NETSCC, HTA

3rd June 2011

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)

Phase IV

Protocol Number:	pRGF/016/09
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NIHR HTA Programme

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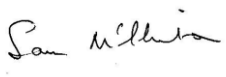

Date: 17 December 2010

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PROTOCOL SUMMARY

QUESTION ADDRESSED	What is the clinical and cost-effectiveness of the use of an α-blocker (tamsulosin) and a calcium channel blocker (nifedipine) in the management of symptomatic urinary stones?
CONSIDERED FOR ENTRY	Male and female patients aged 18 to 65 with a ureteric stone confirmed by non-contrast computed tomography of the kidney, ureter and bladder (CTKUB).
TRIAL ENTRY	Consent to the RCT will be obtained from 1200 eligible patients after written and oral information is provided by local hospital teams. Participants will be randomised to a unique blinded participant numbered pack containing 28 capsules (400 participants to each of the three treatment groups – nifedipine, tamsulosin, and placebo). Participants will take one capsule orally per day for a maximum of 28 days and will be followed-up by postal questionnaires sent from the trial office (CHaRT, Aberdeen) at four and 12 weeks after randomisation. Participants will be reviewed in clinic approximately four weeks after being randomised.
INTERVENTIONS	Participants will take one of the following capsules per day for a maximum of 28 days: - The calcium channel blocker nifedipine, 30mg once per day. - The α-blocker tamsulosin, 0.4mg once per day. - Placebo once per day. The capsules will be over encapsulated to ensure that participants are blind to the medication allocation.
OUTCOME ASSESSMENT	The primary clinical outcome is spontaneous passage of ureteric stones at four weeks (defined as no further intervention required to facilitate stone passage). The primary economic outcome is the incremental cost per quality adjusted life years (QALYs) gained at 12 weeks. QALYs are based on the responses to the EQ-5D.
CO-ORDINATION	**Local**: by local consultant Urologists and local recruitment officers **Central**: by the trial office in Aberdeen (Telephone 01224 559644). **Overall**: by the Project Management Group, and overseen by the Trial Steering Committee and the Data Monitoring Committee.
FUNDER	The National Institute for Health Research (NIHR), Health Technology Assessment (HTA) Programme
Start date:	June 2010
Planned finish date:	November 2013
Planned reporting date:	December 2013
Planned start of recruitment:	September 2010
Planned end of recruitment:	November 2012

GLOSSARY OF ABBREVIATIONS

α-blocker	Drugs that act as antagonists of α adrenergic receptors (α-adrenoceptors).
AUC	Area under the curve
BID	Twice a day
BNF	British National Formulary
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CONSORT	Consolidated Standards of Reporting Trials
CI	Chief Investigator
CRF	Case Report Form
CTKUB	Computed Tomography of the Kidney, Ureter and Bladder
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
ESWL	Extra-corporeal shock wave lithotripsy
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HPLC	High Performance Liquid Chromatography
HTA	Health Technology Assessment
IMP	Investigational Medicinal Product
ISD	Information Statistics Division
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
IVU	Intravenous Urogram
MET	Medical expulsive therapy
MR	Modified release
MRC	Medical Research Counsel
REC	Research Ethics Committee
NCT	National Clinical Trial
NHS	National Health Service
NIHR	National Institute Health Research
NRES	National Research Ethics Service
NRS	Numeric Rating Scale
OD	Once a day
PI	Principal Investigator
PMG	Project Management Group
PQ	Participant Questionnaire
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QID	Four times a day
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration

SUSPEND PERSONNEL

Grant Holders

1 Samuel McClinton (Chief Investigator)
2 James N'Dow (Consultant Urologist)
3 Thomas Lam (Urology Specialist Registrar)
4 Neil Burgess (Principal Investigator)
5 Ken Anson (Principal Investigator)
6 Glen Preminger (Clinical Lead)
7 Robert Pickard (Consultant Urologist)
8 Uday Patel (Radiologist)
9 Kathryn McMullan (Pharmacist)
10 Jennifer Burr (CHaRT director)
11 Graeme MacLennan (Lead Statistician)
12 Mary Kilonzo (Health Economist)
13 Katie Schumm (Trial Manager)
14 Patrick Wright (General Practitioner)
15 Ruth Thomas (Research Manager)
16 Terry Clarke (Patient Group Advisor)

Trial Steering Committee (TSC):

Independent members

1 Mike Bishop
2 Frank Keeley
3 Shaun Treweek

Non Independent members:
Grant holders listed above

Observers:

1 Trial Manager
2 Data co-ordinator
3 CHaRT Senior Trials Manager
4 CHaRT Senior IT Manager

Project Management Group (PMG):
Consists of the grant holders, observers of the TSC and other key members of the trial team (e.g. statistician).

Data Monitoring Committee (DMC) Members:

1 Elaine McColl (Chair)
2 Kenneth John Hastie
3 John Norrie

Trial Office Team:

1 Samuel McClinton
2 CHaRT Director
3 Trial Manager
4 Data Co-ordinator
5 Mary Kilonzo
6 Kathryn McMullan
7 Graeme MacLennan
8 Katie Schumm
9 Ruth Thomas
10 Senior Trials Manager
11 Senior IT Manager
12 Trial statistician

Other Information

International Standard Randomised Controlled Trial Number (ISRCTN)	ISRCTN69423238
REC Reference Number	10/S0501/31
NIHR HTA Project Number	08-71-01
EudraCT Number	2010-019469-26
SUSPEND web site:	http://www.charttrials.abdn.ac.uk/suspend

1. 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[1] and 5–6% for white females[2] with males forming stones three times as often as females. Urinary stones often recur and the lifetime recurrence rate is approximately 50%[3]. The interval between recurrences is variable, with approximately 10% within one year, 35% within five years, and 50% within 10 years[2]. The increased incidence of urinary stones in the industrialised world is associated with improved standards of living (mainly due to the high dietary intake of proteins and minerals) and there is also an association with ethnicity and region of residence[4]. 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)[5] using over 21,500 bed days. The pain leads to a requirement for analgesia, time off work and often repeated hospital admissions for therapeutic interventions.

A clinical guideline on the management of ureteric stones by the European Association of Urology and the American Urological Association[6] estimates that 68% of stones ≤5 mm and 47% of stones 5-10mm in size can be expected to pass spontaneously and concluded that the majority of these stones pass within four to six weeks of presentation. Stones in the distal ureter pass more readily than stones located more proximally. The majority of the studies included in the guideline meta-analysis assessed stones in the distal (lower) ureter only. Consequently, patients with favourable features and with smaller sized stones in the lower ureter are traditionally treated expectantly. Those who fail standard supportive care, (which involves analgesia, anti-emetics if nauseated, and intra-venous fluids if there is associated vomiting), 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. For instance, ESWL is associated with up to 5% risk of sepsis and up to 8% risk of impaction of stone fragments causing urinary obstruction (Steinstrasse), whilst ureteroscopy is associated with up to 4% risk of sepsis and up to 6% risk of ureteric injury[6].

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[7-9]. The selective α-blocker, tamsulosin has specificity for α-1A and α-1D receptor subtypes[10,11], whilst other α-blockers variably block all α-1 receptor sub-types in a non-specific manner [12,13,14]. Similarly, calcium channel blockers such as nifedipine inhibit ureteric smooth muscle contraction[15,16]. The use of both classes of drugs in augmenting the passage of ureteric stones has been termed medical expulsive therapy (MET) and this is proposed as a way to enhance stone passage and avoid the need for further interventions.

Two recent meta-analyses have reported the potential role of α-blockers and calcium channel blockers in MET. Hollingsworth and co-workers[17] included nine randomised controlled trials which included 693 subjects, although all but one trial had serious methodological flaws. Studied interventions included the calcium channel blocker nifedipine and several different α-blockers whilst the comparative control arms included placebo, other vasodilators, antispasmolytics, anticholinergic therapy or corticosteroids. Overall spontaneous stone passage occurred in 47% of the control group whilst patients given MET with either drug were 65% more likely to pass the stone with an absolute risk reduction of 31%. Three studies reported a head to head comparison between nifedipine and α-blockers. Two of these studies did not report any statistically significant

difference in stone passage rates between the two drugs, whilst one study found the α-blocker to be superior to nifedipine with a relative risk reduction of 26%.

In a more recent systematic review and meta-analysis, Singh and colleagues[18] included 22 studies; 13 of which assessed α-blockers, 6 assessed nifedipine, and 3 assessed both drugs against control. In the pooled analysis of 16 studies using α-blockers (n=1,235), those receiving active treatment were 59% more likely to pass the stone with a baseline stone-passage rate of 50% in the control group. The incidence of mild adverse effects was 4%. The corresponding pooled result for nifedipine (9 studies, n=686) showed that active treatment gave a 50% increased likelihood of stone passage with an absolute risk reduction of 26%. The incidence of mild adverse effects was 15%. Both drugs significantly shortened by between 2 and 6 days the average time to stone expulsion[18]. However, the overall quality of trials was poor.

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.

However, more recent results provided by Bensalah and co-workers[19] appear to challenge the notion that α-blockers enhance spontaneous ureteric stone passage. The study, recently presented as an abstract, was a prospective, multi-centre, randomised, double-blind, placebo-controlled trial which evaluated the efficacy of tamsulosin versus placebo in patients with ureteric colic caused by distal ureteric stones. 129 patients were treated for 42 days or until stone expulsion. At 42 days, there was no significant difference between the spontaneous expulsion rates between placebo (70.5%) and tamsulosin (77.0%; P = 0.41), nor in the mean stone passage times (10.1 and 9.6 days respectively). Nevertheless, the overall mean stone diameter was 3.1mm, which is lower than all of the earlier studies included in the meta-analyses by Hollingsworth[17] and Singh[18]. The spontaneous stone passage rate in the placebo arm was high (70.5%) in comparison with other studies included in the two meta-analyses.

There is limited evidence on the cost-effectiveness of MET; an indirect cost-benefit analysis based on cost data from the USA and four European countries suggested that the use of tamsulosin could potentially result in a cost saving of US$1,132 per patient episode over conventional ‘watchful waiting’[20].

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 that described in this protocol to inform the clinical management of patients with ureteric stone disease.

For the purposes of the randomised controlled trial we have chosen to compare tamsulosin versus nifedipine. The weight of available evidence supports the use of tamsulosin as the α-blocker of choice in MET for ureteric stones. In the two previous reviews[17,18] tamsulosin was the agent of choice in 13/16 RCTs. As discussed earlier, there also appears to be a theoretical advantage in using tamsulosin due to its specificity for the α-1A and α-1D adrenergic receptor subtypes. Similarly the reviews also suggest that nifedipine should be the calcium channel blocker of choice. The 8 RCTs identified in

Singh and Hollingsworth[17,18] which examined the efficacy of calcium channel blockers all used nifedipine. Nifedipine is also in widespread use in the NHS for other indications.

The main anticipated risk to participants is that they suffer an adverse reaction to trial medication. Treatment with α-blocker or nifedipine is associated with a small risk of adverse effects. In the report by Singh and colleagues[18] the incidence of mild adverse effects was 4% with α-blocker and 15% with nifedipine. However, both trial drugs are in common use for different indications, and the undesirable effects (such as postural hypotension and tachycardia) are well recognised. Patients with a contraindication to either drug will not be included in the trial. The off-label use of tamsulosin in women is well documented in the literature and there have not been any reports of any specific adverse reactions to treatment in female participants. However, the risks of tamsulosin use during pregnancy are unknown and nifedipine is contraindicated during pregnancy. Two suitable 'highly effective' forms of contraception must be used in women of child bearing potential entering the trial.

The potential benefits to participants are that the pain and discomfort caused by their ureteric stones will be relieved sooner and the avoidance of additional treatment (such as ureteroscopy or extra-corporeal shock wave lithotripsy) by 25% - 45%.

2. Trial Objectives

The aim of this trial is to determine the clinical effectiveness and cost-effectiveness of the use of tamsulosin and nifedipine in the management of symptomatic urinary stones.

In the context of all trial groups receiving standard supportive care two pragmatic comparisons will be made evaluating medical expulsive therapy (MET) for facilitating ureteric stone passage:

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

An α-blocker (tamsulosin) versus a calcium channel blocker (nifedipine).

The hypotheses being tested are:
1) The use of MET will result in an absolute increase in the spontaneous stone passage rate of at least 25% compared with placebo and
2) The use of an α-blocker (tamsulosin) will result in an absolute increase of 10% in the spontaneous stone passage rate compared with a calcium channel blocker (nifedipine).

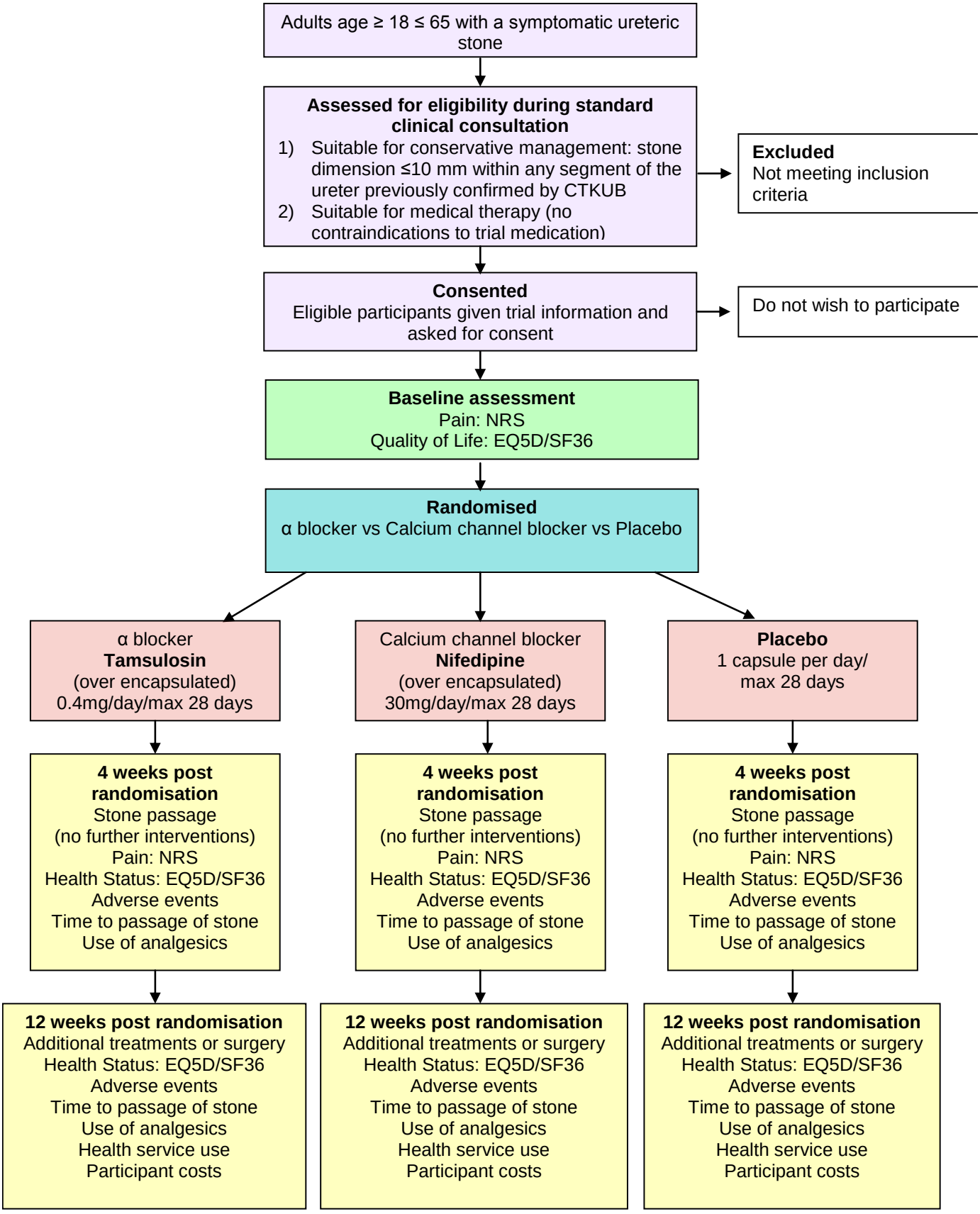
3. Trial Design

A multi-centre, double blind, placebo controlled, randomised trial evaluating two medical expulsive therapy policies (nifedipine or tamsulosin) versus placebo. The trial will be conducted in secondary care units with a high volume of admissions with ureteric stones across the UK. The choice of centres has been informed by a national audit of ureteric stone management undertaken by the British Association of Urological Surgeons (BAUS) Section of Endourology in 2007 (co-led by our group). Co-ordination of the trial will occur at the Centre for Healthcare Randomised Trials (CHaRT), a registered Trials Unit in the Health Services Research Unit, University of Aberdeen. A summary of the trial design is shown in Figure 1.

3.1 Interventions to be evaluated

Two active treatments will be investigated:
1) Tamsulosin, 0.4mg/day up to a maximum of 28 days
2) Nifedipine, 30mg/day up to a maximum of 28 days

Figure 1 Flow diagram - Randomised controlled trial comparing tamsulosin with nifedipine with placebo to facilitate urinary stone passage



3.2 Selection of Participants

As standard practice, clinicians will assess patients presenting with suspected ureteric calculi. A log will be taken of all patients assessed in order to document the reasons for non-inclusion in the study (e.g. reason they were ineligible, declined to participate) to inform the CONSORT diagram. Following adequate pain relief and confirmation of ureteric calculi by CTKUB, eligible patients (according to the inclusion and exclusion criteria given in sections 3.2.1 & 3.2.2) will be provided with a patient information leaflet. The research nurse will identify if the patient is interested in the trial and will ensure any questions that the patients have are answered appropriately. The patients will be given as long as they require, prior to discharge, to make a decision about whether or not to participate. On providing consent, the patient will be asked to complete a baseline questionnaire and will then be randomised to one of the three treatment groups.

3.2.1 Inclusion criteria

- Patients presenting acutely with ureteric colic
- Adults ≥18 to ≤ 65 years of age
- Presence of stone already confirmed by non-contrast computed tomography of the kidney, ureter and bladder (CTKUB).
- Stone within any segment of the ureter
- Unilateral ureteric stone
- Largest dimension of the stone ≤10 mm
- Female subjects must be willing to use two methods of contraception listed in the protocol prior to the start of dosing until at least 28 days after receiving the last dose of trial medication post menopausal (defined as 12 months with no menses without an alternative medical cause) or permanently sterilised
- Capable of giving written informed consent, which includes compliance with the requirements of the trial

3.2.2 Exclusion criteria

- Women who have a known or suspected pregnancy (confirmed by a pregnancy test)
- Women who are breast-feeding
- Asymptomatic incidentally found ureteric stone
- Stone not previously confirmed by CTKUB
- Stone with any one dimension >10 mm
- Kidney stone without the presence of ureteric stone
- Multiple (i.e. ≥ 2) stones within ureter
- Bilateral ureteric stones
- Stone in a ureter draining a solitary kidney (either anatomically or functionally)
- Patients with abnormal renal tract anatomy (such as a duplex system, horseshoe kidney or ileal conduit)
- Presence of urinary sepsis
- Chronic kidney disease stage 4 or stage 5 (eGFR < 30ml/min)
- Patients currently taking an α-blocker
- Patients currently taking a calcium channel blocker
- Patients currently taking PDE5 inhibitors
- Contraindication or allergy to tamsulosin or nifedipine (see Appendix B)
- Patients who are unable to understand or complete trial documentation

3.2.3 Contraception

Women who are eligible to take part in the trial and are of child bearing potential (i.e. are not post menopausal (defined as 12 months with no menses without an alternative

medical cause) or permanently sterilised) will be advised to use two forms of highly effective birth control (i.e. results in a less than 1% per year failure rate) and continue use until at least 28 days after last dose of trial medication. Acceptable forms of contraception include:-

- Established use of oral, transdermal, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) ***plus*** a spermicidal foam/gel/film/cream/suppository.
- Male partner is sterile (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) prior to female entry onto the trial and is the sole partner of the female participant.
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception for trial purposes].

3.3 Informed consent

An information leaflet will be given to each potential participant to inform them of the benefits and known drawbacks of all aspects of this trial. It shall specifically explain that the trial will investigate the effect of two different drugs against a placebo, and explain the likelihood of them receiving each of the three trial treatments. The patient information sheet will be developed in conjunction with the newly formed British Association of Urological Surgeons Section of Endourology Patient Group. Signed informed consent forms will be obtained from the participants in all centres, by an individual who is trained in Good Clinical Practice (GCP). Participants who cannot give informed consent (e.g. due to incapacity) will be not be eligible for participation. We will also seek the participant's permission to inform their general practitioner that they are taking part in this trial.

3.4 Randomisation

Eligible and consenting participants will be randomised to one of the two intervention groups or the placebo group on a 1:1:1 basis using the proven telephone Interactive Voice Response (IVR) randomisation application hosted by the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU) in Aberdeen. The randomisation algorithm will use centre, stone size and stone location as minimisation covariates. Upon randomisation the participant will be allocated a unique participant number and assigned a numbered participant pack containing over-encapsulated trial medication to ensure that the participant, investigator and trial personnel remain blind to treatment.

3.4.1 Code break/ emergency unblinding

Participants will be given a patient card which will have the study title, IMP details, patient trial number and out of hours contact details in case of emergency unblinding. The treatment code should only be broken for valid medical or safety reasons, e.g. in the case of a severe adverse event where it is necessary for the Principal Investigator or treating health care professional to know which treatment the participant is receiving to determine emergency treatment. Where possible the members of the research team should remain blinded, subject always to clinical need,.

In the event of clinical emergency requiring unblinding, the first point of contact is the Urology Department where the participant was recruited to the trial. The participant will

be given a card to carry with details of this telephone number. Contact information will also be available in the participant's hospital notes.

The Principal Investigator, the site Research Nurse or a member of staff at the Urology Department will telephone the Centre for Healthcare Randomised Trials (CHaRT) randomisation service at the number given in the Telephone User Guide. Using the trial centre ID and the participant study number(the study number will be available from the patient card or the participant's hospital notes). The name and position of the person making the call will be recorded. In the unlikely event of randomisation service failure the on-call pharmacist at Aberdeen Royal Infirmary will be contacted and the same procedure followed.

Following any unblinding via the telephone randomisation service, automatic emails will be sent to the Chief Investigator, Trial Manager and members of the CHaRT Management team. The on-call pharmacist will email the same list of people of any unblinding performed by them. These e-mails will not contain the treatment code and the trial team will remain blinded as far as is practicable.

The Chief Investigator will then ascertain why unblinding has taken place. If the participant was unblinded because of a Serious Adverse Event then an SAE form will be completed and will be reported as stipulated in Section 6.2.2 of the Protocol.

3.5 Trial Procedures

Participants will complete three questionnaires. The baseline questionnaire will be completed in hospital after entry into the trial (but before they receive their study medication). Two further postal questionnaires, one at four and one at 12 weeks post randomisation, will be sent from the co-ordinating office (CHaRT, Aberdeen). In addition, participants may be reviewed in clinic at approximately four weeks after randomisation (as is common in routine NHS care). In the event that the participant does not return their questionnaire a reminder letter will be sent out approximately two weeks later and this may be followed up by a phone call approximately three weeks after the reminder letter.

Three case report forms will be completed by the research team at the recruiting site. One at baseline and one at the four week follow up visit (completed from the participants notes if they do not attend the visit). If the participant indicates on their 12 week questionnaire that they have had further interventions since their four week questionnaire a further case report form will be completed by the research nurse from the participant's notes.

The complete trial processes are shown in Figure 2.

3.6 Subject withdrawal

Participants will remain on the trial unless they chose to withdraw consent or if the PI, CI or trial office feel it is no longer appropriate for the participant to continue (i.e. participant becomes unable to complete the trial documentation). Once the participant has been withdrawn from the trial, participant questionnaires will not be collected, however permission will be sought for the research team to continue to collect outcome data from their hospital notes (via the CRFs).

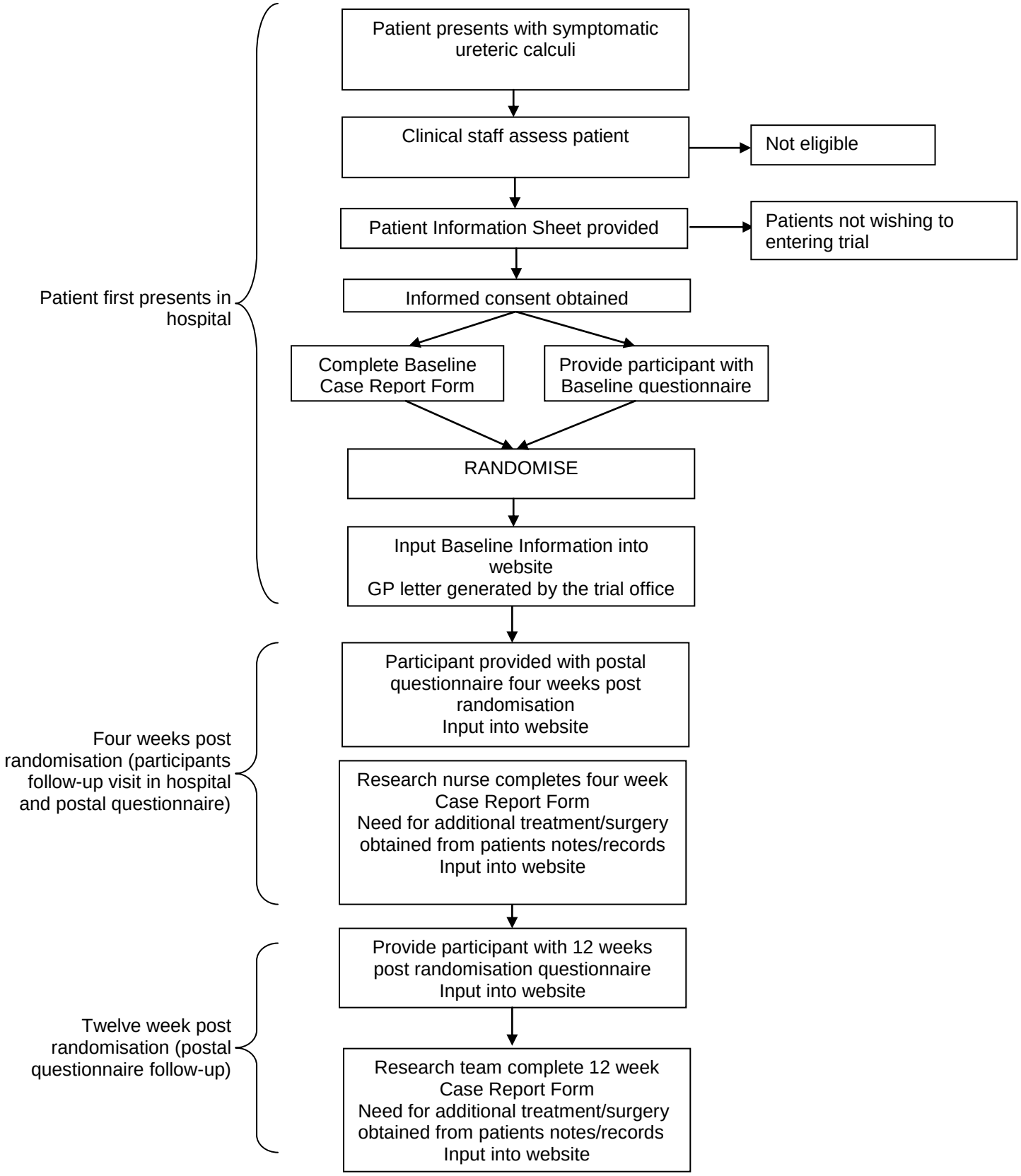
In the event that the participant is withdrawn from the study medication for any reason (i.e. a serious adverse reaction or event occurs) they will still continue in the trial and will be asked to complete the trial documents.

3.7 Duration of trial

Participants will take the trial medication once daily for a maximum of 28 days. End of trial for each participant will be defined as 18 weeks post randomisation to allow for collection of the 12 week questionnaire. End of trial is when the last participant randomised reaches this 18 week timepoint.

The project timetable and milestones can be found in Appendix A.

Figure 2: Trial processes



4. Trial medications

4.1 Investigational medicinal products

Tamsulosin hydrochloride (Petyme) will be sourced by Tayside pharmaceuticals from TEVA UK in the form of 400 microgram MR (modified release) capsules.

Nifedipine (Coracten) will be sourced by Tayside pharmaceuticals from UCB Pharma in the form of 30 mg SR (sustained release) capsules.

The placebo will be manufactured by Tayside Pharmaceuticals.

The medicinal products will be over-encapsulated to maintain the blinding of the trial. Trial medication will be presented as capsules in amber glass containers with a child proof closure and labelled according to Annex 13 of Volume 4 of The Rule Governing Medicinal Products in the EU: Good Manufacturing Practices.

The medicinal products and the placebo will be over-encapsulated, packaged and labelled by Tayside pharmaceuticals according to Good Manufacturing Practice.

4.2 Dosing Regimen

Participants will take one capsule of the trial medication per day until stone passage occurs or for a maximum of 28 days. All trial medication should be taken orally with a little water after the first meal of the day while standing or sitting (not lying down). Capsules should not be broken or chewed, but swallowed whole.

4.3 Drug accountability

Blinded treatment packs will be stored by the local pharmacy according to manufacturer's instructions until dispensed to the participant. Detailed dispensing records will be kept by the pharmacy

4.4 Subject compliance

Upon randomisation each participant will be assigned a unique participant numbered pack of blinded medication. Participants will be instructed to store the medication according to the manufacturer's instructions. The participant will be asked to record whether they completed the full course of treatment in the four week questionnaire. Unused medication and/or empty packaging should be returned by the participant at the four week follow up visit and returned to the pharmacy. If the participant does not attend the four week visit they will be instructed to destroy the medication. Participants will also be treated with usual standard of care at the treating establishment, including prescribed analgesia.

4.5 Concomitant medications

Patients currently taking rifampacin or digoxin are excluded from the trial.

Potential interactions taken from the Summary of Product Characteristics for each product can be found in Appendix B. The participant's GP will also receive this information..

5. Proposed outcome measures

The trial has a primary clinical and a primary economic outcome reflecting the multidimensional nature of the possible effects the intervention may have.

Primary:

Clinical	The primary outcome is spontaneous passage of ureteric stones at four weeks (defined as no further intervention required to facilitate stone passage).
Economic	Incremental cost per quality adjusted life years (QALYs) gained at 12 weeks. QALYs are based on the responses to the EQ-5D.

Secondary:

Patient-reported	Severity of pain as measured by the Numeric Rating scale (NRS)[21,22]. Generic health profile as measured by the SF 36 and use of analgesia.
Clinical	Time to passage of stone; further interventions received at 12 weeks.
Safety	Participant reported discontinuation of trial medications
Economic	NHS primary and secondary care use and costs up to three months, incremental cost per surgical interventions averted; modelled incremental cost per QALY beyond the 12 week trial follow-up.

5.1 Timing and measurement of outcome assessment:

Outcomes will be assessed at four weeks (clinical outcome +/- 2 weeks) and 12 weeks post randomisation as shown in Table 1.

Table 1: Source and timing of measures

Outcome measures	Source	Timing		
		Recruitment	Post randomisation	
			Four weeks	12 weeks
Need for additional intervention	Case Report Form (CRF)		✓	✓
Additional interventions received	Participant Questionnaire (PQ)		✓	✓
Pain (NRS)	(PQ)	✓	✓	
Health profile and status (SF 36, EQ5D)	(PQ)	✓	✓	✓
Use of analgesics	PQ		✓	
Adverse events	PQ		✓	
Time to passage of stone	PQ and CRF		✓	✓
NHS primary and secondary health care use	PQ and CRF			✓
Participant out of pocket costs	PQ			✓

6. Safety

6.1 Timing and recording of safety parameters

Information regarding participant discontinuation of medication due to adverse events will be collected at four weeks in the patient questionnaire.

6.2 Procedures for recording and reporting adverse events

The Medicines for Human Use (Clinical Trials) Regulations 2004 gives the following definitions:-

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for that product (see Appendix D)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death
- Is life-threatening
- Required hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect

6.2.1 Adverse events that will not be reported

Non-serious events will not be collected or reported. Planned hospital visits for conditions other than those associated with the ureteric stone will not be collected or reported. Planned hospital visits associated with the treatment of the ureteric stone will be recorded as an outcome measure, but will not be reported as a serious adverse event.

6.2.2 Procedure for adverse event recording in this trial.

All adverse events will be assessed in respect of severity (serious or not), relationship to trial medication (suspected/not suspected), whether expected or unexpected, duration and, therefore, whether constituting a Serious Adverse Event (SAE). Please refer to the flow chart in Appendix C to determine whether a response is a serious adverse event or reaction.

Participants will be advised to contact their General Practitioner should they experience an adverse event between the period following treatment and the twelve week follow-up questionnaire. This is current clinical practice for participants receiving tamsulosin or nifedipine within the NHS. When notified of trial participation, General Practitioners will be asked to notify the trial office of any serious adverse reactions or events (e.g. unexpected admission to hospital) in a timely manner. This will provide a robust system for the notification of any Serious Adverse Reactions or Serious Adverse Events (both expected and unexpected) occurring outside of the trial visit.

a. Non serious adverse events

Non serious adverse events will not be collected. Participants will be asked whether they discontinued the study medication due to adverse reaction(s) in the four week questionnaire.

b. Serious adverse events

All serious adverse events are to be notified to the Co-Sponsors and CI as soon as the investigator or trial office (via a GP) becomes aware either orally or in writing and this should be followed by a written report on the event.

i). If the adverse event is **serious but potentially expected** (see Appendix D for list of potentially expected adverse reactions), a **serious adverse event report form** should be completed within **seven days** of the local investigator becoming aware. When the web-based form is completed, the Chief Investigator and the trial office will be notified automatically.

ii). If the adverse event is **serious and unexpected** a **serious adverse event report form** should be completed **within 24 hours** of the local investigator being aware of the event. When the web-based form is completed, the Chief Investigator and the trial office will be notified automatically.

6.2.3 Adverse reaction and unexpected adverse reaction reporting

i. Fatal or life threatening SUSARs

The Chief Investigator (or his designee) or Co-Sponsor will forward reports on fatal or life threatening suspected unexpected serious adverse reactions (SUSARs) (i.e. serious unexpected adverse events where a causal link between the drug and the event is suspected) to the MHRA and the Research Ethics Committee within **seven** days of their first knowledge of the minimum criteria using the relevant proforma. A copy will also be sent to the Co-Sponsor, the manufacturer and the DMC. Follow up information will be forwarded to the MHRA and ethics committee within eight days.

ii. Non fatal and non life-threatening SUSARs

The Chief Investigator (or his designee) or Co-Sponsor will forward reports on non fatal and non life-threatening SUSARs to the MHRA and the Research Ethics Committee within **fifteen** days of their first knowledge of the minimum criteria using the relevant proforma. A copy will be sent to the Co-Sponsors, the manufacturer and the DMC. Follow up information will be forwarded to the MHRA and ethics committee within eight days.

iii. All other serious adverse reactions

The trial office, with the assistance of the CI, will prepare a summary of all serious adverse reactions every six months. These will be distributed to the participating investigators, the Co-Sponsors, the manufacturer, the trial steering committee and the DMC.

In addition all suspected serious adverse reactions will be collated annually and submitted to the MREC and MHRA in accordance with the guidance on annual safety reporting.

The DMC will regularly assess the safety data collected for the trial and will have ability to advise that the trial is temporarily or permanently halted based on safety concerns according to the criteria defined in their charter.

6.2.4 Pregnancies

Pregnancy is not regarded as a serious adverse event, but will be recorded and reported. Pregnancy will be prevented as far as is practicable (see section 3.2.4), but in the event a woman does become pregnant on the trial she will be followed throughout her pregnancy and any serious adverse events at delivery will be recorded and reported. If necessary the development of the newborn will be monitored an appropriate period post delivery.

7. Statistics

7.1 Proposed sample size

Combining the data from the two recent meta-analysis[17,18], suggests a relative risk of approximately 1.50 comparing MET (either α-blocker or calcium channel blocker) against 'standard care' on the primary outcome. These reviews indicate a spontaneous stone passage rate of approximately 50% in control groups of included RCTs. Only three of the included RCTs directly compared a calcium channel blocker and an α-blocker, and these suggested that α-blockers are likely to be superior to calcium channel blockers. Combining information from Singh[18] and Hollingsworth[17] stone passage rates in the α-

blocker and calcium channel blockers groups are approximately 85% and 75% respectively. The most conservative sample size is required to detect superiority between the two active treatments and to this end will power the trial. 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 α-blocker group, with type I error rate of 5% and 90% power requires 354 per group, adjusting for 10% loss to follow-up inflates this to 400 per group. Since all treatment comparisons are pre-specified, no adjustment for multiplicity has been made[24]. Recruiting 1200 participants (randomising 400 to each of the three treatment groups; α-blocker, calcium channel blocker and placebo) would provide sufficient power (>90%) for all other comparisons of interest.

7.2 Procedures to minimise bias

To minimise bias all participants will be randomised to treatment (including a placebo arm) using the minimisation criteria detailed in section 3.4. The trial will be conducted double blind, that is the participant, investigator and personnel involved in the trial (with the exception of the DMC members and allocated statistican) will be unaware of each individual's treatment allocation.

7.3 Statistical analysis

Two comparisons will be considered for the primary trial analysis:
1) MET (an α-blocker [tamsulosin] or a calcium channel blocker [nifedipine]) versus placebo
2) An α-blocker (tamsulosin) versus a calcium channel blocker (nifedipine).

Treatment groups will be described at baseline and follow-up using means (with standard deviations), medians (with inter-quartile ranges) and numbers (with percentages) where relevant. Primary and secondary outcomes will be compared using generalised linear models, with adjustment for participant baseline and minimisation covariates: trial centre; stone size (≤5mm or >5mm - 10mm); and location in ureter (upper, mid, or lower). All estimates of treatment effect will be presented with 95% confidence intervals. Statistical significance will be at the 5% level. Primary analyses will be by allocated group (intention to treat). Subgroup analyses (appropriately analysed by testing treatment by subgroup interaction) will explore the possible effect modification of a number of factors (stone size (≤ 5mm or >5mm - 10 mm); location in ureter, (upper, mid, or lower); gender; all using stricter levels of statistical significance ($p<0.01$, 99% confidence intervals)

All statistical analyses and reporting will follow the carefully documented Statistical Analysis Plan (SAP). The Trial Steering Committee and an independent Data Monitoring Committee (DMC) will be asked to review and comment on the SAP prior to any analysis and the SAP will be finalised prior to any unblinding of the data. For SUSPEND a single main analysis will be performed at the end of the trial when all follow-up has been completed. Consideration of the frequency of monitoring reports, interim analysis and any criteria for stopping rules will be discussed and agreed with the DMC prior to recruitment starting. The SAP and DMC charter will document the agreed timings and strategy.

8. Economic evaluation

Economic evaluation will be an integral part of the trial. Resource use and costs will be estimated for each participant. Resource data collected will include the costs of the intervention drugs and simultaneous and consequent use of primary and secondary NHS services by participants. Personal costs such as purchase of medications, time and

travel will also be estimated. The perspective of the trial will be societal as it will include both the NHS costs as well as that of the participants.

8.1 Collection of data

At recruitment, data will be collected on the intervention that the participants receive. At four and 12 weeks post randomisation participants will be asked to provide information about their use of analgesics and at 12 weeks their primary and secondary health care service use. They will also be asked for information about the time they spent travelling to primary and secondary health service providers and the resources they may have used such as mode of transport

8.2 Participant costs

Participant costs will comprise self purchased healthcare and travel and time costs for accessing NHS care. Self-purchased health care will include items such as prescription costs and over the counter medications. Information about these will be collected using the health care utilisation questions. Participants will be asked for information on travel costs and this will be estimated from the number of visits to, for example, their GP, or hospital doctor (estimated from the health care utilisation questions) and the unit cost of making a return journey to each type of health care provider (from a Health Care Unit Cost Questionnaire administered at 12 weeks).

The cost of participant time will be estimated by asking them how long they spent travelling to, and attending, their last visit to each type of health care provider. Participants will also be asked what activity they would have been undertaking (e.g. paid work, leisure, housework) had they not attended the health care provider. These data will be presented in their natural units, e.g. hours, and also costed using standard economic conventions, e.g. the Department of Transport estimates for the value of leisure time. These unit time costs, measured in terms of their natural and monetary terms will then be combined with estimates of number of health care contacts derived as outlined below.

8.3 NHS costs of other health services used

Use of secondary care services following the treatment period will be collected using a case report form (CRF). This form will record information on non-protocol (protocol visits are those scheduled for the purposes of data collection) outpatient visits, readmissions relating to the use and consequences of drug treatment. Use of primary care services such as prescription medications, contacts with primary care practitioners e.g. GPs and practice nurses will be collected via the 'health care utilisation questions' administered at 12 weeks follow-up.

8.4 Cost effectiveness

The cost effectiveness within the trial will be measured in terms of the number of participants needing further treatment during or at the end of the twelve week follow-up and quality adjusted life years (QALYs) at 12 weeks. QALYs will be estimated by combining estimated quantity of life, with quality of life derived from the EQ5D questionnaire (administered at baseline, four weeks and 12 weeks post-randomisation) and UK tariffs[23].

The within trial analysis will be based on 12 weeks follow-up and results will be presented as the incremental cost per further treatments needed during or at the end of the 12 week follow-up and the incremental cost per QALY gained. The results will be 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 are likely to involve bootstrapping estimates of costs, number of further treatments needed, QALYs, incremental cost per further treatments needed and incremental cost per QALY. Incremental cost-effectiveness data will be presented in terms of cost-effectiveness acceptability curves (CEACs). Forms of uncertainty, e.g. concerning the unit cost of a resource from the different centres, will be addressed using deterministic sensitivity analysis. Where feasible the results of the sensitivity analyses will also be presented as CEACs.

A modeling exercise will be performed to extrapolate the estimates of the cost-utility analysis to a longer time horizon than that considered by the trial. This will allow consideration of the costs of any subsequent treatments performed after the trial follow-up period and effects on quality of life prior to this. Consideration will also be given to the relevance of costs and effects on quality of life following subsequent treatment. Individual participant data from the trial as well as both published and unpublished evidence in the field will be used to populate the model. The methods used to assemble additional data will follow recognised methodology, which will vary according to the type of parameter, extent of uncertainty and role within the model. Therefore, comprehensive systematic searching will be limited to those parameters to which the results of the model are likely to be particularly sensitive. The modeling exercise will comply with recent recommendations on good practice for modeling and the results will be presented in terms of incremental cost per additional treatment needed and incremental cost per QALY gained. Parameter and other forms of uncertainty will be addressed using probabilistic and deterministic sensitivity analysis.

9. Trial Oversight Committees

9.1 Data Monitoring Committee

The DMC will be made up of members listed at the start of this protocol, one of whom is an experienced statistician. After the trial has been initiated the DMC will initially meet to agree its terms of reference and other procedures. CHaRT has adopted the DAMOCLES Charter for DMCs and suggests to the independent DMC members that they adopt the Terms of Reference contained within.

The committee will meet regularly to monitor the unblinded trial data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

Progress reports to the DMC will be held in the strictest confidence by its members and securely archived.

9.2 Trial Steering Committee

The trial steering committee will be headed by a member independent to the trial. CHaRT recommends to TSCs that they adopt the MRC CTU template to form the basis for each individual trial's charter. Details of the membership of the TSC can be found at the start of this protocol.

10. Ethics and Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory guidance, including, but not limited to, the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents (and any subsequent amendments) will be submitted for review to the Fife and Forth Valley Research Ethics Committee (FFVREC) and to the Medicine and Healthcare products Regulatory Agency (MHRA) for clinical trial authorisation.

Annual progress and safety reports and a final report at the conclusion of the trial will be submitted to FFVREC and the MHRA within the timelines defined in the regulations.

11. Quality Assurance

The trial will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, GCP and the appropriate legislation (Medicines for Human Use (Clinical Trials) Regulations 2004). The purpose of monitoring will be to ensure that the local site facilities and personnel continue to be fit for purpose. The approach to, and extent of, monitoring (specifying both central and on-site monitoring) will be specified in a trial monitoring plan which is usually initially determined by a risk assessment, undertaken prior to start of trial.

12. Data Handling and Record Keeping

Clinical data will be entered into the database by the local investigator or research nurse working in each hospital site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with local research nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's details will be stored on a secure database under the guidelines of the 1988 Data Protection Act. Participants will be allocated an individual specific trial number and their details will be anonymised on the secure database. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

The Co-sponsors are responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least thirty years following close of study.

13. Financing and insurance

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme.

14. Publication policy

All RCTs conducted by CHaRT have a commitment to publish the findings of the research. At a minimum this trial will have a results paper published in a peer-reviewed medical/scientific journal.

If all grant-holders and research staff fulfil authorship rules, group authorship will be used under the collective title of 'The SUSPEND Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to the named individual(s) and the SUSPEND Trial Group.

For reports which specifically arise from the trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to the named individual(s) for the SUSPEND Trial Group'.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior agreement from the Project Management Group.

We intend to maintain interest in the study by publication of SUSPEND newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final SUSPEND Newsletter to all involved in the trial.

Further details on the publication policy can be found in Appendix E.

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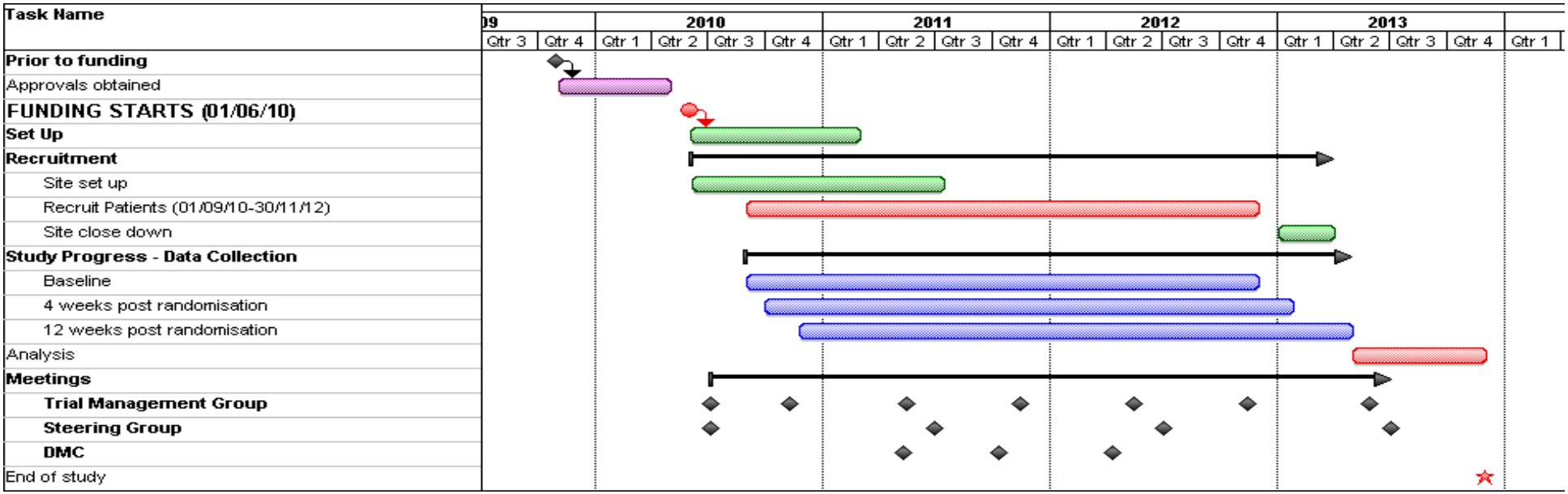
Appendix A
Project timetable and milestones

Study duration; 42 months
Milestones;

- Months 1-3: initiation of study, recruitment of staff, NHS approvals
- Months 4-12 Establish sites and staff, staggered site start up of patient recruitment
- Months 5-30: patient recruitment (all sites by month 16)
- Months 31-35: participant follow up at 3 months
- Months 36-42: analysis of data, economic analysis, interpretation of results and report writing.

Figure 3: GANNT Chart of Project Timetable



Appendix B
Contraindications and interaction with other medicinal products and other forms of interaction

From the Summary of Product Characteristics (SmPC) for Nifedipine (last SmPC revision April 2009) and Tamsulosin (last SmPC revision 15 December 2006)

Nifedipine capsules are contra-indicated in patients with known hypersensitivity to nifedipine or other dihydropyridines because of the theoretical risk of cross reactivity.

Nifedipine 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 nifedipine capsules in malignant hypertension has not been established.

Nifedipine capsules are contra-indicated in patients with acute porphyria.

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

As nifedipine 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.

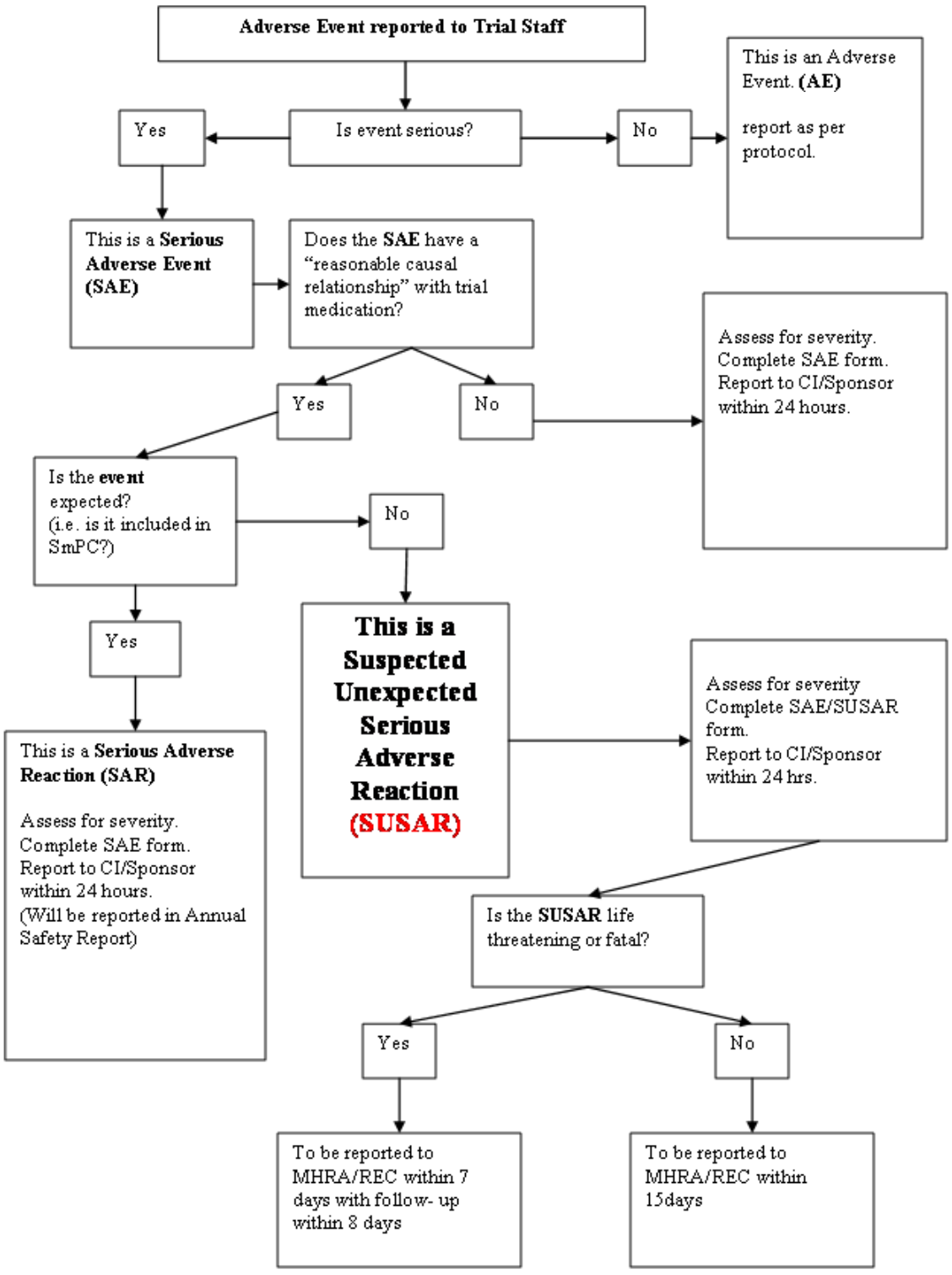
Tamsulosin should not be administered to patients with severe hepatic insufficiency.

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.

Concurrent administration with another α_1-adrenoceptor antagonist may lower blood pressure.

Appendix C
Adverse event/reaction flow chart



Appendix D
Drug specific adverse reactions

From the Summary of Product Characteristics (SmPC):-

Nifedipine (last SmPC revision April 2009)

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.

Less frequently reported side-effects include myalgia, tremor, pemphigoid reaction and visual disturbances.

Rare reactions include; Impotence, mood changes, exacerbation of angina pectoris. Cases of hypersensitivity-type jaundice have been reported rarely. In addition, disturbances of liver function such as intra-hepatic cholestasis may occur. These regress after discontinuation 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.

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

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.

Tamsulosin (last SmPC revision 15 December 2006)

The most common side effect experienced with tamsulosin is dizziness.

More uncommon side effects include headache, tachycardia, rhinitis, orthostatic hypotension, constipation, diarrhoea, nausea, vomiting, rash, itching, uticaria, abnormal ejaculation, asthenia.

Rare and very rare effects are syncope, angio-oedema and priapism (very rare).

Appendix E
Publication Policy

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the international Committee of Medical Journal Editors.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.[1] In such cases the authorship will be presented by the collective title - The SUSPEND Trial Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the by-line 'Jane Doe *and* the Trial Group'.[2] Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the byline would read 'Jane Doe *for* the Trial Group').[2]

b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria[1]:

i. each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.

ii. participation must include three steps:

- conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
- drafting the article or revising it for critically important content; AND
- final approval of the version to be published.

Participation solely in the collection of data is insufficient by itself. Those contributors who do not justify authorship may be acknowledged and their contribution described.[1]

c. Determining authorship

Tentative decisions on authorship should be made as soon as possible.[1] These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

2. AUTHORSHIP FOR PUBLICATION ARISING FROM SUSPEND

a. Operationalising authorship rules

We envisage two types of report (including conference presentations) arising from the SUSPEND trial and its associated projects:

i. *Reports of work arising from the main SUSPEND trial*

If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The SUSPEND Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the SUSPEND Trial Group'.

ii. *Reports of satellite studies and subsidiary projects*

Authorship should be guided by the authorship rules outlined in Section 1 above. Grantholders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules should be recognised in the Acknowledgement section. The role of the SUSPEND Trial Group in the development and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the SUSPEND trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the SUSPEND Trial Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

b. Quality assurance

Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the SUSPEND trial including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the SUSPEND project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertake to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat in Aberdeen at least two weeks prior to the meeting).

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1. Huth EJ (1986). Guidelines on authorship of medical papers. *Annals of Internal Medicine*,
104, 269-274.
2. Glass RM (1992). New information for authors and readers. Group authorship, acknowledgements and rejected manuscripts. *Journal of the American Medical Association*, **268**, 99.