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Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: a multicentre, placebo-controlled, randomised controlled trial and cost-effectiveness analysis of a calcium channel blocker (nifedipine) and an alpha-blocker (tamsulosin) (the SUSPEND trial)

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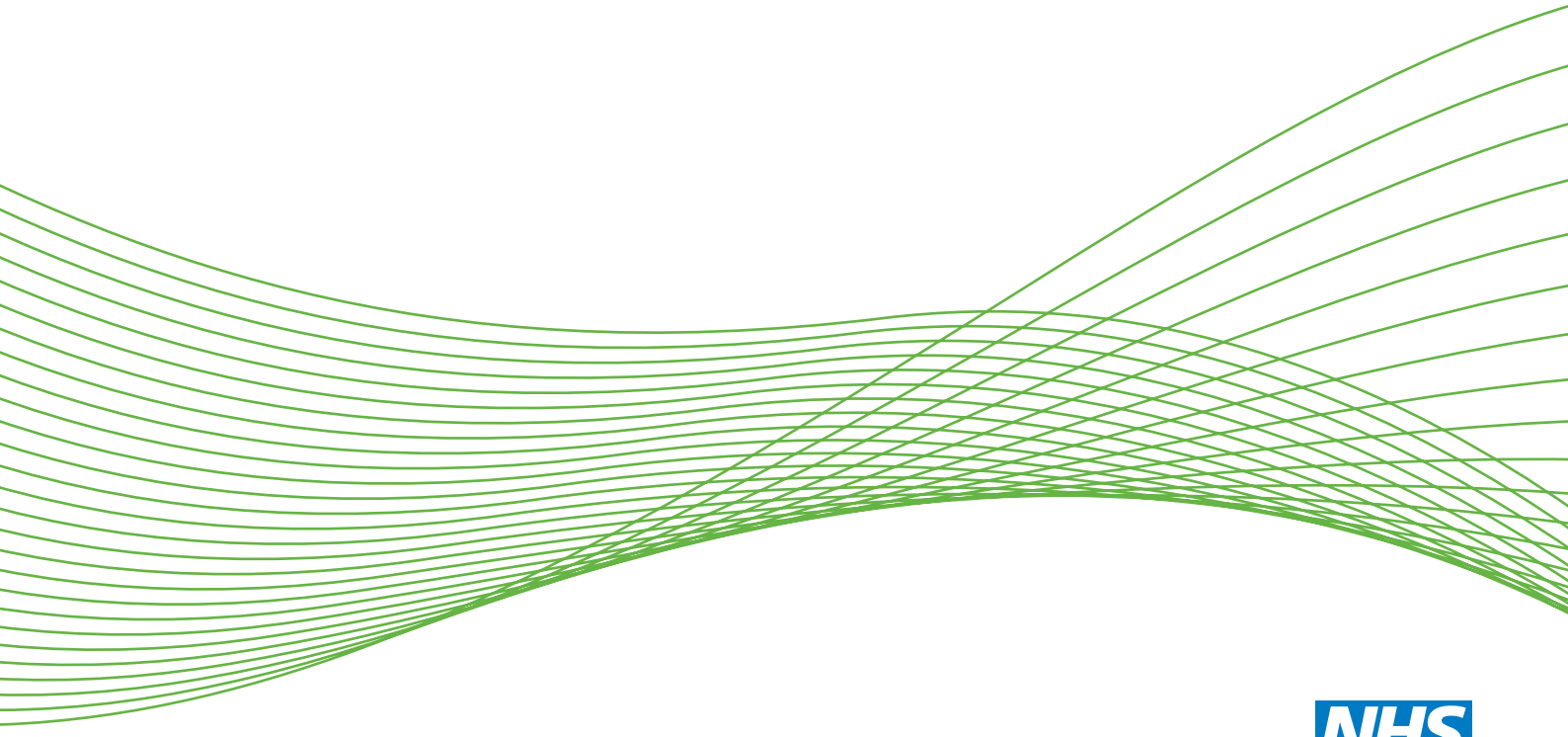

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Abstract

Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: a multicentre, placebo-controlled, randomised controlled trial and cost-effectiveness analysis of a calcium channel blocker (nifedipine) and an alpha-blocker (tamsulosin) (the SUSPEND trial)

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Background: Ureteric colic, the term used to describe the pain felt when a stone passes down the ureter from the kidney to the bladder, is a frequent reason for people to seek emergency health care. Treatment with the muscle-relaxant drugs tamsulosin hydrochloride (Petyme, TEVA UK Ltd) and nifedipine (Coracten®, UCB Pharma Ltd) as medical expulsive therapy (MET) is increasingly being used to improve the likelihood of spontaneous stone passage and lessen the need for interventional procedures. However, there remains considerable uncertainty around the effectiveness of these drugs for routine use.

Objectives: To determine whether or not treatment with either tamsulosin 400 µg or nifedipine 30 mg for up to 4 weeks increases the rate of spontaneous stone passage for people with ureteric colic compared with placebo, and whether or not it is cost-effective for the UK NHS.

Design: A pragmatic, randomised controlled trial comparing two active drugs, tamsulosin and nifedipine, against placebo. Participants, clinicians and trial staff were blinded to treatment allocation. A cost–utility analysis was performed using data gathered during trial participation.

Setting: Urology departments in 24 UK NHS hospitals.

Participants: Adults aged between 18 and 65 years admitted as an emergency with a single ureteric stone measuring ≤ 10 mm, localised by computerised tomography, who were able to take trial medications and complete trial procedures.

Interventions: Eligible participants were randomised 1 : 1 : 1 to take tamsulosin 400 µg, nifedipine 30 mg or placebo once daily for up to 4 weeks to make the following comparisons: tamsulosin or nifedipine (MET) versus placebo and tamsulosin versus nifedipine.

Main outcome measures: The primary effectiveness outcome was the proportion of participants who spontaneously passed their stone. This was defined as the lack of need for active intervention for ureteric stones at up to 4 weeks after randomisation. This was determined from 4- and 12-week case-report forms completed by research staff, and from the 4-week participant self-reported questionnaire. The primary economic outcome was the incremental cost per quality-adjusted life-year (QALY) gained over 12 weeks. We estimated costs from NHS sources and calculated QALYs from participant completion of the European Quality of Life-5 Dimensions health status questionnaire 3-level response (EQ-5D-3L™) at baseline, 4 weeks and 12 weeks.

Results: Primary outcome analysis included 97% of the 1167 participants randomised (378/391 tamsulosin, 379/387 nifedipine and 379/399 placebo participants). The proportion of participants who spontaneously passed their stone did not differ between MET and placebo [odds ratio (OR) 1.04, 95% confidence interval (CI) 0.77 to 1.43; absolute difference 0.8%, 95% CI –4.1% to 5.7%] or between tamsulosin and nifedipine [OR 1.06, 95% CI 0.74 to 1.53; absolute difference 1%, 95% CI –4.6% to 6.6%]. There was no evidence of a difference in QALYs gained or in cost between the trial groups, which means that the use of MET would be very unlikely to be considered cost-effective. These findings were unchanged by extensive sensitivity analyses around predictors of stone passage, including sex, stone size and stone location.

Conclusions: Tamsulosin and nifedipine did not increase the likelihood of stone passage over 4 weeks for people with ureteric colic, and use of these drugs is very unlikely to be cost-effective for the NHS. Further work is required to investigate the phenomenon of large, high-quality trials showing smaller effect size than meta-analysis of several small, lower-quality studies.

Trial registration: Current Controlled Trials ISRCTN69423238. European Clinical Trials Database (EudraCT) number 2010–019469–26.

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List of abbreviations

BAUS	British Association of Urological Surgeons
BNF	*British National Formulary*
CEAC	cost-effectiveness acceptability curve
CHaRT	Centre for Healthcare Randomised Trials
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CT	computerised tomography
CTIMP	clinical trial involving an investigational medicinal product
CT KUB	computerised tomography scanning of the kidneys, ureters and bladder
DMC	Data Monitoring Committee
EQ-5D™	European Quality of Life-5 Dimensions
ESWL	extracorporeal shockwave lithotripsy
GP	general practitioner
HRQoL	health-related quality of life
HSRU	Health Services Research Unit
IT	information technology
MET	medical expulsive therapy
MR	modified release
NIHR	National Institute for Health Research
NMB	net monetary benefit
NRS	numeric rating scale
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PIL	patient information leaflet
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form questionnaire-36 items
SF-6D	Short Form questionnare-6 Dimensions
SUSPEND	Spontaneous Urinary Stone Passage ENabled by Drugs trial
TSC	Trial Steering Committee
WTP	willingness to pay

Plain English summary

About 5% of people suffer from kidney stones that pass down the urine drainage tube (ureter) into the urinary bladder and cause episodes of severe pain (ureteric colic). People with ureteric colic have to attend hospital for pain relief and diagnosis. Although most stones smaller than 10 mm eventually reach the bladder and are passed during urination within 4 weeks, some get stuck and have to be removed using telescopic surgery or shockwave therapy. Previous studies suggest that if people with ureteric colic are treated with drugs that relax the ureter, such as tamsulosin hydrochloride (Petyme, TEVA UK Ltd) or nifedipine (Coracten®, UCB Pharma Ltd), they are more likely to pass their stone without any further procedures. To see if these drugs really work, we carried out a study involving over 1000 patients with ureteric colic. We divided the patients who agreed to take part into three groups, which were treated with either tamsulosin, nifedipine or placebo (pill without active ingredients) for 4 weeks. The treatment each person received was decided by a computer program (random allocation), and the patients and the doctors caring for them did not know which treatment they were taking. We counted how many patients in each group had further procedures to remove the stone. We found that eight out of every 10 (80%) patients in all the groups did not need any procedures during the 4 weeks, with no differences between the tamsulosin, nifedipine and placebo groups. Our conclusion was that giving tamsulosin or nifedipine for 4 weeks to people with ureteric colic is not worthwhile.

Scientific summary

Background

Ureteric colic describes the severe episodic pain people feel when a kidney stone passes down the ureter, which is the muscular tube connecting the kidney to the urinary bladder. It is a common reason for people to seek emergency help from the NHS in the UK, with 31,000 hospital admissions in England from April 2012 to March 2013. Ureteric colic predominantly affects people of working age, disrupting their social and economic activity. The stone will usually pass spontaneously within 4 weeks and patients are generally treated expectantly at home with general advice and painkillers. However, for about 25% of sufferers, failure of stone passage, the development of an infection or kidney damage means that active intervention to drain the affected kidney or remove the stone is required. This is more likely for those with larger stones or with stones higher up in the ureter. Recently, two drugs that relax the ureteric muscle have been identified and a series of small clinical trials suggest that their use during expectant management of people with ureteric colic reduces the likelihood of needing further intervention and hastens stone passage. Combining the results of these small trials in a meta-analysis suggests that people taking either of these drugs are about 50% more likely to pass their stone within 4 weeks compared with control and, when comparing the two drugs, the stone passage rate with tamsulosin hydrochloride (Petyme, TEVA UK Ltd) was about 10% better than with nifedipine (Coracten®, UCB Pharma Ltd). However, the trials were generally single centre and there was considerable clinical and statistical heterogeneity, which limits the applicability of the findings for the evidence base used as the basis for treatment decisions within the UK NHS. As a result, the National Institute for Health Research Health Technology Assessment programme commissioned a trial to determine precisely the effectiveness of these agents as medical expulsive therapy (MET) for people with ureteric colic and hence guide decisions around their use within the UK NHS.

Objectives

The research was designed to determine whether or not the use of MET is worthwhile for the UK NHS in terms of increasing the likelihood of spontaneous stone passage and being cost-effective compared with standard care without MET. The hypothesis for the SUSPEND (Spontaneous Urinary Stone Passage ENabled by Drugs) trial was that MET (tamsulosin or nifedipine) taken for up to 4 weeks would increase the proportion of spontaneous stone passage (measured as the lack of need for further intervention) by at least 25% compared with placebo control, and that tamsulosin would be at least 10% more effective than nifedipine.

We planned two comparisons of equal importance:

- MET (tamsulosin 400 µg or nifedipine 30 mg daily) versus placebo
- tamsulosin 400 µg daily versus nifedipine 30 mg daily.

Methods

Adults with ureteric colic presenting for urgent care, but not requiring immediate active treatment (i.e. without severe infection, uncontrolled pain or impaired kidney function), were identified from 24 UK NHS hospitals. Eligible participants had to have a single stone of a maximum dimension of $\leq$ 10 mm located within the ureter by computerised tomography of kidneys, ureters and bladder (CT KUB); to be able to take the trial drugs; and, for female participants, to agree to avoid pregnancy by using effective contraception during the 4-week trial period. After providing informed consent, eligible participants were randomised in a 1 : 1 : 1 ratio between the three groups using a remote telephone interactive voice response randomisation application that concealed allocation.

Relevant baseline data were collected by trial staff on a case report form (CRF) and from the participants by self-completed questionnaire. Participants were instructed to take the allocated medication once daily for up to 4 weeks, with early discontinuation if the stone passed, if further intervention was planned or if intolerable adverse effects occurred. The medications were supplied from an independent source using identical packaging and overencapsulation to maintain blinding of participants, clinicians and research staff. Outcome data and progress through the trial were recorded by participant questionnaires and CRFs at 4 weeks and 12 weeks after randomisation.

The primary outcome, spontaneous stone passage, was defined as the lack of need for further intervention to facilitate stone passage at 4 weeks. This was recorded on the 4-week patient questionnaire and 4- and 12-week CRFs. This was analysed using an intention-to-treat strategy by logistic regression. Treatment effects were summarised as odds ratios (ORs) and absolute percentage differences, both with 95% confidence intervals (CIs). Adjusted treatment effects were derived from models including fixed effects for stone size ($\leq$ 5 mm or > 5 mm) and stone location (lower, mid or upper ureter) at baseline, and a random effect for centre. The treatment-modifying effect of stone size and stone location was explored using tests of interaction. Secondary outcomes of health-related quality of life, pain and number of days of analgesic use at 4 weeks, and estimated time to stone passage were analysed using linear models. Within-trial cost-effectiveness over 12 weeks was examined by calculating costs in each group from NHS sources and quality-adjusted life-years (QALYs) based on participant completion of the European Quality of Life-5 Dimensions (EQ-5D™) questionnaire at baseline, 4 weeks and 12 weeks. The resultant cost–utility analysis was expressed as an incremental cost-effectiveness ratio and by cost-effectiveness acceptability curves.

Results

We randomised 1167 participants between January 2011 and December 2013, and included 1136 (97%) in our analysis of the primary outcome, thereby exceeding our planned sample size of 1080. There were 17 post-randomisation exclusions. Of these, 14 patients were randomised in error as they were found to be ineligible, whereas a further three were erroneously given open-label tamsulosin after randomisation before the trial medication was dispensed. The primary outcome data could not be determined for 14 participants. Baseline characteristics between the three trial groups were well balanced. Overall, the key characteristics of the SUSPEND trial population were similar to those seen in previous published cases series, except that we included a smaller proportion of women (19%). This was linked to a higher exclusion rate in women, predominantly as a result of lack of CT KUB. Participant-reported premature discontinuation of trial medication owing to intolerable side effects on the 4-week questionnaire was 6%, 10% and 17% in the placebo, tamsulosin and nifedipine groups, respectively. Trial medication contributed to three serious adverse events, but there were no deaths.

At 4 weeks, 303 out of 379 (80%) participants in the placebo group had passed their stone compared with 307 out of 378 (81%) allocated to tamsulosin and 304 out of 379 (80%) allocated to nifedipine. For the planned comparison of MET versus placebo the OR was 1.04 (95% CI 0.77 to 1.43) with an absolute difference of 0.8% (95% CI –4.1% to 5.7%), and for tamsulosin versus nifedipine the OR was 1.06 (95% CI 0.74 to 1.53) with an absolute difference of 1% (95% CI –4.6% to 6.6%). These estimates were unchanged in models adjusting for stone size and stone location. There was no evidence that the treatment effects differed across subgroups. There were no differences between the trial groups in terms of visual analogue pain score at 4 weeks, number of days of analgesic use or time to stone passage. Health status measured by the EQ-5D and Short Form questionnaire-36 items questionnaires improved in all groups between baseline and the 4- and 12-week time points to reach close to the norm for an age-matched UK general population. There were no differences at any time point between the trial groups. There was considerable non-response to participant questionnaires at 4 weeks and 12 weeks, but results were robust to sensitivity analyses exploring the effect of imputation of missing data using values maximally favouring active treatment. There were no differences in cost or gain in QALYs between the trial groups and, consequently, cost–utility analyses were uninformative. The lack of any differences meant that MET would not be considered to be cost-effective using the results from the trial.

Conclusions

The results of this large, multicentre, pragmatic, randomised controlled trial that focused on outcomes important to patients and the NHS show that MET using tamsulosin 400 µg or nifedipine 30 mg daily is not effective for increasing the likelihood of stone passage for people with ureteric colic over the 4 weeks after diagnosis. Estimated treatment effects and CIs rule out pre-specified clinically important differences. Relevant subgroup and sensitivity analyses did not identify any specific patient characteristics where benefit from MET was likely. There was also no evidence that use of MET reduced pain, hastened stone passage or increased quality of life compared with placebo. These results and a lack of any meaningful difference in costs mean that these drugs would be unlikely to be considered cost-effective for use in the UK NHS.

Implications for health care

Widely used clinical guidance documents, in line with the results of available meta-analyses, currently recommend the use of MET as part of the routine management of people with ureteric colic who would be expected to pass their stone spontaneously. Cohort studies suggest that the routine use of MET is increasing, with a recent estimate showing it was used in 60% of the target patient group. The finding of no effect from this large, high-quality trial (set within routine care for this condition) make it necessary for interested clinicians, clinical guideline writers and health-care policy-makers to reappraise the evidence to decide whether or not patients having expectant management for ureteric colic should be offered MET as part of their treatment. Contradiction of positive results derived from a meta-analysis of a series of earlier single-centre, small trials with varying risk of bias by the null results of an adequately powered high-quality trial with low risk of bias is a frequent phenomenon. Recent expert statistician opinion advises that seekers of evidence should make judgements after careful consideration of qualitative and quantitative properties in each specific circumstance, with further sensitivity analyses where possible. The SUSPEND trial clearly demonstrates the ineffectiveness of tamsulosin and nifedipine as MET at the therapeutic dose and duration used with a high degree of precision. Owing to the lack of congruence in trial design, it is not appropriate to combine our results in the previous meta-analyses. Instead, the results should be contrasted from both a quality and statistical perspective to shape clinical opinion and health-care policy.

Implications for research

The SUSPEND secondary outcomes reinforce the understanding that ureteric colic is a painful condition causing considerable disability and, hence, lowering the health state of sufferers. The pain and ill health largely resolve by 4 weeks, although a sizeable minority (20% in this trial) suffer continued problems related to the need for further active treatment to ensure eventual stone passage. The health-care need to lessen requirement for intervention, reduce pain and hasten stone passage therefore remains despite the demonstrated ineffectiveness of tamsulosin and nifedipine for MET. The main implications for research are as follows:

1. The precision of these results ruling out the > 10% effect size that might be considered to be the minimum clinically important difference makes further testing of these drugs futile.
2. A number of putative alternative agents targeted primarily at smooth muscle relaxation are being tested and, if initial assessment of efficacy is promising, should be explored further in a definitive multicentre trial rather than in small, single-institution studies.
3. Small, single-centre studies of novel treatments in urology carried out in different health systems may have limited generalisability as the basis for treatment decisions in the NHS. Clinicians, patients and health policy-makers should seek evidence from large, multicentre, UK-based trials, when available, before initiating change in clinical practice.

Trial registration

This trial is registered as ISRCTN69423238. This trial is also registered as European Clinical Trials Database (EudraCT) number 2010–019469–26.

Funding

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Chapter 1 Introduction

In 2008, the UK Government Department of Health's National Institute for Health Research (NIHR) Health Technology Assessment programme called for a randomised controlled trial (RCT) to answer the following clinical care question: 'What is the effectiveness and cost-effectiveness of the use of calcium channel blockers and α-blockers to facilitate urinary stone passage in people with ureteric colic?' This report describes the research [the SUSPEND (Spontaneous Urinary Stone Passage ENabled by Drugs) trial] that was subsequently commissioned.

The SUSPEND trial was a large, pragmatic, UK-based, multicentre RCT. It aimed to establish whether or not the use of either alpha-blockers or calcium channel blockers was clinically effective as medical expulsive therapy (MET) to facilitate spontaneous stone passage for people requiring emergency care for ureteric colic in comparison with placebo, and whether or not their use was cost-effective from the perspective of the UK NHS.

Background

Target population for trial

Ureteric colic describes the pain felt when a stone formed in the urine collection part of the kidney (usually resulting from the aggregation of calcium-based crystals) passes down the ureter, the urine drainage tube connecting the kidney to the bladder (*Figure 1*). The pain is typically severe and recurrent; each episode usually lasts for an hour or two and is interspersed with periods without pain. Female sufferers consider it to be more intense than the pain experienced during childbirth.[1] Repeated episodes have a detrimental influence on perception of quality of life.[2] Pain is usually felt in the abdomen but can go down into the groin and scrotum in males, and labia in females. Some people also get increased frequency and urgency of urination. The pain is likely to relate to direct contact of the stone with the epithelial cells lining the ureter and sustained contraction (spasm) of the smooth muscle surrounding the ureter in response to the obstruction of urine flow.[3] The severity of the pain leads to secondary symptoms such as nausea, vomiting and fever. Pain episodes generally continue until the stone passes into the bladder from where it can be freely voided by urination. Kidney stone disease is highly prevalent in most countries, where it affects 5% to 10% of the population,[4] and, as there is no effective disease-modifying treatment, sufferers may have repeated episodes following the first bout of colic, with an approximate lifetime risk of recurrence of 50%.[5,6] The cause of kidney stone formation is multifactorial with genetic, environmental and dietary influences all playing a part. In epidemiological terms it is more common in people aged 15–60 years, in men and in those of Caucasian race, and there is a higher incidence during the summer months.[7]

Ureteric colic is one of the most common reasons for people to seek emergency health care, with an annual incidence of around 30 out of 100,000 in high-resource parts of the world.[8] In the UK, 83,000 people required emergency care for ureteric colic in 2009,[9] and NHS England health episode statistics data for 2012–13 showed 31,000 hospital admissions with a 1-day median stay and a NHS tariff cost of £19.3M.[10] In the USA, there were 600,000 emergency room visits in 2000 at an estimated health-care cost of US$490M.[7] In both countries, the incidence of ureteric colic increased by over 50% during the previous decade.[7,9]

Clinical assessment

The diagnosis of ureteric colic is usually straightforward from the characteristic history of pain, the lack of abdominal tenderness and, to some extent, the finding of non-visible haematuria on reagent strip testing of urine.[8] At this point the patient is given effective pain relief in the form of opiates or non-steroidal anti-inflammatory drugs (NSAIDs), alone or in combination.[11,12] Urine is then checked for infection by microscopy and culture, and renal function is estimated by measurement of serum creatinine. Once the patient is comfortable, the presence of a stone in the ureter can be reliably confirmed by imaging using computerised tomography scanning of the kidneys, ureters and bladder (CT KUB) without the use of intravascular contrast agents. Further analysis of the CT KUB

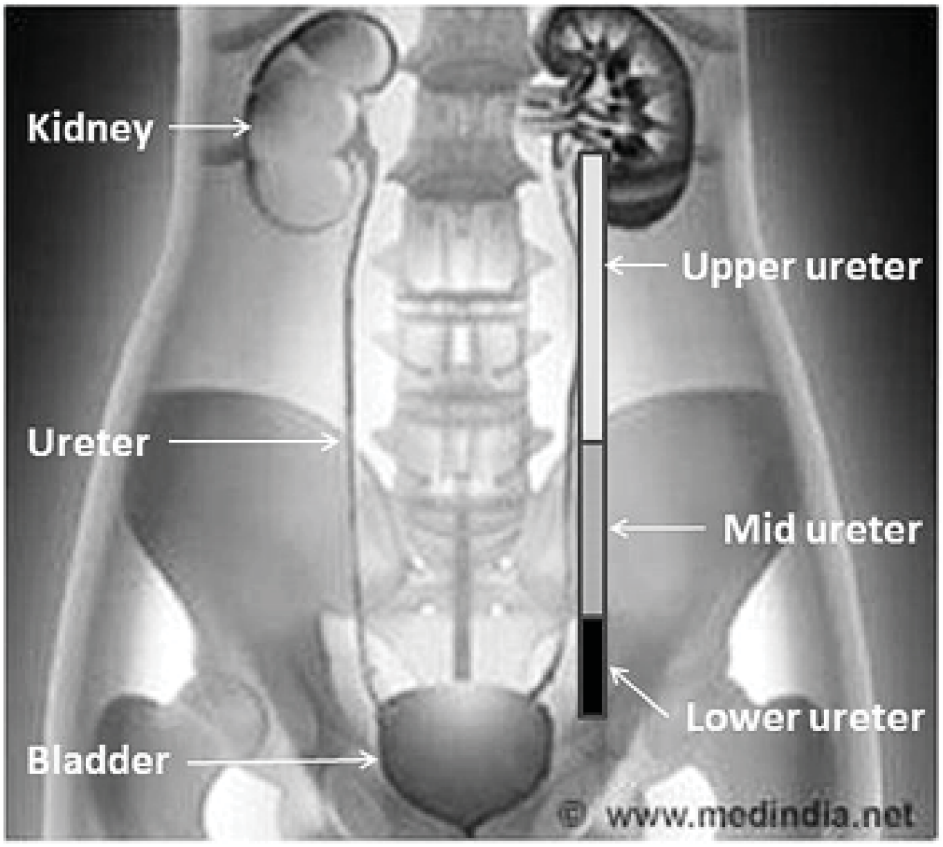

FIGURE 1 Anatomy of urinary tract showing definition of ureteric segments. Reproduced, with permission, from Medindia. URL: www.medindia.net/news/michigan-hospitals-lead-the-way-in-preventing-common-and-costly-urinary-tract-infections-116433-1.htm (accessed July 2015).

images will localise the stone to the upper, mid or lower ureter (see *Figure 1*) and will estimate stone size defined by the maximum linear dimension in millimetres. Less commonly, patients may have evidence of severe urinary and bloodstream infection (urosepsis) as a result of the stone obstructing drainage from the affected kidney; they may have stones in both ureters; or they may have a single kidney, all of which cause marked impairment of renal function. Each of these situations will require resuscitation and urgent intervention and, therefore, such patients are not the focus of this trial.

Interventions for ureteric colic

Guidance on patient management options with summarised relative benefits and harms has been formulated under a joint initiative between the European Association of Urology and the American Urological Association, and form the basis of clinical management for people with kidney and ureteric stones, particularly across Europe and North America.[13] The options for treatment fall under three headings – symptom management, MET and active treatment – and these are discussed below.

Symptom management

For the majority of patients (approximately 75%) without a reason for prompt intervention to drain the affected kidney, management consists of pain relief, antiemetics and encouragement of adequate oral fluid intake. Once the pain is controlled, care can continue at home with oral analgesics but with the facility for rapid readmission if there is deterioration, together with a planned reassessment at approximately 4 weeks to assess whether or not spontaneous stone passage has occurred. Reasons for changing to active management would include poor pain control, the onset of systemic infection or concerns regarding deterioration in kidney function.

Medical expulsive therapy

Patients with ureteric stones face the uncertainty of when spontaneous stone passage and associated episodic pain will occur. Simple adjunctive treatments that lessen stone symptoms, hasten stone passage and increase the likelihood of eventual passage, thus reducing the risk of requiring active treatment, would reduce this burden. After many years of different agents being trialled, recent meta-analyses of multiple RCTs have encouraged clinicians to prescribe MET. An alpha-blocker drug [typically tamsulosin hydrochloride (Petyme, TEVA UK Ltd) 400 µg once daily] or a calcium channel blocker [typically nifedipine (Coracten®, UCB Pharma Ltd) 30 mg once daily] is prescribed to patients who, following assessment and diagnosis, can be treated by symptom management while awaiting spontaneous stone passage.[14,15] The results of most individual trials, and the summarised effects in the meta-analyses, suggest that these two drug classes have efficacy for the three desired outcomes of reduced pain, quicker stone passage and higher rate of eventual stone passage. However, the small sample size and the single-centre nature of the individual trials included limits, certainty and generalisability of the treatment effect, hence the need for a large, more pragmatic, trial such as SUSPEND. Current status of the evidence basis for use of MET is discussed later in this introduction.

Active treatment

Definitive removal of the stone can be achieved in two ways. Extracorporeal shockwave lithotripsy (ESWL) is an ambulatory treatment whereby acoustic waves that can be generated by a number of different energy sources are focused on the stone from outside the body. The physical characteristics of the stone allow it to be fragmented without significant damage to surrounding tissue. The treatment does require continued imaging of the stone by radiography or ultrasound, however, and the patient has to pass the fragments in the urine. Alternatively, stones can be directly visualised by passing a fine endoscope (ureteroscope) up from the bladder. The stone can then be extracted whole or fragmented in situ with a variety of energy sources and removed in pieces. This ureteroscopic technique gives greater certainty of stone removal but does involve a hospital admission and general anaesthetic.[16] Emergency drainage of an obstructed infected kidney can be achieved either by retrograde passage of a drainage tube (ureteric stent) up the ureter to the kidney from below or by direct insertion from above of a tube (nephrostomy) through the skin of the back into the urine collection part of the kidney.

Outcomes of interest

Cohort studies and observations from placebo or standard therapy groups of RCTs suggest that about 50–85% of people with ureteric colic will pass their stone unaided (spontaneous stone passage) within 4 weeks of diagnosis. Speedier passage of the stone would tend to reduce overall pain burden and thereby lessen the impact of any pain on the patient's lifestyle, in terms of time off work and interference in day-to-day activities. From a clinical perspective, confirming stone passage is difficult. Patients are sometimes encouraged to sieve their urine (most stones are the size of a match head), but adherence is doubtful and small fragments can easily be missed. Simple imaging by plain single abdominal radiography or by ultrasound to confirm the absence of a stone has low diagnostic accuracy,[17] whereas further definitive imaging by repeated CT KUB gives levels of radiation exposure that are generally considered to be unacceptable for this predominantly young patient group.[18] Clinical definition of stone passage is, therefore, the absence of pain or other relevant symptoms or signs. For the 30% of patients who continue to experience symptoms, further intervention (sometimes with MET if not previously used, but more usually with active stone removal by ESWL or ureteroscopy) will be required following repeat imaging. The urgency of any active intervention will depend on individual patient circumstances and resource availability in the particular health-care setting. There is an increased likelihood that active treatment will be required with larger stones (conventionally described as > 5 mm) and with stones located in the mid or upper ureter at the time of first presentation (*Table 1*). The need for further treatment is an important and routinely measurable outcome for both patients and providers of health care, as active intervention is associated with harm to patients and increased health-care costs.[13]

TABLE 1 Approximate probability of spontaneous stone passage according to stone characteristics

Characteristic	Probability of spontaneous stone passage (%), mean (range)
Stone size[13]	
≤ 5 mm	68 (46–85)
> 5 mm	47 (36–59)
Stone location[19]	
Lower ureter	75
Mid ureter	60
Upper ureter	48

Current evidence base for use of medical expulsive therapy

Background

Given that care for most patients with ureteric stones is delivered with the expectation of spontaneous stone passage, several strategies aimed at reducing pain, hastening stone passage and increasing the rate of stone passage have been proposed and trialled. Such strategies are termed MET. Agents that initially appeared to be useful but then failed to show efficacy in more robustly designed studies included diuretics and administration of high fluid load to increase urinary hydrostatic pressure above the stone;[20] steroidal anti-inflammatory drugs and NSAIDs to reduce ureteric oedema and inflammation around the stone;[21,22] and antimuscarinic drugs to inhibit ureteric muscular contraction.[23] The two drug classes that appear to show efficacy in repeated small-scale RCTs and subsequent meta-analysis are calcium channel antagonists and alpha-adrenoreceptor antagonists.[24]

Experiments using animal and human tissue models demonstrate that ureteric smooth muscle contraction can be stimulated by activation of adrenergic receptors, particularly the alpha-1D subtype.[25–28] Blockade of alpha-1 receptors by specific pharmacological antagonists (alpha-blockers) such as doxazosin,[29] terazosin,[30] alfuzosin[31] and, most typically, tamsulosin[32,33] results in ureteric smooth muscle relaxation. It was hypothesised that this would translate into clinical benefit for people with ureteric colic. Smooth muscle contraction is stimulated in part by the influx of calcium ions into the smooth muscle cell through specific channels in the cell membrane, which are opened and closed by changes in the degree of electrical polarisation. These channels can be blocked by specific pharmacological antagonists, such as nifedipine, resulting in less calcium influx and reduced smooth muscle contraction. Experimental work demonstrating this effect in vitro encouraged translation to the clinical care of people with ureteric colic.[34–38]

Pharmacological characteristics of putative agents

Tamsulosin is a readily available alpha-blocker which is licensed by the European Medicines Agency and the US Food and Drug Administration at a dose of 400 µg in the form of a modified-release (MR) oral tablet to be taken daily for relief of lower urinary tract symptoms in men.[39,40] It is generally well tolerated but is associated with common (0.1–1%) risks of dizziness and retrograde ejaculation in men. The calcium channel blocker nifedipine is available in the form of MR tablets or capsules in varying doses, ranging from 20 mg to 60 mg, with 30 mg being most often used.[40] The drug is licensed for the treatment of hypertension, Raynaud's phenomenon and prophylaxis of angina, although it has been largely superseded for these indications by more specific and effective calcium channel antagonists. The common side effects (0.1–1%) include headache, dizziness, flushing, constipation and oedema of the lower limbs.

Evidence review for efficacy of tamsulosin and nifedipine as medical expulsive therapy

Multiple RCTs have been carried out testing the efficacy of both alpha-blockers (typically tamsulosin 400 µg) and calcium channel blockers (typically nifedipine 30 mg) compared with placebo, standard care, which may include other interventions, and each other. The medications are prescribed for use either up until the time of spontaneous stone passage or for up to one per month without stone passage. The conduct, quality and results of these trials have been examined by a number of systematic reviews and the results combined in meta-analyses, the findings of which concerning the main outcomes of interest will now be summarised.

Stone clearance

Comparison of the rate of spontaneous stone passage between MET and control is the primary outcome for the great majority of RCTs included in the meta-analyses. The absolute rates of stone passage are likely to vary according to trial eligibility criteria, such as type of diagnostic imaging used, stone location, stone size, the time point at which the outcome is censored and the protocol used to decide whether or not the stone has passed. Variation in these trial features is illustrated from 22 studies included in a Cochrane review[14] that compared tamsulosin 400 µg with control (*Table 2*).

Despite these inconsistencies in trial design, the available meta-analyses all demonstrate an apparent beneficial effect of both tamsulosin and nifedipine as agents to increase the proportion of patients with ureteric colic who spontaneously pass their stone within a reasonable time frame (*Table 3*).

Regarding the effect of stone size, the meta-analysis by Seitz *et al.*[15] reported a relative risk (RR) in favour of tamsulosin versus control of 1.25 [95% confidence interval (CI) 1.12 to 1.40] for stones < 5 mm, and 1.62 (95% CI 1.50 to 1.74) for stones ≥ 5 mm. For nifedipine against control, the RR for stones < 5 mm was 1.49 (95% CI 1.17 to 1.88) and for stones ≥ 5 mm was 1.49 (95% CI 1.31 to 1.69). Similarly, Campschroer *et al.*[14] reported absolute rates of stone clearance for alpha-blocker against control for stones ≤ 5 mm of 83% versus 56%, with a RR of 1.4 (95% CI 1.2 to 1.7), and for stones > 5 mm of 67% versus 39%, with a RR of 1.7 (95% CI 1.3 to 2.1). Summarised results for the effect of stone location on clearance rates for tamsulosin against standard therapy were reported by Fan *et al.*,[43] with a RR of 1.55 for lower ureteral stones (95% CI 1.43 to 1.68) and a RR of 1.28 for upper ureteral stones (95% CI 1.04 to 1.57). Similarly, Campschroer *et al.*[14] reported absolute rates of stone clearance for alpha-blockers against control for stones in the lower (distal) ureter of 79% versus 55% (RR 1.4, 95% CI 1.2 to 1.6) and for stones in the mid or upper ureter of 39% versus 27% (RR 1.5, 95% CI 0.9 to 2.4). The results of these meta-analyses should be interpreted with caution given the uncertainties associated with estimating effect size in subgroups of the overall trial population. Overall, it does appear that these drugs demonstrate efficacy for passage of larger stones and for stones in the upper section of the ureter that are considered to be less likely to pass without active intervention.[8]

TABLE 2 Variation in key trial design characteristics

Trial features	Option 1 (*n*)	Option 2 (*n*)	Option 3 (*n*)
Diagnostic imaging	CT KUB (4)	Any imaging (15)	Unclear (3)
Stone size	≤ 10 mm (10)	4–10 mm (4)	Other (8)
Stone location	Distal (20)	Proximal (1)	Any (1)
Follow-up duration	< 4 weeks (11)	4 weeks (10)	> 4 weeks (1)
Follow-up assessment	CT KUB (3)	Imaging (10)	Unclear (9)
Primary outcome	Rate of stone passage (20)	Time to stone passage (2)	

n, number of trials using this option.
Data extracted from Campschroer *et al.*[14]

TABLE 3 Summarised stone expulsion rates after tamsulosin or nifedipine therapy from meta-analysis

Review	Comparators	Stone clearance			
		Stone free	RR (95% CI)	Number of studies	Number of participants
Hollingsworth *et al.*, 2006[24]	Tamsulosin vs. control[a]	72% vs. 47%	1.5 (1.2 to 1.9)	4	222
EAU/AUA, 2007[13]	Tamsulosin vs. control	NA	29% (20% to 37%)[b]	5	280
Singh *et al.*, 2007[41]	Alpha-blocker vs. control	80% vs. 52%	1.6 (1.4 to 1.8)	16[c]	1235
Seitz *et al.*, 2009[15]	Tamsulosin vs. control	82% vs. 59%	1.4 (1.3 to 1.6)	10	816
Campschroer *et al.*, 2014[14]	Tamsulosin vs. placebo	80% vs. 65%	1.5 (1.3 to 1.7)	6[d]	629
Lu *et al.*, 2012[42]	Tamsulosin vs. standard care[e]	75% vs. 50%	1.4 (1.1 to 1.7)	9	661
Fan *et al.*, 2013[43]	Tamsulosin vs. control	80% vs. 52%	1.5 (1.4 to 1.7)	15	1593
Campschroer *et al.*, 2014[14]	Alpha-blocker vs. control	78% vs. 49%	1.6 (1.3 to 1.9)	21[f]	1565
Campschroer *et al.*, 2014[14]	Tamsulosin vs. standard	77% vs. 52%	1.5 (1.3 to 1.7)	24	1875
EAU/AUA, 2007[13]	Tamsulosin vs. nifedipine	NA	20% (–7% to 45%)[b]	2	Not stated
Lu *et al.*, 2012[42]	Tamsulosin vs. nifedipine	84% vs. 73%	1.2 (1.0 to 1.3)	6	597
Campschroer *et al.*, 2014[14]	Tamsulosin vs. nifedipine	94% vs. 73%	1.2 (1.0 to 1.4)	4	3486
Hollingsworth *et al.*, 2006[24]	Nifedipine vs. control	71% vs. 47%	1.5 (1.1 to 1.9)	2	135
EAU/AUA, 2007[13]	Nifedipine vs. control	NA	9% (–7% to 25%)[b]	4	160
Singh *et al.*, 2007[41]	Nifedipine vs. control	78% vs. 52%	1.5 (1.3 to 1.7)	9	686
Seitz *et al.*, 2009[15]	Nifedipine vs. control	79% vs. 53%	1.5 (1.3 to 1.7)	9	686

AUA, American Urological Association; CI, confidence interval; EAU, European Association of Urology; NA, not applicable; RR, relative risk.
a Control, any comparator except nifedipine.
b Change in absolute risk (95% credible interval).
c Thirteen trials used tamsulosin.
d Five trials used tamsulosin.
e Standard, alternative medical therapy (e.g. steroid), excluding nifedipine.
f Sixteen trials used tamsulosin.

Time to stone passage

Shorter duration of stone episode is likely to be associated with less pain and less social inconvenience, such as time off work, which may be of benefit to patients. Most RCTs examined time to stone passage as a secondary outcome, although the degree to which this was reported varied, thus making meta-analysis difficult. However, the direction of effect was consistent in favouring tamsulosin or nifedipine (*Table 4*). It should also be noted that censoring of exact time of passage is reliant on precise patient report or timing of follow-up imaging leading to reporting inaccuracy.

Pain episodes/use of analgesia

Pain is likely to be the main reason for continued ill health in people with ureteric stones and it drives both transient quality-of-life detriment and the need for further intervention. However, it is difficult to measure in an ambulatory setting, particularly for conditions such as ureteric colic which are characterised by episodic pain of varying severity and frequency. The RCTs and subsequent meta-analyses reported this outcome, but the differences in definition make measurement of comparative effect uncertain (*Table 5*).

TABLE 4 Summarised results for time to stone expulsion after tamsulosin or nifedipine therapy from meta-analysis

Review	Comparators	Time to stone passage (days)			
		Absolute number of days	RR (95% CI)	Number of studies	Number of participants
Singh *et al.*, 2007[41]	Tamsulosin vs. control[a]	5 vs. 8	–	8	584
Lu *et al.*, 2012[42]	Tamsulosin vs. control[a]	–	–3 (–5 to –2)	6	454
Fan *et al.*, 2013[43]	Tamsulosin vs. control	–	–3 (–5 to –3)	7	555
Campschroer *et al.*, 2014[14]	Alpha-blocker vs. placebo	–	–2 (–4 to 1)	4[b]	293
Campschroer *et al.*, 2014[14]	Alpha-blocker vs. standard[c]	–	–3 (–4 to –1)	18[d]	1388
Singh *et al.*, 2007[41]	Nifedipine vs. control[a]	8 vs. 13	–	9	686

a Control, any comparator except nifedipine.
b Three trials used tamsulosin.
c Standard, alternative medical therapy (e.g. steroid) excluding nifedipine.
d Fifteen trials used tamsulosin.

TABLE 5 Summarised results for number of pain episodes after tamsulosin or nifedipine therapy from meta-analyses

Review	Comparators	Number of pain episodes			
		Absolute rate	RR (95% CI)	Number of studies	Number of participants
Lu *et al.*, 2012[42]	Tamsulosin vs. control[a]	–	–0.4 (–0.7 to –0.1)	8	633
Fan *et al.*, 2013[43]	Tamsulosin vs. control[a]	24% vs. 40%	–	4	326
Campschroer *et al.*, 2014[14]	Tamsulosin vs. placebo	–	–0.7 (–1.3 to –0.1)	1	96
Campschroer *et al.*, 2014[14]	Tamsulosin vs. standard[b]	–	–0.5 (–1.0 to –0.0)	6	555

a Control, any comparator except nifedipine.
b Standard, alternative medical therapy (e.g. steroid) excluding nifedipine.

Need for hospitalisation

The final main outcome of interest is the proportion of patients that require further active management, which will mainly consist of stone removal using ESWL or ureteroscopy. Within the RCTs and subsequent meta-analyses this is mainly reported as the rate of further hospital admissions for treatment of a ureteric stone (*Table 6*).

Cost-effectiveness

A cost-minimisation study has been performed which assessed the potential health economic benefit of MET compared with observation alone.[44] A decision analytical model was used to predict comparative costs and resource use for a MET strategy using tamsulosin based on cost data obtained from the USA and four European countries, and efficacy data from existing meta-analyses. The costs of adverse events and other treatment-related complications were not included and a cost–utility analysis was not performed. The study found that use of tamsulosin for MET might lead to a saving of US$1132 over observation, with this conclusion being unchanged by sensitivity analyses. The cost-effectiveness of MET for different health-care systems remains unknown.

TABLE 6 Summarised hospitalisation rates after tamsulosin or nifedipine therapy from meta-analysis

Review	Comparators	Need for active intervention			
		Absolute rate	RR (95% CI)	Number of studies	Number of participants
Seitz *et al.*, 2009[15]	Tamsulosin vs. control[a]	5% vs. 25%	–	5	480
Fan *et al.*, 2013[43]	Tamsulosin vs. control[a]	12% vs. 34%	0.4 (0.2 to 0.6)	5	325
Campschroer *et al.*, 2014[14]	Alpha-blocker vs. standard[b]	14% vs. 37%	0.4 (0.1 to 1.0)	4[c]	313
Seitz *et al.*, 2009[15]	Nifedipine vs. control[a]	20% vs. 34%	–	1	140

a Control, any comparator except nifedipine.
b Standard, alternative medical therapy (e.g. steroid) excluding nifedipine.
c Three trials used tamsulosin.

Summary

All seven meta-analyses using different selection criteria and reporting protocols appear to suggest that treatment with either tamsulosin or nifedipine at the time of presentation with acute ureteric colic increases the likelihood of eventual spontaneous stone passage, hastens the time to stone passage and reduces the risk of unwanted consequences such as pain and the need for an intervention to remove the stone. This leads the authors of these reviews to conclude that the balance of evidence supports routine use of these therapies, although with caveats regarding individual trial quality and trial size, with all but one trial having fewer than 100 participants in each group (*Table 7*). One large trial compared the use of tamsulosin (400 µg) against nifedipine (30 mg) as MET for stones sized 4–7 mm located in the very distal ureter (ureter course within the bladder wall) across 10 centres in China.[45] The trial randomised 3189 patients, and, at 4 weeks, the stone expulsion rate was 96% for tamsulosin and 74% for nifedipine with no further details given, although the Cochrane review[14] gave a RR of 1.3 (95% CI 1.2 to 1.4) and found the trial to have low risk of bias. However, limited details given in the trial report makes quality assessment difficult; there was no sample size calculation to justify the large sample and diagnosis was by any imaging method, although follow-up and primary

TABLE 7 Summary of conclusions of meta-analyses

Review	Blinding	Overall quality	Ascertainment bias	Publication bias	Research recommendation	Recommendation for practice
Hollingsworth *et al.*, 2006[24]	Majority unblinded	Not assessed	Mediterranean setting mainly	No	High-quality RCT	Viable option
Fan *et al.*, 2013[43]	27% low risk	Variable	Good	Unlikely	None	None
Lu *et al.*, 2012[42]	Varied: potential source of bias	Varied	Varied	Yes	Large RCT	Tamsulosin recommended for distal stones of < 10 mm
Singh *et al.*, 2007[41]	Majority unblinded	Poor	NA	No risk for nifedipine; small risk for tamsulosin	Large RCT	Promising but await large trial
Seitz *et al.*, 2009[15]	Majority not blinded	NA	Varied imaging	Yes	Large study	MET for < 10 mm
Campschroer *et al.*, 2014[14]	Noted lesser effect size in placebo studies	Variable	NA	Small risk	Large, multicentre RCT with CT for diagnosis	Alpha-blocker for distal < 10 mm

CT, computerised tomography; NA, not applicable.

outcome assessment was by weekly CT KUB until stone passage or up to 4 weeks. Mean time to stone passage was given as 78.35 hours in the tamsulosin group and 137.93 hours in the nifedipine group. This duration of stone episode appears much shorter than that recorded in previous trials and may relate to the inclusion criteria and recruitment policies for this particular study. Additionally, the Jadad quality score was low (one) and the trial was supported by a manufacturer of tamsulosin.

The possibility that the conclusion from published meta-analyses regarding the benefits of MET is incorrect has to be borne in mind, as up to one-third of meta-analyses that show positive outcomes of a therapy are later altered by the inclusion of results from single, large, multicentre, robust, well-designed RCTs.[46] In the case of MET trials it is noted that use of less diagnostically accurate methods of imaging for participant inclusion prior to the widespread availability of CT KUB may lead to selection bias, because either smaller or radiolucent stones are missed, or people without a stone are included. Similarly, older, less accurate methods of imaging were widely used to decide if the stone had passed. This, together with lack of blinding in non-placebo-controlled studies, could lead to ascertainment bias in favour of the intervention group.

Need for a further trial and implications for design

The change of practice recommendations in some of the published meta-analyses has led to the adoption of MET for people with expectantly managed ureteric colic. The most widely used care guidance document gives a 'Grade A' recommendation for use of an alpha-blocker with follow-up within 14 days.[47] The extent of use of MET is hard to measure, but a survey of urologists in the USA suggests that 25% would recommend its use for stones in the mid and upper ureter and 32% would recommend its use for stones in the distal ureter.[48] The routine use of MET appears to be increasing, at least in the USA, with rates of 14% in 2009[49] rising to 64% in 2012.[50] In the UK, anecdotal discussion at the British Association of Urological Surgeons (BAUS), Section of Endourology, meetings suggests that use is also widespread in response to the EAU guideline recommendation. Despite this practice recommendation and widespread adoption of MET, the uncertainties expressed by most meta-analyses and associated suggestions of the need for a large RCT should be borne in mind. This is of particular importance as the use of ineffective treatment is both wasteful and potentially harmful.

Conclusions

Ureteric stone disease is a significant health problem in the UK and worldwide in terms of its impact on patients and the use of resources. A large proportion of patients with a ureteric stone will ultimately experience spontaneous stone passage. However, any drug treatment that facilitates and increases the chance of this (i.e. MET) will bring added benefit in terms of reduced pain, a reduced need for active intervention and a quicker return to normal activity. Provided the drug is effective and safe, the benefits of use will probably lead to cost savings for the NHS and society as a whole. The available evidence from meta-analyses of a high number of predominantly small, underpowered studies with a high degree of clinical and statistical heterogeneity suggest that MET with either tamsulosin or nifedipine may have some of those advantages over standard therapy of observation and supportive therapy, which has led to increasing adoption as part of routine care. However, as a result of significant uncertainties and knowledge gaps within the evidence base, it was clear that a large, multicentre, well-designed trial was required. From an effectiveness perspective, any trial would also need to measure the impact on pain burden, quality of life and cost-effectiveness from the perspective of the NHS.

Trial objectives

The aim of the SUSPEND trial was to determine the clinical effectiveness and cost-effectiveness of the use of tamsulosin and nifedipine in the management of people with symptomatic ureteric stones. The following question was addressed:

In patients with a symptomatic ureteric stone of ≤ 10 mm in maximum dimension, what is the clinical benefit and cost-effectiveness of using either tamsulosin 400 µg or nifedipine 30 mg once a day for up to 4 weeks over placebo?

In the context of a trial group receiving placebo, two pragmatic comparisons of equal importance were made in the evaluation of MET for facilitating ureteric stone passage:

- tamsulosin 400 µg or nifedipine 30 mg once daily versus placebo
- tamsulosin 400 µg once daily versus nifedipine 30 mg once daily.

The hypotheses being tested were:

1. The use of tamsulosin or nifedipine will result in an absolute increase in the spontaneous stone passage rate of at least 25% compared with placebo (from 50% to 75%).
2. The use of tamsulosin will result in an absolute increase of 10% in the spontaneous stone passage rate compared with nifedipine (from 75% to 85%).

Chapter 2 Trial design

The SUSPEND trial was a multicentre, randomised, placebo-controlled trial evaluating the benefit of two drugs as MET, the alpha-blocker tamsulosin and the calcium channel blocker nifedipine to increase stone clearance rate for UK NHS patients with symptomatic ureteric stones.

The trial protocol has been published by McClinton *et al.*[51]

Participants

Potential participants were adults presenting as an emergency with a diagnosis of ureteric colic at UK NHS hospitals and identified according to the inclusion and exclusion criteria specified below.

Inclusion criteria

- Patients presenting acutely with ureteric colic.
- Patients aged ≥ 18 years to ≤ 65 years.
- Presence of stone confirmed by non-contrast CT KUB.
- Stone within any segment of the ureter.
- Unilateral ureteric stone.
- Largest dimension of the stone ≤ 10 mm.
- Female participants who were willing to use two of the listed methods of contraception prior to taking any trial medication until at least 28 days after receiving the last dose of trial medication, who were post menopausal (defined as 12 months with no menses and without an alternative medical cause) or who had undergone permanent sterilisation. Acceptable forms of contraception for trial purposes included:
    - Established use of hormonal methods of contraception.
    - Placement of an intrauterine device or intrauterine system.
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) plus a spermicidal foam/gel/film/cream/suppository.
    - Male partner was sterile (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) prior to a woman partner starting the trial and was the sole partner of the female participant.
    - True abstinence: when this was in line with the preferred and usual lifestyle of the person willing to take part in the trial. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception for trial purposes.
- Capable of giving written informed consent, which includes compliance with the requirements of the trial.

Exclusion criteria

- Women who have a known or suspected pregnancy (confirmed by a pregnancy test).
- Women who are breastfeeding.
- Women intending to become pregnant during anticipated period of participation in trial.
- Asymptomatic incidentally found ureteric stone.
- Stone not previously confirmed by CT KUB.
- Stone with any one dimension of > 10 mm on CT KUB.
- Kidney stone without the presence of ureteric stone.
- Multiple (i.e. ≥ 2) stones within one ureter.

- Bilateral ureteric stones.
- Stone in a ureter draining an either anatomically or functionally solitary kidney.
- Patients with abnormal upper urinary tract anatomy (such as a duplex system, horseshoe kidney or ileal conduit).
- Presence of urinary sepsis.
- Chronic kidney disease stage 4 or worse (estimated glomerular filtration rate of < 30 ml/minute).
- Patients currently taking an alpha-blocker.
- Patients currently taking a calcium channel blocker.
- Patients currently taking a phosphodiesterase type 5 inhibitor.
- Contraindication or allergy to tamsulosin or nifedipine.
- Patients who are unable to understand or complete trial documentation.

Participants were randomised to one of the three trial groups on a 1 : 1 : 1 basis. The randomisation algorithm used trial centre (site), stone size (≤ 5 mm, > 5 mm) and stone location (upper, middle or lower ureter) as minimisation covariates. A remote telephone interactive voice response randomisation application hosted by the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU) at the University of Aberdeen, UK, was used to perform randomisation.

The main criterion for selection of UK NHS hospital sites where participant recruitment could take place was a high rate (> 15 per month) of patient emergency admissions owing to ureteric colic. Information on admission rates was obtained from a national audit of ureteric stone management undertaken by the BAUS Section of Endourology in 2007 (see www.BAUS.org.uk). A total of 24 UK NHS sites took part in the trial (*Figure 2*). These were Aberdeen Royal Infirmary, Aberdeen; Addenbrooke's Hospital, Cambridge; Bristol Royal Infirmary, Bristol; Broadgreen Hospital, Liverpool; Cheltenham General Hospital, Cheltenham; Derriford Hospital, Plymouth; Freeman Hospital, Newcastle upon Tyne; Guy's Hospital, London; Manchester Royal Infirmary, Manchester; Morriston Hospital, Swansea; Norfolk and Norwich University Hospital, Norwich; Pinderfields Hospital, Wakefield; Queen Elizabeth Hospital, Birmingham; Raigmore Hospital, Inverness; Royal Hallamshire Hospital, Sheffield; Southampton General Hospital, Southampton; Southmead Hospital, Bristol; St George's Hospital, London; St James's University Hospital, Leeds; Sunderland Royal Hospital, Sunderland; The James Cook University Hospital, Middlesbrough; Torbay Hospital, Torquay; University Hospital of South Manchester, Manchester; and the Western General Hospital, Edinburgh.

Trial interventions

Two active treatments were being investigated and compared with a placebo group and each other:

1. tamsulosin hydrochloride 400 µg MR once daily up to a maximum of 28 days
2. nifedipine 30 mg MR once daily up to a maximum of 28 days
3. placebo [lactose-filled capsule (Tayside Pharmaceuticals)] once daily up to a maximum of 28 days.

Medication was overencapsulated to ensure that both participants and trial staff remained blinded to the identity of allocated medication.

Apart from allocated trial medication, all participants received the standard care for expectant management of people with ureteric colic. This included other medications to relieve symptoms, such as analgesics and antiemetics, advice on general measures, such as adequate fluid intake and resumption of normal activity, and appropriate review arrangements to detect stone passage, progressive symptoms or complications such as sepsis. No other adjunctive medications thought to promote stone passage, such as corticosteroids, are approved for use in the UK and clinical staff were asked to avoid use of such agents at site initiation visits.

FIGURE 2 The UK location of the 24 SUSPEND trial sites.

Duration of interventions

Participants took one capsule of trial medication per day until stone passage occurred or further intervention was decided upon, up to a maximum of 28 days after randomisation.

Comparisons

Two pragmatic comparisons were made evaluating MET for facilitating ureteric stone passage:

- tamsulosin (alpha-blocker) or nifedipine (calcium channel blocker) versus placebo
- tamsulosin versus nifedipine.

Outcome measures

Primary outcome measures

Clinical effectiveness

The primary outcome was spontaneous passage of ureteric stones at 4 weeks after randomisation. This was defined as no further intervention planned or carried out to facilitate stone passage at up to 4 weeks. A further intervention was classified as any clinical record entry detailing actual interventions reported to have been carried out within 4 weeks or any further planned intervention. This information was reported on the 4- and 12-week case report form (CRF). Patients' returned questionnaires at 4 weeks and 12 weeks were also assessed for additional interventions that may not have been captured by the CRF.

Health economic

The health economic outcome was incremental costs per quality-adjusted life-years (QALYs) gained at 12 weeks. QALYs were calculated from participant responses to the European Quality of Life-5 Dimensions questionnaire 3 level response (EQ-5D-3L™)[52] completed at baseline, 4 weeks and 12 weeks post randomisation, and costs from use of primary and secondary NHS health-care services from the responses to the 12-week participant questionnaire and the 4- and 12-week CRFs.

Secondary outcome measures

Patient reported

Patient-reported secondary outcomes were:

- severity of pain
- health-related quality of life (HRQoL)
- self-reported use of analgesics
- time to stone passage
- self-reported discontinuation of trial medication (and reasons).

Severity of pain related to the pain on the day of completion of the 4-week questionnaire as measured by the numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain imaginable).[53,54] Analgesic use was measured using the self-reported number of days that pain medication was used up to the time of completion of the 4-week participant questionnaire. HRQoL was measured using the generic health profile measure Short Form questionnaire-36 items (SF-36),[55] and the generic health status measure European Quality of Life-5 Dimensions (EQ-5D™),[56] at baseline, 4 weeks and 12 weeks. Time to stone passage was derived from the 4-week CRF where there was passage of stone confirmed by imaging. Self-reported stone passage was not used to assess time to stone passage. Discontinuation of trial medication up to 4 weeks after randomisation was measured in the 4-week participant questionnaire.

Chapter 3 Methods

Research ethics and regulatory approvals

The SUSPEND trial was a clinical trial involving investigational medicinal products (CTIMPs). It was conducted under the European Union Clinical Trials Directive and was reviewed and approved by the UK Medicines and Healthcare products Regulatory Agency and allocated the EudraCT number 2010–019469–26. The trial was also given a favourable opinion prior to commencement by the East of Scotland Research Ethics Service Research Ethics Committee 2 (reference 10/S0501/31). It was approved by the sponsors (NHS Grampian and University of Aberdeen) and by the research and development departments of the NHS organisations at each participating site prior to trial commencement at each site. The trial was conducted in accordance with the principles of good clinical practice and was registered on the UK Clinical Research Network Portfolio (UKCRN Study ID 9184) and assigned an International Standard Randomised Clinical Trial number (ISRCTN69423238). Prior to starting recruitment at each site, a site initiation visit took place where central trial staff detailed and explained trial procedures to the local principal investigator and clinical research team, and provided a trial-specific site file.

Participants

Trial flow

The flow of participants through the trial is detailed in *Figure 3*.

Identification of patients (screening)

Patients were identified by clinicians working in the urology or accident and emergency departments of participating sites, who were supported by local clinical research teams. Approved trial publicity material in the form of posters was used to help alert staff that the trial was taking place at specific sites.

Recruitment process

Clinicians assessed patients presenting with suspected ureteric calculi in accordance with standard practice. A screening log was completed and included all patients assessed at participating sites to document the reasons for inclusion or non-inclusion in the trial. Following adequate pain relief and confirmation of a single ureteric stone by CT KUB, identified eligible patients were given a patient information leaflet (PIL; see *Appendix 1*) to inform them of the purpose and need for the trial as well as the uncertainties around the clinical usefulness of MET. The PIL was developed in conjunction with the BAUS Section of Endourology Patient Group. Following receipt of the PIL, a member of the local research team asked the patient if they were interested in the trial and ensured any questions that the patients had were answered appropriately. Further checking against eligibility criteria, particularly around the use of tamsulosin and nifedipine as MET, was performed by local research staff. When a patient was eligible and happy to take part in the trial they were asked to sign a trial consent form (see *Appendix 2*).

Randomisation and intervention allocation

Eligible and consenting participants were allocated using minimisation to one of the two intervention groups or the placebo group on a 1 : 1 : 1 basis using the telephone interactive voice response randomisation application hosted by the CHaRT, HSRU, at the University of Aberdeen. The minimisation algorithm used the trial centre (site), stone size (≤ 5 mm, > 5 mm) and stone location (upper, middle, lower ureter) as covariates.

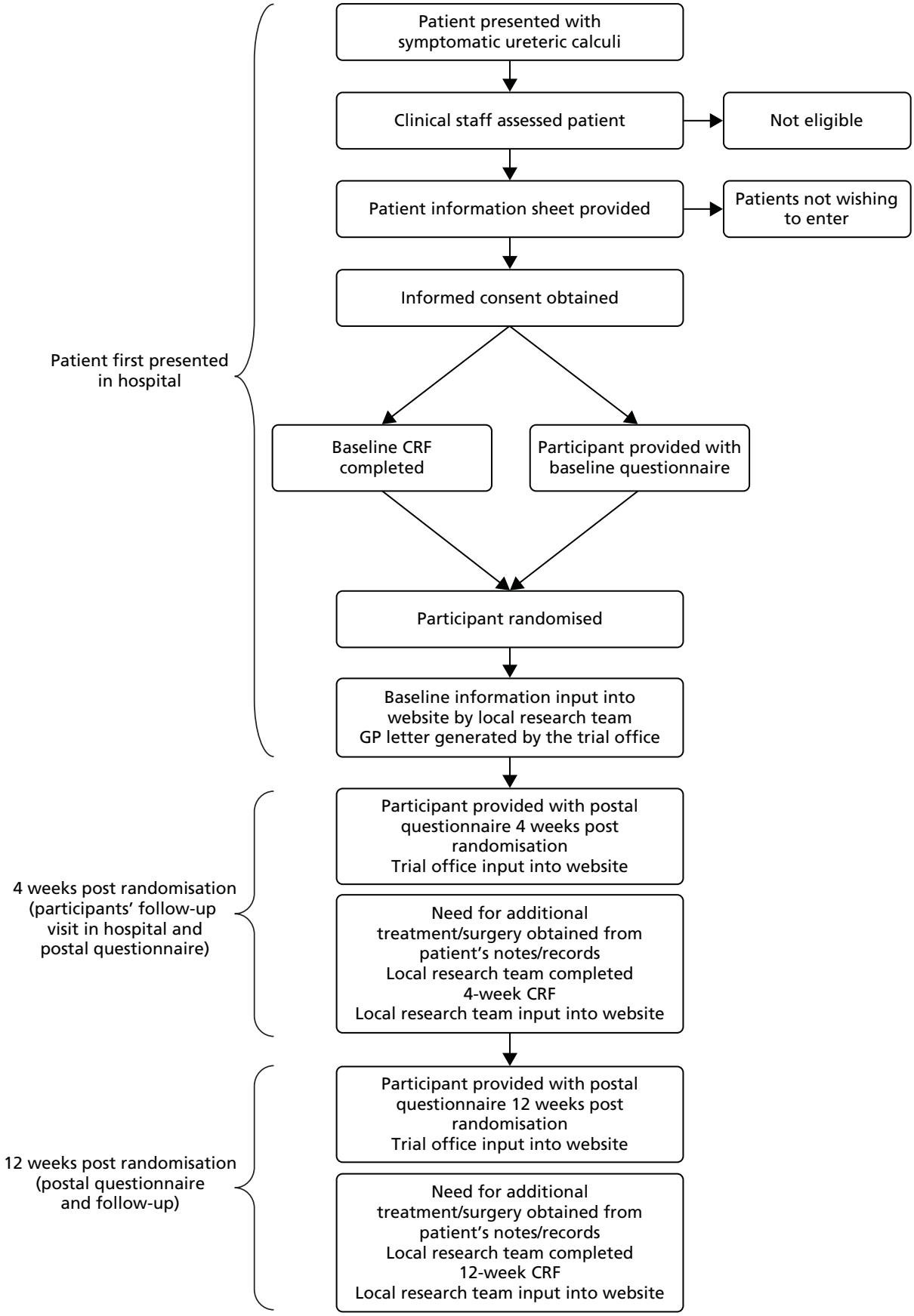

FIGURE 3 Flow of participants through the trial. GP, general practitioner.

Blinding

At randomisation, the participant was allocated a unique participant study number and assigned a numbered participant pack. The packs were provided by an independent supplier containing the overencapsulated trial medication to ensure that the participant, local investigator and trial personnel remained blinded to treatment allocation.

Unblinding

The treatment code was broken only in the case of a serious adverse event (SAE), when it was necessary for the principal investigator at site or treating health-care professional to know which intervention the participant was receiving to determine a management plan.

Each participant was given a card to carry with details of a contact telephone number at the site to be used in the event that unblinding was necessary. Contact information was also available in the participant's hospital records. If unblinding was necessary, a member of the research team or a member of clinical staff at the local recruiting site telephoned the dedicated randomisation service at the CHaRT in Aberdeen on the number provided using the trial centre identification and the participant study number. In the unlikely event of the randomisation service not being able to field the query, the on-call pharmacist at Aberdeen Royal Infirmary was contacted and the same procedure followed.

Following any unblinding via the telephone randomisation service, automatic e-mails were sent to the chief investigator, trial manager and members of the CHaRT management team. If an on-call pharmacist performed the unblinding they would e-mail the same list of people. These e-mails did not contain the treatment code, and the trial team remained blinded as far as was practicable. The chief investigator then ascertained why unblinding had taken place. If the patient was unblinded because of a SAE this was then reported.

Interventions

The trial interventions were:

1. tamsulosin hydrochloride in the form of 400-µg MR capsules
2. nifedipine in the form of 30-mg MR capsules
3. placebo (lactose-filled capsules).

A summary of product characteristics for each of the investigational medicinal products (tamsulosin hydrochloride and nifedipine) used in the trial is included in *Appendix 3*.

All the medicinal products were overencapsulated to maintain the blinding of the trial. Trial medication was presented as capsules in amber plastic containers with a childproof closure and labelled in accordance with Annex 13 of Volume 4 of *The Rules Governing Medicinal Products in the European Union: Good Manufacturing Practices*.[57] All disguised drug packs were stored at site pharmacies under temperature-controlled conditions until dispensed to participants. The medicinal products and the placebo were overencapsulated, packaged and labelled by Tayside Pharmaceuticals, Ninewells Hospital, Dundee, UK, in accordance with Good Manufacturing Practice.

Participants were instructed to store the medication in accordance with the manufacturer's instructions. Unused medication and/or empty packaging were returned to the site by the participant at the 4-week follow-up visit or returned directly to the pharmacy; alternatively, if participants did not attend the 4-week visit, they were instructed to dispose of surplus trial medication appropriately.

Data collection

Questionnaires were designed to obtain information on stone passage or further intervention, pain, HRQoL and resource use, including NHS and personal costs. Participants were asked to complete trial questionnaires at baseline, 4 weeks post randomisation and 12 weeks post randomisation. The baseline questionnaire was completed in hospital before randomisation. Further questionnaires were sent to each participant by post from

the trial office (CHaRT, Aberdeen) with pre-paid envelopes at 4 weeks and 12 weeks post randomisation (see *Appendix 4*). If a participant did not return the questionnaire a reminder letter was sent out approximately 2 weeks later with a short form of the questionnaire containing the EQ-5D only (see *Appendix 4*).

In addition, CRFs were completed by the research team at the recruiting site at baseline and at the follow-up visit 4 weeks after randomisation (see *Appendix 5*). If the participant did not attend the follow-up visit, the CRF was completed from the participant's health-care records. If participants indicated on their 12-week questionnaire that they had received further intervention for their stone since their 4-week questionnaire, or if they completed only a short form of the questionnaire, or if no 12-week questionnaire was returned, a further CRF was completed 12 weeks post randomisation from their health-care records (see *Appendix 5*). The outcome measures collected and their timings of measurement are described in *Table 8*.

Safety reporting

Non-serious adverse events were not collected or reported. Planned hospital visits for conditions other than those associated with the ureteric stone were not collected or reported. Hospital admissions (planned or unplanned) associated with the treatment of the ureteric stone diagnosed at the time of entry to the trial were expected to occur for a proportion of participants. These were recorded as an outcome measure, but were not recorded or reported as SAEs.

All suspected SAEs were assessed in respect of severity, potential relationship to trial medication and whether they were expected or unexpected. Confirmed SAEs were reported to the Trial Office and then to the chief investigator and sponsor, who subsequently provided their assessment and action plan.

Participants who had left hospital were advised to contact their general practitioner (GP) should they experience an adverse event. This is current standard clinical practice for participants receiving tamsulosin or nifedipine within the NHS. As part of their notification that one of their patients was participating in the trial, GPs were asked to inform the trial office of any SAEs or reactions. This provided a robust system for the notification of any serious adverse reactions or SAEs occurring outside hospital research sites.

TABLE 8 Source of timing of outcome measures

Outcome measure	Source	Timing		
		Recruitment	4 weeks post randomisation	12 weeks post randomisation
Further intervention planned	CRF		✓	✓
Pain (NRS)	PQ	✓	✓	
Use of analgesics	PQ		✓	
Further interventions received	PQ and/or CRF		✓	✓
Health status: SF-36 and EQ-5D	PQ	✓	✓	✓
Adverse events	PQ		✓	✓
Time to passage of stone	PQ and CRF		✓	✓
NHS primary and secondary health-care use	PQ and CRF		✓	✓
Participant personal costs	PQ			✓

PQ, participant questionnaire.

Change of status/withdrawal

The trial status of some participants changed during the trial for a number of reasons. These included post-randomisation exclusion, participant withdrawal and medical withdrawal. Participants were free to withdraw from the trial at any time without giving a reason. If a participant withdrew from receiving the trial questionnaires, permission was sought for the research team to continue to collect outcome data from their hospital records. In the event that a participant was told to stop taking trial medication by clinical or trial staff for any reason, the participant continued in the trial and was asked to complete the trial documents unless he or she did not wish to do so.

Data management

Clinical data were entered into the electronic SUSPEND database through the trial web portal (https://viis.abdn.ac.uk/HSRU/suspend/), together with data from participant questionnaires, by the research team working at each hospital site. Questionnaires returned by post to the trial office were entered into the database by the central research team. Staff in the trial office worked closely with the local research teams to ensure that the data were complete and accurate. All trial staff and the statistician responsible for analysing the data remained blinded to allocation until completion of the trial and locking of the database.

Data collected during the course of the research were kept strictly confidential and accessed only by members of the trial team. Participants' details were stored on a secure database under the guidelines of the Data Protection Act 1998, including encryption of any identifiable data.[58] Participants were allocated an individual specific trial number and all data, other than personal data, were identified only by this unique study number.

A random 10% sample of all trial data was generated by the database for re-entry by the trial office to validate correct data entry input. Any discrepancies between original data entry and the re-entered data were reviewed against the original paper copy and incorrect entries corrected accordingly. An initial data entry error rate of > 5% would have triggered a requirement to re-enter the entire data set from that questionnaire. This was not found to be necessary.

Trial oversight committees

The trial Data Monitoring Committee (DMC) comprised three independent individuals who met initially at the beginning of the trial when terms of reference and other committee procedures were agreed. The DMC then met a subsequent four times during the course of the trial to monitor unblinded trial baseline and outcome data provided by the trial statistician and details of SAEs. The DMC reported any recommendations to the chairperson of the Trial Steering Committee (TSC).

The TSC was chaired by a clinician independent from the trial and consisted of two other independent members as well as the grant holders. The TSC met five times over the duration of the trial.

Patient and public involvement

A patient representative was involved in the study design and conduct, with input into production of the PIL and other trial documentation, and membership of both the trial management group and the TSC. The patient representative contributed to, and reviewed, the trial protocol and final report. Additionally, the PIL for the trial (see *Appendix 1*) was developed in conjunction with the BAUS Section of Endourology Patient Group.

Important changes to methods after trial commencement

Serious adverse events

During the initial stages of the trial, a number of SAEs were reported and recorded which, on investigation, were found to be a result of readmissions for continuing treatment of the participant's ureteric stone (i.e. the primary outcome). These were, therefore, being recorded as a SAE as well as an

outcome. To ensure that such events were recorded only as an outcome, the wording regarding the collection of these events was clarified to state:

> *Hospital admissions (planned or unplanned) associated with the treatment of the ureteric stone diagnosed at the time of entry to the trial are expected. These will be recorded as an outcome measure, but will not be recorded or reported as serious adverse events.*

Strategies to improve questionnaire return rate

A number of strategies were implemented during the trial to improve participant questionnaire return rate. A substudy investigating the use of text message notification to participants to inform them that their questionnaire would arrive shortly, combined with e-mail delivery of questionnaires with a link to complete an online version, did not affect response rate. A short version of the 4- and 12-week questionnaires designed to collect the information needed for the primary outcomes of the trial was sent instead of the full questionnaire as a reminder to encourage completion.[59] This did not have any effect on response rate.

A Cochrane review on strategies to improve retention in RCTs found monetary incentives to be one of the few approaches to be effective in increasing response rates to participant questionnaires.[60] Part-way through the trial, a £5 high-street voucher was sent out with the 12-week questionnaire to encourage response. This appeared effective, in that response rate increased from 46% to 57%, but influence from other confounders cannot be ruled out.

Statistical methods and trial analysis

Sample size and power calculation

We combined the data from two meta-analyses,[24,41] which suggested a RR of approximately 1.50 comparing MET (either alpha-blocker or calcium channel blocker) against 'standard care' as the primary outcome. These reviews indicated that the percentage of spontaneous stone passage was approximately 50% in control groups of included RCTs. Only three of the included RCTs directly compared a calcium channel blocker and an alpha-blocker, and these suggested that alpha-blockers were potentially superior to calcium channel blockers. From an analysis of data from Singh *et al.*[41] and Hollingsworth *et al.*,[24] we estimated that proportions of stone passage in the alpha-blocker and calcium channel blocker groups were approximately 85% and 75%, respectively. The most conservative sample size was required to detect superiority between the two active treatments, and the trial was powered on this basis. To detect an increase of 10% in the primary outcome (spontaneous stone passage) from 75% in the calcium channel blocker group to 85% in the alpha-blocker group, with type I error rates of 5% and 90% power, required 354 participants per group (1062 in total); adjusting for 10% loss to follow-up inflated this to 400 per group. We aimed to recruit 1200 participants (randomising 400 to each of the three treatment groups: alpha-blocker, calcium channel blocker and placebo) to provide sufficient power (> 90%) for all other comparisons of interest, and allowing for an anticipated 10% loss to follow-up.

General methods

Treatment groups were described at baseline and follow-up using means [with standard deviations (SDs)], medians (with interquartile ranges) and numbers (with percentages) where relevant. Primary and secondary outcomes were compared using generalised linear models. Treatment effects were estimated from unadjusted and adjusted models. Adjusted models included the trial centre (random effect), stone size (≤ 5 mm, > 5 mm) and stone location (upper, middle or lower ureter). All estimates of treatment effect are presented with 95% CIs. The analysis strategy was by allocated group (intention to treat). Two a priori comparisons were considered for the primary trial analysis:

1. MET [an alpha-blocker (tamsulosin) or a calcium channel blocker (nifedipine)] versus placebo
2. an alpha-blocker (tamsulosin) versus a calcium channel blocker (nifedipine).

We also made two post-hoc comparisons between tamsulosin and placebo, and nifedipine versus placebo. All analyses were carried out using Stata® 13 (StataCorp LP, College Station, TX, USA).

Primary outcome

The primary outcome was analysed using logistic regression. We summarised treatment effects as odds ratios (ORs) and absolute percentage differences, from both adjusted and unadjusted models and presented with 95% CIs. Subgroup analyses (appropriately analysed by testing treatment by subgroup interaction) explored the possible effect modification of stone size (≤ 5 mm or > 5 mm to 10 mm), location in ureter, (upper, mid or lower) and sex, all using stricter levels of statistical significance (99% CIs; p-value < 0.01).[61] Subgroup analyses were also summarised visually using forest plots.[62] There was no correction for multiple testing.[63] During the planning of the SUSPEND trial it was anticipated that there would be few or no missing primary outcome data (owing to the algorithm specifying the primary outcome) and the primary outcome was analysed using complete-case analysis. The pragmatic nature of the trial made assessing the adherence unreliable, and no attempt was made to incorporate any analysis of treatment received.

Secondary outcomes

The secondary outcomes were analysed in a similar manner to the primary outcome using the appropriate link functions. Quality-of-life data were analysed using a mixed model that allowed treatment effects to vary at each time point.

Timings and frequency of analysis

The DMC considered interim inspection of the data on four occasions during the trial. The committee met to review and consider data on outcome measures and SAEs after randomisation of 300, 600 and 900 participants had occurred. Having seen and considered these data, the DMC did not make any recommendations to alter the progression of the trial on any of the occasions on which they met.

Algorithm for primary outcome

The primary clinical outcome is spontaneous passage of ureteric stones at 4 weeks (defined as no further intervention required to facilitate stone passage at up to 4 weeks). The algorithm to create this outcome can be found in *Appendix 6*.

Missing data

Baseline data were collected prior to randomisation. Where baseline data were missing, no imputation was undertaken for the reporting of the baseline covariates of the trial cohort. If there were missing data for covariates that were used in the analyses of the trial outcomes, single imputation was performed using the guidelines set out in White and Thompson[64] (i.e. centre-specific means for continuous variables and an indicator for categorical variables). It was anticipated that the nature of the clinical condition and the algorithm to generate the final outcome would result in few cases of missing primary outcome data and, as such, no plan was made to impute missing primary outcome data. Participants with missing primary outcome data were excluded from analysis of the primary outcome. For other outcomes, participants were included where they provided data under a missing-at-random assumption. Sensitivity analyses were planned to follow guidelines laid out by White *et al.*[65] to assess the impact of any missing outcome data on quality-of-life data from patient questionnaires. The analysis of quality-of-life outcomes was repeated using multiple imputation models with predictions based on all baseline covariates collected. Results were combined across 10 imputed data sets. The robustness of the results was then tested using pattern mixture models, which imputed missing data across a range of potential values from minus half of the observed SD to plus half of the SD of the outcome being analysed.

Economic methods

Introduction

Given that the condition under study was anticipated to be a short-term resolving problem for patients and the NHS, the main planned economic analysis was a 'within-trial' economic evaluation using data collected during the 12 weeks of individual participation. The question addressed was: 'What is the cost-effectiveness of medical expulsive therapy using either tamsulosin or nifedipine compared to no treatment (placebo)?' The trial was set within the perspective of the NHS, although it included both the NHS costs as well as those health-care costs falling on the participants.

Measurement of resource utilisation

Resource use and costs were estimated for each participant. Resource data collected included the costs of the intervention drugs and simultaneous and consequent use of primary and secondary NHS services by participants. Personal health-care costs, such as purchase of medication, were also estimated.

At recruitment, data were collected on the intervention that the participants received, the diagnostic tests conducted and the medications prescribed at the admission. At 12 weeks post randomisation, participants were asked to provide information by questionnaire of their primary and secondary health-care service use. They were asked for details of medications purchased, the cost of these and whether or not they had any visits to non-NHS health-care providers.

The consequential use of health services was recorded prospectively for each participant in the trial. Resource utilisation data were based on responses to the participant questionnaires and the CRFs completed by the local research teams. The CRFs recorded information on non-protocol visits (protocol visits are those scheduled for the purposes of data collection), outpatient visits and readmissions relating to the use and consequences of drug treatment. Use of primary care services, such as prescription medications, and contacts with primary care practitioners (e.g. GPs and practice nurses) were collected via the health-care utilisation questions administered in the participant 12-week questionnaire. Details of the sources used to estimate resource utilisation are included in *Table 9*.

TABLE 9 National Health Service resource use during the 12 weeks of participation

Resource	Relevant variable	Source	Reported outcome
Intervention	Drug (e.g. tamsulosin)	CRF[a]	Number
	Diagnostic tests	CRF[a]	Number
	Analgesic/antibiotics	CRF[a]	Number
Primary care visits	GP doctor visits	PQ	Number
	GP nurse visits	PQ	Number
Secondary care	Outpatient visit	CRF[a] and PQ	Number
	Active further intervention (e.g. insertion of stent)	CRF[a] and PQ	Number
	Admissions days	CRF[a] and PQ	Number

PQ, participant questionnaire.
a CRF completed with reference to the participant's health-care record.

Identification of unit costs

Unit costs were obtained from published sources such as the *British National Formulary* (BNF)[40] and NHS reference costs.[66] The unit cost data source year was 2012–13 and the currency was British pounds.

The cost of the trial intervention included the cost of the drug to which the participants were allocated, the costs of diagnostic tests performed to confirm ureteric stone and the cost of the medications or antibiotics prescribed at diagnosis. The unit costs of medications were obtained from the BNF[40] and the diagnostic tests costs were obtained from NHS reference costs.[66] The unit costs of medicines given on admission were assumed to be those of the most commonly used drugs. The unit cost of NSAIDs was that of diclofenac (50 mg) given as a tablet, and the cost of opiates was based on the cost of morphine (10-mg injection). Antibiotic costs were based on the unit cost of a 3-day course of ciprofloxacin (500 mg). The initial secondary care attendances prior to and at recruitment were not included as costs because they were considered to be the same across all trial groups. The unit cost for the diagnostic test received was based on the average NHS reference cost for a computerised tomography (CT) scan ordered by the urology department.

The costs of subsequent resource use comprised costs to both the primary (GP appointments) and secondary (outpatient appointments and admissions) NHS care services. Unit costs for GP visits were obtained from the Personal Social Services Research Unit costs of primary care.[67] Outpatient visit unit cost was based on the average NHS tariff for a urology department consultant-led outpatient appointment obtained from the reference costs.[66] A summary of the unit costs of the resources used is provided in *Table 10*.

Unit costs of further active intervention for the ureteric stone were derived from costs associated with different urology Healthcare Resource Group codes as detailed in *Table 10*. For occasions when a participant received two interventions on the same day, unit cost use was defined as the average cost of treatment of urinary tract stone disease with intervention. For those that had an admission with no intervention, the cost of urinary stone disease without intervention was used. As the median stay in the urology department was 1 day, any extra admissions days were costed using the long-stay excess days tariff.[66]

The participant resource use data and unit cost were combined for each of the primary and secondary NHS care services to give an estimate of the total health-care cost per participant, as well as the average cost for each identified resource and the average total cost for each group of the trial.

TABLE 10 Unit costs and their sources

Resource	Unit cost	Source	Notes
Drug			
Alpha-blocker (tamsulosin)	£4.76	BNF[40]	The 28-day cost of the non-proprietary tamsulosin hydrochloride, daily cost of £0.17
Calcium channel blocker (nifedipine)	£6.95	BNF[40]	The 28-day cost of the non-proprietary nifedipine, daily cost of £0.25
Diagnostic test	£60.00	Reference costs[66]	RA08A CT scan, one area, no contrast, 19 years and over, diagnostic imaging: direct access[a]
Analgesia			
NSAID	£2.49	BNF[40]	Based on cost of diclofenac (Voltarol®, Novartis)
Opiate	£2.60	BNF[40]	Based on cost of morphine injection
Other	£2.55	Average of above 2	

continued

TABLE 10 Unit costs and their sources (*continued*)

Resource	Unit cost	Source	Notes
Antibiotic used	£0.80	BNF[40]	Based on most frequently administered antibiotic (ciprofloxacin, non-proprietary)
Cost additional day in hospital	£264.00	Reference costs[66]	LB05G intermediate percutaneous kidney or ureter procedures, 19 years and over, with CC score of 0 [non-elective inpatient (long-stay) excess bed-days]
Percutaneous insertion of nephrostomy tube	£1207.00	Reference costs[66]	LB09D intermediate endoscopic ureter procedures, 19 years and over [non-elective inpatients (short stay)]
	£691.00		Day case
Antegrade insertion of stent into ureter	£647.00	Reference costs[66]	LB05G intermediate percutaneous kidney or ureter procedures, 19 years and over, with CC score of 0–2 [non-elective inpatients (short stay)]
	£566.00		Day case
Therapeutic ureteroscopic operations	£1458.00	Reference costs[66]	LB65E major endoscopic kidney or ureter procedures, 19 years and over with CC score 0–2 [non-elective inpatients (short stay)]
	£1434.00		Day case
Endoscopic insertion/ removal of stent into ureter	£524.00	Reference costs[66]	LB72A diagnostic flexible cystoscopy, 19 years and over [non-elective inpatients (short stay)]
	£402.00		Day case
ESWL of calculus in ureter	£775.00	Reference costs[66]	LB36Z ESWL [non-elective inpatients (short stay)]
	£504.00		Day case
Hospital admission without procedure	£470.00	Reference costs[66]	LB40G urinary tract stone disease without interventions, with CC score of 0–2 [non-elective inpatients (short stay)]
	£456.00		Day case
More than one intervention	£1719.00	Reference costs[66]	LB40D urinary tract stone disease with interventions, with CC score of 0–2 [non-elective inpatients (short stay)]
Outpatient visit	£101.00	Reference costs[66]	Based on the average unit cost of outpatient attendances (both consultant- and non-consultant-led) to urology department
Practice nurse visit	£15.50		Based on cost per consultation
GP visit	£44.46		Per surgery consultation lasting 11.7 minutes
Cost of visit to other health-care professionals	As indicated by participant		Based on information on PQ
Medications	As indicated by participant		Based on information on PQ
Visits to non-NHS providers	As indicated by participant		Based on information on PQ

CC, complications and comorbidities; PQ, participant questionnaire.
a Information includes the currency code, currency description and sheet name.

Participant costs

Participant costs comprised self-purchased health care, such as prescription costs (for participants who pay prescription charges), over-the-counter medications and visits to non-NHS health-care providers. Information about participant resource use was collected using the 12-week health-care utilisation questionnaire (see *Appendix 4*).

Health status

Health-related quality-of-life measures were collected at baseline, 4 weeks and 12 weeks by participant completion of the EQ-5D and the SF-36 questionnaires. The EQ-5D divides health status into five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each of these dimensions has three levels, so 243 possible health states exist. Responses on the participants' EQ-5D questionnaires were transformed using a standard algorithm to produce a health-state utility at each time point for each participant. The utility scores obtained at baseline, 4 weeks and 12 weeks were used to estimate the mean QALY score for each group[52] over the 12-week (approximately 0.25 years) period of observation.

Responses from the SF-36 questionnaire were also used as the basis of QALYs as a sensitivity analysis to validate the EQ-5D scores. They were mapped onto the existing Short Form questionnare-6 Dimensions (SF-6D) measure using a standard algorithm[68] to allow utility values to be estimated for each time point. These utility scores were transformed to QALYs using the methods described above to provide an alternative measure of QALYs for each participant.

Data analysis

Resource use, cost and QALY data were summarised and analysed using Stata 13. As data were collected over a short (12-week) period, discounting was not carried out. The main cost-effectiveness analysis reports the results of participants with complete data. All the difference estimates are presented with 95% CIs. Data reported as mean costs for both active treatment groups and the placebo group were derived for each item of resource use and then compared using unpaired Student's *t*-test and linear regression adjusted for baseline values. The mean incremental costs were estimated using general linear models, with adjustment for minimisation variables [centre at which participant was recruited, stone size (≤ 5 mm, > 5 mm), stone location at diagnosis (lower, mid or upper ureter) and sex]. The general linear model allowed for heteroscedasticity by specifying a distributional family which reflects the relationship between mean and variance.[69] A modified Park's test was conducted to identify the appropriate family, which identified a gamma family. This allows for the skewness of cost data and assumes that variance is proportional to the square of the means as appropriate. A link function needs to be identified for the general linear model to specify the relationship between the set of regressors and the conditional mean. The link test recognised the identity link as the appropriate link function. The identity link leaves the interpretation of the coefficients unchanged from that of the ordinary least squares, as the covariates act additively to the mean. The mean incremental QALYs were estimated using ordinary least squares and were adjusted for minimisation factors, as well as for the baseline EQ-5D score.

Incremental cost-effectiveness

Cost-effectiveness of the trial interventions from the perspective of the NHS during the period of observation was measured in terms of the number of participants needing further treatment within 12 weeks, and in terms of QALYs accrued by participants in each group at 12 weeks. The results are presented as point estimates of mean incremental costs, number of further treatments needed, QALYs, incremental cost per further treatment needed and incremental cost per QALY. Measures of variance for these outcomes required bootstrapping of the point estimates. Incremental cost-effectiveness data are presented by cost-effectiveness acceptability curves (CEACs). Forms of uncertainty (e.g. concerning the unit cost of a resource from the different centres) are addressed using deterministic sensitivity analysis.

As the data were not normally distributed, non-parametric bootstrapping was used to generate 1000 estimates of mean costs and QALYs for each treatment group. CEACs were generated using these 1000 estimates, using the net monetary benefit (NMB) approach. The NMB associated with a given treatment option is given by the formula:

$$\text{NMB} = (\text{Effect} \times \text{Rc}) - \text{cost}, \quad (1)$$

where effects are measured in QALYs and Rc is the ceiling ratio of willingness to pay (WTP) per QALY. Using this formula, the strategy with greatest NMB is identified for each of the 1000 bootstrapped replicates of the analysis, for different ceiling ratios of WTP per QALY. Plotting the proportion of bootstrap iterations favouring each treatment option (in terms of the NMB) against increasing WTP per QALY produces the CEAC for each treatment option. These curves graphically present the probability of each treatment strategy being considered optimal at different levels of WTP per QALY gained.

The degree of missing data for the variables used in the derivation of costs was very low, and the data that were missing were considered to be missing completely at random. However, the number of participants with completely missing data for EQ-5D scores at 4 weeks and 12 weeks used for the derivation of QALYs was high (available data: tamsulosin group = 164/383; nifedipine group = 165/383; and placebo group = 157/384). Several methods of imputation were used as described in the sensitivity analysis.

Sensitivity analysis

There are elements of uncertainty owing to the lack of available information; therefore, various sensitivity analyses were conducted to explore the importance of such uncertainties. One-way sensitivity analyses using extreme values were performed around the QALY estimates. As the base-case analyses were performed using participants with complete cases, multiple imputation was carried out using chained equations in Stata 13 to replace missing cost and EQ-5D variables with a plausible value in 20 imputed data sets.

There was uncertainty around the QALY estimates as they were derived using the EQ-5D. There was some uncertainty over whether or not the dimensions in the EQ-5D are sensitive enough to capture the loss in quality of life, particularly in reference to acute pain. Therefore, SF-36 responses were mapped on the SF-6D measure using the algorithm by Brazier *et al.*[68] to validate the estimate of utility value for each time point derived from the EQ-5D. These scores were used in the same way as the EQ-5D to provide an alternative measure of QALYs for each participant.

A modelling exercise had been planned to extrapolate the estimates of the cost–utility analysis to a longer time horizon than that considered by the trial. However, the decision was taken not to perform any further analysis as the trial data suggested that there were very few cases that had not resolved by the end of the 12-week trial period and there was no chance of recurrence of the same stone.

Chapter 4 Participant baseline characteristics

Trial recruitment

In total, 1167 patients presenting to 24 UK NHS hospitals for emergency treatment of ureteric colic were randomised during the 35 months between January 2011 and December 2013, and followed up to March 2014. The trajectory of recruitment from all sites during the course of the trial is shown in *Figure 4*, and *Table 11* lists the recruiting sites and individual recruitment duration, total recruitment and average recruitment rate per month.

Participant flow

The progress of participants through the trial from screening to final outcome measurement at 12 weeks after randomisation is shown in *Figure 5*, which complies with current recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement.[70] A total of 17 participants were withdrawn following randomisation and have not been included in the main analysis, for the reasons stated in *Table 12*. Fourteen participants did not have any primary outcome data recorded, which left 1136 (97%) randomised participants included in the primary outcome analysis.

Baseline characteristics

Our randomisation algorithm, including minimisation by the variables of stone size and location, ensured that the three trial groups were well balanced across all relevant and measured covariates (*Table 13*). Participants were drawn from the expected age range within the limits imposed by the nature of the trial as a CTIMP set at 18–65 years. Those over 65 years old were not included as there is a requirement to titrate the dose of nifedipine in this age group (see *Appendix 3*) which was not possible. Women accounted for 19% of the trial population. The groups were well balanced for opiate and NSAID use prior

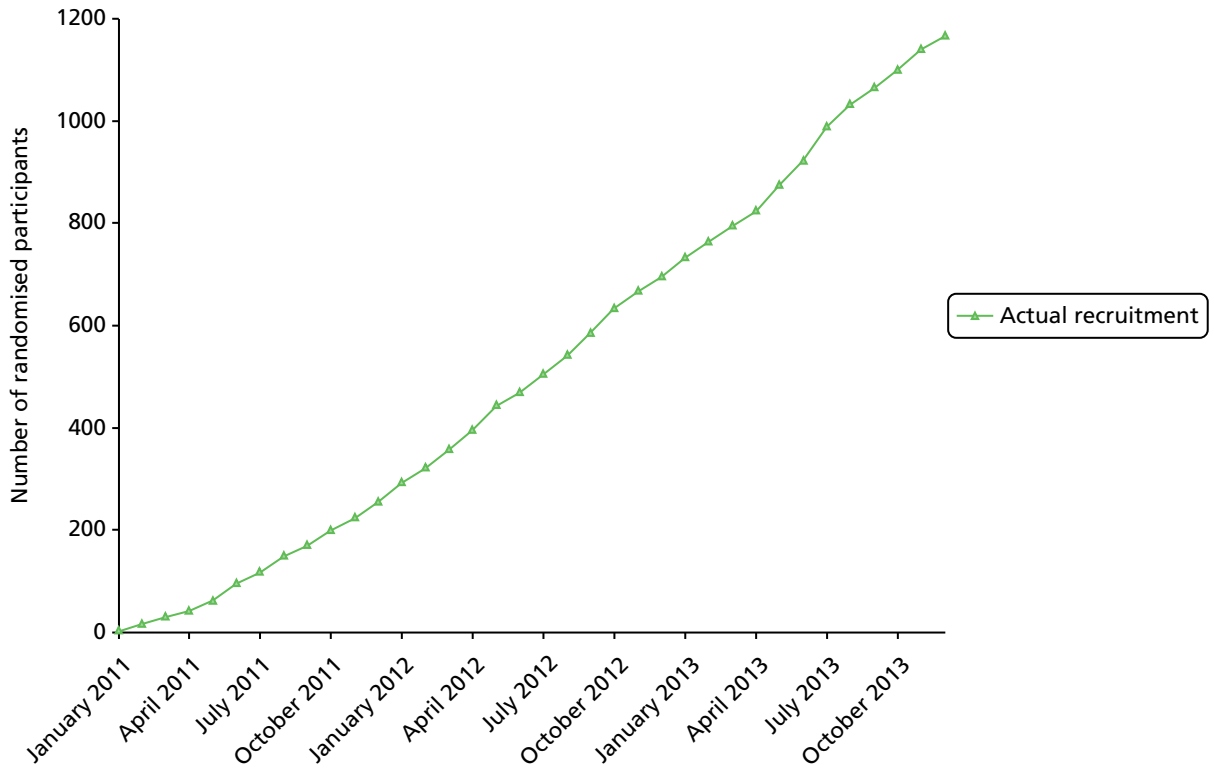

FIGURE 4 SUSPEND recruitment over time.

TABLE 11 SUSPEND recruitment by centre

Recruiting site	Number randomised	Percentage of total recruitment ($n = 1167$)	Number of recruiting months	Average number recruited per month
Freeman Hospital, Newcastle	211	18	36	5.86
Pinderfields General Hospital, Wakefield	154	13	32	4.81
Southmead Hospital, Bristol	109	9	24	4.54
Norfolk and Norwich University Hospital, Norwich	86	7	32	2.69
Cheltenham General Hospital, Cheltenham	24	2	9	2.67
Morriston Hospital, Swansea	75	6	33	2.27
Wythenshawe Hospital, Manchester	36	3	17	2.12
Aberdeen Royal Infirmary, Aberdeen	75	6	36	2.08
St George's Hospital, London	56	5	31	1.81
St James' University Hospital, Leeds	25	2	14	1.79
Addenbrooks Hospital, Cambridge	35	3	21	1.67
Royal Hallamshire Hospital, Sheffield	41	4	25	1.64
The James Cook University Hospital, Middlesbrough	46	4	29	1.59
Derriford Hospital, Plymouth	53	5	34	1.56
Southampton General Hospital, Southampton	19	2	13	1.46
Sunderland Royal Infirmary, Sunderland	34	3	25	1.36
Bristol Royal Infirmary, Bristol	7	1	6	1.17
Raigmore Hospital, Inverness	29	2	26	1.12
Queen Elizabeth Hospital, Birmingham	2	0	2	1.00
Torbay Hospital, Torquay	20	2	27	0.74
Guy's Hospital, London	8	1	11	0.73
Broadgreen Hospital, Liverpool	18	2	27	0.67
Manchester Royal Infirmary, Manchester	3	0	16	0.19
Western General Hospital, Edinburgh	1	0	13	0.08

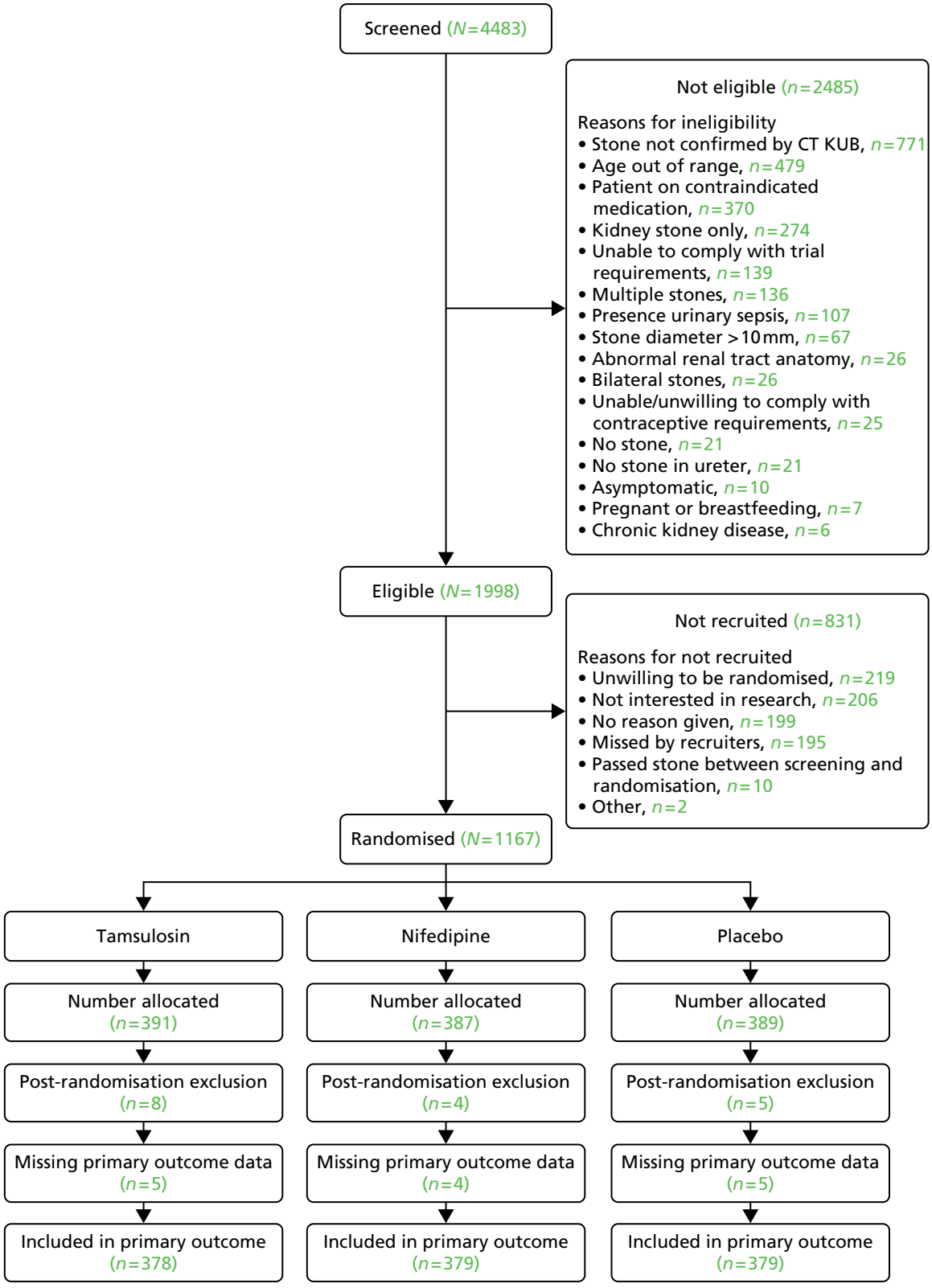

FIGURE 5 The SUSPEND trial CONSORT diagram.

TABLE 12 Reasons for post-randomisation exclusion

Reason for exclusion	Intervention		
	Tamsulosin ($n = 8$)	Nifedipine ($n = 4$)	Placebo ($n = 5$)
Age out of range	5	2	5
Given tamsulosin after randomisation	3		
Found to have multiple stones		1	
Stone not within ureter		1	

TABLE 13 Baseline characteristics

Baseline characteristics	Intervention		
	Tamsulosin ($N = 383$)	Nifedipine ($N = 383$)	Placebo ($N = 384$)
Age (years), mean (SD)	43.1 (11.5)	42.3 (11.0)	42.8 (12.3)
Female, *n* (%)	68 (17.8)	66 (17.2)	85 (22.1)
Stone size (mm), mean (SD)	4.6 (1.6)	4.5 (1.6)	4.5 (1.7)
≤ 5 mm, *n* (%)	287 (74.9)	286 (74.7)	286 (74.5)
> 5 mm, *n* (%)	96 (25.1)	97 (25.3)	98 (25.5)
Stone location			
Upper ureter, *n* (%)	94 (24.5)	89 (23.2)	93 (24.2)
Mid ureter, *n* (%)	40 (10.4)	43 (11.2)	44 (11.5)
Lower ureter, *n* (%)	249 (65.0)	251 (65.5)	247 (64.3)
History of previous stone episode, *n* (%)	130 (33.9)	118 (30.8)	137 (35.7)
Duration of pain (days), mean (SD)	3.0 (5.1)	2.6 (3.3)	3.2 (5.5)
Pain visual analogue score, mean (SD)	4.0 (3.4)	3.9 (3.4)	3.6 (3.2)
Analgesic medication pre-admission, *n* (%)			
NSAID	132 (34.5)	110 (28.7)	117 (30.5)
Opiate	63 (16.4)	67 (17.5)	81 (21.1)
Other	79 (20.6)	86 (22.5)	79 (20.6)
Analgesic medication on admission, *n* (%)			
NSAID	279 (72.8)	289 (75.5)	278 (72.4)
Opiate	224 (58.5)	230 (60.1)	230 (59.9)
Other	127 (33.2)	141 (36.8)	133 (34.6)
Antibiotic medication on admission, *n* (%)	38 (9.9)	46 (12.0)	41 (10.7)
SF-36 physical component summary, mean (SD)	47.0 (9.0)	46.5 (9.2)	46.1 (9.7)
SF-36 mental component summary, mean (SD)	50.2 (10.8)	50.6 (10.8)	49.6 (11.6)
EQ-5D, mean (SD)	0.677 (0.311)	0.674 (0.332)	0.701 (0.306)

to randomisation, in line with a similar duration of pain symptoms prior to randomisation. The overall proportion of participants that fell into the pre-specified subgroups related to stone size and location was similar to previous cohorts and they were well balanced between the three groups. One-third of participants had suffered a previous stone episode at some point in the past.

Site staff and participant response rates

Completion rates for the 4- and 12-week CRFs from site staff, and participant response rates for the 4- and 12-week questionnaires are detailed in *Table 14*. Average response rates were 63% for the 4-week participant questionnaire and 49% for the 12-week participant questionnaire with no differences between trial groups. Denominators in the results sections are the number of participants that were included in that specific analysis and reflect the number of participants with available data.

TABLE 14 Response to 4- and 12-week questionnaires, and CRFs

	Intervention		
Type of response	Tamsulosin ($N = 383$)	Nifedipine ($N = 383$)	Placebo ($N = 384$)
4-week questionnaire, *n* (%)	247 (64.5)	241 (62.9)	231 (60.2)
4-week CRF, *n* (%)	378 (98.7)	379 (99.0)	379 (98.7)
12-week questionnaire, *n* (%)	187 (48.8)	194 (50.7)	183 (47.7)
12-week CRF, *n* (%)	357 (93.2)	356 (93.0)	358 (93.2)

Chapter 5 Outcomes and results

Primary outcome

A primary outcome was attributed to 1136 of the 1150 included participants (99%), with 14 participants (1%) completely lost to follow-up. The occurrence of the primary outcome at any time up to 4 weeks after randomisation (number of participants not requiring further intervention for the symptomatic ureteric stone) was 307 out of 378 (81.2%) in the tamsulosin group and 304 out of 379 (80.2%) in the nifedipine group, compared with 303 out of 379 (79.9%) for those randomised to placebo. These primary results are described in more detail in *Table 15* using both raw and adjusted analyses. The full logistic regression model is detailed in *Appendix 7*.

We also recorded the number of participants having an intervention planned between 4 weeks and 12 weeks on the 12-week CRF. A further 27 (7.1%) participants in the tamsulosin group, 25 (6.4%) in the nifedipine group and 28 (7.4%) in the placebo group were recorded as having had an intervention between these time points.

TABLE 15 Primary outcome: stone passage at 4 weeks (defined as number of participants not requiring further intervention)

	Intervention		
Analyses type	**Tamsulosin (*N* = 378)**	**Nifedipine (*N* = 379)**	**Placebo (*N* = 379)**
No further intervention, *n* (%)	307 (81.2)	304 (80.2)	303 (79.9)
	OR, 95% CI;* p-*value		***Risk difference, 95% CI***
MET vs. placebo			
Unadjusted	1.04, 0.77 to 1.43; 0.76		0.8%, –4.1% to 5.7%
Adjusted	1.06, 0.70 to 1.60; 0.78		0.9%, –5.1% to 6.8%
Tamsulosin vs. nifedipine			
Unadjusted	1.07, 0.74 to 1.53; 0.73		1.0%, –4.6% to 6.6%
Adjusted	1.06, 0.73 to 1.53; 0.77		0.8%, –4.5% to 6.1%
Tamsulosin vs. placebo			
Unadjusted	1.08, 0.76 to 1.56; 0.76		1.2%, –4.4% to 6.9%
Adjusted	1.09, 0.67 to 1.78; 0.73		1.3%, –5.7% to 8.3%
Nifedipine vs. placebo			
Unadjusted	1.02, 0.71 to 1.45; 0.93		0.2%, –5.4% to 5.9%
Adjusted	1.03, 0.68 to 1.56; 0.88		0.5%, –5.6% to 6.5%

Adjusted analyses include stone location lower, middle, upper ureter, stone size (< 5 mm, > 5 mm) and a random effect for centre.

Secondary outcomes

Estimated time to stone passage

The outcome for time to passage of stone as measured by clinical report, and confirmed by imaging, was available for 237 (21%) participants and showed no difference between groups (*Table 16*).

Pain

Participants scored the severity of pain during the day of completion of the baseline and 4-week questionnaire using the NRS.[53,54] The duration of pain and use of analgesic medication was recorded as the number of days pain medication was used on the 4-week participant questionnaire. The results are shown in *Table 17*.

Health status

Generic health profile as measured by the SF-36 and EQ-5D at baseline and 4 weeks and 12 weeks after randomisation is shown in *Table 18* and *Figure 6*.

On both the EQ-5D and the SF-36 physical component summary, participants had impaired HRQoL at baseline which returned to population average (SF-36) or full health (EQ-5D) levels by 12 weeks. There was no evidence of a difference between any groups when comparing MET to placebo or tamsulosin to nifedipine at either of the time points. Owing to the high proportion of missing data, the robustness of these results was tested using multiple imputation and pattern mixture models. Younger participants and those with higher baseline SF-36 physical and mental component summary scores were less likely to respond at 4 weeks and 12 weeks. Multiple imputation models gave practically identical treatment effect estimates but with slightly tighter CIs for all treatment effect estimates in *Table 18*. The results were also robust when varying the pattern of missing data for all but implausible scenarios; for example, missing data in MET group were no different from observed data, but in the placebo group the missing data were over one-third of a SD lower (i.e. 3 points on the SF-36 physical component summary) than observed data. This was the case for all treatment effects summarised in *Table 18*.

TABLE 16 Time to stone passage

	Intervention		
Analyses type	**Tamsulosin ($n = 79$)**	**Nifedipine ($n = 74$)**	**Placebo ($n = 84$)**
Time to stone passage (days)			
Mean (SD)	16.5 (12.6)	16.2 (14.5)	15.9 (11.3)
Median (25th, 75th centile)	14 (5, 27)	13 (4, 26)	14 (5, 25)
MET vs. placebo (difference, 95% CI; p-value)			
Unadjusted	0.5, –2.9 to 3.9; 0.78		
Adjusted	0.6, –2.6 to 4.0; 0.71		
Tamsulosin vs. nifedipine (difference, 95% CI; p-value)			
Unadjusted	0.4, –3.7 to 4.4; 0.86		
Adjusted	0.6, –2.5 to 3.7; 0.72		

TABLE 17 Pain outcomes

Outcome	Intervention		
	Tamsulosin (*N* = 247)	Nifedipine (*N* = 239)	Placebo (*N* = 231)
Any self-reported pain medication during first four weeks, *n*/*N* (%)	139/245 (56.7)	133/239 (55.6)	136/231 (58.9)
Number of days of pain medication use[a]			
Mean (SD)	11.6 (8.7)	10.7 (9.0)	10.5 (8.2)
Median (25th, 75th centile)	10 (4, 17)	7 (4, 14)	7 (4, 14)
MET vs. placebo (difference, 95% CI; *p*-value)	0.6, –1.6 to 2.8; 0.45		
Tamsulosin vs. nifedipine (difference, 95% CI; *p*-value)	0.8, –1.6 to 3.2; 0.50		
EQ-5D pain domain at 4 weeks	(*N* = 244)	(*N* = 239)	(*N* = 229)
No pain or discomfort, *n* (%)	170 (69.7)	159 (66.5)	154 (67.2)
Moderate pain or discomfort, *n* (%)	66 (27.0)	71 (29.7)	65 (28.4)
Extreme pain or discomfort, *n* (%)	8 (3.3)	9 (3.8)	10 (4.4)
MET vs. placebo (OR, 95% CI; *p*-value)	0.94, 0.73 to 1.21; 0.66		
Tamsulosin vs. nifedipine (OR, 95% CI; *p*-value)	0.82, 0.62 to 1.09; 0.17		
VAS pain scale at 4 weeks[a]	(*N* = 233)	(*N* = 231)	(*N* = 216)
Mean (SD)	1.0 (2.0)	1.3 (2.2)	1.2 (2.2)
MET vs. placebo (difference, 95% CI; *p*-value)	0.0, –0.4 to 0.4; 0.96		
Tamsulosin vs. nifedipine (difference, 95% CI; *p*-value)	–0.3, –0.7 to 0.1; 0.095		
EQ-5D pain domain at 12 weeks	(*N* = 183)	(*N* = 188)	(*N* = 177)
No pain or discomfort, *n* (%)	126 (68.9)	136 (72.3)	133 (75.1)
Moderate pain or discomfort, *n* (%)	50 (27.3)	46 (24.5)	41 (23.2)
Extreme pain or discomfort, *n* (%)	7 (3.8)	6 (3.2)	3 (1.7)
MET vs. placebo (OR, 95% CI; *p*-value)	1.26, 0.87 to 1.82; 0.21		
Tamsulosin vs. nifedipine (OR, 95% CI; *p*-value)	1.14, 0.84 to 1.56; 0.39		

VAS, visual analogue scale.

a Percentages are derived from the number of responses available for each variable. All estimates adjusted for stone size, stone location and centre (random effect). ORs compare any pain (moderate or extreme) reported on EQ-5D between groups.

TABLE 18 Quality-of-life scores

Quality-of-life measures	Intervention		
	Tamsulosin (*N* = 383)	Nifedipine (*N* = 383)	Placebo (*N* = 384)
SF-36 physical component summary,* n *[mean] (SD)			
Baseline	369 [46.5] (9.2)	372 [47.0] (9.0)	369 [46.1] (9.7)
4 weeks	229 [48.0] (9.4)	228 [47.9] (9.7)	213 [47.9] (8.8)
12 weeks	177 [51.2] (9.7)	177 [51.4] (9.2)	167 [51.6] (9.0)
Effect estimates, 95% CI; p-*value*			
	MET vs. placebo		***Tamsulosin vs. nifedipine***
4 weeks	–0.2, –1.4 to 1.0; 0.83		0.4, –1.0 to 1.8; 0.61
12 weeks	0.0, –1.4 to 1.3; 0.96		0.8, –0.7 to 2.3; 0.30
SF-36 mental component summary,* n *[mean] (SD)			
Baseline	369 [50.6] (10.8)	372 [50.2] (10.8)	369 [49.6] (11.6)
4 weeks	229 [47.7] (11.9)	228 [47.7] (11.9)	213 [46.5] (11.8)
12 weeks	177 [49.3] (11.7)	177 [50.4] (10.3)	167 [51.3] (9.9)
Effect estimates, 95% CI; p-*value*			
	MET vs. placebo		***Tamsulosin vs. nifedipine***
4 weeks	0.5, –1.0 to 2.0; 0.53		–0.3, –2.1 to 1.4; 0.70
12 weeks	–1.5, –3.1 to 0.2; 0.09		–1.5, –3.4 to 0.4; 0.11
EQ-5D,* n *[mean] (SD)			
Baseline	373 [0.674] (0.332)	369 [0.677] (0.311)	373 [0.701] (0.306)
4 weeks	243 [0.837] (0.271)	238 [0.853] (0.241)	226 [0.846] (0.242)
12 weeks	182 [0.859] (0.242)	187 [0.868] (0.240)	175 [0.898] (0.184)
Effect estimates, 95% CI; p-*value*			
	MET vs. placebo		***Tamsulosin vs. nifedipine***
4 weeks	0.001, –0.035 to 0.037; 0.96		–0.003, –0.045 to 0.038; 0.87
12 weeks	–0.028, –0.068 to 0.011; 0.16		0.002, –0.043 to 0.048; 0.91

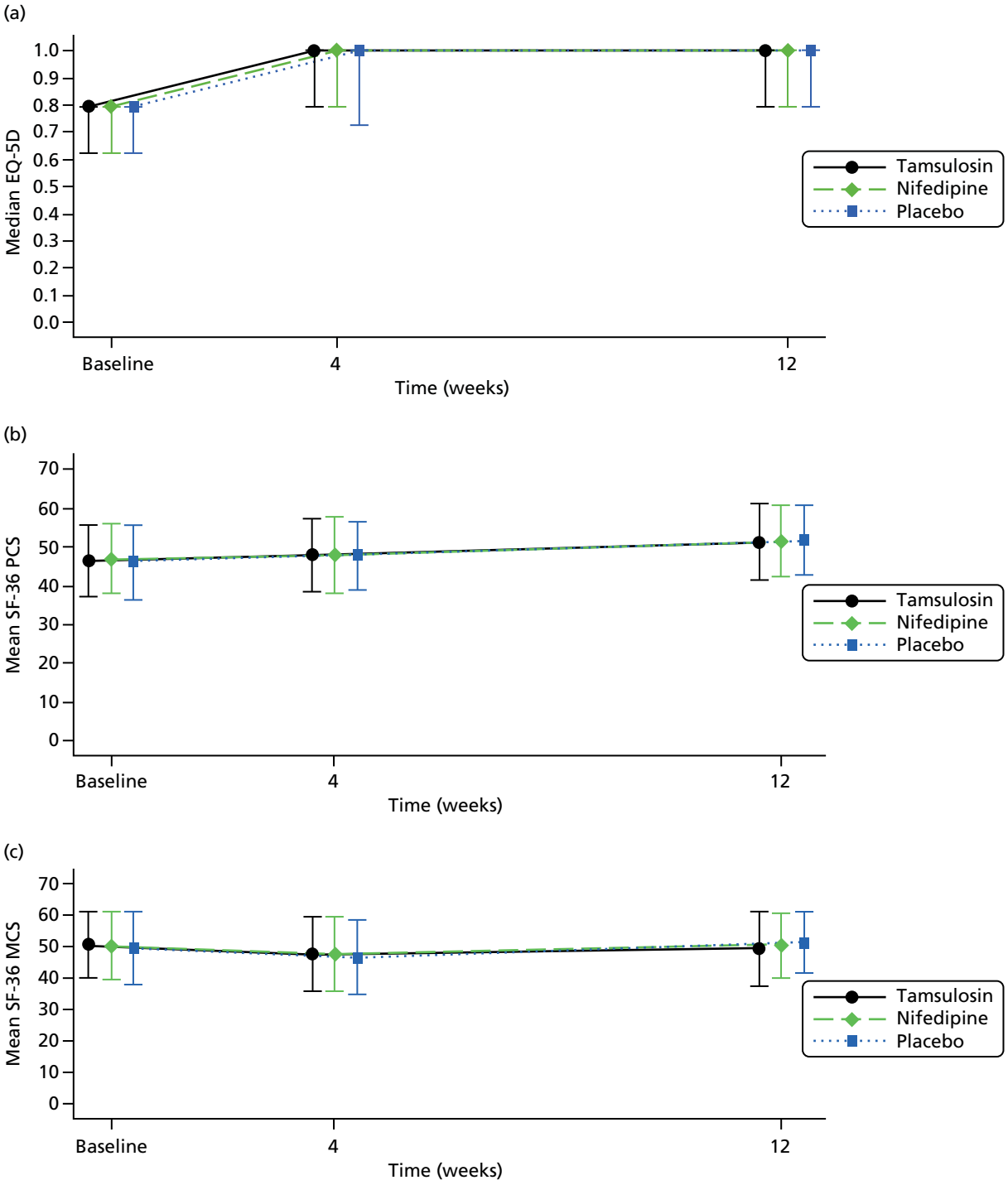

FIGURE 6 Quality-of-life scores measured at baseline, 4 weeks and 12 weeks. Graphs summarise mean and SD for SF-36 physical component summary (PCS) and mental component summary (MCS), median and 25th to 75th centiles for the EQ-5D.

Duration of hospitalisation

The number of participants with further hospital admissions was low and similar in all the groups (see *Table 21*). The average stay of additional hospital admissions up to 12 weeks after randomisation was 0.17 days (SD 0.64 days) in the tamsulosin group, 0.23 days (SD 1.06 days) in the nifedipine group and 0.25 days (SD 1.13 days) in the placebo group.

Significant clinical events

Participant discontinuation of trial medication was reported from responses to a single question on the 4-week participant questionnaire. Discontinuation rates solely as a result of side effects were 10% (25/247) for tamsulosin, 17% (40/241) for nifedipine and 6% (15/231) for placebo (*Table 19*). Serious adverse reactions (defined as SAEs that were thought to be possibly or definitely related to trial medication) were recorded by sites using a SAE form. The event rates are shown in *Table 19* with further details of the reactions reported in *Table 20*.

TABLE 19 Discontinuation and serious adverse reaction rates

	Intervention		
Quality-of-life measures	Tamsulosin ($N = 247$)	Nifedipine ($N = 241$)	Placebo ($N = 231$)
Participant discontinuation of medication as a result of side effects, *n* (%)	25 (10)	40 (17)	15 (6)
Serious adverse reactions, *n*	0	3	1

TABLE 20 Details of reported serious adverse reactions

	Intervention		
Description of serious adverse reaction	Tamsulosin ($n = 0$)	Nifedipine ($n = 3$)	Placebo ($n = 1$)
Right loin pain, diarrhoea, vomiting[a]	0	1	0
Headache, dizziness, light-headedness, chronic abdominal pain	0	0	1
Malaise, headache, chest pain[a]	0	1	0
Severe chest pain, difficulty breathing, left arm pain	0	1	0

a Emergency unblinding was required to facilitate further treatment.

Subgroup analysis

We explored the potential moderating effect of several factors previously reported in the literature by analysing the following subgroups:

- sex
- stone size (≤ 5 mm, > 5 to 10 mm)
- stone location (upper, mid, lower ureter).

Use of analgesia was considered as a subgroup analysis. However, as 98% of participants had used analgesia prior to randomisation it was therefore felt that any subgroup analysis would be uninformative.

Results of the subgroup analysis are summarised graphically using forest plots in *Figures 7* and *8* for MET versus placebo and tamsulosin versus nifedipine, respectively. The forest plots present ORs and 99% CIs. There was no evidence of any subgroup by treatment interaction. The *p*-values for the interaction terms were 0.59 for sex, 0.23 for stone size, and 0.12 for upper and 0.04 for mid ureter (with lower ureter as the reference location) for stone location comparing MET versus placebo. For tamsulosin versus nifedipine, these *p*-values were 0.39 for sex, 0.13 for stone size, 0.54 for upper ureter and 0.70 for mid ureter. The full breakdown of primary outcome by subgroup is summarised in *Appendix 8*.

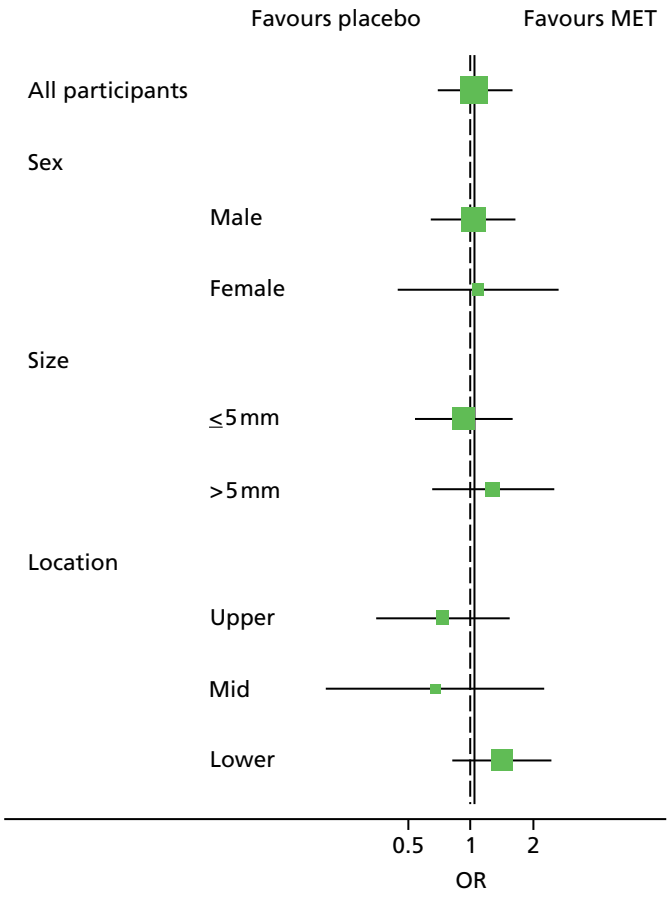

FIGURE 7 Subgroup analysis: stone size and stone location on stone passage (MET vs. placebo).

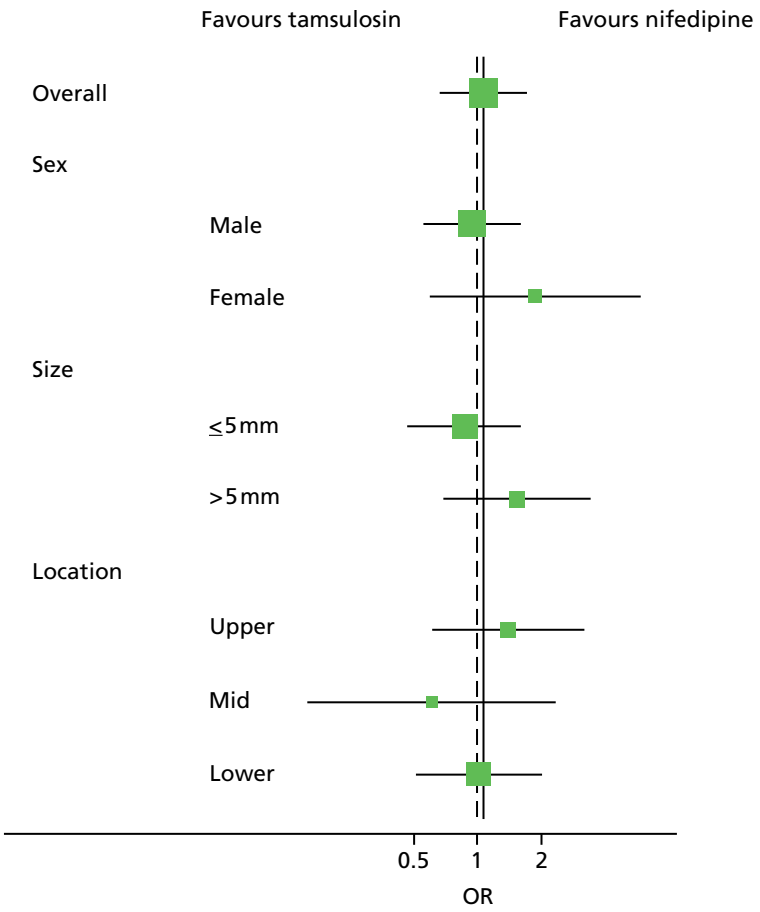

FIGURE 8 Subgroup analysis: stone size and stone location on stone passage (tamsulosin vs. nifedipine).

Chapter 6 Resource use, costs and cost-effectiveness

The average total resource use for the interventions and the subsequent use of health services over the 12 weeks are detailed in *Table 21*. The pattern of resource use was similar across all three groups and there were no statistically significant differences between the three groups. Very few participants used resources, as indicated by the zero median value, and resource use was skewed, with most participants having little or no resource use and a few having high resource use.

Costs

In terms of the costs incurred after the intervention was delivered, the mean total cost per participant in the tamsulosin group was £326 (SD £594), in the nifedipine group was £335 (SD £557) and in the placebo group was £367 (SD £619) (*Table 22*). On average, costs in the placebo group were higher than in either intervention group, which were mainly driven by the further interventions received and inpatient admissions. There was, however, no evidence of a statistically significant difference in the subsequent services used. Similar to the resource use, the cost data were skewed, as indicated by the many zero values in the summary statistics.

TABLE 21 Resource use

	Intervention {*n*, mean [median] (SD)}		
Resource	Tamsulosin	Nifedipine	Placebo
Analgesics and antibiotics	383, 1.84 [2] (0.87)	383, 1.74 [2] (0.88)	384, 1.78 [2] (0.86)
Diagnostic tests[a]	383, 1.60 [2] (0.66)	383, 1.56 [2] (0.60)	384, 1.61 [2] (0.69)
Doctor visits	329, 0.20 [0] (0.68)	331, 0.18 [0] (0.68)	325, 0.14 [0] (0.54)
Nurse visits	329, 0.04 [0] (0.31)	330, 0.02 [0] (0.15)	325, 0.07 [0] (0.90)
Outpatient visits[b]	377, 0.72 [1] (0.73)	378, 0.63 [1] (0.67)	379, 0.67 [1] (0.69)
Percutaneous insertion of nephrostomy tube[c]	378 [0]	379 [0]	379 [0]
Antegrade insertion of stent	378, 0.01 [0] (0.09)	379, 0.01 [0] (0.10)	379, 0.03 [0] (0.16)
Ureteroscopic operations	378, 0.10 [0] (0.30)	379, 0.10 [0] (0.30)	379, 0.11 [0] (0.31)
Endoscopic insertion of stent	378, 0.06 [0] (0.24)	379, 0.07 [0] (0.25)	379, 0.08 [0] (0.27)
ESWL	378, 0.06 [0] (0.24)	379, 0.07 [0] (0.27)	379, 0.08 [0] (0.29)
Other	378, 0.12 [0] (0.34)	379, 0.12 [0] (0.35)	379, 0.10 [0] (0.33)
All interventions[d]	378, 0.29 [0] (0.65)	379, 0.30 [0] (0.71)	379, 0.31 [0] (0.70)
Excess admissions days[e]	375, 0.17 [0] (0.64)	377, 0.23 [0] (1.06)	375, 0.25 [0] (1.13)

a Includes tests conducted at baseline, 4 weeks and participant-reported tests.
b Includes 4-week clinic attendance and participant-reported outpatient visits.
c Only two participants had percutaneous insertion of nephrostomy tube.
d A summary of all reported further interventions received by participants.
e Consists of duration of admissions reported on the CRF minus the median 1-day admissions as well as participant-reported admissions.

TABLE 22 Summary of costs

	Intervention {*n*, mean [median] (SD)}		
Resource	Tamsulosin	Nifedipine	Placebo
Intervention	383, £4.96	383, £6.95	384, £0
Analgesics and antibiotics	383, £4 [5] (2)	383, £4 [5] (2)	384, £4 [5] (2)
Diagnostic tests[a]	383, £96 [120] (40)	383, £94 [120] (36)	383, £98 [120] (41)
Doctor visits	329, £9 [0] (30)	331, £8 [0] (30)	325, £6 [0] (24)
Nurse visits	329, £0.57 [0] (5)	330, £0.28 [0] (2)	325, £1.14 [0] (14)
Outpatient visits[b]	377, £73 [101] (74)	378, £64 [101] (67)	379, £67 [101] (70)
All interventions[c]	378, £250 [0] (581)	379, £267 [0] (608)	379, £291 [0] (632)
Excess admissions days[d]	375, £44 [0] (169)	377, £62 [0] (279)	375, £65 [0] (298)
Total costs[e]	325, £326 [228] (494)	329, £335 [227] (557)	323, £367 [223] (619)

a Includes tests conducted at baseline, 4 weeks and participant-reported tests.
b Includes 4-week clinic attendance and participant-reported outpatient visits.
c Cost of all interventions as some participants had more than one intervention in a visit.
d Consists of duration of admissions reported in the CRF minus the median 1-day admission (urology department) as well as participant-reported admissions.
e Estimates based on participants with complete cost data.

Quality-adjusted life-years

The EQ-5D scores for each group of the trial at baseline, 4 weeks and 12 weeks are shown in *Table 23*. EQ-5D data were complete for just over 40% of trial participants in each group. The estimated mean QALY gained over the 12 weeks of trial participation was 0.19 (SD 0.05) for the tamsulosin group, 0.20 (SD 0.04) for the nifedipine group and 0.20 (SD 0.04) for the placebo group.

Medical expulsive therapy versus placebo

The results of the analysis undertaken to compare MET against placebo are reported in *Tables 24* and *25*. The pattern of resource use was similar across both groups without any statistically significant differences. Resource use was low, as indicated by the zero median value, and skewed, with most participants having little or no resource use.

TABLE 23 Quality of life based on responses to the EQ-5D score

	Intervention {*n*, mean [median] (SD)}		
EQ-5D score at	Tamsulosin	Nifedipine	Placebo
Baseline	373, 0.70 [0.80] (0.31)	369, 0.70 [0.80] (0.29)	373, 0.72 [0.80] (0.29)
4 weeks	243, 0.85 [1.00] (0.25)	238, 0.86 [1.00] (0.22)	226, 0.86 [1.00] (0.22)
12 weeks	185, 0.87 [1.00] (0.23)	187, 0.87 [1.00] (0.23)	175, 0.91 [1.00] (0.17)
QALY	165, 0.19 [0.21] (0.05)	164, 0.20 [0.21] (0.04)	157, 0.20 [0.21] (0.04)

TABLE 24 Resource use (MET vs. placebo)

Resource	Intervention {*n*, mean [median] (SD)}	
	MET	Placebo
Analgesics and antibiotics	766, 1.80 [2] (0.87)	384, 1.78 [2] (0.86)
Diagnostic tests[a]	766, 1.58 [2] (0.63)	384, 1.61 [2] (0.69)
Doctor visits	660, 0.20 [0] (0.68)	325, 0.14 [0] (0.54)
Nurse visits	659, 0.04 [0] (0.25)	325, 0.07 [0] (0.90)
Outpatient visits[b]	754, 0.68 [1] (0.70)	379, 0.67 [1] (0.69)
Percutaneous insertion of nephrostomy tube[c]	757, 0.00 [0]	379, 0.00 [0]
Antegrade insertion of stent	757, 0.01 [0] (0.10)	379, 0.03 [0] (0.16)
Ureteroscopic operations	757, 0.10 [0] (0.30)	379, 0.11 [0] (0.31)
Endoscopic insertion of stent	757, 0.07 [0] (0.25)	379, 0.08 [0] (0.27)
ESWL	757, 0.07 [0] (0.26)	379, 0.08 [0] (0.29)
Other	757, 0.12 [0] (0.34)	379, 0.10 [0] (0.33)
All interventions[d]	757, 0.30 [0] (0.69)	379, 0.31 [0] (0.70)
Excess admissions days[e]	752, 0.20 [0] (0.87)	375, 0.25 [0] (1.13)

a Includes tests conducted at baseline, 4 weeks and participant-reported tests.
b Includes 4-week clinic attendance and participant-reported outpatient visits.
c Only two participants had percutaneous insertion of nephrostomy tube.
d A summary of all reported further interventions received by participants.
e Consists of duration of admissions reported on the CRF minus the median 1-day admissions as well as participant-reported admissions.

TABLE 25 Summary of costs (MET vs. placebo)

Resource	Intervention {*n*, mean [median] (SD)}	
	MET	Placebo
Intervention	766, £4.96	384, £0
Analgesics and antibiotics	766, £4 [5] (2)	384, £4 [5] (2)
Diagnostic tests[a]	766, £95 [120] (38)	383, £97 [120] (41)
Doctor visits	660, £8 [0] (30)	325, £6 [0] (24)
Nurse visits	659, £0.42 [0] (4)	325, £1.14 [0] (14)
Outpatient visits[b]	754, £68 [101] (71)	379, £67 [101] (70)
All interventions[c]	757, £258 [0] (594)	379, 291 [0] (632)
Excess admissions days[d]	752, £53 [0] (230)	375, £65 [0] (298)
Total costs[e]	654, £330 [228] (526)	323, £367 [223] (619)
Unadjusted mean difference (95% CI)	–£35 (–£39 to £110)	
Adjusted mean difference (95% CI)	£3 (–£67 to £70)	

a Includes tests conducted at baseline and 4 weeks and participant-reported tests (not reported on the CRFs).
b Includes 4-week clinic attendance and participant-reported outpatient visits (not reported on the CRFs).
c Cost of all interventions as some participants had more than one intervention in a visit.
d Consists of duration of admissions reported on the CRFs minus the median 1-day admission (urology department) as well as participant-reported admissions.
e Estimates based on participants with complete cost data.

Costs

In terms of costs incurred after the intervention was delivered, the mean total cost per participant in the MET group was £330 (SD £526) and in the placebo group was £367 (SD £619) (see *Table 25*). On average, the MET group had lower costs than the placebo group, which were mainly driven by the further interventions received and inpatient admissions. The data were skewed, as indicated by the many zero values in the summary statistics. The unadjusted mean difference was –£35 (95% CI –£39 to £110) and favoured the MET group. The adjusted mean difference estimated using a generalised linear model fitted and adjusting for the minimisation factors and clustering for the centres between MET and placebo was £3 (95% CI –£67 to £70) and favoured the placebo group. There was, however, no evidence of a statically significant difference in the costs.

The EQ-5D results in *Table 26* followed a similar pattern to those reported in *Table 23* as, on average, the MET group had slightly lower QALY scores of 0.19 (SD 0.05), compared with 0.20 (SD 0.04) for placebo. The unadjusted mean difference was –0.003 (96% CI –0.006 to 0.011) and the adjusted mean difference was –0.001 (95% CI –0.007 to 0.006), but these differences were not statistically significant.

The incremental cost difference based on the complete cases (participants with both QALY and cost data) was –£42 (95% CI –£188 to £104) and the incremental QALY difference was –0.001 (95% CI –0.008 to 0.006) (*Table 27*). These values are based on a smaller sample than the raw cost and QALY data in *Tables 25* and *26*. Thus, on average, costs in the MET group were lower but MET was also less effective than placebo. The probabilities that MET would be considered cost-effective at various thresholds of WTP are shown in *Table 27*.

TABLE 26 Quality of life based on responses to the EQ-5D (MET vs. placebo)

	Intervention {*n*, mean [median] (SD)}	
EQ-5D score at	MET	Placebo
Baseline	742, 0.70 [0.80] (0.30)	373, 0.72 [0.80] (0.29)
4 weeks	481, 0.86 [1.00] (0.24)	226, 0.86 [1.00] (0.22)
12 weeks	369, 0.87 [1.00] (0.23)	175, 0.91 [1.00] (0.17)
QALY	329, 0.19 [0.21] (0.05)	157, 0.20 [0.21] (0.04)
Unadjusted QALY difference, 95% CI	–0.003 (–0.006 to 0.011)	
Adjusted QALY difference, 95% CI	–0.001 (–0.007 to 0.006)	

TABLE 27 Cost-effectiveness results from the complete case analysis using QALYs generated using EQ-5D scores (MET vs. placebo)

Cost effectiveness results	
Difference in costs, mean (95% CI)	–£42 (–£188 to £104)[a]
Difference in QALYs, mean (95% CI)	–0.001 (–0.008 to 0.006)
ICER	£4355[b]
Probability active is cost-effective when threshold is £0 per QALY	71%
Probability active is cost-effective when threshold is £20,000 per QALY	56%
Probability active is cost-effective when threshold is £30,000 per QALY	51%
Probability active is cost-effective when threshold is £50,000 per QALY	46%

ICER, incremental cost-effectiveness ratio.
a This value differs from that reported on *Table 25* as it is based on respondents that had both cost and EQ-5D data.
b Reflects the cost saving per QALY lost.

The empirical estimates of the joint distribution of mean costs and QALYs obtained using the results of the bootstrap replicates are shown in *Figure 9*. The figure shows that in most cases costs were lower in the MET group than in the placebo group, but QALYs gained were also lower.

The probability that the MET intervention group would be considered to be cost-effective at different thresholds of WTP was 56% at £20,000 and 51% at £30,000, as illustrated in *Figure 10*.

Tamsulosin versus nifedipine

Resource use

The average total resource use in terms of the interventions and the subsequent use of health services over the 12 weeks of the trial are detailed in *Table 28*. The pattern of resource use was similar across both groups and there were no statistically significant differences between the groups. Very few participants used resources, as indicated by the zero median value; resource use was skewed, with most participants having little or no resource use and a few of them having high resource use.

Costs

In terms of the costs incurred after the intervention was delivered, the mean total cost per participant in the tamsulosin group was £326 (SD £594) and in the nifedipine group was £335 (SD £557) (*Table 29*). On average, the nifedipine group had higher costs than the tamsulosin group. These costs were mainly driven by the further interventions received and inpatient admissions. There was, however, no evidence of a statistically significant difference in the subsequent use of services. Cost data were skewed, as indicated by the many zero values in the summary statistics. The adjusted mean difference was –£25 (95% CI –£84 to £34) favouring tamsulosin.

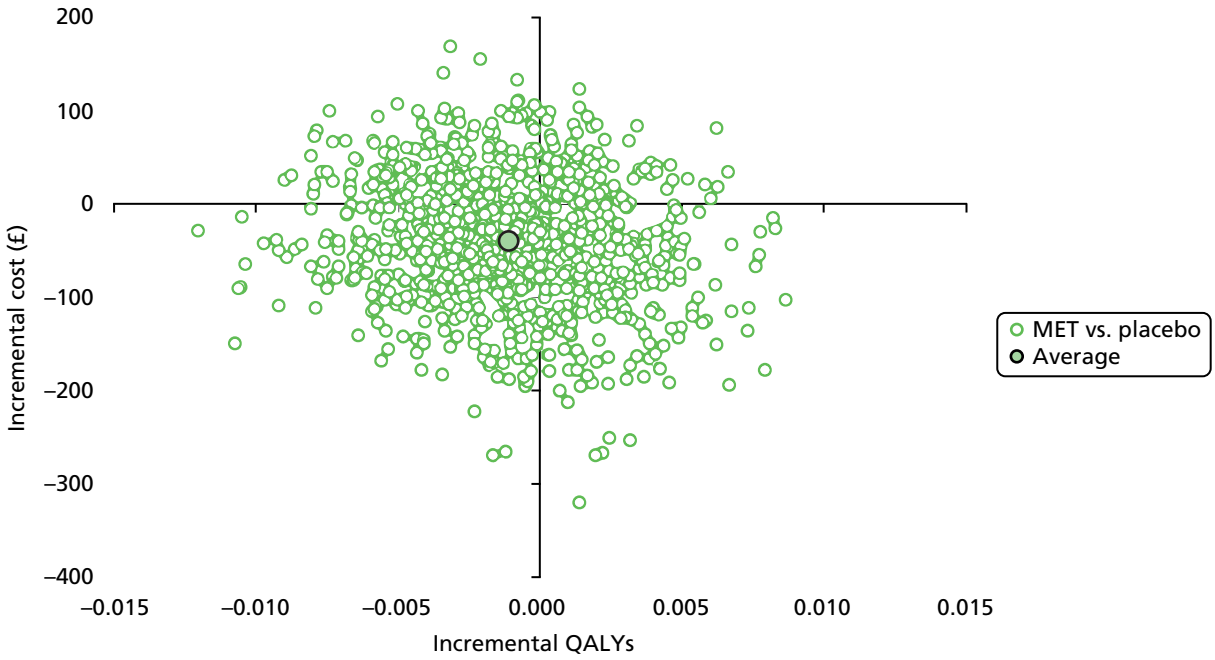

FIGURE 9 Representation of the uncertainty in differential mean costs and QALYs based on EQ-5D responses (MET vs. placebo). Strategy costs are costs incurred for each of the two treatment arms, MET and placebo.

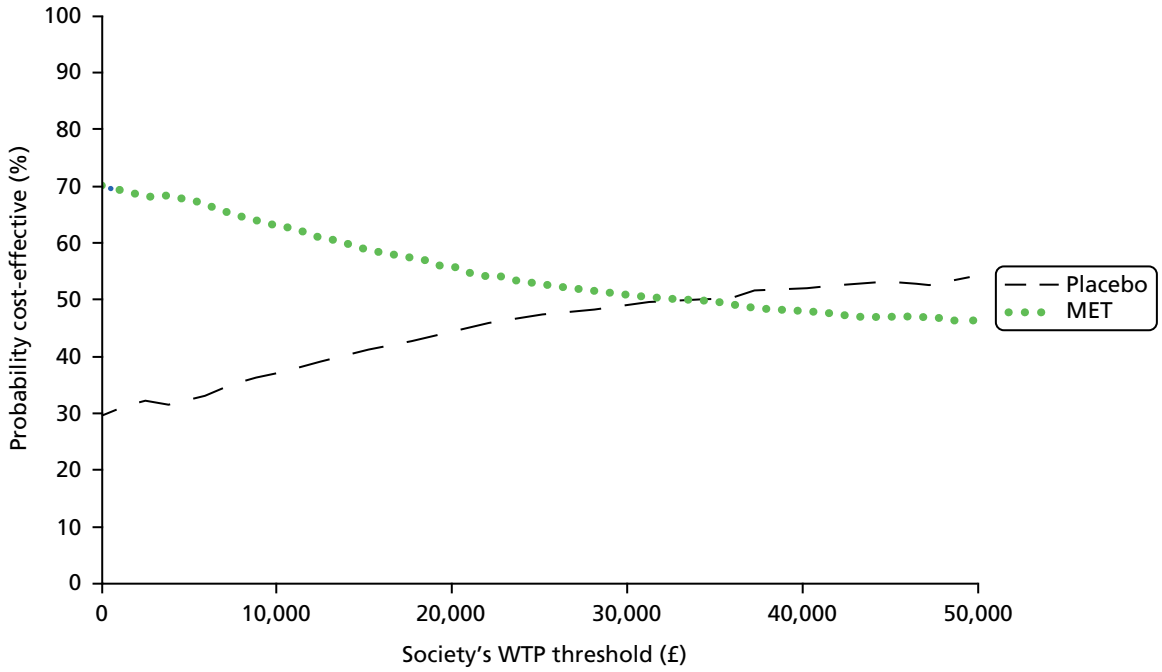

FIGURE 10 Cost-effectiveness acceptability curve using QALYs based on EQ-5D responses (MET vs. placebo).

TABLE 28 Resource use (tamsulosin vs. nifedipine)

	Intervention {*n*, mean [median] (SD)}	
Resource	**Tamsulosin**	**Nifedipine**
Analgesics and antibiotics	383, 1.84 [2] (0.87)	383, 1.74 [2] (0.88)
Diagnostic tests[a]	383, 1.60 [2] (0.66)	383, 1.56 [2] (0.60)
Doctor visits	329, 0.20 [0] (0.68)	331, 0.18 [0] (0.68)
Nurse visits	329, 0.04 [0] (0.31)	330, 0.02 [0] (0.15)
Outpatient visits[b]	377, 0.72 [1] (0.73)	378, 0.63 [1] (0.67)
Percutaneous insertion of nephrostomy tube[c]	378 [0]	379 [0]
Antegrade insertion of stent	378, 0.01 [0] (0.09)	379, 0.01 [0] (0.10)
Ureteroscopic operations	378, 0.10 [0] (0.30)	379, 0.10 [0] (0.30)
Endoscopic insertion of stent	378, 0.06 [0] (0.24)	379, 0.07 [0] (0.25)
ESWL	378, 0.06 [0] (0.24)	379, 0.07 [0] (0.27)
Other	378, 0.12 [0] (0.34)	379, 0.12 [0] (0.35)
All interventions[d]	378, 0.29 [0] (0.65)	379, 0.30 [0] (0.71)
Excess admissions days[e]	375, 0.17 [0] (0.64)	377, 0.23 [0] (1.06)

a Includes tests conducted at baseline, 4 weeks and participant-reported tests.
b Includes 4-week clinic attendance and participant-reported outpatient visits.
c Only two participants had percutaneous insertion of nephrostomy tube.
d A summary of all reported further interventions received by participants.
e Consists of duration of admissions reported on the CRF minus the median 1-day admissions as well as participant-reported admissions.

TABLE 29 Summary of costs (tamsulosin vs. nifedipine)

Resource	Intervention {*n*, mean [median] (SD)}	
	Tamsulosin	Nifedipine
Intervention	383, £4.96	383 £6.95
Analgesics and antibiotics	383, £4 [5] (2)	383, £4 [5] (2)
Diagnostic tests[a]	383, £96 [120] (40)	383, £94 [120] (36)
Doctor visits	329, £9 [0] (30)	331, £8 [0] (30)
Nurse visits	329, £0.57 [0] (5)	330, £0.28 [0] (2)
Outpatient visits[b]	377, £73 [101] (74)	378, £64 [101] (67)
All interventions[c]	378, £250 [0] (581)	379, £267 [0] (608)
Excess admissions days[d]	375, £44 [0] (169)	377, £62 [0] (279)
Total costs[e]	325, £326 [228] (494)	329, £335 [227] (557)
Unadjusted mean difference (95% CI)	−£9 (−£90 to £72)	
Adjusted mean difference (95% CI)	−£25 (−£84 to £34)	

a Includes tests conducted at baseline and 4 weeks and patient-reported tests (not reported in the CRFs).
b Includes 4-week clinic attendance and patient-reported outpatient visits (not reported in the CRF).
c Cost of all interventions as some patients had more than one intervention in a visit.
d Consists of duration of CRF-reported admissions minus the median 1-day admission (urology department) as well as patient-reported admissions.
e Estimates based on patients with complete cost data.

Quality-adjusted life-years

Table 30 shows the EQ-5D scores for each group of the trial at baseline, 4 weeks and 12 weeks. The proportion of total trial participants with complete EQ-5D data at each time point was slightly greater than 40% for each group. The estimated mean QALYs were 0.19 (SD 0.05) for the tamsulosin group and 0.20 (SD 0.04) for the nifedipine group. The mean QALY difference (–0.003) between tamsulosin and nifedipine after adjusting for minimisation factors and baseline EQ-5D favoured the nifedipine group, but this was not statistically significant.

Estimation of cost-effectiveness

For the initial base-case analysis, a generalised linear model adjusting for baseline EQ-5D and minimisation factors for complete case (respondents that had both cost and QALY data) was employed. An ordinary least squares model adjusting for baseline EQ-5D and the minimisation factors was used to estimate the QALY differences. As noted in *Table 31*, these values differ from those reported in *Tables 29* and *30* as they are based on a smaller sample, as a result of the missing EQ-5D data. The incremental analysis in *Table 31* reflects that, on average, the tamsulosin group was less costly than the nifedipine group but the tamsulosin group had lower QALYs than the nifedipine group.

The empirical estimates of the joint distribution of mean costs and QALYs obtained using the results of the bootstrap replicates are shown in *Figure 11*.

The probability that the tamsulosin intervention group would be considered to be cost-effective at different thresholds of WTP was 61% at £20,000 and 55% at £30,000 (*Figure 12*).

TABLE 30 Quality of life based on responses to the EQ-5D (tamsulosin vs. nifedipine)

EQ-5D measure at	Intervention {*n*, mean [median] (SD)}	
	Tamsulosin	Nifedipine
Baseline	373, 0.70 [0.80] (0.31)	369, 0.70 [0.80] (0.29)
4 weeks	243, 0.85 [1.00] (0.25)	238, 0.86 [1.00] (0.22)
12 weeks	185, 0.87 [1.00] (0.23)	187, 0.87 [1.00] (0.23)
QALY	165, 0.19 [0.21] (0.05)	164, 0.20 [0.21] (0.04)
Unadjusted QALY difference (95% CI)	−0.006 (−0.016 to 0.004)	
Adjusted QALY difference (95% CI)	−0.003 (−0.014 to 0.009)	

TABLE 31 Cost-effectiveness results from the complete case analysis tamsulosin vs. nifedipine using QALYs generated using EQ-5D scores

Cost-effectiveness results	
Difference in costs, mean (95% CI)	−£87 (−£200 to £26)[a]
Difference in QALYs, mean (95% CI)	−0.002 (−0.013 to 0.010)
ICER	£43,500[b]
Probability that tamsulosin is cost-effective when threshold is £0 per QALY	85%
Probability that tamsulosin is cost-effective when threshold is £20,000 per QALY	61%
Probability that tamsulosin is cost-effective when threshold is £30,000 per QALY	55%
Probability tamsulosin is cost-effective when threshold is £50,000 per QALY	48%

ICER, incremental cost-effectiveness ratio.
a Based on responders who had both cost and EQ-5D data.
b Reflects the cost saving per QALY lost.

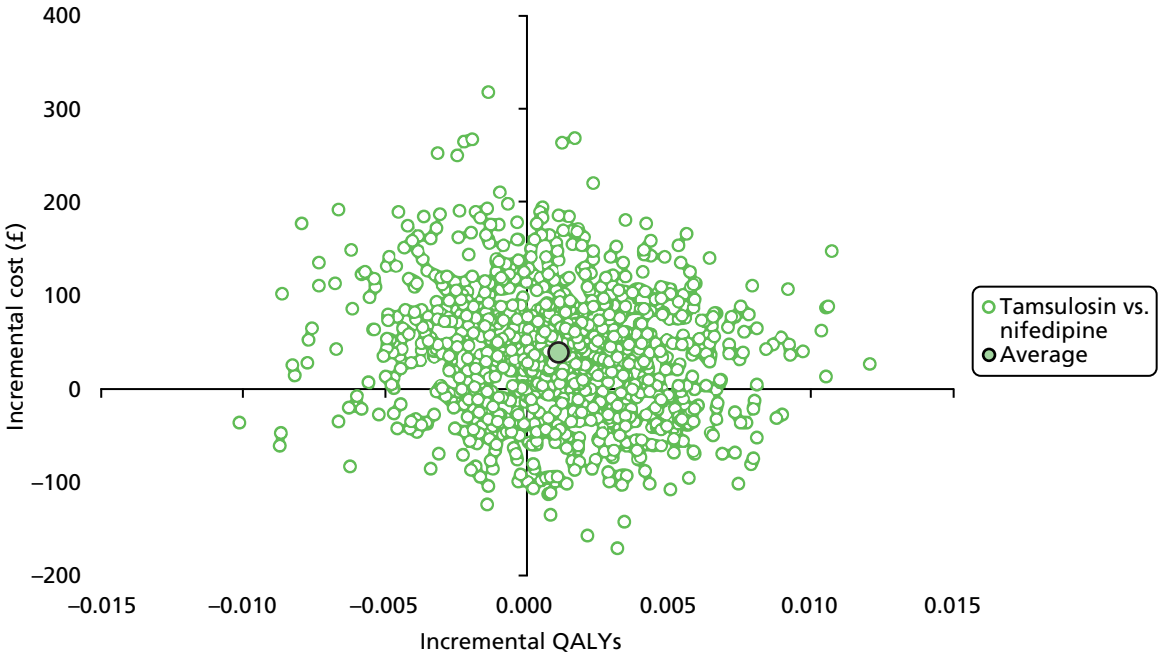

FIGURE 11 Representation of the uncertainty in differential mean costs and QALYs based on EQ-5D responses (tamsulosin vs. nifedipine). Strategy costs are costs incurred for each of the two treatment arms, tamsulosin and nifedipine.

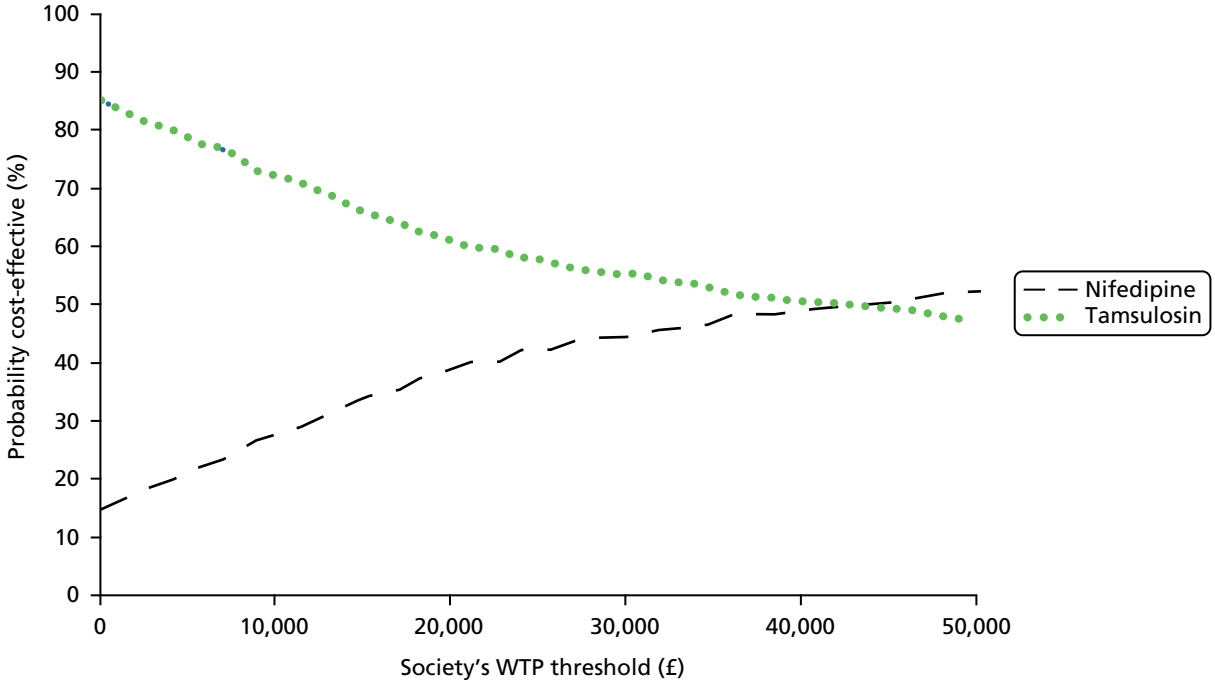

FIGURE 12 Cost-effectiveness acceptability curve using QALYs based on EQ-5D responses (tamsulosin vs. nifedipine).

Sensitivity analysis using quality-adjusted life-years generated using Short Form questionnaire-36 items

Medical expulsive therapy versus placebo

The results of the analysis using the utility scores (*Table 32*) from the SF-6D were similar to the base-case analysis, although there were fewer respondents with complete data.

The cost-effectiveness results indicate that, on average, the MET group was £37 less costly than the placebo group, but it was also 0.003 QALYs less effective than placebo (*Table 33*). The empirical estimates of the joint distribution of mean costs and QALYs obtained using the results of the bootstrap replicates are shown in *Figure 13*.

The empirical estimates of the joint distribution of mean costs and QALYs obtained using the results of the bootstrap replicates are shown in *Figure 11*.

The probability that the MET intervention group would be considered cost-effective at different thresholds of WTP was 41% at £20,000 and 32% at £30,000, as shown in *Figure 14*.

TABLE 32 Quality of life based on responses to the SF-6D (MET vs. placebo)

	Intervention {*n*, mean [median] (SD)}	
SF-6D measure at	MET	Placebo
Baseline	729, 0.72 [0.71] (0.15)	367, 0.71 [0.69] (0.15)
4 weeks	441, 0.72 [0.74] (0.15)	213, 0.72 [0.74] (0.15)
12 weeks	348, 0.79 [0.85] (0.15)	165, 0.80 [0.85] (0.14)
QALY	292, 0.17 [0.18] (0.03)	141, 0.17 [0.18] (0.03)
Unadjusted difference in QALYs (95% CI)	−0.001 (−0.005 to 0.007)	
Adjusted difference in QALYs (95% CI)	−0.003 (−0.008 to 0.002)	

TABLE 33 Cost-effectiveness results from the completed case analysis using QALYs generated using the SF-6D (MET vs. placebo)

Cost effectiveness results	
Difference in costs, mean (95% CI)	–£37 (–£151 to £77)
Difference in QALYs, mean (95% CI)	–0.003 (–0.008 to 0.002)
ICER	£12,333[a]
Probability intervention is cost-effective when threshold is £0 per QALY	75%
Probability intervention is cost-effective when threshold is £20,000 per QALY	41%
Probability intervention is cost-effective when threshold is £30,000 per QALY	32%
Probability intervention is cost-effective when threshold is £50,000 per QALY	22%

ICER, incremental cost-effectiveness ratio.
a Reflects the amount society is willing to save to accept a reduction in QALYs.

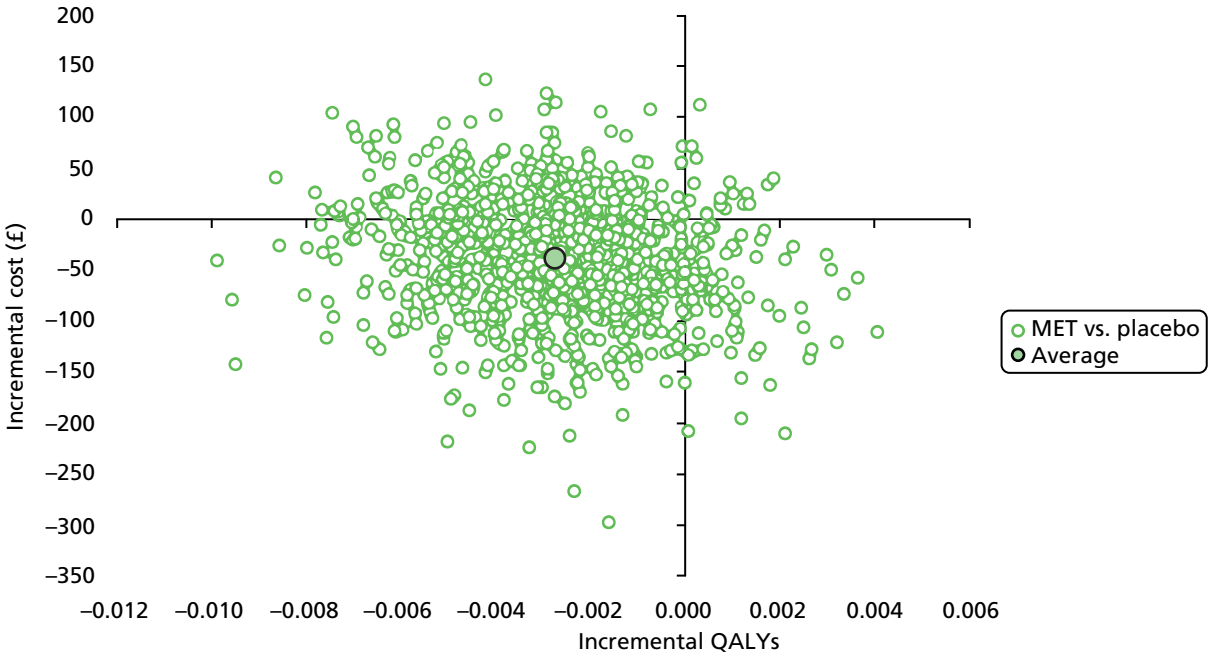

FIGURE 13 Representation of the uncertainty in differential mean costs and QALYs based on SF-6D responses (MET vs. placebo). Strategy costs are costs incurred for each of the two treatment arms, MET and placebo.

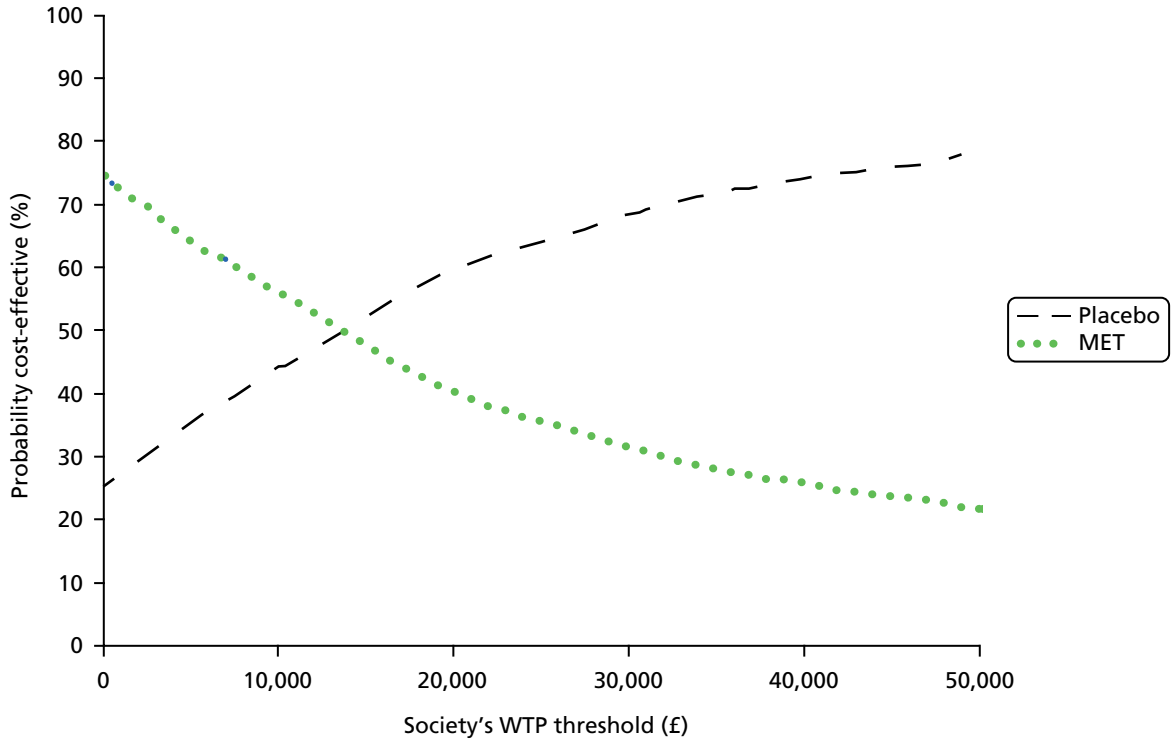

FIGURE 14 Cost-effectiveness acceptability curve using QALYs based on SF-6D responses (MET vs. placebo).

Tamsulosin versus nifedipine

The results of the analysis using the utility scores (*Table 34*) from the SF-6D were similar to the base-case analysis, although there were fewer respondents with complete data.

The results of the incremental analysis are reported in *Table 35*. On average, the tamsulosin group had lower costs and lower QALYs than the nifedipine group. None of the differences was statistically significant.

The empirical estimates of the joint distribution of mean costs and QALYs obtained using the results of the bootstrap replicates are shown in *Figure 15*.

The probability that tamsulosin would be considered cost-effective at different thresholds of WTP was 57% at £20,000 and 54% at £30,000, as illustrated in *Figure 16*.

TABLE 34 Quality of life based on responses to the SF-6D (tamsulosin vs. nifedipine)

	Intervention {*n*, mean [median] (SD)}	
SF-6D measure at	Tamsulosin	Nifedipine
Baseline	363, 0.72 [0.70] (0.15)	366, 0.720 [0.73] (0.15)
4 weeks	220, 0.82 [0.73] (0.15)	221, 0.73 [0.74] (0.15)
12 weeks	174, 0.78 [0.85] (0.16)	174, 0.79 [0.83] (0.14)
QALY	147, 0.17 [0.17] (0.03)	145, 0.17 [0.18] (0.03)
Difference in QALYs (95% CI)	–0.001 (–0.006 to 0.008)	

TABLE 35 Cost-effectiveness results from the completed case analysis using QALYs generated using the SF-6D (tamsulosin vs. nifedipine)

Cost-effectiveness results	
Difference in costs, mean (95% CI)	–£14 (–£146 to £117)
Difference in QALYs, mean (95% CI)	–0.0006 (–0.0050 to 0.0040)
ICER	£23,000[a]
Probability intervention is cost-effective when threshold is £0 per QALY	63%
Probability intervention is cost-effective when threshold is £20,000 per QALY	57%
Probability intervention is cost-effective when threshold is £30,000 per QALY	54%
Probability intervention is cost-effective when threshold is £50,000 per QALY	51%

ICER, incremental cost-effectiveness ratio.
a Reflects the saving per QALY lost.

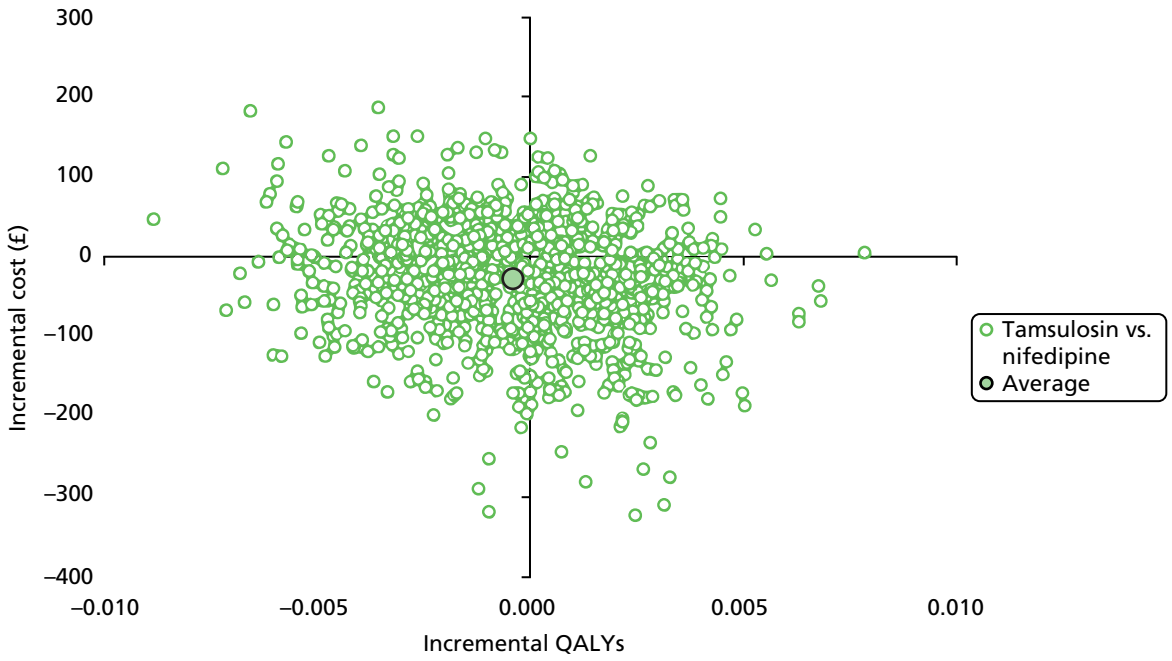

FIGURE 15 Representation of the uncertainty in differential mean costs and QALYs based on SF-6D responses (tamsulosin vs. nifedipine). Strategy costs are costs incurred for each of the two treatment arms, tamsulosin and nifedipine.

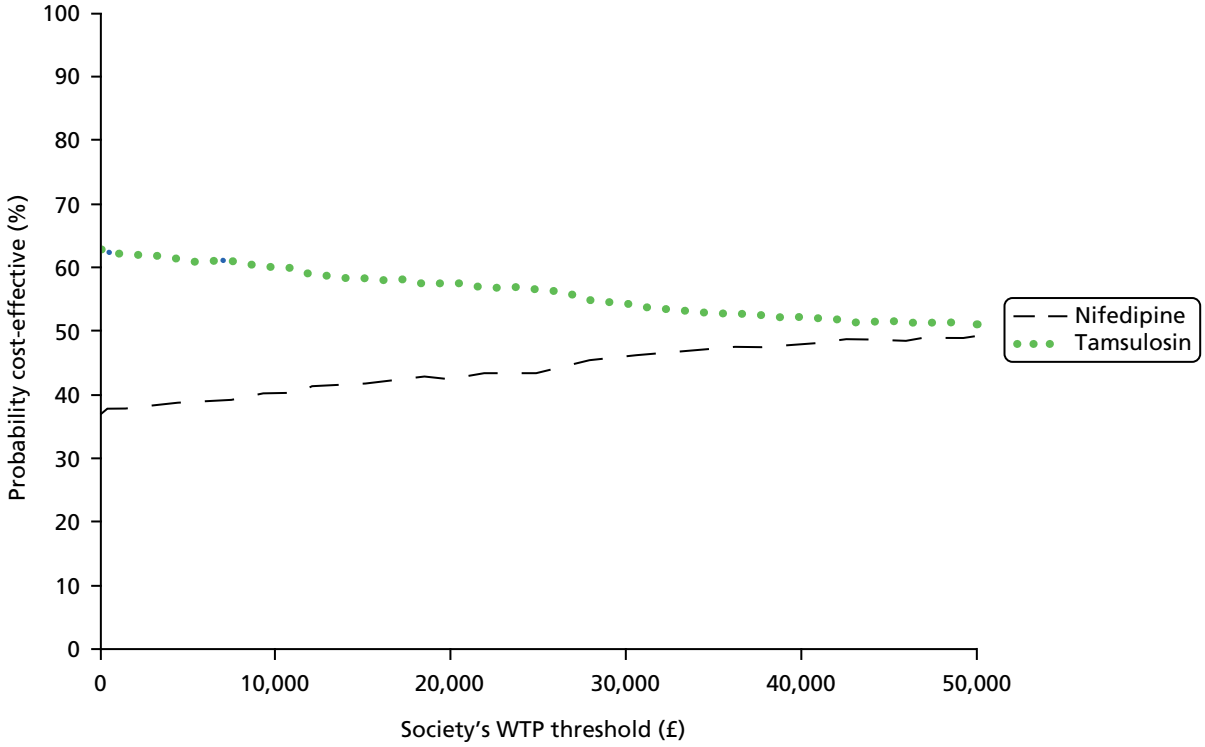

FIGURE 16 Cost-effectiveness acceptability curve using QALYs based on the SF-6D responses (tamsulosin vs. nifedipine).

Sensitivity analysis using extreme European Quality of Life-5 Dimensions scores

The first one-way sensitivity analysis replaced all the missing QALY data with the highest EQ-5D score for the specific group at that particular time point. As illustrated by *Tables 36* and *37*, this did not change the results.

Sensitivity analyses using multiple imputation

Medical expulsive therapy versus placebo

The results of the imputation are presented in *Table 38*. The cost and QALY differences between the two groups are similar to those of the complete case analysis; on average, MET is less costly and less effective than placebo. The cost difference reduced from –£42 (95% CI –£188 to £104) (see *Table 27*) to –£6 (96% CI –£106 to £92) (see *Table 38*). The QALY difference remained the same with a very small change in the 95% CI. However, none of these differences was statistically significant.

The probability that MET will be cost-effective compared with placebo at a given WTP per QALY gained threshold reduced from 56% (see *Table 27*) to 33% for the £20,000 threshold, and from 51% (see *Table 27*) to 29% for the £30,000 threshold (*Figures 17* and *18*).

TABLE 36 Quality of life replacing missing EQ-5D data with full health score

	Intervention {mean [median] (SD)}		
EQ-5D measure at	Tamsulosin ($n = 383$)	Nifedipine ($n = 383$)	Placebo ($n = 384$)
Baseline EQ-5D	0.70 [0.80] (0.31)	0.71 [0.80] (0.29)	0.73 [0.80] (0.29)
4 weeks	0.91 [1.00] (0.21)	0.92 [1.00] (0.19)	0.92 [1.00] (0.18)
12 weeks	0.94 [1.00] (0.17)	0.94 [1.00] (0.17)	0.96 [1.00] (0.12)
QALY	0.20 [0.2] (0.04)	0.21 [0.21] (0.03)	0.21 [0.22] (0.03)

TABLE 37 Quality of life replacing missing EQ-5D data with the worse-case scenario

	Intervention {mean [median] (SD)}		
EQ-5D measure at	Tamsulosin ($n = 383$)	Nifedipine ($n = 383$)	Placebo ($n = 384$)
Baseline EQ-5D	0.66 [0.80] (0.37)	0.65 [0.80] (0.37)	0.69 [0.80] (0.36)
4 weeks	0.45 [0.80] (0.56)	0.45 [0.80] (0.56)	0.40 [0.70] (0.57)
12 weeks	0.29 [–0.24] (0.58)	0.30 [–0.24] (0.58)	0.28 [–0.24] (0.58)
QALY	0.10 [0.11] (0.10)	0.10 [0.12] (0.10)	0.10 [0.11] (0.10)

TABLE 38 Cost-effectiveness results from the completed case analysis using QALYs generated using the EQ-5D imputation results (MET vs. placebo)

Cost-effectiveness results	
Difference in costs, mean (95% CI)	–£6 (–£106 to £92)
Difference in QALYs, mean (95% CI)	–0.001 (–0.007 to 0.004)
ICER	£6000[a]
Probability intervention is cost-effective when threshold is £0 per QALY	53%
Probability intervention is cost-effective when threshold is £20,000 per QALY	33%
Probability intervention is cost-effective when threshold is £30,000 per QALY	29%
Probability intervention is cost-effective when threshold is £50,000 per QALY	26%

ICER, incremental cost-effectiveness ratio.
a Reflects the saving per QALY lost.

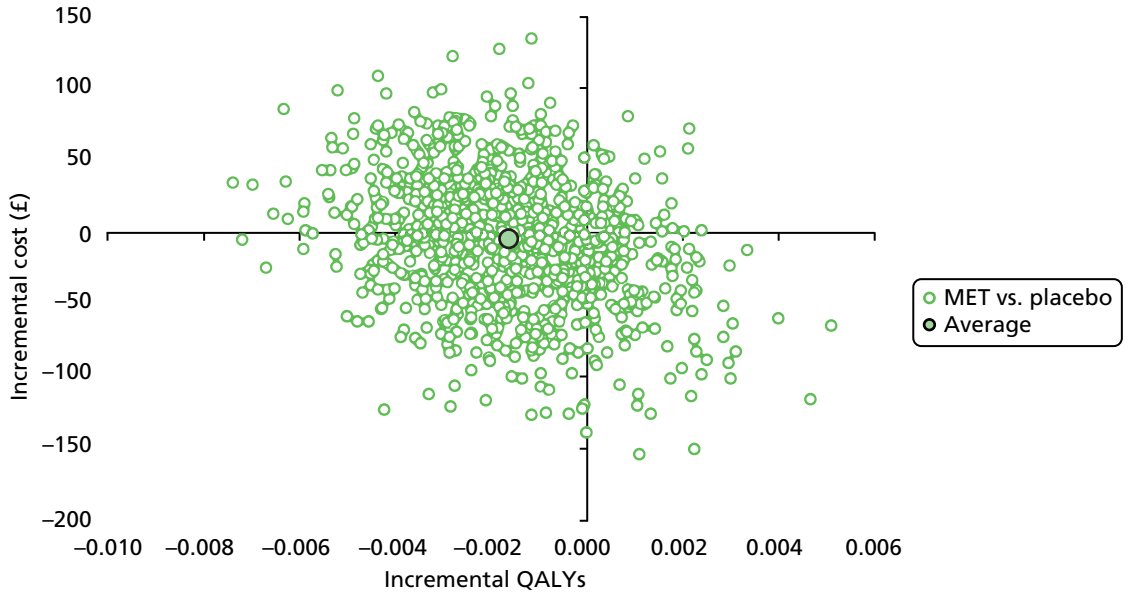

FIGURE 17 Representation of the uncertainty in differential mean costs and QALYs based on EQ-5D imputation results (MET vs. placebo). Strategy costs are costs incurred for each of the two treatment arms, MET and placebo.

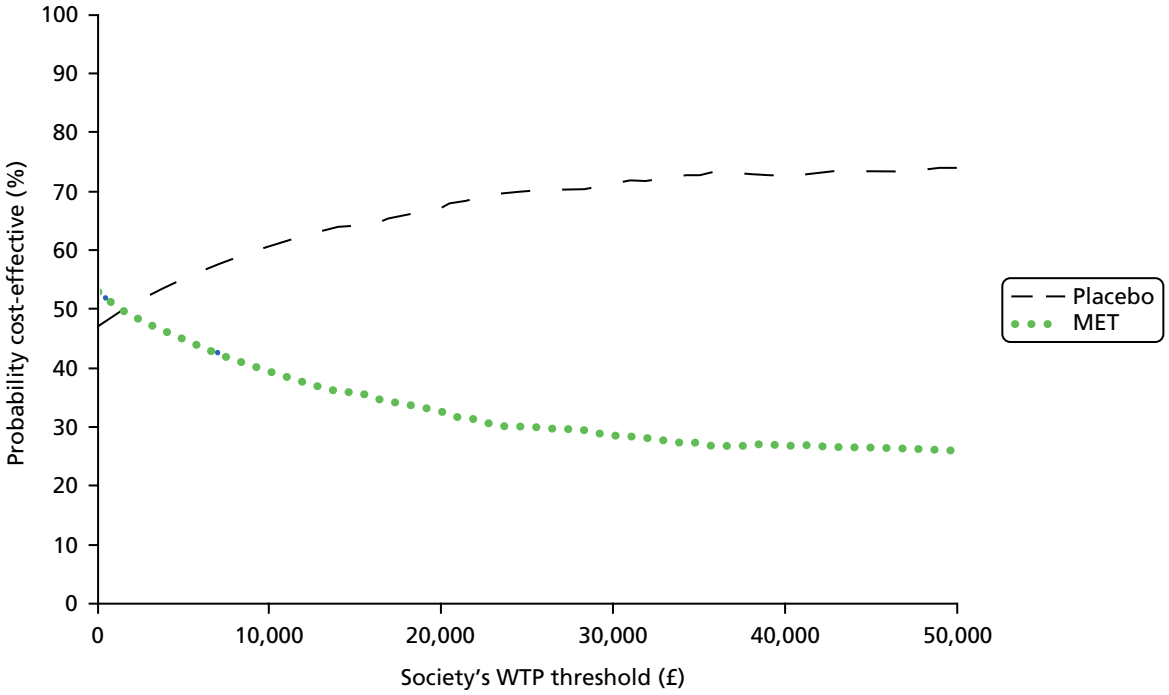

FIGURE 18 Cost-effectiveness acceptability curve using QALYs based on EQ-5D imputation results (MET vs. placebo).

Tamsulosin versus nifedipine

The results of the imputation for the tamsulosin and nifedipine comparison are presented in *Table 39*. None of these differences was statistically significant. The direction of the difference in costs and QALYs changed from negative to positive compared with the complete case analysis using EQ-5D (*Table 31*), with tamsulosin costing more than nifedipine but also being more effective.

The shape of the CEAC also changed, with the chance that tamsulosin would be considered to be cost-effective increasing over different thresholds and that of the nifedipine group decreasing compared with the complete case analysis using the EQ-5D reported in *Table 31* (*Figures 19* and *20*).

TABLE 39 Cost-effectiveness results from the completed case analysis using QALYs generated using the EQ-5D imputation results (tamsulosin vs. nifedipine)

Cost-effectiveness results	
Difference in costs, mean (95% CI)	£11 (–£57 to £80)
Difference in QALYs, mean (95% CI)	0.0004 (–0.0070 to 0.0040)
ICER	£24,677
Probability intervention is cost-effective when threshold is £0 per QALY	43%
Probability intervention is cost-effective when threshold is £20,000 per QALY	50%
Probability intervention is cost-effective when threshold is £30,000 per QALY	53%
Probability intervention is cost-effective when threshold is £50,000 per QALY	54%

ICER, incremental cost-effectiveness ratio.

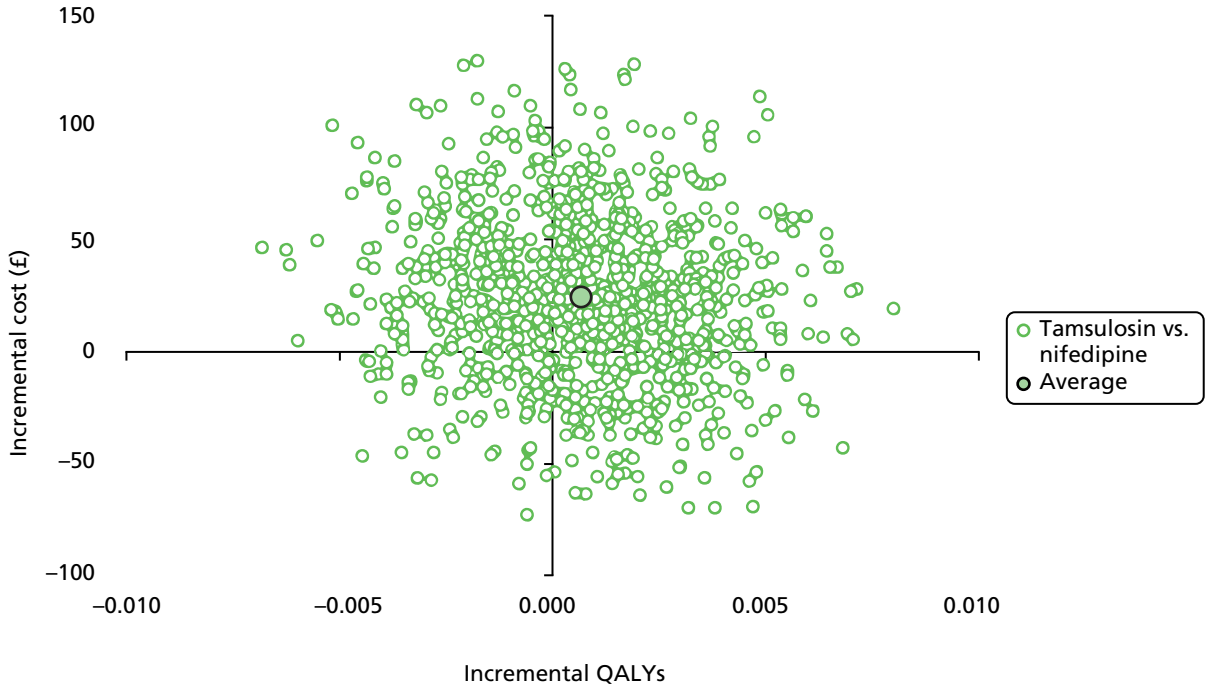

FIGURE 19 Representation of the uncertainty in differential mean costs and QALYs based on EQ-5D imputation results (tamsulosin vs. nifedipine). Strategy costs are costs incurred for each of the two treatment arms, MET and placebo.

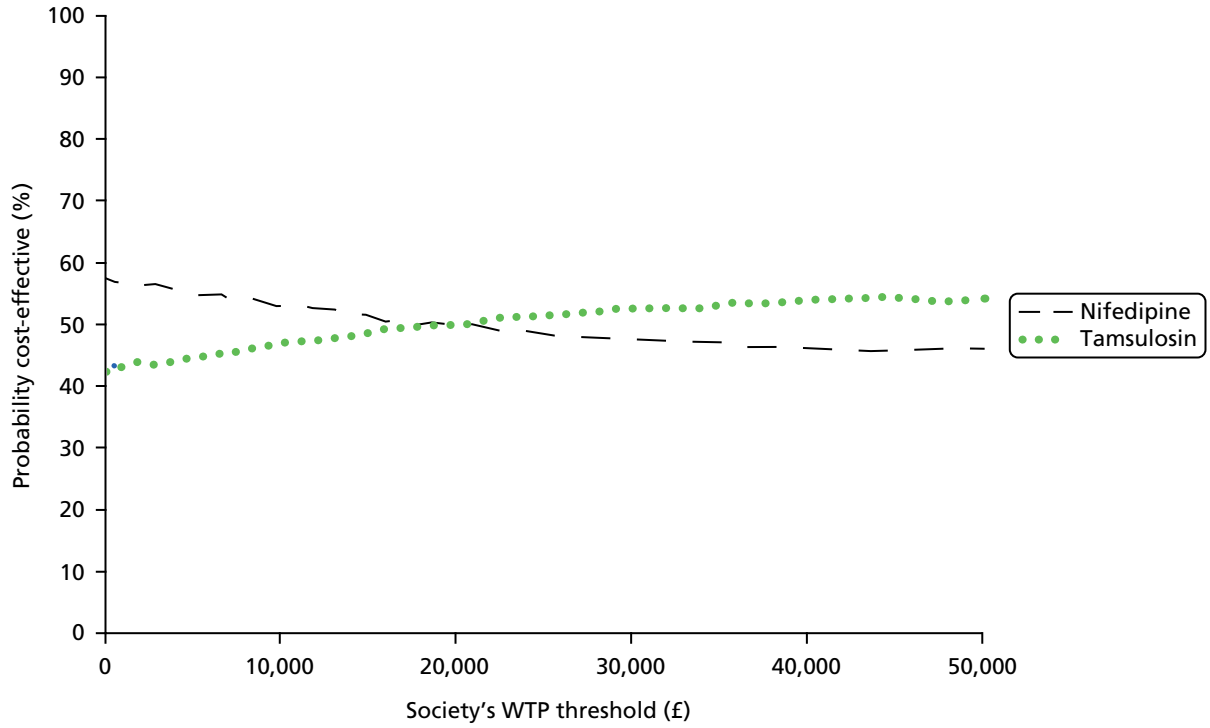

FIGURE 20 Cost-effectiveness acceptability curve using QALYs based on EQ-5D imputation results (tamsulosin vs. nifedipine).

Interpretation of results

The results were not sensitive to the different assumptions applied and concur with the clinical results that reflected that there were no statistically significant differences in the clinical outcome. The utility scores indicated a general improvement in quality of life from baseline to 12 weeks; however, there was no statistically significant difference between the groups. The sensitivity analyses using data imputation to determine the possible effects of missing data did not lead to any change in the overall conclusions. The imputation analysis comparing MET and placebo resulted in a smaller cost difference, that was not statistically significant, and a reduction in the probability of MET being considered to be cost-effective at the £20,000 and £30,000 WTP thresholds. The complete case analysis tended to favour tamsulosin over nifedipine in cost, but the imputed analysis favoured tamsulosin in QALYs; however, neither of these results was statistically significant. The chance of tamsulosin being considered to be cost-effective in the imputed analysis with nifedipine, at the £20,000 and £30,000 WTP thresholds also reduced. The incremental cost-effectiveness ratios (apart from those in the imputation analysis reported in *Table 39*) all reflected the saving per QALY lost. For the MET to be considered cost-effective, these values would have to be greater than £30,000. These results have to be interpreted taking into account the uncertainty surrounding the estimates. The results emphasise that there are no significant differences in both the costs and QALYs, and if the National Institute for Health and Care Excellence-recommended thresholds of £20,000 to £30,000 are considered, none of the active treatments has much higher than a 50% chance of being considered cost-effective, meaning that none has any cost-effectiveness advantage over placebo.

Chapter 7 Discussion

Statement of principal findings

Primary outcome

The SUSPEND trial was designed, firstly, to determine whether or not the possible benefit of MET for expectantly managed ureteric colic suggested by meta-analyses of a number of small previous RCTs was borne out in a large, controlled, effectiveness trial carried out in a routine care setting. Secondly, the trial investigated which of the two candidate classes of agent was superior in facilitating stone passage. The results showed no benefit for either tamsulosin (an alpha-blocker) or nifedipine (a calcium channel blocker) over 4 weeks in altering the rate of stone passage as measured by the lack of need for further intervention. The finding of no effect is robust in that the trial recruited to the planned sample size with near-complete collection of the primary outcome, delivering the necessary power to detect what was established as the minimum clinically important difference of a 25% (50–75%) increase in spontaneous stone passage. Indeed, the trial results have sufficient precision to rule out a 10% absolute benefit between both active drugs and placebo at the 95% confidence level. These results were unchanged by pre-planned sensitivity analyses examining interaction with stone size, stone location, sex of participant and place of treatment.

Secondary outcomes

Pain is a significant burden for this patient population and has an impact on state of health. Improved pain control would therefore be of benefit to sufferers of ureteric colic and would also relieve burden on the health-care system in terms of contact with health-care professionals for advice and to obtain analgesia. For the 61% of participants who completed and returned the 4-week questionnaire, there was no benefit of either drug compared with placebo for the outcomes of degree of pain at 4 weeks, measured on a Likert-type pain score, and the recollected number of days of analgesia use over 4 weeks. Concerning quality of life, baseline scores for health status taken just prior to randomisation showed the expected detriment caused by an acute episode of ureteric colic across all five domains. Subsequently, there was progressive improvement over the 12 weeks of the trial back to the level of the general population.[52] For the outcome of recovery of general health, there were no statistically significant differences in any of the time points between the groups, thus indicating no benefit from the drugs tested.

Time to stone passage was determined from the date of stone passage recorded on the CRFs, which were completed by local research staff. This question also established whether or not stone passage was confirmed by repeat imaging. Imaging during follow-up was not required as part of the trial protocol and this was performed only if directed by the local clinical team on the basis of local practice or clinical need. There was no clear record of stone passage for 79% of participants, which is to be expected in the routine care setting, given that once the stone is in the bladder it then passes during micturition without further discomfort. Therefore, although the best estimate of time to stone passage showed no evidence of any difference between groups, it is acknowledged that there are uncertainties concerning these data owing to the limited sample.

In line with the clinical findings, there was no evidence that the drugs tested offered any advantage in terms of cost-effectiveness, because QALY gain was equivalent across the three groups. In addition, the costs were broadly in line with the low drug costs for tamsulosin and nifedipine, and with the similar rates of further costly intervention to remove a stone between the groups.

The results of this large, pragmatic, UK-based, multicentre RCT set within routine care provide no support for the continued use of MET. Neither tamsulosin (400 µg) nor nifedipine (30 mg) reduced the need for further intervention over 4 weeks compared with placebo as part of the expectant phase of management for people presenting with a symptomatic ureteric stone.

Strengths and weakness of trial

Strengths

The SUSPEND trial was commissioned by the UK NHS to define whether or not drugs to increase the rate of ureteric stone passage, and thereby benefit patients and reduce health-care costs, were clinically useful. The SUSPEND trial was designed to fulfil this brief and, in particular, sought to embed the trial within the current standard NHS care pathway using the primary outcome measure of 'need for further intervention'. This outcome was reliable and valid in terms of recording, attribution and relevance to patients and the NHS. The trial design and outcome measure used allows immediate implementation of the findings into routine NHS care.

During protocol development, the need to include only those people presenting for emergency treatment of a single ureteric stone was clear, because this was the group in which MET would potentially be used in the UK NHS. To achieve this, mandatory identification of a single ureteric stone by CT KUB, which has 98% diagnostic accuracy,[71] was incorporated as the main inclusion criterion. During the recruitment period a number of sites were in the later stages of transition between previous imaging modalities and CT KUB recommended by the relevant guidelines.[47] Overall, this resulted in 17% of patients screened being ineligible for the trial because CT KUB had not been performed. Ineligibility as a result of a lack of CT KUB was high in the first 6 months of recruitment, but fell markedly during the recruitment period (*Figure 21*) as the slower adopting centres successfully implemented CT KUB as a mandatory part of their loin pain emergency care pathway during the course of the SUSPEND trial. This supports our strategy of requiring CT KUB for trial entry, which anticipated this key pathway change (see *Figure 21*).

As expected for a large trial, baseline characteristics that might influence stone passage rates were similar between groups, with no differences in age and sex distribution, or in stone size and stone location. In addition, the characteristics of the SUSPEND trial population were similar to those recently published in a cohort of people presenting with ureteric colic.[72] The proportion of participants requiring further intervention by 4 weeks in the SUSPEND trial (20%) was similar to previous RCTs that used this as a measured outcome (20%)[14] and from a recent case series (14%).[72] In this trial, only 345 of the 4483 (7.6%) screened patients had a contraindication to the trial medication, suggesting that MET would be widely applicable as a therapeutic option. However, subsequent treatment discontinuation rates owing to perceived drug adverse effects were significantly higher for tamsulosin (10%) and nifedipine (17%) than for placebo (6%), which would limit routine application. Stone characteristics were also similar to the most recently reported case series, with 75%

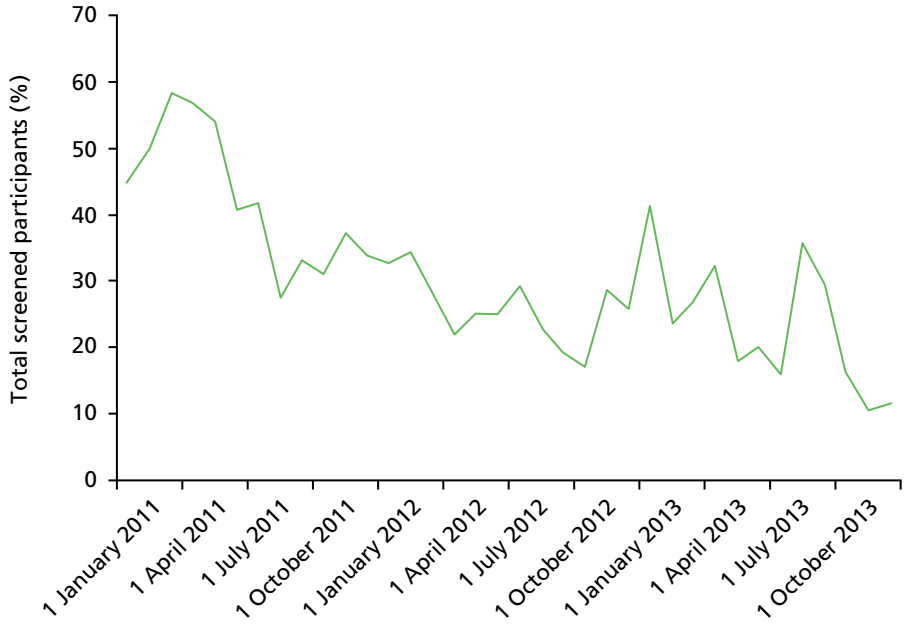

FIGURE 21 Percentage of screened participants found to be ineligible owing to lack of CT KUB during the trial.

being sized at 5 mm or less and 65% being found in the lower ureter, compared with 88% being sized at 5 mm or less and 66% being found in the lower ureter in the recent case series from the Republic of Korea.[72] The design used for the SUSPEND trial ensured inclusion of only people with a single ureteric stone that could be managed expectantly as well as recruitment of a population with similar key characteristics to case series of people with ureteric colic.[72] The equivalence of the SUSPEND trial population to the total population of people who might be considered for MET means that the finding of no effect is generalisable across the target population for MET both within the UK and worldwide.

A key aspect of the trial design was to ensure that allocation of participants to trial group was concealed from participants, clinical staff, and local and central trial staff. Selection bias in terms of clinical subgroups was not present, as emphasised by the equivalence of baseline characteristics. The well-established safety profile of the medications used meant that cases of unblinding were few (six in total; 0.5%) and that blinding was maintained until trial completion and database locking, thereby minimising the risk of ascertainment bias. Given the variation in spontaneous stone passage rates observed in control groups of previous RCTs, a placebo control was chosen despite the presumed likely efficacy of the active drugs. The continued need for the placebo group was monitored throughout the trial and supported by the DMC.

By using established clinical research networks within the UK and promotion by relevant professional organisations, it was ensured that the trial recruited effectively to the planned sample size. Over the 35-month recruitment window, 1167 participants were randomised and 1136 (97%) of these had the primary outcome recorded against the targets of 1200 and 1080 set out at the start of the trial, ensuring that the findings were robust.

It was anticipated that patient-driven outcomes, such as health status and pain, would be difficult to collect and that it would not be possible to estimate time to stone passage reliably without non-routine repeated imaging for all participants. The primary outcome, need for further intervention, was chosen because it aligned with the evidence needs of patients, clinicians and health-care providers. The avoidance of further intervention is a key outcome for patients as this involves invasive procedures each with a benefit and harm profile, together with the social and economic inconvenience of further hospital attendance and recovery time. For clinicians working in managed health-care systems such as the UK NHS, reduction in demand from emergency presentations makes planned service delivery more straightforward and avoids disruption to more efficient elective care delivery. For providers of health care, any reduction in interventions will reduce requirement for non-elective activity and cost and, hence, increase efficiency. A further advantage, considering the target population of a predominantly younger working age group with stable domicile, was that the recording of the primary outcome was achievable in a high percentage and could be validated locally through routinely collected NHS data. The success of this strategy is shown by attribution of primary outcome to 98% of the trial population, allowing an unbiased precise estimate of treatment effect.

Weaknesses

The conversion rate from screening to randomisation was 26%, which may have resulted in a degree of inclusion bias, although this was not evident from the similarity of baseline characteristics between our trial population and the previous unselected case series from the Republic of Korea.[72] The proportion of women in the trial population (19%) was lower than that recorded in other cohorts such as Hospital Episode Statistics data for 2012–13 [Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (fourth revision) (OPSC) code N23; 39.5%] and the recent Korean case series (32%).[72] However, the proportion of women was balanced across the groups of the trial and there was no evidence of interaction between sex and treatment for the primary outcome. Women were more likely to be excluded from the screened population, mainly as a result of not having a diagnostic CT KUB and having a stone located within the kidney rather than ureter. An additional small number were excluded because of the need to comply with the regulatory requirements regarding contraceptive use, as tamsulosin is not licensed for use in women.[73] Despite being unable to include patients older than 65 years, owing to restrictions in nifedipine use, the overall age range was identical with previous series as was the proportion of previous stone formers.

During the trial design, a number of methods of measurement of the event of stone passage were considered before deciding on the need for further active intervention. Most previous trials in this area have recorded stone passage rates up to a suitable cut-off time, usually at 4 weeks. These trials used various methods of measuring stone passage, which were predominantly based on the absence of visible stone on repeat imaging. In the routine NHS care pathway, repeat imaging following an episode of ureteric colic is not used for asymptomatic patients, regardless of whether or not they feel they have passed the stone. Those with continued pain or signs of infection are reimaged either by ultrasound with a full bladder and plain abdominal film of kidneys, ureters and bladder or, sometimes, by repeat CT KUB. For the purposes of detecting stone passage, a combination of ultrasound and plain radiography has the advantage of low radiation dose and, despite lower diagnostic accuracy (approximately 60%) compared with CT KUB, is recommended in current guidance.[17] Repeat CT KUB has been used in a number of trials and will give a high degree of certainty regarding the presence of a stone but exposes the patient to a significant radiation dose, equivalent to about 2.5 years of background.[18] A recent report from the UK Government[18] has emphasised the need for clinicians to justify every CT scan requested because of the risks of increased radiation exposure. For a single CT carried out in a 44-year-old person, this would amount to a lifetime additional cancer risk of 240 in 1 million. For this reason, repeat imaging at 4 weeks was not required to censor stone passage in our trial protocol. Rather, the active outcome of need for further intervention was measured, which has immediate consequences for the patient, clinician and health-care provider, and we were successful in documenting this for 98% of our trial population.

Reducing time to stone passage has been used as an important marker for the efficacy of MET; however, it is less appropriate for an effectiveness trial such as SUSPEND set within routine care. To measure this outcome accurately requires regular and frequent imaging, which was not logistically, ethically or economically feasible within our research setting. A strict set of criteria for inclusion of participants for this outcome was used, including (1) being reported by trial staff on the 4-week CRF; (2) being confirmed by imaging that a stone had passed; and (3) having a credible date of stone passage entered by the local research team on the 4-week CRF. Using these criteria, time to stone passage was confirmed for only 237 (21%) participants, with no difference between groups. Given that stone passage is often unnoticed following presentation with ureteric colic (except by absence of continuing pain) and considering repeat imaging was not mandatory, our results for time to stone passage have limited reliability and validity. Nevertheless, the lack of any discernible benefit from the tested drugs regarding time to stone passage from available data is consistent with the findings regarding the primary and other secondary outcomes.

The primary outcome was censored at 4 weeks, using the reasoning that most stone episodes would be completed by this time and that this end point aligned with previous trials. It could be thought, however, that a 4-week period of treatment with MET might reduce symptoms without stone passage, with symptoms returning once treatment had been completed. Data were collected up to 12 weeks and showed that a further 27 (7.1%) participants in the tamsulosin group, 25 (6.4%) in the nifedipine group and 28 (7.4%) in the placebo group had an intervention between 4 weeks and 12 weeks that was not planned at 4 weeks post randomisation. Inclusion of these data as a sensitivity analysis to the main results did not alter the finding of no difference.

The other possible benefit of MET is that it may reduce the amount of pain suffered by people as the stone descends down the ureter. The episodic nature of the pain and the community setting of stone episode follow-up presented challenges to reliable measurement of pain severity and duration during the 4-week observation period of the SUSPEND trial. Pain symptoms were recorded by responders to the 4-week participant questionnaire as the number of days that pain medication was taken for in the 4 weeks post-randomisation, a NRS for pain severity at the 4-week time point and the level of pain over the past 4 weeks on the EQ-5D. Although none of these measures showed any differences between treatment groups and the responses were consistent across the three measurements, recorded outcomes were available for only 63% of participants at 4 weeks and only 50% of participants at 12 weeks. There was no difference in response rates between trial groups, and the only baseline characteristic associated with failure to return a questionnaire was younger age, which is in accordance with findings from a previous community-based trial.[74] A number of interventions aimed at increasing questionnaire response rates were implemented throughout the trial, including pre-notification of

questionnaire delivery by short message service (SMS) text message; e-mail delivery of reminder questionnaires; sending out a shortened questionnaire format; and including a monetary incentive as recognition of the burden required for questionnaire completion and appreciation for trial involvement. A £5 high-street voucher sent out with the 12-week questionnaire successfully increased response rate from 46% to 57%. There was a small, non-significant, increase in response rate to the 4-week (but not the 12-week) questionnaire following a SMS text pre-notification on questionnaire response rate (response rate was increased from 52% to 57%). The remaining interventions did not have any impact on response rate.

Results in context

Previous efficacy studies

In general, previous studies have sought to demonstrate efficacy for MET using a primary outcome of stone passage rates directly measured as no stone seen on repeat imaging. Rates of further intervention are infrequently recorded in published work, with only three trials, involving 248 participants, of tamsulosin versus control (standard therapy), reporting a mean rate of 18% compared with 31% (RR 0.58, 95% CI 0.38 to 0.90),[14] and one trial, involving 140 participants, comparing nifedipine with an antispasmodic, phloroglucinol, reporting a rate of 20% versus 34% (p-value = 0.8).[15] The overall rate of further intervention in the SUPEND trial is in line with these previous reports, but in our large sample no difference was found across trial groups. Adding the SUSPEND trial results for tamsulosin into the Cochrane meta-analysis[14] using a random-effects model for this outcome gave a RR of 0.76 (95% CI 0.55 to 1.05; p-value = 0.1) (*Figure 22*).

It is difficult to place these results in the context of the previous studies and associated meta-analyses because of marked differences in design, size, conduct and outcome measures. Specifically, this trial was planned to provide a 'stand-alone' definitive answer to whether or not MET is a clinically useful intervention in the appropriate health-care setting. This was achieved by using definitive diagnostic confirmation of the target condition by CT KUB, using broad inclusion criteria, particularly in relation to stone size and location, and recruiting to a sample size sufficient to detect an effect size that may be considered to be the minimum required to change practice. To guard against allocation and ascertainment bias, robust methods of randomisation, allocation concealment and protection of blinding until trial completion were used. A placebo control group was used in case of a no-effect result, which indeed transpired. The primary outcome was chosen to reflect the chief concern of patients, clinicians and health-care providers, while being straightforward to collect and minimising waste of trial resources. These elements set this trial apart, and it is not felt that addition of these data to previous meta-analyses is valid. Instead, it is more appropriate for seekers of evidence concerning the advisability of use of MET to consider the positive results seen from meta-analysis of a series of small efficacy-focused RCTs against the no-effect results of this large effectiveness trial.

Meaning of trial

Ureteric colic continues to be a common reason for younger people of working age to seek emergency health care, with over 30,000 episodes resulting in hospital admission recorded for NHS England in 2012–13.[66] Simple, safe therapies to reduce the need for invasive interventions and alleviate pain associated with upper urinary tract stones would probably be welcomed by patients suffering ureteric colic as well as by the clinicians treating them and providers of health care. Unfortunately, the promise shown for tamsulosin, an alpha-blocker, and nifedipine, a calcium channel blocker, in meta-analysis of smaller trials has not been borne out by this large, pragmatic, multicentre RCT set within the routine care setting in the UK NHS. Patients with ureteric colic, their clinicians and clinical guidance authorities need to consider our results in conjunction with other evidence and decide whether or not to use MET for people presenting with ureteric colic. This does require urgent consideration as the prevalence of use of MET appears to be increasing, at least in the USA, from 14% in 2009[49] to 64% in 2012.[50] In our view, the results of the SUSPEND trial are clear and show that MET is not effective using the agents, dose and duration tested, suggesting that this trend of increased use should be reversed.

Study or subgroup	Alpha-blocker Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Autorino 2005[75]	5	50	11	46	9.8	0.42 (0.16 to 1.11)
Erturhan 2007[76]	1	30	2	30	1.8	0.50 (0.05 to 5.22)
SUSPEND 2015	71	378	76	379	58.6	0.94 (0.70 to 1.25)
Yencilek 2010[77]	14	42	26	50	29.8	0.64 (0.39 to 1.06)
Total (95% CI)		**500**		**505**	**100**	**0.76 (0.55 to 1.05)**
Total events	91		115			

Heterogeneity: $\tau^2=0.02$; $\chi^2=3.71$, df=3 ($p=0.29$); $I^2=19\%$

Test for overall effect: $z=1.64$ ($p=0.10$)

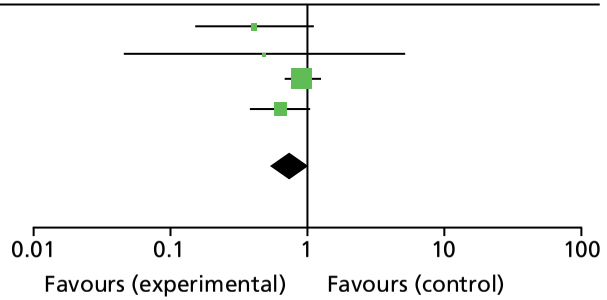

FIGURE 22 Forest plot showing inclusion of the SUSPEND trial result for comparison of tamsulosin vs. control for the outcome of hospitalisation for further intervention within a previous meta-analysis conducted as part of the Cochrane review.[14] The SUSPEND study refers to the current report. df, degrees of freedom; M–H, Mantel–Haenszel.

Chapter 8 Recommendations and further research

Medical expulsive therapy had no effect in this large, pragmatic, UK-based, adequately powered, high-quality RCT with a low risk of bias. This should be considered by interested clinicians, guideline writers and health-care policy-makers, especially against the positive findings from previous meta-analyses of a number of predominantly small, low-quality trials. In particular, the key design aspects of the SUSPEND trial that directly relate to the current care pathway for people with ureteric colic in the UK NHS (including accurate diagnosis by CT KUB, expectant management at home after a short hospital stay and the outcome of need for further intervention) should be given due weight. The routine use of MET is currently recommended by relevant clinical guidance bodies, and recent cohort studies suggest that the majority of patients with ureteric colic are prescribed one of the agents, predominantly tamsulosin, although this remains an unlicensed use of the drug. The SUSPEND trial results should reverse this trend, and guideline writers will need to reconsider clinical practice recommendations and their strength in the light of our reliable and precise estimates of effect size. This is especially in light of the higher rate of participants in both the tamsulosin and nifedipine groups who discontinued trial medication owing to adverse effects compared with placebo. It is of particular importance for women (especially those of child-bearing age) prescribed tamsulosin, as this medication is not licensed for use in this patient group and, therefore, the necessary safety profile has not been established.

Our baseline measurements reinforce previous understanding that ureteric colic is associated with considerable pain and disturbance to health state, with the consequent increased use of health services and disruption of social and economic activity. The degree of ill health does appear to resolve for most sufferers of ureteric colic within 4 weeks, but there remains a minority (20% in this trial) of patients who fail to pass their stone spontaneously and in whom further intervention is required to remove it. This intervention inevitably leads to a further period of disability and ongoing use of health-care resources. Therefore, despite the null results concerning the clinical effectiveness of tamsulosin and nifedipine, there remains a need for simple treatments that can reduce the need for intervention, help relieve pain and hasten stone passage, and a number of agents are in the early phases of development. We consider research priorities to be:

1. continued early-phase work to identify putative drugs or simple devices that show efficacy to hasten or increase likelihood of stone passage
2. promising agents should be tested in multicentre studies adequately powered to demonstrate a useful treatment effect and designed to minimise important biases
3. further work is required to investigate the phenomenon of large, high-quality trials showing smaller effect size than meta-analysis of several small, lower-quality studies. In particular, uncertainty regarding the results of these meta-analyses should be better communicated to the seeker of evidence both statistically and in the written conclusions of published papers
4. work should be done to ensure that guideline-producing bodies and their writers are well-informed regarding the need for careful consideration and interpretation of findings from published meta-analyses and grade their practice recommendations cautiously.

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Professor Samuel McClinton (Professor of Urology) was the chief investigator of the study; he had complete involvement and oversight of the study design, execution and data collection, and was responsible for the final report.

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Data sharing statement

All available data will be made available by contacting the corresponding author.

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Appendix 1 Spontaneous Urinary Stone Passage ENabled by Drugs trial patient information leaflet

PATIENT INFORMATION SHEET

<<INSERT NHS TRUST/BOARD LOGO>>

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INVITATION TO TAKE PART

You are being invited to take part in a research study related to the treatment of your ureteric stone. Before you decide if you would like to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with relatives, friends and your doctor or nurse if you wish. Please feel free to ask questions if the information is not clear or if you would like more information.

WHY HAVE I BEEN INVITED TO TAKE PART?

You have been chosen because you have been diagnosed with a stone in your ureter (the tube which drains the urine from the kidney to the bladder).

DO I HAVE TO TAKE PART?

No. It is entirely up to you whether or not to take part. Please take as much time as you feel you need to make this decision. You can read this information sheet as many times as you wish and ask your doctor or research nurse as many questions as you need.

Whether you decide to take part or not you will still receive standard care for your ureteric stone.

If you decide to take part we will ask you to sign a consent form confirming your agreement. However, even after you have signed this form, you are still free to withdraw at any time and without giving a reason. A decision to withdraw from the study will not affect the standard of care you receive.

BACKGROUND TO THE CONDITION

Ureteric stones are very common; 2-3% of the general population have suffered from this condition. Ureteric stones have been found to have an impact on individual's quality of life due to the severe pain produced which requires prescription of pain killing medicines, admission to hospital and time off work and social activities.

There are a number of different treatments used to get rid of ureteric stones. These include a number of telescopic procedures which remove the stone or else shock wave treatment can be applied from outside the body to break up the stone. In recent years the benefit of drugs to help pass the stone has been tested. These drugs relax the muscle fibres of the ureter and it is thought that this may make the stone come out quicker. Tamsulosin and nifedipine are two different drugs that have this action. These drugs are already in common use to treat other health problems such as high blood pressure or bladder problems. The new use of these drugs to encourage ureteric stones to come out more quickly is known as medical expulsive therapy (MET). It may be that the use of MET can reduce the risk of associated complications present with other treatments.

WHAT IS THE PURPOSE OF THE STUDY?

This study will test whether drug treatment with either nifedipine or tamsulosin will make ureteric stones come out more easily and quickly.

HAVE ANY STUDIES LIKE THIS BEEN DONE BEFORE?

Preliminary studies into the use of MET to treat ureteric stones have been conducted, but these studies had a small number of participants taking part and did not directly compare these medicines with a non-active 'dummy' capsule (placebo). As the benefit of this treatment remains unclear the research authority of the NHS, the National Institute of Health Research, have decided to carry out a comprehensive study. The study is called SUSPEND and it is a large UK wide study that will compare the benefit of nifedipine, tamsulosin and a non-active 'dummy' capsule (placebo) to see whether nifedipine or tamsulosin are worth introducing as standard treatment for people with ureteric stones in the NHS.

HOW WILL WE DO THIS?

Patients who agree to take part in SUSPEND will be randomly allocated to be given one of the following treatments: nifedipine or tamsulosin or placebo (non-active 'dummy' capsule). The particular treatment given to each person in the study will be decided by a computer system (see the table below for the treatment groups). If you decide to take part this means that neither you nor your doctors can decide which treatment you will receive. There is an equal chance you will be placed into any one of the three treatment groups below. To take part in this study you must be happy to take any one of these treatments for up to 28 days.

Group number	Group name	Treatment
Group 1	Calcium Channel Blocker	Nifedipine (one 30 mg oral capsule each day for up to 28 days)
Group 2	Alpha Blocker	Tamsulosin (one 0.4 mg capsule each day for up to 28 days)
Group 3	Placebo	Placebo (one non-active 'dummy' capsule each day for up to 28 days)

To collect the information we need everyone in the study will be followed up in exactly the same way for a period of 12 weeks after starting the treatment. We will ask you to complete three short questionnaires; one before you start the study, one four weeks after you start and one 12 weeks after you start. The questionnaires will ask you to detail the symptoms you experience due to your ureteric stones and how this affects your day-to-day life. We will send you the questionnaires in the post and may send you a reminder by post or e-mail. If you have a mobile phone we may send you a text message to let you know your questionnaire is on its way.

The study nurse or doctor involved in the study will also collect information from your hospital and family doctor records during the 12 weeks after you join the study.

After your initial hospital visit for your ureteric stone you will be asked to come back to an outpatient clinic at your hospital to check how you are getting on. If your ureteric stone symptoms are still not adequately controlled you may receive further treatment in the same way people with ureteric stones are usually treated. All the

care that you receive on the study will be the same as the standard care that is usually given apart from the capsules you will take as part of the study.

WHAT WILL HAPPEN NEXT?

You will be given time to consider the information given in this sheet and your doctor or nurse will further explain the study and what you need to do if you want to take part. You will have the opportunity to ask the doctor or research nurse as many questions as you need to fully understand your participation in the SUSPEND study.

If you do not wish to take part in the SUSPEND trial you do not have to give a reason and this will not affect the healthcare you will be given.

If you are happy to take part in the SUSPEND study you will be asked a series of questions to make sure that your particular circumstances make you suitable for inclusion in the study. If you are suitable, you will be asked to sign a consent form and complete the first questionnaire. Your details will be entered into a computer system and you will be randomly allocated to receive one of the three possible study treatments we are testing. Neither you nor the doctors or nurses treating you will know which treatment you are taking. This information will however be known at the study office and can be released to the doctors treating you if needed. You will be given a pack of study medication and asked to take one capsule every day until you pass the stone or until you finish the pack. You will also be given an information leaflet about the medicine and a telephone number to contact in case you have any concerns about the study treatment while you are taking it.

WHAT ARE THE POSSIBLE BENEFITS TO ME OF TAKING PART?

You will receive the same proper health care from your doctors whether or not you choose to participate in the study or not. You may not benefit personally from taking part in this study. There is no guarantee that MET therapy will be successful, however you will be offered other treatment if your symptoms get worse or do not improve.

By taking part in this study you will be directly helping us to inform the treatment of future patients diagnosed with ureteric stones. The results of the study will help plan effective services offered by the NHS.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

The disadvantages of taking part in this study include possible reactions to the study medication which you are randomised to. Some people could have side effects with the medications used in the SUSPEND study, but these are usually mild and disappear after a short while. The medications used are not new drugs and have been in routine use for many years for other health problems.

Side effects that have been reported with these medications include:-

<u>Common (less than 1 in 10, more than 1 in 100)</u>
Dizziness, headache, constipation, abnormal ejaculation.

Uncommon (less than 1 in 100, more than 1 in 1,000)
Rapid heartbeat, palpitations, runny and itchy nose, diarrhoea, nausea, vomiting, indigestion, itching, rash, increased frequency of urination, fainting, mood changes.

Rare (less than 1 in 1,000, more than 1:10,000)\
Feeling of pins and needles, swollen gums, impotence, swelling.

Very Rare (less than 1 in 10,000 or rate unknown)
Feeling of weakness, lethargy, eye pain, shortness of breath, prolonged and painful erection, allergic reactions including swelling of lips face and neck, blurred or impaired vision, nose bleeds, exfoliative dermatitis.

If you decide to participate in the SUSPEND study, you will be provided with an information leaflet with your medicine. Please, read all the information contained in this leaflet about your treatment.

WHAT SHOULD I TELL MY DOCTOR IF I DO DECIDE TO TAKE PART?

Please tell your doctor if you have previously had a reaction to nifedipine or tamsulosin. Please also tell your doctor about other medicines you take, either prescribed or those you buy for yourself including herbal remedies.

If there is a possibility you are pregnant please tell your doctor as you will be required to take a pregnancy test before entering the study. If you are pregnant you cannot take part in the study.

If you are a woman of child bearing potential you will need to use a highly effective form of contraception while you are taking the study medication and for at least 28 days after. Acceptable forms of contraception include:-

- Combined oral contraceptive pill, progesterone only pill (mini-pill), transdermal patch, depot-provera injection or implanon implant.
- Intra-uterine system (Mirena) or device.
- Condom or Occlusive cap (diaphragm or cervical/vault caps) ***plus*** a spermicidal foam/gel/film/cream/suppository.
- Female sterilisation or sole male partner is sterile.

Since no contraceptive method is 100% reliable on its own, we advise the use of additional methods of contraception from the start of the study.

If you require any further advice on contraception during this study please ask.

WHAT IF THERE IS A PROBLEM?

We do not expect any harm to come to you by taking part in this study. However, if you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek compensation through the research sponsors of the study, University of Aberdeen and NHS Grampian. Contact details for both research sponsors are available through the research team.

As a patient of the NHS if you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of

this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

If you have a concern about any aspect of this study you should ask to speak to the researchers who will answer your questions (contact details of your local study nurse and the SUSPEND study office can be found at the end of this information sheet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints mechanisms (or Private Institution). Contact details can be obtained from your local hospital. In addition to this, you may contact the chairman of the SUSPEND Trial Steering Committee (an experienced, retired doctor who is independent from the study) through the SUSPEND study office.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

Your doctor will continue your care and treatment as standard.
In the unlikely event you are unable to continue in SUSPEND we will withdraw you from the study and ask you to stop taking the study medication. Your doctor will continue to treat you as standard. If this happens we will keep the relevant information already collected about you for the study results. This information will remain confidential and will not be used for any other purpose.

WHO WILL KNOW I AM TAKING PART IN THE STUDY?

All information that is collected about you during the course of the study will be kept strictly confidential and will be held securely in accordance with the Data Protection Act. Only certain members of the research team will have access to your information in order, for instance, to send you the questionnaires.

If you participate in the study we will tell your GP you are taking part, but only with your permission. We will also ask your GP to contact us if you visit them with any problems that may relate to the study. Data for all participants in the study, including those who withdraw, will be kept for a minimum of 30 years.

WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?

You can withdraw from the study at any time, but you will need to continue attending appointments with your consultant and/or GP in order to have your ureteric stones monitored as part of your standard care.

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

If a new treatment or information becomes available during the study, you will be made aware of this and you can decide if you would like to continue taking part. You may decide this at any time and your decision will not affect your long-term care. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results of the study will be used to make recommendations on treatments for patients with ureteric stones. The results of this study will also be published in scientific journals and presented at scientific meetings. You will not be identified in any publication of results of the study. We will let you know the results of the study when it is finished unless you tell us that you do not wish to know.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

The study has been designed by UK urological medical doctors and researchers. Patients will be recruited at different hospitals in England, Wales and Scotland. The study is being funded by the UK National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme. It is being co-ordinated by The Centre for Healthcare Randomised Trials (CHaRT), a UKCRC registered clinical trials unit, at the University of Aberdeen.

WHO HAS REVIEWED THE STUDY?

This study has been reviewed by a NHS Research Ethics Committee, which has responsibility for scrutinising proposals for medical research on humans, in accordance with the Clinical Trials Regulations. In this case, the reviewing Committee was the Fife and Forth Valley Research Ethics Committee who have raised no objections from the point of view of medical ethics. In addition the study has also been reviewed and approved by the Medicines and Healthcare Products Regulatory Agency, the Research & Development department of your local hospital and the study funder (NHS NIHR HTA).

It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from the University of Aberdeen, NHS Grampian and the Regulatory Authorities whose role it is to check that research is properly conducted and the interests of those taking part are adequately protected.

THANK YOU

Patients and doctors rely increasingly on the results of clinical studies, such as SUSPEND, to make sure they are making the right decisions about treatment. Thank you for taking the time to read this information leaflet. We hope that it has been helpful in enabling you to decide if you would like to participate in the SUSPEND study.

FURTHER INFORMATION AND CONTACT DETAILS

If you have any questions or would like any more information, please contact:

Study Office contact details:

SUSPEND Study Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
University of Aberdeen
3rd Floor, Health Sciences Building
Foresterhill
Aberdeen AB25 2ZD
Telephone: [redacted]
Email: [redacted]
Website:
[redacted]

Local contact details:

<<Insert contact details of local PI and/or Research Nurse>>

Appendix 2 Spontaneous Urinary Stone Passage ENabled by Drugs trial consent form

SUSPEND
Spontaneous Urinary Stone Passage Enabled by Drugs

TRIAL CONSENT FORM

Participant Study No

Please initial ALL boxes

By signing this form and initialling each box:

1) I agree that I have

- been given the Information Sheet about the study (Version number 1.4, date 21 Oct 2013) ☐
- had the opportunity to discuss the study and all my questions have received satisfactory answers ☐
- understood the purpose of the study and I know what my involvement will be ☐
- received advice regarding the use of contraception while involved in the trial ☐

2) I understand that

- my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected ☐
- information relevant to the SUSPEND Trial may be collected from my hospital and NHS records, including Office of National Statistics (ONS) and NHS central registers ☐
- relevant sections of my medical notes and data collected during the study may be looked at by individuals directly involved in the trial, from regulatory authorities or from the NHS Health Boards or Trusts, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
- my personal contact details will be kept confidentially and securely by the study office in Aberdeen. I agree that the study co-ordinators can use my contact details to send me relevant study information and questionnaires. ☐
- my family doctor (GP) will be told that I am taking part in this trial ☐

I agree to take part in the study ☐

Your signature (participant) _____

Your name in block capitals _____

Date _____

For office use only

I confirm that I have explained to the person named above, the nature and purpose of the study and the procedures involved

Signature _____

Name in block capitals _____

Date _____

The SUSPEND Trial Office, Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD
Tel [redacted]; Fax [redacted]; [redacted]

Copies: 1 for trial office in Aberdeen (top copy); 1 for patient; 1 for site file, 1 to be filed with hospital notes.

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Appendix 3 Summary of product characteristics for the investigational medicinal products

Tamsulosin summary of product characteristics

Much of this information is reproduced from Medicines & Healthcare products Regulatory Agency[78]

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Petyme 400 micrograms MR Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 400 micrograms of tamsulosin hydrochloride.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified-release capsule, hard
Orange/olive-green capsule, with the black printed mark TSL 0.4 and with a black stripe at both ends. The capsules contain white to off-white pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

One capsule a day after breakfast or the first meal of the day. The capsule is swallowed whole with a glass of water while standing or sitting (not lying down). The capsule should not be broken or pulled apart as this may have an effect on the release of the long-acting active ingredient.

No dose adjustment is warranted in renal impairment. No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see also section 4.3).

Paediatric population
There is no relevant indication for use of tamsulosin in children. The safety and efficacy of tamsulosine in children <18 years have not been established. Currently available data are described in section 5.1

4.3 Contraindications

Hypersensitivity to tamsulosin, including drug-induced angio-oedema, or to any of the excipients. Orthostatic hypotension observed earlier (history of orthostatic hypotension).
Severe hepatic insufficiency.

4.4. Special warnings and precautions for use

As with other α 1-adrenoceptors antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared.

Before therapy with tamsulosin is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.

The treatment of patients with severe renal impairment (creatinine clearance of < 10 ml/min) should be approached with caution as these patients have not been studied.

Angio-oedema has been rarely reported after the use of tamsulosin. Treatment should be discontinued immediately, the patient should be monitored until disappearance of the oedema, and tamsulosin should not be re-administered.

The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not yet been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to cataract surgery.

The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract surgery is scheduled is not recommended.

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4 (see section "4.5").

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

No interactions have been seen when tamsulosin hydrochloride was given concomitantly either with atenolol, enalapril, or theophylline. Concomitant cimetidine, brings about a rise in plasma levels of tamsulosin, whereas furosemide, a fall, but as levels remain within the normal range posology need not be adjusted. .

In vitro, neither diazepam nor propranolol, trichlormethiazide, chlormadinone, amitriptyline, diclofenac, glibenclamide, simvastatin and warfarin change the free fraction of tamsulosin in human plasma. Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide and chlormadinone.

Diclofenac and warfarin may increase the elimination rate of tamsulosin.

Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 may lead to increased exposure to tamsulosin hydrochloride. Concomitant administration with ketoconazole (a known strong CYP3A4 inhibitor) resulted in an increase in AUC and Cmax of tamsulosin hydrochloride by a factor of 2.8 and 2.2, respectively.

Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype.

Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4.

Concomitant administration of tamsulosin hydrochloride with paroxetine, a strong inhibitor of CYP2D6, resulted in a Cmax and AUC of tamsulosin that had increased by a factor of 1.3 and 1.6, respectively, but these increases are not considered clinically relevant.
Concurrent administration of other α_1-adrenoreceptor antagonists could lead to hypotensive effects.

4.6 Fertility, pregnancy and lactation

Tamsulosin is not indicated for use in women.

Ejaculation disorders have been observed in short and long term clinical studies with tamsulosin. Events of ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported in the post authorization phase.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However patients should be aware of the fact that dizziness can occur.

4.8. Undesirable effects

The frequencies of adverse reactions are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

	Common	Uncommon	Rare	Very rare	Not known
Nervous system disorders	Dizziness	Headache	Syncope		
Eye disorder					vision blurred, visual impairment
Cardiac disorders		Palpitations			
Vascular disorders		Orthostatic hypotension			
Respiratory, thoracic and mediastinum-related disorders		Rhinitis			epistaxis

Gastrointestinal disorders		Constipation, diarrhoea, nausea, vomiting			
Skin and subcutaneous tissue disorders		Rash, itching, urticaria	Angio-oedema	Stevens-Johnson syndrome	erythema multiforme, dermatitis exfoliative
Reproductive systems and breast disorders	Ejaculation disorder, Retrograde ejaculation, Ejaculation failure			Priapism	
General disorders and administration site conditions		Asthenia			

During cataract surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been associated with therapy of tamsulosin during post-marketing surveillance (See also Section 4.4).

Post-marketing experience
In addition to the adverse events listed above, the following adverse reactions have been reported in association with tamsulosin use:

Cardiac disorders
Not Known: Atrial fibrillation, arrhythmia, tachycardia

Respiratory, thoracic and mediastinal disorders
Not known: Dyspnoea

Because these spontaneously reported events are from the worldwide post marketing experience, the frequency of events and the role of tamsulosin in their causation cannot be reliably determined.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:
www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms
Overdosage with tamsulosin hydrochloride can potentially result in severe hypotensive effects. Severe hypotensive effects have been observed at different levels of overdosing.

Treatment
In case of acute hypotension occurring after overdosage cardiovascular support should be given. Blood pressure can be restored and heart rate brought back to normal by lying the patient down. If this does not help then volume expanders and, when necessary, vasopressors could be employed. Renal function should be monitored and general supportive measures applied. Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins.

Measures, such as emesis, can be taken to impede absorption. When large quantities are involved, gastric lavage can be applied and activated charcoal and an osmotic laxative, such as sodium sulphate, can be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Tamsulosin is an α_{1A} adrenoreceptor antagonist. The medicinal product is only used for the treatment of prostatic conditions.
ATC code: G04CA02

Mechanism of action
Tamsulosin binds selectively and competitively to postsynaptic α_{1A} adrenoreceptors, which convey smooth muscle contraction, thereby relaxing prostatic and urethral smooth muscle.

Pharmacodynamic effects
Tamsulosin increases the maximum urinary flow rate by relaxing prostatic and urethral smooth muscle, thus relieving obstruction.

The medicinal product also improves the irritative and obstructive symptoms in which the contraction of smooth muscle in the lower urinary tract plays an important role.

Alpha-blockers can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin in normotensive patients.

The medicinal product's effect on storage and voiding symptoms are also maintained during long-term therapy, as a result of which the need for surgical treatment is significantly postponed.

Paediatric population
A double-blind, randomized, placebo-controlled, dose ranging study was performed in children with neuropathic bladder. A total of 161 children (with an age of 2 to 16 years) were randomized and treated at 1 of 3 dose levels of tamsulosin (low [0.001 to 0.002 mg/kg], medium [0.002 to 0.004 mg/kg], and high [0.004 to 0.008 mg/kg]), or placebo. The primary endpoint was number of patients who decreased their detrusor leak point pressure (LPP) to <40 cm H2O based upon two evaluations on the same day. Secondary endpoints were: Actual and percent change from baseline in detrusor leak point pressure, improvement or stabilization of hydronephrosis and hydroureter and change in urine volumes obtained by catheterisation and number of times wet at time of catheterisation as recorded in catheterisation diaries. No statistically significant difference was found between the placebo group and any of the 3 tamsulosin dose groups for either the primary or any secondary endpoints. No dose response was observed for any dose level.

5.2 Pharmacokinetic properties

Absorption
Tamsulosin is rapidly absorbed from the intestines and its bioavailability is almost complete. Absorption is slowed down if a meal has been eaten before taking the medicinal product. Uniformity of absorption can be assured by always taking tamsulosin after breakfast.
Tamsulosin shows linear kinetics.

Peak plasma levels are achieved at approximately six hours after a single dose of tamsulosin taken after a full meal. The steady state is reached by day five of multiple dosing, when C_{max} in patients is about two-thirds higher than that reached after a single dose. Although this has been demonstrated only in the elderly, the same result would also be expected in younger patients.
There are huge inter-patient variations in plasma levels of tamsulosin, both after single as well as multiple dosing.

Distribution
In humans, tamsulosin is more than 99% bound to plasma proteins and the volume of distribution is small (about 0.2 l/kg).

Biotransformation
Tamsulosin has a low first pass metabolic effect. Most tamsulosin is found unaltered in plasma. The substance is metabolised in the liver.

In studies on rats, tamsulosin was found to cause only a slight induction of microsomal liver enzymes.

Excretion
Tamsulosin and its metabolites are mainly excreted in the urine with about 9% of the dose being present in unchanged form.

The elimination half-life of tamsulosin in patients is approximately 10 hours (when taken after a meal) and 13 hours in the steady state.

5.3 Preclinical safety data

Toxicity after a single dose and multiple dosing has been investigated in mice, rats and dogs. Reproductive toxicity has also been investigated in rats, carcinogenicity in mice and rats, and genotoxicity *in vivo* and *in vitro*.

The common toxicity profile found with large doses of tamsulosin is equivalent to the pharmacological effect associated with alpha adrenergic antagonists.
Changes in ECG readings were found with very large doses in dogs. This is not, however, assumed to be of any clinical significance. Tamsulosin has not been found to have any significant genotoxic properties.

Greater proliferative changes in the mammary glands of female rats and mice have been discovered on exposure to tamsulosin. These findings, which are probably indirectly linked to hyperprolactinaemia and only occur as a result of large doses having been taken, are considered clinically insignificant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content of capsule
Microcrystalline cellulose
Methacrylic acid-ethyl acrylate copolymer
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate
Talc

Capsule body
Gelatine
Indigotine (E 132)
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)

Black iron oxide (E 172)

Ink
Shellac
Black iron oxide (E 172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Blister packs: Store in the original package.
Tablet containers: Keep the container tightly closed.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blister packs in cardboard boxes and HDPE tablet containers with PP child-resistant closures containing 10, 14, 20, 28, 30, 50, 56, 60, 90, 100, 180 or 200 modified-release capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road
Hampden Park

Eastbourne
East Sussex
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0860

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 02/02/2006
Date of latest renewal: 23/03/2010

10 DATE OF REVISION OF THE TEXT

7/08/2013

Nifedipine summary of product characteristics

Much of this information is reproduced from Medicines & Healthcare products Regulatory Agency[79]

UCB Pharma Limited
208 Bath Road, Slough, Berkshire, SL1 3WE
Telephone: [redacted]
Fax: [redacted]
Medical Information Direct Line: [redacted]
Medical Information e-mail: [redacted]
Customer Care direct line: [redacted]
Need to contact this company?

Summary of Product Characteristics last updated on the eMC: 20/04/2009

Coracten XL Joint SPC 30mg, 60mg

1. NAME OF THE MEDICINAL PRODUCT

Coracten XL 30mg.

Coracten XL 60mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 30mg Nifedipine Ph.Eur in sustained release form.

Each capsule contains 60mg Nifedipine Ph.Eur in sustained release form.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Prolonged release capsule, hard

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Coracten XL capsules are indicated for the treatment of hypertension and the prophylaxis of chronic stable angina pectoris.

4.2 Posology and method of administration

The capsules are for oral administration and should be swallowed whole with a little fluid.

Dosage - Angina Pectoris and Hypertension

Adults only: Normally treatment is initiated with one 30mg Coracten XL capsule every 24 hours. Dosage may be titrated to a higher level as clinically warranted. The dose may be adjusted to 90mg every 24 hours.

Children: Coracten XL capsules are not recommended for use in children.

Elderly: The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Hepatic impairment: As Coracten XL is a long acting formulation, it should not be administered to patients with hepatic impairment.

Renal impairment: Dosage adjustments are not usually required in patients with renal impairment.

4.3 Contraindications

Coracten XL capsules are contra-indicated in patients with known hypersensitivity to nifedipine or other dihydropyridines because of the theoretical risk of cross reactivity. They should not be used in nursing mothers and women who are or who may become pregnant (see section 4.6. Pregnancy and Lactation).

Coracten XL capsules should not be used in clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction. They should not be used in patients in cardiogenic shock.

Coracten XL capsules should not be used for the treatment of acute attacks of angina, or in patients who have had ischaemic pain following its administration previously.

The safety of Coracten XL capsules in malignant hypertension has not been established.

Coracten XL capsules should not be used for secondary prevention of myocardial infarction.

Coracten XL capsules are contra-indicated in patients with acute porphyria.

Coracten XL capsules should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction.

As Coracten XL is a long acting formulation, it should not be administered to patients with hepatic impairment.

4.4 Special warnings and precautions for use

The dose of nifedipine should be reduced in patients with hepatic impairment (***see section 4.2. Posology and Method of Administration***). Nifedipine should be used with caution in patients who are hypotensive; in patients with poor cardiac reserve; in patients with heart failure or significantly impaired left ventricular function as their condition may deteriorate; in diabetic patients as they may require adjustment of their diabetic therapy; and in dialysis patients with malignant hypertension and irreversible renal failure with hypovolaemia, since a significant drop in blood pressure may occur due to the vasodilator effects of nifedipine.

Excessive falls in blood pressure may result in transient blindness. If affected do not attempt to drive or use machinery (see also section 4.8. Undesirable Effects).

Since nifedipine has no beta-blocking activity, it gives no protection against the dangers of abrupt withdrawal of beta-blocking drugs. Withdrawal of any previously prescribed beta-

blockers should be gradual, preferably over 8 to 10 days.

The dose of nifedipine should be reduced in patients with hepatic impairment (see section 4.2.Posology and Method of Administration).

Nifedipine may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Nifedipine will not prevent possible rebound effects after cessation of other anti-hypertensive therapy.

4.5 Interaction with other medicinal products an other forms of interaction

As with other dihydropyridines, nifedipine should not be taken with grapefruit juice because bioavailability is increased.

The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and hence an increase in the plasma digoxin. Digoxin levels should be monitored and, if necessary, the digoxin dose reduced.

Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid falsely. However, HPLC measurements are unaffected.

Coracten XL capsules should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see section 4.3. Contra-indications).

Increased plasma levels of nifedipine have been reported during concomitant use of H_2-receptor antagonists (specifically cimetidine), other calcium channel blockers (specifically diltiazem), alcohol, cyclosporin, macrolide antibiotics, gingko biloba and ginseng. Azole antifungals may increase serum concentrations of nifedipine.

Decreased plasma levels of nifedipine have been reported during concomitant use of antibacterials (specifically rifampicin), and probably also antiepileptics and St John's Wort.

When used in combination with nifedipine, plasma concentrations of quinidine have been shown to be suppressed regardless of quinidine dosage. The plasma concentrations of phenytoin, theophylline, non-depolarising muscle relaxants (e.g. tubocurarine) and possibly digoxin are increased when used in combination with nifedipine. Tacrolimus concentrations may be increased by nifedipine.

Enhanced hypotensive effect of nifedipine may occur with: aldesleukin, alprostadil, anaesthetics, antipsychotics, diuretics, phenothiazides, prazosin and intravenous ionic X-ray contrast medium. Profound hypotension has been reported with nifedipine and intravenous magnesium sulphate in the treatment of pre-eclampsia.

Ritonavir and quinupristin/dalfopristin may result in increased plasma concentrations of nifedipine.

Effective plasma levels of nifedipine may not be achieved due to enzyme induction with concurrent administration of erythromycin, carbamazepine and phenobarbitone.

There is an increased risk of excessive hypotension, bradycardia and heart failure with β-blockers.

An increased rate of absorption of nifedipine from sustained release preparation may occur if given concurrently with cisapride.

Nifedipine may result in increased levels of mizolastine due to inhibition of cytochrome CYP3A4.

Nifedipine may increase the neuromuscular blocking effects of vecuronium.

4.6 Pregnancy and lactation

Pregnancy

Because animal studies show embryotoxicity and teratogenicity, nifedipine is contraindicated during pregnancy (see also section 4.3. Contra-indications). Embryotoxicity was noted at 6 to 20 times the maximum recommended dose for nifedipine given to rats, mice and rabbits, and teratogenicity was noted in rabbits given 20 times the maximum recommended dose for nifedipine.

Lactation

Nifedipine is secreted in breast milk, therefore, Coracten XL capsules are not recommended during lactation.

4.7 Effects on ability to drive and use machines

Dizziness and lethargy are potential undesirable effects. If affected do not attempt to drive or use machinery (see also section 4.8. Undesirable Effects).

Excessive falls in blood pressure may result in transient blindness. If affected do not attempt to drive or use machinery (see also section 4.8. Undesirable Effects).

4.8 Undesirable effects

Most side-effects are consequences of the vasodilatory effects of nifedipine.

Side-effects are generally transient and mild, and usually occur at the start of treatment only. They include headache, flushing and, usually at higher dosages, nausea, dyspepsia, heartburn, constipation, diarrhoea, dizziness, lethargy, skin reactions (rash, urticaria and pruritus), paraesthesia, hypotension, palpitation, tachycardia, dependent oedema, increased frequency of micturition, eye pain, depression, fever, gingival hyperplasia ,telangiectasia and erythema multiforme.

Other less frequently reported side-effects include myalgia, tremor, pemphigoid reaction and visual disturbances. Impotence may occur rarely. Mood changes may occur rarely.

Excessive falls in blood pressure may result in cerebral or myocardial ischaemia or transient blindness.

As with other sustained release dihydropyridines, exacerbation of angina pectoris may occur rarely at the start of treatment with sustained release formulations of nifedipine. The occurrence of myocardial infarction has been described

although it is not possible to distinguish such an event from the natural course of ischaemic heart disease. Ischaemic pain has been reported in a small proportion of patients following the introduction of nifedipine therapy. Although a 'steal' effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

There are reports in older men on long-term therapy of gynaecomastia which usually regresses upon withdrawal of therapy.

Side-effects which may occur in isolated cases are photosensitivity, exfoliative dermatitis, systemic allergic reactions, purpura and a worsening of myasthenia gravis. Usually, these regress after discontinuation of the drug.

Rare cases of hypersensitivity-type jaundice have been reported. In addition, disturbances of liver function such as intra-hepatic cholestasis may occur. These regress after discontinuation of therapy.

4.9 Overdose

Clinical effects

Reports of nifedipine overdosage are limited and symptoms are not necessarily dose-related. Severe hypotension due to vasodilation, and tachycardia and bradycardia are the most likely manifestations of overdose.

Metabolic disturbances include hyperglycaemia, metabolic acidosis and hypo- or hyperkalaemia.

Cardiac effects may include heart block, AV dissociation and asystole, and cardiogenic shock with pulmonary oedema.

Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, hypoxia and unconsciousness to the point of coma.

Treatment

As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority.

After oral ingestion, gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

Elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

Activated charcoal should be given in 4-hourly doses of 25g for adults, 10g for children.

Blood pressure, ECG, central arterial pressure, pulmonary wedge pressure, urea and electrolytes should be monitored.

Hypotension as a result of cardiogenic shock and arterial vasodilation should be treated with elevation of the feet and plasma expanders. If these measures are ineffective, hypotension may be treated with 10% calcium gluconate 10-20 ml intravenously over 5-10 minutes. If the effects are

inadequate, the treatment can be continued, with ECG monitoring. In addition, beta-sympathomimetics may be given, e.g. isoprenaline 0.2 mg slowly i.v. or as a continuous infusion of 5µg/min. If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required.

Additional fluids should be administered with caution to avoid cardiac overload.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C08C A05

Nifedipine is a potent calcium-channel blocker which, by dilating peripheral arterial smooth muscle, decreases cardiac work and myocardial oxygen requirement. It also dilates coronary arteries, thereby improving myocardial perfusion and reducing coronary artery spasm. In hypertension, it reduces blood pressure but has little or no effect in normotensive subjects. It has no therapeutic antiarrhythmic effect.

5.2 Pharmacokinetic properties

Coracten XL capsules are a sustained release formulation of nifedipine designed to provide less fluctuation and more prolonged nifedipine blood concentrations than standard immediate release preparations.

Nifedipine is highly protein bound. It undergoes hepatic oxidation to inactive metabolites which are excreted in the urine (80%) and faeces (20%).

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:

Lactose monohydrate

Microcrystalline Cellulose

Hydroxylpropyl methylcellulose K100

Povidone K30

Magnesium Stearate

Hydroxypropylcellulose

Ammonio methacrylate copolymer type B

Polyethylene Glycol 6000

Dibutylphthalate

Titanium dioxide E171

Talc

30 mg - Capsule shells (size 3):

Yellow iron oxide E172

Red iron oxide E172

Titanium dioxide E171

Gelatin

60 mg - Capsule shells (size 1)

Red iron oxide E172

Titanium dioxide E171

Gelatin

The printing ink is made of shellac, purified water, black iron oxide (E172) with 2 ⁻ ethoxyethanol, soya lecithin, anitfoam and IMS or with ethyl alcohol, isopropyl alcohol, n ⁻ butyl alcohol, propylene glycol, ammonium hydroxide and potassium hydroxide.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Coracten XL capsules are available in blister strips packed in cartons containing 28, 30, 56 and 60 capsules. The blister strips are formed from PVC with a coating of PVdC backed with aluminium foil.

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma Limited

208 Bath Road

Slough

Berkshire

SL1 3WE

UK

8. MARKETING AUTHORISATION NUMBER(S)

30 mg - PL 00039/0506

60 mg - PL 00039/0507

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 October 1998

10. DATE OF REVISION OF THE TEXT

April 2009

POM

Appendix 4 Spontaneous Urinary Stone Passage ENabled by Drugs trial participant questionnaires

BASELINE QUESTIONNAIRE

Participant Study No

SUSPEND

Spontaneous Urinary Stone Passage Enabled by Drugs

Baseline QUESTIONNAIRE

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research Health Technology Assessment Programme

ISRCTN69423238

Version 1.0, 11 May 2010

The following questionnaire is broken down into three sections (Section A - Section C). Please work through all the sections as best you can from start to finish.

Some of the sections ask you to indicate your answers to the questions by placing a cross **(X)** in the appropriate box, and other sections ask you to circle your answer.

Please read the questions carefully and answer each one as accurately as you can.

The sections covered in this questionnaire are as follows:

Section A: Your Pain Today

Section B: Describing Your Own Health Today (EQ-5D)

Section C: Your General Health (SF-36©)

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

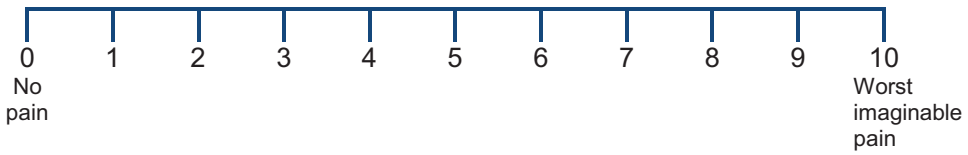
Please start here:

Date questionnaire filled in D D / M M / Y Y Y Y

SECTION A – YOUR PAIN TODAY

A1. Please rate the level of pain that you are experiencing TODAY.
The following line represents pain of increasing intensity from 'no pain' to 'worst imaginable pain'. The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain).

Please circle the most appropriate number that describes your pain today.



SECTION B - DESCRIBING YOUR OWN HEALTH TODAY(EQ-5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

B1. Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐
B2. Self-care	I have no problems with self-care	☐
	I have some problems washing or dressing myself	☐
	I am unable to wash or dress myself	☐

B3. Usual Activities *(e.g. work, study, housework, family or leisure activities)*

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

B4. Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

B5. Anxiety/ Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

SECTION C - YOUR GENERAL HEALTH (SF-36©)

Please fill in all the questions by crossing the relevant box of the answer that applies to you.

These questions ask for your views about your health and how you feel about life in general. Do not spend too much time in answering as your immediate response is likely to be the most accurate, but please make sure you answer every question.

C1. In general, would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

C2. Compared to one year ago, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

C3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes limited a lot	Yes limited a little	No not limited at all
a)	**Vigorous activities**, such as running, lifting heavy, objects participating in strenuous sport	☐	☐	☐
b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking **more than one mile**	☐	☐	☐
h)	Walking **several hundred yards**	☐	☐	☐
i)	Walking **one hundred yards**	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

C4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐	☐	☐	☐	☐

C5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily regular activities as a result of any emotional problems? (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Did work or other **activities less carefully than usual**	☐	☐	☐	☐	☐

C6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

C7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

C8. During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

C9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐
b) Have you been very nervous?	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐
f) Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐
h) Have you been happy?	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐

C10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

C11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b) I am as healthy as anybody I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
c) My health is excellent	☐	☐	☐	☐	☐

THANK YOU FOR YOUR HELP IN COMPLETING THIS FORM

The SUSPEND Trial Office
Health Services Research Unit
Health Sciences Building
Foresterhill
Aberdeen
AB25 2ZD
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Email: [redacted]
[redacted]

4 WEEK QUESTIONNAIRE

Participant Study No

SUSPEND

Spontaneous Urinary Stone Passage Enabled by Drugs

4 week QUESTIONNAIRE

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research
Health Technology Assessment Programme

ISRCTN69423238

Version 1.1, 01 Sept 2010

The following questionnaire is broken down into four sections (Section A - Section D). Please work through all the sections as best you can from start to finish.

Some of the sections ask you to indicate your answers to the questions by placing a cross **(X)** in the appropriate box, and other sections ask you to circle your answer.

Please read the questions carefully and answer each one as accurately as you can.

The sections covered in this questionnaire are as follows:

Section A: Stone Passage

Section B: Your Pain

Section C: Describing Your Own Health Today (EQ-5D)

Section D: Your General Health (SF-36©)

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Please start here:

Date questionnaire filled in D D / M M / Y Y Y Y

SECTION A- STONE PASSAGE

Please fill in all the questions by placing a cross in the relevant box of the answer that applies to you or writing in the information requested.

A1. Have you passed the stone? Yes ☐ No ☐ Don't know ☐

If Yes, when did you pass the stone
(if you're not sure please give an approximate date) D D / M M / Y Y Y Y

A2. Did you complete the 28 days course of treatment? Yes ☐ No ☐

If No,

How many days of treatment did you take? ☐☐ Days

If you did not complete the 28 day course, was it because:

The stone passed? Yes ☐ No ☐

The treatment was making you unwell? Yes ☐ No ☐

Other reason Yes ☐ No ☐

SECTION B – YOUR PAIN

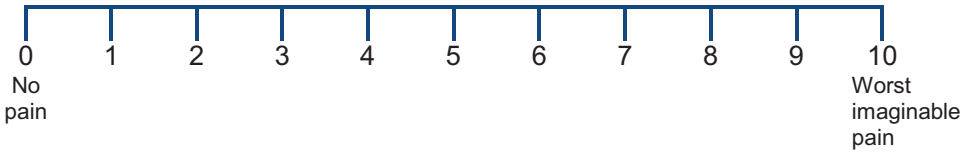
B1. In the past FOUR WEEKS have you had pain related to your ureteric stone?

Yes ☐ No ☐

If Yes,
How many days (approximately) have you taken pain medication? ☐☐ days
(If you have not taken any, please write zero in the box provided)

B2. Please rate the level of pain that you are experiencing TODAY.
The following line represents pain of increasing intensity from 'no pain' to 'worst imaginable pain'. The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain).

Please circle the most appropriate number that describes your pain.



SECTION C - DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

C1. Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐
C2. Self-care	I have no problems with self-care	☐
	I have some problems washing or dressing myself	☐
	I am unable to wash or dress myself	☐
C3. Usual Activities *(e.g. work, study, housework, family or leisure activities)*	I have no problems with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
C4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
C5. Anxiety/Depression		
	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

SECTION D - YOUR GENERAL HEALTH (SF-36©)

Please fill in all the questions by crossing the relevant box of the answer that applies to you.

These questions ask for your views about your health and how you feel about life in general. Do not spend too much time in answering as your immediate response is likely to be the most accurate, but please make sure you answer every question.

D1. In general, would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

D2. Compared to one year ago, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

D3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes limited a lot	Yes limited a little	No not limited at all
a)	**Vigorous activities**, such as running, lifting heavy objects participating in strenuous sport	☐	☐	☐
b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking **more than one mile**	☐	☐	☐
h)	Walking **several hundred yards**	☐	☐	☐
i)	Walking **one hundred yards**	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

D4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐	☐	☐	☐	☐

D5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily regular activities as a result of any emotional problems? (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Did work or other **activities less carefully than usual**	☐	☐	☐	☐	☐

D6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely ☐

D7. How much bodily pain have you had during the past 4 weeks?

None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe ☐

D8. During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?

Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely ☐

D9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐
b) Have you been very nervous?	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐
f) Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐
h) Have you been happy?	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐

D10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

D11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b) I am as healthy as anybody I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

THANK YOU FOR YOUR HELP IN COMPLETING THIS QUESTIONNAIRE

Once you have completed the form, please return it in the pre-paid envelope provided or to the following address:

The SUSPEND Trial Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
Health Sciences Building
Foresterhill
Aberdeen
AB25 2ZD
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

4 WEEK QUESTIONNAIRE

Participant Study No

SUSPEND

Spontaneous Urinary Stone Passage Enabled by Drugs

4 week QUESTIONNAIRE REMINDER

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research
Health Technology Assessment Programme

ISRCTN69423238

Version 1.0 20 Feb 2013

The following questionnaire is broken down into three sections (Section A - Section C). Please work through all the sections as best you can from start to finish.

Some of the sections ask you to indicate your answers to the questions by placing a cross **(X)** in the appropriate box, and other sections ask you to circle your answer.

Please read the questions carefully and answer each one as accurately as you can.

The sections covered in this questionnaire are as follows:

Section A: Stone Passage

Section B: Your Pain

Section C: Describing Your Own Health Today (EQ-5D)

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Please start here:

Date questionnaire filled in D D / M M / Y Y Y Y

SECTION A- STONE PASSAGE

Please fill in all the questions by placing a cross in the relevant box of the answer that applies to you or writing in the information requested.

A1. Have you passed the stone? Yes ☐ No ☐ Don't know ☐

D D / M M / Y Y Y Y

If Yes, when did you pass the stone
(if you're not su re please give an ap proximate date)

A2. Did you complete the 28 days course of treatment? Yes ☐ No ☐

If No,

How many days of treatment did you take? ☐☐ Days

If you did not complete the 28 day course, was it because:

The stone passed? Yes ☐ No ☐

The treatment was making you unwell? Yes ☐ No ☐

Other reason Yes ☐ No ☐

SECTION B – YOUR PAIN

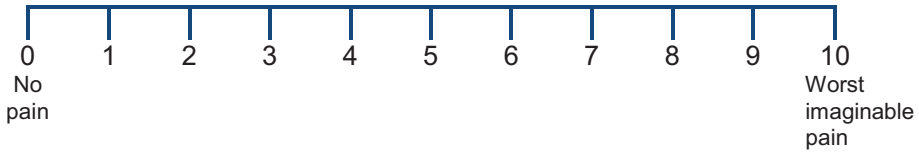
B1. In the past FOUR WEEKS have you had pain related to your ureteric stone?

Yes ☐ No ☐

If Yes,
How many days (approximately) have you taken pain medication?
(If you have not taken any, please write zero in the box provided) ☐☐ days

B2. Please rate the level of pain that you are experiencing TODAY.
The following line represents pain of increasing intensity from 'no pain' to 'worst imaginable pain'. The best rating is marked 0 (no pain) and the worst rating is marked 10 (worst imaginable pain).

Please circle the most appropriate number that describes your pain.



SECTION C - DESCRIBING YOUR OWN HEALTH TODAY (EQ-5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

C1. Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐
C2. Self-care	I have no problems with self-care	☐
	I have some problems washing or dressing myself	☐
	I am unable to wash or dress myself	☐
C3. Usual Activities *(e.g. work, study, housework, family or leisure activities)*	I have no problems with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
C4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
C5. Anxiety/Depression		
	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

THANK YOU FOR YOUR HELP IN COMPLETING THIS QUESTIONNAIRE

Once you have completed the form, please return it in the pre-paid envelope provided or to the following address:

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Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
Health Sciences Building
Foresterhill
Aberdeen
AB25 2ZD
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

12 WEEK QUESTIONNAIRE

Participant Study No

SUSPEND

Spontaneous Urinary Stone Passage Enabled by Drugs

12 WEEK QUESTIONNAIRE

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research
Health Technology Assessment Programme

ISRCTN69423238

Version 1.2, 07 December 2012

The following questionnaire is broken down into three sections (Section A - Section C). Please work through all the sections as best you can from start to finish.

Some of the sections ask you to indicate your answers to the questions by placing a cross **(X)** in the appropriate box, and other sections ask you to circle your answer.

Please read the questions carefully and answer each one as accurately as you can.

The sections covered in this questionnaire are as follows:

Section A: Describing Your Own Health Today (EQ-5D)

Section B: Health Service Use and Costs

Section C: Your General Health (SF-36©)

There are no right or wrong answers.

Please try to complete the whole questionnaire even though some questions may appear similar.

Your answers will be treated with complete confidentiality.

Thank you for your time in completing this questionnaire.

Once you have completed the form,
please return it in the pre-paid envelope provided or to the following address:

The SUSPEND Trial Office
Centre for Healthcare Randomised Trials (CHaRT)
Health Services Research Unit
Health Sciences Building
Foresterhill Aberdeen
AB25 2ZD
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

ISRCTN69423238 Version 1.2, 07 December 2012

Please start here:

Date questionnaire filled in D D / M M / Y Y Y Y

SECTION A- DESCRIBING YOUR OWN HEALTH TODAY – (EQ- 5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

A1. Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐
A2. Self-care	I have no problems with self-care	☐
	I have some problems washing or dressing myself	☐
	I am unable to wash or dress myself	☐
A3. Usual Activities *(e.g. work, study, housework, family or leisure activities)*	I have no problems with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
A4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
A5. Anxiety/Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

SECTION B - HEALTH SERVICE USE AND COSTS

Please fill in all the questions by crossing the relevant box of the answer that applies to you or writing in the information requested.

B1. Have you had any other investigation (e. g. scan, X-ray) for your ureteric stone symptoms since you started the study treatment approximately 3 months ago?

Yes ☐ No ☐ Don't know ☐

B1a. *If Yes,* please give details, e.g. what investigation and when?

B1b. If this occurred at a different hospital to the one you received your study treatment from please tell us where you went:

B2. Have you had any further treatment or surgery to treat your ureteric stone symptoms? Yes ☐ No ☐

B2a. *If Yes,* please give details, e. g. what treatment and when?

B3. Were you re-admitted to hospital for any reason, since you started your study treatment for your ureteric stone during the last 3 months? Yes ☐ No ☐

B3a. *If Yes,* how many nights were you admitted for in total? (*If you were admitted only as a day case, write 0 in the box provided*) ☐☐

B3b. *If Yes,* why were you admitted? (*Please give details):*

B4. Have you seen your GP, in relation to your ureteric stone symptoms in the last 3 months? Yes ☐ No ☐

B4a. If yes how many times did you see your GP? ☐☐ times

B5. Have you seen a practice nurse in relation to your ureteric stone symptoms in the last 3 months? Yes ☐ No ☐

B5a. If yes, how many times did you see the nurse? ☐☐ times

B6. Were you prescribed any medicines by a doctor or nurse in relation to your ureteric stone symptoms in the last 3 months? Yes ☐ No ☐

B6a. If yes, what were you prescribed?

B7. Did you buy any medicines over the counter to treat your ureteric stone symptoms in the last 3 months? Yes ☐ No ☐

B7a. If yes how much in total did you spend? £ ☐☐ . ☐☐

B8. Excluding your study visits have you visited NHS hospital outpatients to see a doctor, in relation to your ureteric stone symptoms in the last 3 months? Yes ☐ No ☐

B8a. If yes specify whom you have seen and the number of times you have seen them:

B9. Excluding your study visits have you visited any other NHS health care professional, in relation to your ureteric stone symptoms in the last 3 months? Yes ☐ No ☐

B9a. If yes specify whom you have seen and the number of times you have seen them:

B10. Did you pay to see any private health care professional, in relation to your ureteric stone symptoms in the last 3 months? Yes ☐ No ☐

B10a. If yes how much in total did you spend? £ ☐☐ . ☐☐

SECTION C - YOUR GENERAL HEALTH (SF-36©)

Please fill in all the questions by crossing the relevant box of the answer that applies to you.

These questions ask for your views about your health and how you feel about life in general. Do not spend too much time in answering as your immediate response is likely to be the most accurate, but please make sure you answer every question.

C1. In general, would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

C2. Compared to one year ago, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

C3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? *If so,* how much?

		Yes limited a lot	Yes limited a little	No not limited at all
a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sport	☐	☐	☐
b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking **more than one mile**	☐	☐	☐
h)	Walking **several hundred yards**	☐	☐	☐
i)	Walking **one hundred yards**	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

C4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐	☐	☐	☐	☐

C5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily regular activities as a result of any emotional problems? (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b) **Accomplished less** than you would like	☐	☐	☐	☐	☐
c) Did work or other **activities less carefully than usual**	☐	☐	☐	☐	☐

C6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

C7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

C8. During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

C9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐
b) Have you been very nervous?	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐
f) Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐
h) Have you been happy?	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐

C10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

C11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b) I am as healthy as anybody I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

THANK YOU FOR YOUR HELP IN COMPLETING THIS QUESTIONNAIRE
PLEASE RETURN USING THE PRE-PAID ENVELOPE

12 WEEK QUESTIONNAIRE

Participant Study No

SUSPEND

Spontaneous Urinary Stone Passage Enabled by Drugs

12 week QUESTIONNAIRE REMINDER

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research
Health Technology Assessment Programme

ISRCTN69423238

Version 1.0, 20 Feb 2013

Date questionnaire filled in D D / M M / Y Y Y Y

DESCRIBING YOUR OWN HEALTH TODAY – (EQ- 5D)

By placing a cross in one box in each group below, please indicate which statements best describe your own health state today

A1. Mobility	I have no problems in walking about	☐
	I have some problems in walking about	☐
	I am confined to bed	☐
A2. Self-care	I have no problems with self-care	☐
	I have some problems washing or dressing myself	☐
	I am unable to wash or dress myself	☐
A3. Usual Activities *(e.g. work, study, housework, family or leisure activities)*	I have no problems with performing my usual activities	☐
	I have some problems with performing my usual activities	☐
	I am unable to perform my usual activities	☐
A4. Pain/Discomfort	I have no pain or discomfort	☐
	I have moderate pain or discomfort	☐
	I have extreme pain or discomfort	☐
A5. Anxiety/Depression	I am not anxious or depressed	☐
	I am moderately anxious or depressed	☐
	I am extremely anxious or depressed	☐

THANK YOU FOR YOUR HELP IN COMPLETING THIS QUESTIONNAIRE PLEASE RETURN IN THE PREPAID ENVELOPE

Email: [redacted] **Tel:** [redacted]

Appendix 5 Spontaneous Urinary Stone Passage ENabled by Drugs case report forms

SUSPEND SCREENING LOG FORM

Outline data on patients who do not fulfil the inclusion criteria, fulfil the exclusion criteria or who decline participation

Inclusion criteria

- Patient presenting acutely with renal pain (ureteric colic)
- Adult ≥18 to ≤65 years of age
- Presence of stone confirmed by computed tomography of the kidney, ureter and bladder (CTKUB)
- Stone within any segment of the ureter
- Unilateral ureteric stone
- Stone diameter ≤10mm in size
- Female subject is willing to use 2 methods of contraception as advised, or is post menopausal or permanently sterilised
- Capable of giving written informed consent, which includes compliance with the requirements of the trial

Q1 Date of attempted recruitment D D / M M / Y Y Y Y

Q2 Year of Birth Y Y Y Y

Q3 Gender (please tick) Male ☐ Female ☐

Q4 Is the patient eligible to participate? Yes ☐ No ☐

If NO, please give the reason(s) they do not meet the inclusion/exclusion criteria (overleaf)

ISRCTN69423238 Version 1.2, 13 Dec 2010

Please give the reason(s) they do not meet the inclusion/exclusion criteria

- Patient <18 or >65 years of age ☐
- Stone not previously confirmed by CTKUB ☐
- Stone diameter >10mm in size ☐
- Female subject is pregnant or breast-feeding ☐
- Female subject is not willing to comply with contraceptive requirements ☐
- Asymptomatic incidentally found ureteric stones ☐
- Kidney stone without the presence of ureteric stones ☐
- Multiple (i.e ≥2) stones present within ureter ☐
- Bilateral ureteric stones ☐
- Stone is in a ureter draining a solitary kidney (either anatomically or functionally) ☐
- Patient has abnormal renal tract anatomy (such as a duplex system, horseshoe kidney or ileal conduit) ☐
- Presence of urinary sepsis ☐
- Patient has chronic kidney disease stage 4 or stage 5 (eGFR < 30ml/min) ☐
- Patient currently taking an alpha blocker ☐
- Patient currently taking a calcium channel blocker ☐
- Patient currently taking PDE5 inhibitors ☐
- Patient has a contraindication or allergy to tamsulosin or nifedipine ☐
- Participant unable to give informed consent or cannot understand/comply with the requirements of the trial ☐

Q5 Is the patient interested in taking part? YES ☐ NO ☐

If NO, please specify reason (if given)

- No reason given ☐
- Patient not interested in the research study ☐
- Patient does not want to be randomised ☐

Q6 Patient randomised YES ☐ NO ☐

If NO, please specify reason

BASELINE CRF

Participant Study No

BASELINE CASE REPORT FORM (CRF)

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research
Health Technology Assessment Programme

ISRCTN69423238 Version 1.2, 14 Mar 2012

***PATIENT DETAILS (*Sticker may be used below)**

Title ☐ Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Other

First name:	
Surname:	
Address:	
Postcode:	
Mobile telephone number (or other contact number)	
E-mail Address:	
Date of birth:	D D / M M / Y Y Y Y
Gender:	Male ☐ Female ☐
NHS number:	
CHI number (if appropriate):	

CONSULTANT DETAILS

Initials: Surname:

GP DETAILS

Initials: Surname:

Address:

2

CLINICAL DATA

Date of baseline assessment D D / M M / Y Y Y Y

MEDICAL HISTORY

Duration of current pain due to ureteric stone: _____ Days

History of previous stone disease Yes ☐ No ☐

Current pre-admission analgesic medications Yes ☐ No ☐

If Yes, please select type of medication:

Non-steroidal ☐ Opiate ☐ Other ☐

If Other, please specify _____

Diagnosis of ureteric stone confirmed by:

Test		Date of test
Plain X-ray KUB	☐	D D / M M / Y Y Y Y
IVU	☐	D D / M M / Y Y Y Y
CT KUB	☐	D D / M M / Y Y Y Y

Medications prescribed at this admission.

Analgesics Yes ☐ No ☐

If Yes, please specify: Non-steroidal ☐ Opiates ☐ Other ☐

Antibiotics Yes ☐ No ☐

RANDOMISATION INFORMATION

Telephone Randomisation Service Number: [redacted]

Ureteric stone size (*largest dimension)*: ☐ mm

Stone Location: Upper Ureter ☐ Middle Ureter ☐ Lower Ureter ☐

Participant Study No: ☐☐☐☐☐

Pack ID Number: ☐☐☐☐

4

<<ON SUSPEND HEADED>> <<TRUST LOGO OF RECRUITING CENTRE>>

Dr <<GP Name>>
<<GP Address 1>>
<<GP Address 2>>
<< GP Address 3>>
<< GP Address 4>>
<< GP Postcode>>

Date

Dear Dr <<Surname>>

Patient name: <<Name>> **Date of birth: <<dob>>**
Patient address: <<address>>

Title of study: Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: a multicentre placebo controlled randomised trial of calcium channel blockers (nifedipine) and alpha blockers (tamsulosin)

Your patient has consented to take part in this study which is a multi centre trial funded by the NIHR Health Technology Assessment Programme. The aim of the trial is to provide robust data to guide the treatment of patients with symptomatic ureteric stones. Your patient has been given written information about the trial, including contact details at the hospital and of the central office in Aberdeen.

Your patient has been randomised to take oral capsules containing nifedipine (30 mg) or tamsulosin (0.4 mg) or placebo once daily for a maximum of 28 days. Participants will be followed up in the hospital approximately 4 weeks after commencing treatment for clinical examination. In addition, participants will be sent postal questionnaires from the central co-ordinating office in Aberdeen to complete four and 12 weeks after randomisation.

In the event that your patient suffers a serious adverse event (SAE) that maybe due to the study medication please could you complete the enclosed SAE form and return it to us as soon as possible after you become aware of this. A serious event is defined as one that results in death, hospitalisation, significant/persistent disability/incapacity or is life threatening.

The study is double blinded. Your patient has been given a card to carry with them during the study with a phone number that can be used to unblind them. In the event of an emergency where it is necessary to know what study medication your patient is receiving to make treatment decisions, this phone number should be used.

Female participants have been advised to use two forms of contraception while taking the study drug and for 28 days afterwards. If your patient is female and becomes pregnant in the next two months please report this to the trial office as soon as possible using any of the contact details given.

ISRCTN69423238 Version 2.1, 21 Oct 2013

A more detailed description of the study background is on the back of this letter and we have enclosed information on potential interactions of the study medication for your information. The use of α-blockers, calcium channel blockers, PDE5 inhibitors, rifampacin and digoxin are contraindicated in the trial.

Please do not hesitate to contact us if you have any concerns about your patient being included in this study.

Yours sincerely,

<<Signature>>

<<Name>>, Research Nurse
<<Contact details>>

Mr Sam McClinton, Chief Investigator
[redacted]

GP INFORMATION SHEET

Title of project

Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: a multicentre placebo controlled randomised trial of a calcium channel blocker (nifedipine) and an α-blocker (tamsulosin)

Background

Urinary stone disease is very common with an estimated prevalence among the general population of 2-3% and an estimated lifetime risk of 1 in 8 for white males and 5-6% for white females, with males forming stones three times as often as females. Urinary stones often recur and the lifetime recurrence rate is approximately 50%. All urinary tract stones and ureteric stones in particular, have a significant impact on patients' quality of life. They are a common cause of emergency hospital admission due to severe pain with over 15,000 hospital admissions in England annually (HES data 2006-2007) using over 21,500 bed days, resulting in significant calls on health service resources. The pain leads to a requirement for analgesia, time off work and often repeated hospital admissions for therapeutic interventions.

Patients with with smaller sized stones in the lower ureter are traditionally treated expectantly. Those who fail standard supportive care or who subsequently develop complications undergo active treatment such as extra-corporeal shock wave lithotripsy (ESWL), ureteric stenting, ureteroscopy with stone retrieval or in situ lithotripsy, or percutaneous nephrostomy insertion. However, such interventions are expensive, require urological expertise and carry a risk of complications.

In recent years, a growing understanding of ureteric function and pathophysiology has led to the hypothesis that drugs which cause relaxation of ureteric smooth muscle can enhance the spontaneous passage of ureteric stones. This has been termed medical expulsive therapy (MET). Two recent meta-analyses have reported the potential role of α-blockers and calcium channel blockers in MET. In both meta-analyses, the majority of studies involved stones <10 mm located in the lower (distal) ureter. Both reviews concluded that a large, high quality randomised controlled trial is required to confirm their findings; suggesting that MET with either drug class can enhance spontaneous stone passage rate. In addition, several studies have previously reported that MET can significantly reduce the pain burden amongst patients in terms of reducing the frequency of pain episodes, pain severity and analgesic requirements.

In summary, the role of MET in reducing the morbidity and economic costs associated with ureteric stone disease is promising. The majority of clinical trials conducted to date have been small and of poor to moderate quality in terms of trial methodology or design. Furthermore they have lacked a comprehensive economic evaluation. There is thus an urgent need for a definitive randomised controlled trial such as SUSPEND to inform the clinical and cost-effectiveness management of patients with ureteric stone disease.

Brief outline of the study

Ethical and regulatory approvals have been obtained for this trial and written consent has been obtained from participants. Participants may be reviewed in outpatients approximately four weeks after randomisation as per normal clinical practice. Participants are sent postal questionnaires approximately four and 12 weeks after randomisation. The primary clinical outcome of the trial (measured at four weeks) is the spontaneous passage of the stone as measured by the need for further intervention in the treatment of the stone. To reflect the multidimensional nature of the possible effects the intervention may have, there is also a primary health economic outcome of incremental cost per quality adjusted life years (QALYs) gained.

Contraindications, interactions with other medicinal products and other forms of interactions

Taken from the Summary of Product Characteristics (SmPC) for Coracten XL (Nifedipine - last SmPC revision April 2009) and Petyme (Tamsulosin - last SmPC revision 07 August 2013)

Nifedipine is contra-indicated in patients with known hypersensitivity to nifedipine or other dihydropyridines because of the theoretical risk of cross reactivity. It should not be used in clinically

significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction. It should not be used in patients in cardiogenic shock, for the treatment of acute attacks of angina, or in patients who have had ischaemic pain following its administration previously. The safety of nifedipine capsules in malignant hypertension has not been established.

Nifedipine is contra-indicated in patients with acute porphyria. Nifedipine should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction. As this is a long acting formulation, it should not be administered to patients with hepatic impairment.

Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid falsely. However, HPLC measurements are unaffected.

Increased plasma levels of nifedipine have been reported during concomitant use of H_2-receptor antagonists (specifically cimetidine), other calcium channel blockers **(**specifically diltiazem), alcohol, cyclosporin, macrolide antibiotics, gingko biloba and ginseng**.** Azole antifungals may increase serum concentrations of nifedipine. Decreased plasma levels of nifedipine have been reported during concomitant use of antibacterials (specifically rifampicin), and probably also antiepileptics and St John's Wort.

When used in combination with nifedipine, plasma concentrations of quinidine have been shown to be suppressed regardless of quinidine dosage. The plasma concentrations of phenytoin, theophylline, non-depolarising muscle relaxants (e.g. tubocurarine) and possibly digoxin are increased when used in combination with nifedipine. Tacrolimus concentrations may be increased by nifedipine.

Enhanced hypotensive effect of nifedipine may occur with: aldesleukin, alprostadil, anaesthetics, antipsychotics, diuretics, phenothiazides, prazosin and intravenous ionic X-ray contrast medium. Profound hypotension has been reported with nifedipine and intravenous magnesium sulphate in the treatment of pre-eclampsia.

Ritonavir and quinupristin/dalfopristin may result in increased plasma concentrations of nifedipine. Effective plasma levels of nifedipine may not be achieved due to enzyme induction with concurrent administration of erythromycin, carbamazepine and phenobarbitone.

There is an increased risk of excessive hypotension, bradycardia and heart failure with β-blockers.

An increased rate of absorption of nifedipine from sustained release preparation may occur if given concurrently with cisapride. Nifedipine may result in increased levels of mizolastine due to inhibition of cytochrome CYP3A4.

Nifedipine may increase the neuromuscular blocking effects of vecuronium.

Tamsulosin is contraindicated in patients with a hypersensitivity to Tamsulosin, including drug-induced angio-oedema, and those with a history of orthostatic hypotension. Tamsulosin should not be administered to patients with severe hepatic insufficiency.

Concomitant cimetidine brings about a rise in plasma levels of tamsulosin, and furosemide a fall, but as levels remain within the normal range change in dosage is not required. Diclofenac and warfarin may increase the elimination rate of tamsulosin.

There is a theoretical risk of enhanced hypotensive effect when tamsulosin is given concurrently with drugs which may reduce blood pressure, including anaesthetic agents and other α_1-adrenoceptor antagonists.

Tamsulosin should not be given in combination with strong inhibitors of CYP34A in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin should be used with caution in combination with strong and moderate inhibitors of CYP34A.

4 WEEK CRF

Participant Study No

SUSPEND

Spontaneous Urinary Stone Passage Enabled by Drugs

4 WEEK CASE REPORT FORM (CRF)

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research
Health Technology Assessment Programme

ISRCTN69423238 Version 1.1, 01 Sept 2010

Q1. Did the patient attend the clinic visit?

Yes ☐ No ☐

If Yes, please specify Date of the visit D D / M M / Y Y Y Y

If No, please specify Date of CRF completion D D / M M / Y Y Y Y

Q2. Tests performed at this visit

☐ Plain X-Ray KUB ☐ IVU ☐ CT KUB ☐ None ☐ Other

If other, please give details:

_____

Q3. Has the stone passed?

Yes ☐ No ☐ Don't know ☐

If Yes, when did the patient pass the stone: D D / M M / Y Y Y Y

(If you're not sure please give an approximate date)

Q4. Further Interventions since joined the trial

Has the patient received any other ureteric stone treatment (excluding randomised medication)?

YES ☐ NO ☐

If Yes, please specify date of intervention:

	Yes	DATE OF INTERVENTION
Percutaneous insertion of nephrostomy tube (M13)	☐	D D / M M / Y Y Y Y
Antegrade insertion of stent into ureter (M33)	☐	D D / M M / Y Y Y Y
Therapeutic ureteroscopic operations (includes calculus fragmentation/removal)(M27)	☐	D D / M M / Y Y Y Y
Endoscopic insertion/removal of stent into ureter (M29)	☐	D D / M M / Y Y Y Y
ESWL of calculus of ureter (M31)	☐	D D / M M / Y Y Y Y
Other	☐	D D / M M / Y Y Y Y

If Other treatment, please specify _____

Please provide admission and discharge date(s)

	Date of Admission	Date of Discharge
Admission One	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y
Admission Two	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y

Q5. Further treatment/surgery planned

Is further treatment/surgery planned for persistent ureteric stone? Yes ☐ No ☐

If Yes, please indicate what is intended (*please tick all that are appropriate*):

Percutaneous insertion of nephrostomy tube (M13)	☐	Endoscopic insertion/removal of stent into ureter (M29)	☐
Antegrade insertion of stent into ureter (M33)	☐	ESWL of calculus of ureter (M31)	☐
Therapeutic ureteroscopic operations (includes calculus fragmentation/removal) (M27)	☐	Other	☐

If Other treatment, please specify: _____

12 WEEK CRF

Participant Study No

SUSPEND

Spontaneous Urinary Stone Passage Enabled by Drugs

12 WEEK CASE REPORT FORM (CRF)

CONFIDENTIAL

This study is funded by the NHS National Institute for Health Research Health Technology Assessment Programme

ISRCTN69423238

Version 1.0, 11 May 2010

Please specify date of CRF completion D D / M M / Y Y Y Y

Further Interventions since joined the trial

Has the patient received any other ureteric stone treatment (excluding randomised medication)?

If Yes, please specify date of intervention:

	Yes	DATE OF INTERVENTION
Percutaneous insertion of nephrostomy tube (M13)	☐	D D / M M / Y Y Y Y
Antegrade insertion of stent into ureter (M33)	☐	D D / M M / Y Y Y Y
Therapeutic ureteroscopic operations (includes calculus fragmentation/removal) (M27)	☐	D D / M M / Y Y Y Y
Endoscopic insertion/removal of stent into ureter (M29)	☐	D D / M M / Y Y Y Y
ESWL of calculus of ureter (M31)	☐	D D / M M / Y Y Y Y
Other	☐	D D / M M / Y Y Y Y

If Other treatment, please specify _____

Was admission required for any of the above? **Yes** ☐ **No** ☐

If Yes, please provide admission and discharge date(s)

	Date of Admission	Date of Discharge
Admission One	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y
Admission Two	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y

SUSPEND
Spontaneous Urinary Stone Passage Enabled by Drugs

CHANGE OF STATUS

To be completed on withdrawal/change of status from study

Participant Study Number

Q1 Date of withdrawal D D / M M / Y Y Y Y

Reason for withdrawal

Q2 Participant decided to withdraw? (state reason)

Q3 Any medical reason for withdrawal? (please state reason)

What is participant withdrawing from?

Q4 Follow-up clinic visits?

Yes ☐ No ☐

Q5 Completing questionnaires?

Yes ☐ No ☐

Q6 Relevant outcome data being collected (via hospital and GP records)?

Yes ☐ No ☐

Q7 Contact by telephone from a member of the SUSPEND team?

Yes ☐ No ☐

ISRCTN69423238 Version 1.0, 01 Sept 2010

SUSPEND
Spontaneous Urinary Stone Passage Enabled by Drugs

Serious Adverse Event Form Page 1

Participant Study Number

FOR TRIAL OFFICE USE ONLY

REPORT NO.

DATE REPORTED TO TRIAL OFFICE

D D M M Y Y Y Y

Date of report D D M M Y Y Y Y

Initial Report ☐ Follow Up Report ☐

Is this a possible SUSAR? **Yes** ☐ **No** ☐

Subject Details

Initials ☐☐☐ Date of Birth D D M M Y Y Y Y Gender: Male ☐ Female ☐

Serious Adverse Event

Seriousness criteria (Check all that apply):

Resulted in death ☐ Life-threatening ☐ Hospitalisation/Prolongation of hospitalisation ☐

Persistent/Significant Disability/Incapacity ☐ Congenital anomaly/ Birth defect ☐ Other medically important condition ☐

If Resulted in Death

Date of Death D D M M Y Y Y Y

Cause of Death:

Cause of Death determined by Autopsy Yes ☐ No ☐

Action taken: Drug withdrawn ☐ Dose reduced ☐ Dose increased ☐

Dose not changed ☐ Unknown ☐ Not applicable ☐

Expectedness: Expected ☐ Unexpected ☐ Onset Date: D D M M Y Y Y Y

Diagnosis: _____

Relationship to Study Drug: None ☐ Possible ☐ Definite ☐

Severity: Mild ☐ Moderate ☐ Severe ☐

Outcome:

Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Not recovered ☐ Unknown ☐ Fatal ☐

Date of Recovery D D M M Y Y

Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU), University of Aberdeen
3rd Floor, Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD
Tel: [redacted], Fax: [redacted], Email: [redacted]

Version 1.1, 01 Sept 2010

SUSPEND
Spontaneous Urinary Stone Passage Enabled by Drugs

Serious Adverse Event Form Page 2

Participant Study Number

Event Narrative	Provide any information regarding the circumstances, sequence, diagnosis and treatment of the event(s) not otherwise reported on this form

Protocol Treatment(s):

Did the patient take any study medication? Yes ☐ No ☐

Did the subject have to be unblinded? Yes ☐ No ☐

If yes, was subject on placebo? Yes ☐ No ☐

If subject was unblinded and not on placebo please complete below

Study Drug	Dose	Frequency	Start Date (DD/MM/YYYY)	Stop Date (DD/MM/YYYY)	Tick if still ongoing	Route	Batch No

Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU), University of Aberdeen
3rd Floor, Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD
Tel: [redacted], Fax: [redacted], Email: [redacted]

Version 1.1, 01 Sept 2010

SUSPEND
Spontaneous Urinary Stone Passage Enabled by Drugs

Serious Adverse Event Form Page 3

Participant Study Number

Medical History
Provide relevant medical history below or include copy of the Medical History case report form page. Include other illnesses present at time of event, previous study emergent adverse events, and pre-existing medical conditions. If additional space is necessary, use further copies of this page.

☐ Check box if a copy of Medical History page of the case report form is included with this report.

	Condition	Start Date (DD/MM/YYYY)	End Date (DD/MM/YYYY)	Tick if still ongoing	Medication Required
1					☐ Yes ☐ No
2					☐ Yes ☐ No
3					☐ Yes ☐ No
4					☐ Yes ☐ No
5					☐ Yes ☐ No
6					☐ Yes ☐ No

Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU), University of Aberdeen
3rd Floor, Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD
Tel: [redacted], Fax: [redacted], Email: [redacted]

Version 1.1, 01 Sept 2010

SUSPEND
Spontaneous Urinary Stone Passage Enabled by Drugs

Serious Adverse Event Form Page 4

Participant Study Number

Concomitant Medications

	Medication	Start Date (DD/MM/YYYY)	End Date (DD/MM/YYYY)	Tick if ongoing	Dose	Frequency	Route	Indications	Suspect Drug (tick)	Interaction with study drug (tick)
1										
2										
3										
4										
5										
6										

Relevant Tests List only relevant confirmatory test results for event(s), for example from blood tests, diagnostic imaging

	Test	Date (DD/MM/YYYY)	Result	Normal Range-Low	Normal Range-High	Comments
1						
2						
3						

Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU), University of Aberdeen
3rd Floor, Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD
Tel: [redacted], Fax: [redacted], Email: [redacted]

Version 1.1, 01 Sept 2010

SUSPEND
Spontaneous Urinary Stone Passage Enabled by Drugs

Serious Adverse Event Form Page 5

Participant Study Number

Rechallenge Information

1.Did the reaction abate after stopping suspected drug?	Yes		No		N/A	
2. Did the reaction reappear after re-introduction of suspect drug?	Yes		No		N/A	

Primary Source

Name:	Email address:
Address:	
Telephone number:	Fax number:

Qualification: Physician ☐ Pharmacist ☐ Other Health Professional ☐ Trial Team ☐

To be signed by the Principal Investigator or designee

I am the Principal Investigator Yes ☐ No ☐

If No, Please state designation

I confirm that this is a SAE

Name: (PRINT) _____

Signature: _____

Date: D D M M Y Y Y Y

To be signed by the Chief Investigator or designee in the event of a SUSAR

I am the Chief Investigator Yes ☐ No ☐

If No, Please state designation

I confirm that this is a SUSAR

Name: (PRINT) _____

Signature: _____

Date: D D M M Y Y Y Y

Reported ☐

Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU), University of Aberdeen
3rd Floor, Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD
Tel: [redacted], Fax: [redacted], Email: [redacted]

Version 1.1, 01 Sept 2010

SUSPEND
Spontaneous Urinary Stone Passage Enabled by Dr

GP Serious Adverse Event Form Page 1

FOR TRIAL OFFICE USE ONLY

REPORT NO.	DATE REPORTED TO TRIAL OFFICE
	D D M M Y Y Y Y

Subject Details

Initials | | | | Date of Birth D D M M Y Y Y Y Gender Male ☐ Female ☐

Subject I.D./Randomisation No | | | | | |

Serious Adverse Event

Seriousness criteria (Check all that apply):

Resulted in death ☐ Life-threatening ☐ Hospitalisation/Prolongation of hospitalisation ☐

Persistent/Significant Disability/Incapacity ☐ Congenital anomaly/ Birth defect ☐ Other medically important condition ☐

Diagnosis:

Relationship to Study Drug: None ☐ Possible ☐ Definite ☐

Action taken: Drug withdrawn ☐ Unknown ☐ Not applicable ☐

If Resulted in Death

Date of Death	Cause of Death:	Cause of Death determined by Autopsy:
D D M M Y Y Y Y		Yes ☐ No ☐

Protocol Treatment(s):

Did the patient take any study medication?	Yes ☐	No ☐	Unknown ☐
Did the subject have to be unblinded?	Yes ☐	No ☐	Unknown ☐
If yes, was subject on placebo?	Yes ☐	No ☐	Unknown ☐

Event Narrative **Provide any information regarding the circumstances, sequence, diagnosis and treatment of the event(s) not otherwise reported on this form**

The SUSPEND trial, Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU), University of Aberdeen, 3rd Floor, Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD
Tel: [redacted], Fax: [redacted], Email: [redacted]

Version 1.0, 11 May 2010

GP Serious Adverse Event Form Page 2

Details of Person Reporting	
Name	Email
Address	**Telephone**
Country	Fax
Qualification GP ☐ Other Health Professional ☐ Other ☐ Please state _____	

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SUSPEND
Spontaneous Urinary Stone Passage Enabled by Dr

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R&D reference | Centre ID

Eudract No. | Subject ID | Subject initials

DO NOT SEND IDENTIFIABLE DATA OR SOURCE DOCUMENTS WITH THIS REPORT

1. MATERNAL INFORMATION

Date of Birth D D M M Y Y Y Y

Date of last menstrual period D D M M Y Y Y Y

Expected date of delivery D D M M Y Y Y Y

Methods of contraception _____

Contraception used as instructed **Yes** ☐ **No** ☐ **Uncertain** ☐

2. MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy. If none mark N/A)

3. PREVIOUS OBSTETRIC HISTORY

	Gestation week	Outcome including any abnormalities
1		
2		
3		
4		
5		

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Centre ID | | |

Eudract No. | | | | | | | | | | |

Subject ID | | | | | | | | |

Subject initials | | |

4. DRUG INFORMATION (list all therapies taken prior to and during pregnancy)

Name of drug	Daily dose	Route	Date Started	Date Stopped	Treatment Start (week of pregnancy)	Treatment Stop (week of pregnancy)
			D D M M Y Y	D D M M Y Y	D D	D D
			D D M M Y Y	D D M M Y Y	D D	D D
			D D M M Y Y	D D M M Y Y	D D	D D

5. PRENATAL INFORMATION

Have any specific tests e.g. amniocemtesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far? **Yes** ☐ **No** ☐ **Uncertain** ☐

If yes please specify test date and results

	Test	Date	Result
1		D D M M Y Y	
2		D D M M Y Y	
3		D D M M Y Y	

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6. PREGNANCY OUTCOME

(a) Abortion **Yes** ☐ **No** ☐
If yes
Therapeutic ☐ Planned ☐ Spontaneous ☐
Please specify the reason and any abnormalities (if known):

(b) Delivery **Yes** ☐ **No** ☐
If yes
Normal ☐ Forceps/Ventouse ☐ Caesarean ☐
Maternal complications or problems related to birth:

Date of abortion D D M M Y Y Y Y

Delivery date D D M M Y Y Y Y

7. MATERNAL PREGNANCY ASSOCIATED EVENTS

If the mother experiences an SAE during the pregnancy, please indicate here and complete and SAE form and submit it to the Trial Office immediately.

8. CHILD OUTCOME

Normal ☐ Abnormal ☐ Stillbirth ☐
If any abnormalities please specify and provide dates

Sex	**Male** ☐ **Female** ☐	**Agpar Scores:**	
Height	**cm**	**1 min**	
Weight	**kg**	**5 mins**	
Head circumference	**cm**	**10 mins**	

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9. ASSESSMENT OF SERIOUSNESS (OF PREGNANCY OUTCOME)

Non serious ☐ Involved prolonged inpatient hospitalisation ☐ Results in persistent or significant disability/incapacity ☐
Life Threatening ☐ Congenital anomaly/birth defect ☐ Other significant medical events ☐

Mother died ☐ Date of death D D M M Y Y Y Y
Stillbirth/neonate died ☐ Date of death D D M M Y Y Y Y

10. ASSESSMENT OF CAUSALITY (OF PREGNANCY OUTCOME)

Please indicate the relationship between pregnancy outcome
Unrelated ☐ Possibly* ☐ Probably* ☐ Definitely* ☐
If any of the fields marked* have been checked, the outcome is considered RELATED to the study drug.

11. ADDITIONAL INFORMATION

12. INFORMATION SOURCE

Name _____
Position _____
Address _____
Signature _____
Date of Report D D M M Y Y Y Y

To be signed by the Chief Investigator

SUSAR
I confirm that this is a SUSAR ☐
Name (PRINT) _____

Signature _____ Date D D M M Y Y
Reported ☐

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Appendix 6 Algorithm to determine primary outcome

From the questions in the 4-week CRF, 'Has the patient received any other ureteric stone treatment (excluding randomised medication)?' and 'Is further treatment/surgery planned for persistent ureteric stone?', if any box was recorded as 'yes' then that participant has had further treatment for this episode of stone and has not spontaneously passed the stone within 4 weeks of randomisation in accordance with the definition of the primary outcome. In addition, if any box is ticked as 'yes' on the 12-week CRF in response to the question 'Has the patient received any other ureteric stone treatment (excluding randomised medication)?' and the date entered is prior to the 4-week endpoint for that individual participant, then that participant has had further treatment for this episode of stone and has not spontaneously passed the stone within 4 weeks in accordance with the definition of the primary outcome. All other participants are coded as having passed their stone spontaneously. A second validation check on this is provided by the question in the 4-week CRF: 'Have you passed the stone?'.

Appendix 7 Full logistic regression models for the primary outcome

TABLE 40 Full logistic regression model for MET vs. placebo to predict primary outcome

Covariate	OR	95% CI	*p*-value
MET	1.06	0.70 to 1.60	0.780
Stone > 5 mm	0.34	0.25 to 0.45	< 0.001
Stone in upper ureter	0.45	0.32 to 0.64	< 0.001
Stone in mid ureter	0.66	0.41 to 1.04	0.070

Placebo, stones ≤ 5 mm and stones in lower ureter were the reference categories.

TABLE 41 Full logistic regression model for tamsulosin vs. nifedipine vs. placebo to predict primary outcome

Covariate	OR	95% CI	*p*-value
Nifedipine	1.03	0.68 to 1.56	0.880
Tamsulosin	1.09	0.67 to 1.78	0.730
Stone > 5 mm	0.34	0.25 to 0.45	< 0.001
Stone in upper ureter	0.45	0.32 to 0.64	< 0.001
Stone in mid ureter	0.65	0.41 to 1.03	0.068

Placebo, stones ≤ 5 mm and stones in lower ureter were the reference categories.

Appendix 8 Full breakdown of primary outcome subgroup summary

TABLE 42 Primary outcome subgroup summary

	Intervention		
Primary outcome subgroup summary	**Tamsulosin (*N* = 378)**	**Nifedipine (*N* = 379)**	**Placebo (*N* = 379)**
No further intervention, *n* (%)	307 (81.2)	304 (80.2)	303 (79.9)
Subgroup,* n/N *(%)			
Sex			
Male	252/313 (81)	254/312 (81)	239/297 (80)
Female	55/65 (85)	50/67 (75)	64/82 (78)
Stone size, *n*/*N* (%)			
≤ 5 mm	240/284 (85)	246/285 (86)	246/285 (86)
> 5 mm	67/94 (71)	58/94 (62)	57/94 (61)
Stone location, *n*/*N* (%)			
Upper ureter	62/88 (70)	58/92 (63)	65/89 (73)
Mid ureter	29/41 (71)	32/40 (80)	36/44 (82)
Lower ureter	216/249 (87)	214/247 (87)	202/246 (82)

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HTA
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