meta-analysis. 4 RCTs directly comparing PDE-5 inhibitors used for direct comparison (all reporting patient preference). About half of vardenafil and a third of tadalafil trials used enriched enrolment (exclusion of those not responding to sildenafil).	Sildenafil, tadalafil, vardenafil	Sildenafil, tadalafil, vardenafil, or placebo. Heterogeneity assessed.	All PDE-5 inhibitors resulted in a significant improvement in IIEF-EF domain scores and IIEF Q3 and Q4 scores. Men with other medical conditions (DM, depression, CVD, prostate cancer, MS, colorectal cancer, schizophrenia, liver and renal failure) were significantly more likely to have an improvement with PDE-5 inhibitors. For men with severe ED absolute improvements were greater but had worse post treatment scores than man with less severe ED. PDE-5 inhibitor vs PDE-5 inhibitor. Direct comparisons were made in 4 trials with small or insignificant differences between treatments. The trials could not be pooled with three of the trials describes as low quality RCTs. Differences in adverse events between PDE-5 inhibitors were not significant.	Significant evidence of publication bias identified.

Summary of evidence of effectiveness of PDE-5 inhibitors:
The largest evidence base pertains to sildenafil as the first marketed drug for ED. The meta-analysis for all three drugs considered in this paper demonstrates the effectiveness of these drug treatments compared with placebo. Comparative effectiveness of the three drugs does not show any convincing difference in effectiveness of the three medications. The pharmaco-kinetic differences between the drugs make tadalafil and vardenafil more convenient for patients, requiring less planning of sexual activity.

Psychosexual interventions:
The Cochrane review of treatments for ED following treatments for cancer (7) found a single trial assessing sexual counselling with and without the female partner following radiotherapy for prostate cancer. Presence of the female partner made no significant difference in this study using the IIEF score. Counselling improved baseline IIEF score of men in both groups. Another trial assessed counselling in men using intracavernosal injections of prostaglandin E1 for ED following radical pelvic surgery or cystectomy. There was no difference in ED in those who received counselling compared with those who did not, though all of those receiving counselling completed the trial as compared with 71% of those who did not receive counselling. Another single small trial (n=15) of a male peer partner intervention showed no significant benefit of the intervention.

Melnik et al, 2008, conducted a systematic review and meta-analysis of psychological interventions for ED.(15) Trials were identified by a comprehensive well-described search. Psychological interventions varied greatly and were categorised as sex group therapy (comprising 8-16 sessions of therapy addressing sexual anxiety, education, communication, sexuality and pleasuring with homework assignments), modified Masters Johnsons therapy (a combination of education, homework assignments and counselling), educational intervention and systematic desensitisation. Most trials included men with predominantly psychogenic ED. Sample sizes were small, ranging from 16 to 70 across trials.

Group psychotherapy showed a significant improvement in the outcome of 'persistence of ED' compared with no treatment (RR=0.40, 0.17 – 0.98; n=100, NNT=2) in a meta-analysis of five trials. No significant differences were found with rational emotive therapy, systematic desensitisation, and modified Masters and Johnson technique. A single previous study by the same author found group therapy to be better than sildenafil and a combination of sildenafil and group therapy to be better than sildenafil alone. Single studies comparing sex therapy in addition to intra-cavernosal injection and vacuum devices found no significant differences while sex therapy was estimated to be 25% more expensive than intra-cavernosal injections.

Summary of evidence for psychosexual interventions:
Overall the Cochrane review finds insufficient evidence to establish the effectiveness of psychosexual counselling. The systematic review and meta-analysis comprise weak evidence of some additional benefits from group therapy for ED from inadequately described trials that have not been assessed for quality. The evidence relates to the use of psychosexual counselling in addition to other treatments for additional benefit but do not establish the benefits of counselling alone in improving ED.

Prostaglandin E1 (alprostadil)
Intracavernosal injections:
Alprostadil injected locally into the penis is used for the treatment of erectile dysfunction. A well-conducted systematic review of male ED following spinal cord injury by DeForge et al(16) (search date June 2003) found 8 non-comparative case series from which data could be pooled for injection of vasoactive substances into the penis (papaverine, phentolamine and alprostadil). The studies were from the US, Europe, Australia, India and China. A random effects pooled estimate of 'satisfactory erections' of 90% (83% - 97%) was derived. In addition a single small study (n=18) evaluated vacuum erection devices (VED) with phentolamine and found no difference in effect.

Literature search identified one study of the effectiveness of alprostadil in men with ED not responding to sildenafil. One RCT comparing effectiveness of alprostadil compared with sildenafil in men with arteriogenic ED, one RCT comparing intracavernous alprostadil and intraurethral alprostadil.

Shabsigh (2000)(17) evaluated intracavernosal alprostadil in 134 men with a score of 3 or less for either Q3 or Q4 of the IIEF and who were unresponsive to sildenafil in an open label study. Of the 134 men enrolled, 85 did not respond to sildenafil and 80 of these responded to a trial of alprostadil, with only 67 choosing to use this at home. Overall 62.7% of patients treated with alprostadil achieved a score of 4 or 5 to both questions 3 and 4 of the IIEF.

Shabsigh (2000)(18) reported a crossover RCT comparing alprostadil injection with intra-urethral instillation in 111 men with ED of mixed etiology. Patients were randomised initially to injections or intra-urethral instillation treatment, followed by crossover to the alternative treatment. Outcomes were assessed by patient and physician grading of the erections on a 0-4 point scale with 4 being the best score and IIEF scores. The study found that success rates were significantly higher with injections as assessed by patients and physicians. IIEF ED domain scores were also significantly better with alprostadil injections. In addition, following the study period when patients could choose the treatment they wished to continue with a significantly higher number chose to continue with injections.

Mancini (2004)(19) reported an RCT of alprostadil compared with sildenafil in a population of men with ED of arteriogenic origin. 35 patients with vasculogenic ED and 20 ED of other causes were randomised to receive alprostadil injections, sildenafil or placebo (oral tablet). Outcomes assessed were peak systolic velocity of blood flow in the penis as assessed by Doppler ultrasound scan and IIEF score. The study was apparently unblinded. Blood flow in the penis was significantly better with alprostadil and sildenafil, though how this correlates with a satisfactory sexual experience is not clear, particularly as the study also found a significant improvement in the IIEF score from baseline with both treatments but not in the placebo group.

Summary of evidence for effectiveness of intracavernosal injections of prostaglandin E1:
There is a small volume of evidence for the use of alprostadil injections for ED but the trial by Mancini suggests that alprostadil injections are comparable to sildenafil and

the study by Shabsigh suggests that alprostadil injections may be useful to patients unresponsive to oral medications.

Intra-urethral instillation

Literature search identified two studies of intra-urethral alprostadil for inclusion in this paper. The study by Shabsigh (2000)(18) has been discussed above and shows a greater effectiveness with injectable alprostadil than intraurethral instillation and a higher patient preference for injection treatment following the study period.

The second study McCullough (2010)(20) evaluated intraurethral alprostadil with sildenafil in the recovery of erectile function following radical prostatectomy in a randomised controlled trial (n=212). This was a well conducted RCT that did not show a significant difference between the two treatments for recovery of erectile function following radical prostatectomy. Compliance for sildenafil was higher (98%) than for intra-urethral alprostadil (79%).

Vacuum erection devices (VED):

The Cochrane review of treatments for ED following treatments for cancer(7) found a single trial for vacuum erection devices (VED) in a population of men who had undergone retropubic prostatectomy for prostate cancer (n=109). Eighty-one percent of those using the VED successfully had intercourse, with a significant difference in overall sexual function with VED and no significant difference between the two trial arms. Twenty three percent of those in the intervention group discontinued treatment, mostly due to discomfort or penile bruising.

The systematic review by DeForge(16) evaluating treatments for ED in a population of patients with spinal cord injury found a small case series of 20 men reporting good device efficacy and sex life satisfaction.

The literature search identified two randomised controlled trials evaluating the effectiveness of VED in a population of men with ED following radical prostatectomy.

A randomised controlled trial by Kohler,(21) (2007, USA) included 28 men with a pre-operative IIEF score of >11 undergoing unilateral or bilateral nerve sparing radical prostatectomy, randomised into an early intervention group (use of VED 1 month after surgery) and a delayed intervention group (use of VED 6 months after surgery). The method of randomisation is not described; however, the groups had no significant differences in baseline characteristics. Blinding of participants may not have been possible and blinding of assessors and researchers has not been reported. Both groups had similar IIEF scores pre-operatively and 1 month post-operatively and a significant difference in favour of the intervention group at 3 and 6 months (p=0.033 at 6 months). At last follow up (mean 9.5 months) there was no significant difference between the groups.

The second RCT by Raina (2005, USA)(22) included 109 consecutive men undergoing unilateral or bilateral nerve sparing radical prostatectomy with IIEF scores >15. They were randomised into a VED group (n=74) and a no treatment group (n=35). The method of randomisation and baseline characteristics of the two groups are not described. Blinding of assessors has not been described in the paper. 80% of patients in the VED group attempted to use their device. The study reports a significant improvement in mean IIEF 5 score of 4.83 points compared with the no treatment group. This would represent a substantial improvement in erectile function. Reasons

for discontinuation of VED use comprised discomfort (55%), penile bruising (20%), social inconvenience (17%) and inability to get an airtight seal (8%). This study was included in the Cochrane review discussed above.

No studies evaluating the use of VED in a general population of men with ED were identified.

Summary of evidence for the effectiveness of VED:
There is weak evidence for the benefit in ED with the use of VED from two methodologically limited RCTs, one of which has been considered in the Cochrane review. Both studies were conducted in men with ED following radical prostatectomy and no evidence for the use of VED in a general population of men with ED identified in the search.

Implantation of penile prosthesis:
The systematic review by DeForge(16) identified five case series of penile implants for ED alone or ED with urinary incontinence. The review concludes that penile implants are satisfactory for those who do not have complications but consistently across studies close to 10% had serious complications. Further implantation and removal of the implants are likely to have damaged penile tissues that would make them unresponsive to treatment with intracavernosal injections and VED.

The literature search identified 7 case series (Table 2) reporting effectiveness of penile implantation. These studies are limited in their methodology with only two prospective studies, a lack of comparators, diverse outcomes often not using standard scales such as the IIEF score. Overall these studies suggest a complication rate of up to 25% and a serious complication rate of up to 20%. At least 10% of implants need to be removed and/or replaced due to complications or malfunction. In addition, the study by Carson suggests that over 20% of those with a functioning prosthesis do not use it.

Table 2: Summary of case series reporting effectiveness of all types of penile prosthesis (malleable and inflatable)

	Patients	Intervention	Comparator	Outcomes	Comments
Montorsi, 2000	200 consecutive patients retrospectively included. Mean follow up 59 months (range 12 – 130 months)	Inflatable penile implant	None	92.5% engaging in sexual intercourse. 98% reported prosthetic erections as satisfactory or excellent. Implant removal and replacement required in 10% of patients.	
Minervini, 2005	Retrospective review of notes of 447 men with 504 penile prosthesis implantations. 22 men lost to follow up.	Penile implants, malleable (393) and inflatable (111).	None	Complications following surgery in 24.2% of patients, major complications in 17.5%. implant removal needed in 10%. 71% of prosthesis led to patient satisfaction (higher for malleable implants).	
Mulhall, 2003	96 men prospectively enrolled.	Inflatable penile implant.	Baseline pre-surgery IIEF scores	Significant improvement in IIEF and IIEF ED domain score at 3 and 6 months.	
Natali, 2008	Retrospective chart review of 253 consecutive patients, 53 lost to follow up.	Malleable (40 patients) and inflatable (160 patients) implants.	None	Intra-operative complications in 7.5% of procedures. Post operative complications in 25.5% (major complications in 20%). Satisfaction of 97% and 81% with two types of inflatable prosthesis and 75% with a malleable prosthesis.	
Wilson, 2007	Retrospective review of 2,384 patients with inflatable penile implants	Four models of inflatable penile implants. Evaluation of long term (10 and 15 year implant survival).	None	Overall 10 year revision free survival was 68.5% and 15 year revision free survival was 59.7%.	
Ferguson, 2003	94 prospectively enrolled patients.	Malleable penile implant.	None	9% of implants needed removal. Satisfactory rigidity and continued sexual activity reported by 76% of patients.	
Carson, 2000	Retrospective review of 372 men undergoing penile implantation and telephone interview of 207 patients.	Inflatable penile implant.	None	19.9 % had replacement, revision or other device related surgery. The five year Kaplan-Meier survival rate for freedom from revision from any cause was 78.5%. Prosthesis used for coitus by 78.7% of men.	

				Satisfaction measured on a scale of 1-5 (1-not at all satisfied, 5 - extremely satisfied). Satisfaction of 4 or 5 reported by76.2% of men surveyed.	

Summary of evidence for the effectiveness of penile prosthesis:
The evidence for the effectiveness of penile prosthesis is poor, being based on methodologically weak case series. Overall penile prosthesis surgery is associated with a high rate of complications and about 10% of implants need revision, replacement or removal. Damage to penile tissues due to implantation and removal may leave few other effective treatment options for those requiring this.

4.2 Evidence of cost-effectiveness

The literature search identified a single publication assessing the cost effectiveness of sildenafil by Smith, 2000, USA.(23) This study assessed cost effectiveness from a societal and third party payer perspective with discounting at the rate of 3% per year. The average utility value for men 60 years of age was derived from the time-tradeoff method and disutility for ED obtained from men in the context of prostate cancer screening decisions. The disutility of erectile dysfunction is difficult to assess as the relationship between the improvement in sexual life and the improvement in overall life is not established. A sensitivity analysis was conducted and effectiveness of sildenafil, morbidity and mortality of treatment, disutility of ED and cost of sildenafil were sensitive to variation. A willingness to pay threshold of $50,000 was used in this study. The incremental cost effectiveness ratio (ICER) of sildenafil from a societal perspective was $11,290 and from the third party payer perspective was $11,230. The paper acknowledges that the success of treatment for ED may be debatable, however, an increase in utility of 0.05 was sufficient to achieve an ICER of $50,000.

Stolk, 2000, published a cost utility analysis of sildenafil compared with papaverine-phentolamine injections from a societal perspective.(24) Utility values for ED were derived from the time trade-off method with a survey of 169 members of the general public in Rotterdam. The mean utility gain for treatment with sildenafil was 0.11. The ICER for sildenafil compared with papaverine-phentolamine treatment £3,639 per QALY in the first year decreasing to £2,630 per QALY in the second year.

A sensitivity analysis was performed. Doubling the frequency of use from once a week increased the cost per QALY by 45% in the first year and by 85% in subsequent years. In addition to frequency of use, effectiveness and acceptability also influenced the results significantly. The worst case ICER reported was £9,343 in the first year and £4,691 in the subsequent years.

No cost effectiveness analyses were identified for any of the other treatments discussed in this paper.

Summary of evidence for cost effectiveness:
Cost effectiveness evaluations were only identified for sildenafil and these suggest that cost effectiveness of sildenafil is well within usually accepted thresholds provided the disutility of the ED is an accurate reflection of the overall quality of life.

4.3 Other data sources (e.g. audit)

The literature search identified an audit of implanted penile prosthesis in the UK by Agrawal et al, 2006.(25) The stated objective of the audit was to assess whether the outcomes of implanting penile prosthesis was related to the number of prostheses implanted by the surgeons. The data source used was the patient information form

completed by surgeons for the manufacturer for each prosthesis implanted. This included initial implantation and revision procedures. The audit found no correlation between revision rate and number of implants performed. A revision rate of 24% was calculated from the numbers of revision implants performed, higher than the expected worldwide rate of 5% considered in the paper.

4.4 Safety

PDE-5 inhibitors:
The meta-analysis of harms by Tsertsvadze in section 4.1(14) identified headache, flushing, dyspepsia and visual disturbances as the harms with a higher relative risk as compared to men treated with placebo. There was no significant difference in serious adverse events (AEs) in men treated with sildenafil as compared with placebo. The most common cardiovascular event was palpitations and occurance of serious cardiovascular events was rare. Overall the meta-analysis finds sildenafil to be a well-tolerated drug with mainly mild to moderate AEs. Meta-analyses by Moore and Fink also did not show a significant increase in serious AEs at any dose of sildenafil with the common AEs being dyspepsis, headache and vasodilatation.

A retrospective study of the cardiovascular safety of tadalafil by Kloner,(26) 2006, included 12,487 tadalafil treated patients and 2,047 placebo treated patients. There was no significant difference in serious cardiovascular adverse events (including myocardial infarction and death) between the two groups. A second meta-analysis by Jackson, 2004, reported similar findings with no significant difference in serious AEs with tadalafil.

The meta-analysis by Guiliano(27) and Markou,(11) 2004, report a similar safety profile for vardenafil with headache, rhinitis, flushing and dyspepsia the most common AEs.

Psychosexual interventions: There were no safety concerns in the reports of psychosexual treatments for ED.

Prostaglandin E1 intracavernosal injections:
Adverse events described with intracavernosal alprostadil use included priapism (prolonged and painful erection which may need surgical treatment), haematoma, induration and pain at the injection site.

Vacuum erection devices:
Adverse events reported with the use of VED comprised testicular swelling and penile bruising and discomfort.

Implantation of penile prosthesis:
Implantation of penile prosthesis was associated with significant risks with complications occurring in upto 25% of patients and major complications in 10-20% of patients undergoing surgery. These may range from device malfunction to deep infection and about 10% of implants may need to be removed or replaced. Replacement surgery may have higher risks for overall and major complications. In addition following removal of implants the damage to penile tissues may greatly reduce the prospect of treatment with other therapies.

4.5 Summary of section 4

Good quality evidence was available for PDE-5 inhibitors from well conducted meta-analysis showing a clinical effectiveness for all three drugs. The largest number of studies have been conducted on sildenafil which was the first to be launched for this indication. Overall the evidence from placebo controlled studies shows that these drugs are effective for the treatment of ED and represent the least invasive treatment option. Comparisons between the drugs do not show a compelling greater effectiveness for any single drug. The pharmacokinetic properties for vardenafil and tadalafil may have some advantages for patients in requiring less planning for sexual intercourse. These drugs have a similar profile of adverse events with an increase in mild to moderate adverse events but no significant increase in serious adverse events.

The evidence for psychosexual interventions is weak with few studies and a large variation in the therapies used. Some studies have reported benefits with psychosexual therapy, particularly when used in combination with another intervention.

Vacuum erection devices have been evaluated mainly in the population of men with ED following treatment for prostate cancer to enhance the recovery of erectile function and there is limited evidence of effectiveness in this group of patients. No evidence of effectiveness in the general population of men with ED was identified. There were minor adverse events reported but no serious adverse events identified.

Intracavernosal injections of prostaglandin E1 into the penis is a more invasiveness treatment option that not all men with ED may choose to use. There is some evidence that the effectiveness of this is similar to PDE-5 inhibitors and that they may be effective in those unresponsive to oral medications. This would be plausible as with intracavernosal injections alprostadil is delivered into penile tissues, and the mechanism of action is different from PDE-5 inhibitors. This is more invasive in its delivery and is associated with a risk of priapism which may require surgical treatment.

The evidence for penile implants comprises reports of case series that suggest that although implants are satisfactory for those who do not have complications, complications are frequent with about 10% of implants requiring removal or replacement. A reported audit suggests that in UK clinical practice removal and replacement is more frequent than these case series suggest.

Evidence of cost effectiveness was only available for sildenafil and shows this to be a cost effective treatment.

5 Implementation

5.1 Current local activity and costs

Across South Central the highest costs are incurred with medical treatment and surgery for erectile dysfunction, and activity data is discussed below.

PDE-5 inhibitors:

Prescription of PDE-5 inhibitors accounts for a high proportion of the cost of treatment of ED and has been rising year on year. Costs of the individual drugs are presented in Table 3.

Table 3: Costs of PDE-5 inhibitors

	4 tab pack	8 tab pack
Sildenafil (Viagra) 25 mg	16.59	33.19
Sildenafil (Viagra) 50 mg	19.34	38.67
Tadalafil (Cialis) 10 mg	26.99	
Tadalafil (Cialis) 20 mg	26.99	53.98
Vardenafil (Levitra) 10 mg	21.68	43.36
Vardenafil (Levitra) 20 mg	24.09	48.16

Source: British National Formulary, 2010

The total spend on PDE-5 inhibitors in 2009/10 was £4.7 million across South Central with significant variation across the region.

There has been an 8% increase in prescribing costs for South Central PCTs between 2008/09 and 2009/10, compared to an 11% increase in England.

The funnel plot (Figure 2) for prescribing of PDE-5 inhibitors for South Central PCTs shows the wide variation in prescribing across the region.

Figure 2: Funnel plot of prescribing of phosphodiesterase inhibitors (sildenafil, tadalafil and vardenafil), South Central PCTs

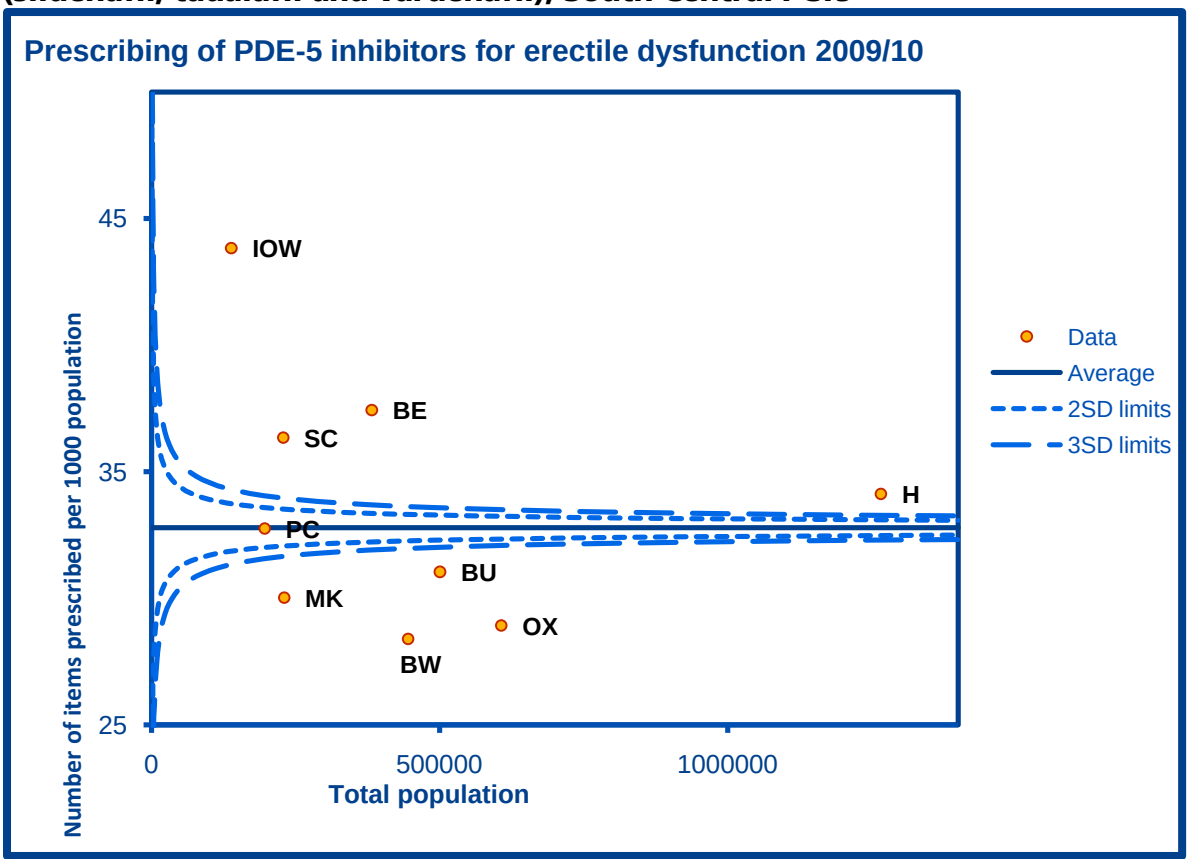


Table 4 shows prescribing costs for PDE-5 inhibitors in South Central and Table 5 the prescribing costs of alprostadil.

Table 4: Prescribing costs for phosphodiesterase inhibitors (sildenafil, tadalafil and vardenafil), South Central PCTs, 2008/09 and 2009/10.

PCT Name	2008/09	2009/10
BERKSHIRE EAST	463,839	496,660
BERKSHIRE WEST	365,094	398,230
BUCKINGHAMSHIRE	480,345	517,804
HAMPSHIRE	1,323,850	1,482,403
ISLE OF WIGHT NHS	160,016	182,768
MILTON KEYNES	193,494	219,532
OXFORDSHIRE	568,400	618,541
PORTSMOUTH CITY TEACHING	215,508	232,234
SOUTHAMPTON CITY	255,975	256,818
Total	**4,026,520**	**4,404,990**

Source: Epact data, December 2010

The prescribing costs of alprostadil are presented in Table 4. This comprises both intracavernosal injections and intra-urethral instillations. Alprostadil injections cost £9.50 for a single dose of 5-20mcg; and intra-urethral instillations cost from £9.89 for a single 125mcg applicator to £11.01 for a single 1mg applicator.

Table 4: Prescribing costs for alprostadil, South Central PCTs, 2008/09 and 2009/10.

PCT Name	2008/09	2009/10
BERKSHIRE EAST	38,281	33,070
BERKSHIRE WEST	37,019	38,313
BUCKINGHAMSHIRE	33,524	33,199
HAMPSHIRE	113,375	112,089
ISLE OF WIGHT NHS	11,290	11,840
MILTON KEYNES	20,331	19,647
OXFORDSHIRE	39,377	34,918
PORTSMOUTH CITY TEACHING	7,439	9,187
SOUTHAMPTON CITY	13,104	10,560
Total	**313,740**	**302,824**

Source: Epact data, December 2010

The hospital cost of penile implants varies from £2,263 to £2,289 with a separate charge for the implant. The cost for injection of therapeutic substance into the penis varies from £706 to £2,104 when performed as an admission and a charge of £96 to £194 when performed as part of an outpatient appointment. The number of procedures for "insertions of penile prosthesis" has remained stable over the three year period in South Central PCTs. There were 126 penile prosthesis insertions in total

from 2007/08 to 2009/10 (Table 6). There were 33 penile injections over the same period (Table 7). These penile injections reported in the HES data are likely to have been performed as day case procedures.
Insertion of 36 penile prostheses in 2009/10 would be expected to cost between £81,468 to £82,404 with an additional cost for the implant, a PBR exclusion and longer hospital stays due to complications. Assuming the 7 injections of therapeutic substance into the penis in 2009/10 were conducted as day case procedures they could be expected to cost between £4,942 to 14,728.

Table 6: Procedures for insertions of penile prostheses (N29), South Central PCTs, 2007/08, 2008/09, 2009/10

PCT	2007/08	2008/09	2009/10
MILTON KEYNES PCT	0		*
PORTSMOUTH CITY TEACHING PCT	*		*
SOUTHAMPTON CITY PCT	*	*	*
HAMPSHIRE PCT	*	*	14
BUCKINGHAMSHIRE PCT	*	11	8
OXFORDSHIRE PCT	*	*	*
BERKSHIRE WEST PCT	*	*	*
BERKSHIRE EAST PCT	13	*	6
ISLE OF WIGHT NHS PCT	*		*
Grand Total	**53**	**37**	**36**

Source: HES data
* indicates fewer than 5 procedures, data suppressed to protect patient confidentiality

Table 7: Procedures for injection of therapeutic substance into penis (N324), South Central PCTs, 2007/08, 2008/09, 2009/10

PCT	2007/08	2008/09	2009/10
MILTON KEYNES PCT	*		0
PORTSMOUTH CITY TEACHING PCT	0		*
SOUTHAMPTON CITY PCT	0	*	*
HAMPSHIRE PCT	*	*	5
BUCKINGHAMSHIRE PCT	*	5	0
OXFORDSHIRE PCT	*	*	0
BERKSHIRE WEST PCT	0	*	*
BERKSHIRE EAST PCT	0	*	0
ISLE OF WIGHT NHS PCT	0		0
Grand Total	**12**	**14**	**7**

Source: HES data
* indicates fewer than 5 procedures, data suppressed to protect patient confidentiality

5.2 Economic model

The health service circular recommends a usual frequency of dosing with PDE-5 inhibitors of once a week. Reducing the dose by 25% to three tablets per month

would reduce the prescribing cost for these medications to about £3.3 million per year, a saving of about £1.1 million and a 50% reduction in frequency of prescribing to once every two weeks would result in savings of about £2.2 million per year.

If penile prosthesis implantation was made low priority, this would result in about 35 men with persisting ED and a saving of between £81,468 to £82,404 and an additional saving by avoiding the longer hospital stays and morbidity of complications.

5.3 Other implementation issues (e.g. training, capacity)

None Identified.

6 Ethical issues

Should men with ED from some causes, such as ED following treatments for prostate cancer or complications of diabetes, have access to treatments for ED when these treatments are not available for other men with ED?

7 Discussion and conclusions

Good quality evidence from meta-analysis suggests that PDE-5 inhibitors are effective and safe in the treatment of ED. Studies of cost effectiveness for PDE-5 inhibitors show sildenafil to be cost effective. The evidence for psychosexual interventions is of poor quality and does not consistently demonstrate effectiveness compared with no treatment or placebo though psychosexual interventions may provide some additional benefit in combination with other treatments for ED. The evidence for the effectiveness of VED is weak and only available for patients who have undergone treatments for prostate cancer. There is evidence for the effectiveness of intracavernosal injection of alprostadil available from randomised controlled trials that suggest that this is an effective treatment and may be effective in men unresponsive to sildenafil treatment, making this a potentially beneficial second line treatment. The evidence for the effectiveness of penile prosthesis is based on case series that suggest that this is an effective treatment, but is associated with a high rate of complications. A published UK audit suggests that the rate of implant removal and replacement is higher in the UK than in the published case series. Evidence of cost effectiveness is limited to PDE-5 inhibitors and is not available for the other treatments discussed. Surgical implantation of a penile prosthesis may be appropriate in a small carefully selected sub-group of patients unresponsive to other therapies and distressed by their ED. These patients may be considered on an individual basis.

8 Options for Priorities Committees

PDE-5 inhibitors:

Funding for treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors is RECOMMENDED in view of the evidence of effectiveness and cost effectiveness.

Funding for treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors is RECOMMENDED for the groups identified in HSC 1999/177 with a maximum frequency of dosing of three times per month.

Funding for treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors is LOW PRIORITY.

Psychosexual interventions:
Funding for treatment of erectile dysfunction with psychosexual interventions is RECOMMENDED.

Funding for treatment of erectile dysfunction with psychosexual interventions is LOW PRIORITY in view of limited evidence for effectiveness and cost effectiveness.

Vacuum erection devices:
Funding for treatment of erectile dysfunction with vacuum erection devices is RECOMMENDED.

Funding for treatment of erectile dysfunction with vacuum erection devices is LOW PRIORITY in view of limited evidence for effectiveness and cost effectiveness.

Intracavernosal injections of prostaglandin E1:
Funding for treatment of erectile dysfunction with intracavernosal injections of prostaglandin E1is RECOMMENDED.

Funding for treatment of erectile dysfunction with intracavernosal injections of prostaglandin E1 is RECOMMENDED for the groups identified in HSC 1999/177 and those not responding to treatment with oral medications.

Funding for treatment of erectile dysfunction with intracavernosal injections of prostaglandin E1is LOW PRIORITY in view of limited evidence for effectiveness and cost effectiveness.

Penile implants:
Funding for treatment of erectile dysfunction with penile implants is RECOMMENDED.
Funding for treatment of erectile dysfunction with penile implants is RECOMMENDED for the groups identified in HSC 1999/177 and those not responding to treatment with oral medications and intracavernosal injections of prostaglandin E1.

Funding for treatment of erectile dysfunction with penile implants is LOW PRIORITY in view of limited evidence for effectiveness and cost effectiveness.

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10 Appendix

10.1 Search strategy

Medline search strategy:

1. (erectile dysfunction or impotence).tw.
2. (sexual dysfunction and (male* or men)).tw.
3. *Erectile Dysfunction/
4. 1 or 2 or 3
5. (pde type 5 inhibitor* or pde 5 inhibitor* or pde5 inhibitor* or phosphodiesterase type 5 inhibitor* or sildenafil or viagra or vardenafil or levitra or tadalafil or cialis).tw.
6. Alprostadil/
7. Papaverine/
8. Phentolamine/
9. Vasodilator Agents/
10. (alprostadil or papaverine or phentolamine or vasodilator* or intracavernosal injection* or intra-cavernosal injection*).tw.
11. Penile Prosthesis/
12. ((penile or penis) adj3 (implant* or prosthe*)).tw.
13. (vaccum or inflatable).tw.
14. counsel*.ti. or counsel*.ab.
15. counseling/ or sex counseling/
16. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 4 and 16
18. limit 17 to english language
19. limit 18 to yr="2000 - 2010"
20. limit 19 to "reviews (specificity)"
21. limit 19 to "therapy (specificity)"
22. limit 21 to ("costs (optimized)" or "economics (optimized)")

10.2 International Index of Erectile Function:

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

HOSPITAL NUMBER (IF KNOWN) ☐☐☐☐☐☐☐

NAME .....

DATE OF BIRTH ☐☐/☐☐/☐☐ AGE ☐☐

ADDRESS .....

.....

.....

Patient Questionnaire

TELEPHONE .....

These questions ask about the effects that your erection problems have had on your sex life <u>over the last four weeks</u>. Please try to answer the questions as honestly and as clearly as you are able. Your answers will help your doctor to choose the most effective treatment suited to your condition. In answering the questions, the following definitions apply:

- sexual activity includes intercourse, caressing, foreplay & masturbation
- sexual intercourse is defined as sexual penetration of your partner
- sexual stimulation includes situation such as foreplay, erotic pictures etc.
- ejaculation is the ejection of semen from the penis (or the feeling of this)
- orgasm is the fulfilment or climax following sexual stimulation or intercourse

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	<u>Over the past 4 weeks:</u>	*Please check one box only*
☐ Q1	How often were you able to get an erection during sexual activity?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q3	When you attempted intercourse, how often were you able to penetrate (enter) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q4	During sexual intercourse, <u>how often</u> were you able to maintain your erection after you had penetrated (entered) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q5	During sexual intercourse, <u>how difficult</u> was it to maintain your erection to completion of intercourse?	0 Did not attempt intercourse 1 Extremely difficult 2 Very difficult 3 Difficult 4 Slightly difficult 5 Not difficult

☐ Q6	How many times have you attempted sexual intercourse?	0 No attempts 1 One to two attempts 2 Three to four attempts 3 Five to six attempts 4 Seven to ten attempts 5 Eleven or more attempts
☐ Q7	When you attempted sexual intercourse, how often was it satisfactory for you?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q8	How much have you enjoyed sexual intercourse?	0 No intercourse 1 No enjoyment at all 2 Not very enjoyable 3 Fairly enjoyable 4 Highly enjoyable 5 Very highly enjoyable
☐ Q9	When you had sexual stimulation or intercourse, how often did you ejaculate?	0 No sexual stimulation or intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q10	When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q11	How often have you felt sexual desire?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q12	How would you rate your level of sexual desire?	1 Very low or none at all 2 Low 3 Moderate 4 High 5 Very high
☐ Q13	How satisfied have you been with your overall sex life?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q14	How satisfied have you been with your sexual relationship with your partner?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q15	How do you rate your confidence that you could get and keep an erection?	1 Very low 2 Low 3 Moderate 4 High 5 Very high