Percutaneous Nephrolithotomy, Flexible Ureterorenoscopy and Extracorporeal Shockwave Lithotripsy for lower pole kidney stones

The clinical and cost effectiveness of surgical interventions for stones in the lower pole of the kidney: The Percutaneous nephrolithotomy, flexible Ureterorenoscopy and Extracorporeal shockwave lithotripsy for lower pole kidney stones Randomised Controlled Trial (PUrE RCT)

PROTOCOL

A UK Collaborative Trial funded by the National Institute for Health Research Health Technology Assessment Programme (NIHR HTA)

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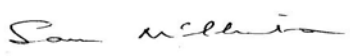
Signature

The CI agrees to abide by this protocol

Prof S McClinton: 

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G MacLennan: signature

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VERSION HISTORY:

Amendment no.	**Protocol version no.**	**Description of changes (*incl. author(s) of changes*)**	**Date Effective**
1	01	Administrative updates, clarification of questionnaire time points - *KS*	23 Mar 2016

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PROTOCOL SUMMARY

Question addressed	For people needing removal of stones in the lower pole of the kidney what is the relative clinical effectiveness and cost effectiveness of using flexible ureterorenoscopy (FURS) compared with extracorporeal shockwave lithotripsy (ESWL) or percutaneous nephrolithotomy (PCNL).
Considered for entry	Male and female patients aged ≥16 years with a stone (or stones) in the lower pole of either kidney confirmed by non-contrast computed tomography of the kidney, ureter and bladder (CTKUB).
Populations	Participants requiring treatment for a stone of maximum dimension ≤10 mm and able to undergo FURS or ESWL (RCT1). Participants presenting with a stone of maximum dimension >10 mm to ≤25 mm and able to undergo FURS or PCNL (RCT2).
Trial entry	We will require 1044 (522 in each of RCT1 and RCT2) eligible patients to consent to participate in the study after considering written and spoken information provided by local clinical and research teams. Eligible and consenting participants, who have a CTKUB to confirm the presence and size of stone will be categorised according to maximum stone dimension and randomised to one of the interventions in RCT1 (FURS or ESWL) or one of the interventions in RCT2 (FURS or PCNL). Randomisation will be minimised by centre within each RCT. Participants will be followed-up by questionnaires sent from the trial office every week up to 12 weeks post intervention and at 12 months post-randomisation.
Interventions	Experimental: Flexible ureterorenoscopy with laser lithotripsy (FURS) Standard: Extracorporeal shockwave lithotripsy (ESWL) or Percutaneous nephrolithotomy (PCNL)
Outcome assessment	The primary clinical outcome is health status measured by the area under the curve (AUC) calculated from multiple measurements of EQ-5D-5L up to 12 weeks post-intervention. The primary economic outcome is the incremental cost per quality adjusted life year (QALYs) gained at 12 months post-randomisation based on estimated healthcare costs and participant responses to the EQ-5D up to 12 months after randomisation.
Co-ordination	**Overall**: by the Project Management Group chaired by the Chief Investigator, and overseen by the Steering Committee and the Data Monitoring Committee. **Central**: by Trial Office in Aberdeen within the Centre for Healthcare Randomised Trials (CHaRT). Telephone 01224 438112. **Local**: By the site Principal Investigator, NHS Trust Research and Development Department, clinical urology team and research team.

GLOSSARY OF ABBREVIATIONS	
A&E	Accident and Emergency
AE	Adverse event
AUC	Area under the curve
BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Confidence interval
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CTKUB	Computed tomography, kidneys, ureters and bladder
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EAU	European Association of Urology
EQ-5D	EuroQol Group's 5 dimension health status questionnaire
ESWL	Extracorporeal shockwave lithotripsy
FURS	Flexible ureterorenoscopy
GCP	Good Clinical Practice
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	Health related quality of life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ISD	Information Statistics Division
ISF	Investigator site file
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive voice response (randomisation)
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NHSG	National Health Service Grampian
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
NRS	Numeric Rating Scale
PI	Principal Investigator
PIL	Patient information leaflet
PMG	Project Management Group
PCNL	Percutaneous nephrolithotomy
PQ	Participant questionnaire
QALY	Quality adjusted life year
RCT	Randomised controlled trial
R&D	Research and Development
REC	Research Ethics Committee
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard operating procedure
TMF	Trial master file
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen

TRIAL PERSONNEL

Chief Investigator

1 Sam McClinton (Professor of Urology and Consultant Urologist)

Grant Holders

1 Ken Anson (Consultant Urologist)
2 Terry Clark (Patient Group Advisor)
3 Rodolfo Hernández (Senior Health Economist)
4 Thomas Lam (Senior Lecturer and Consultant Urologist)
5 Graeme MacLennan (Trial Statistician)
6 Steven MacLennan (Research fellow)
7 John Norrie (CHaRT Director)
8 Robert Pickard (Professor of Urology)
9 Daron Smith (Consultant Urologist)
10 Kath Starr (Trial Manager)
11 Ruth Thomas (Research Manager)
12 Ben Turney (Consultant Urologist)
13 Oliver Wiseman (Consultant Urologist)

Project Management Group (PMG)

This group is comprised of the grant holders along with representatives from the PUrE central trial team:

1 Trial Manager(s)
2 Data Co-ordinator
3 Health Economist
4 Junior Statistician
5 Senior Trials Manager
6 Senior IT Manager

Trial Office Team

This group will contribute to strategic management of the trial including meeting organisation, communication and financial aspects

1 Chief Investigator
2 CHaRT Director
3 Trial Manager(s)
4 Data Co-ordinator
5 Senior Trials Manager
6 Senior IT Manager
7 Trial statistician
8 Trial secretary

Trial Steering Committee (TSC) Members

The membership of this committee comprises of three independent members along with the Chief Investigator (Professor S. McClinton) or a nominated delegate as an additional voting member. The other PUrE grant holders and key members of the central office (e.g. the trial manager) may attend TSC meetings as non-voting observers.

Independent TSC Members

1 Nigel Parr (Chair)
2 Jeff Hussey
3 Lynda Harper

Data Monitoring Committee (DMC) Members

This committee is comprised of three independent members and the trial statistician will contribute as appropriate. The CI and or a nominated delegate may contribute to the open session of the meetings as appropriate.

1 Steve Payne (Chair)
2 Robert Hills
3 David Douglas

1. INTRODUCTION

1.1 Background

Renal tract stone disease is very common, with a lifetime prevalence of approximately 10% in the adult population across the world.[1] It mainly affects adults of working age and the incidence has been increasing over the past decades.[2, 3] This is partly due to people with obesity or diabetes being more likely to suffer renal stone disease and results in a higher burden for healthcare and associated costs for high resource countries.[4] Approximately 50% of people with renal tract stones will experience symptoms, typically kidney pain, and about 25% of patients with stones will require active treatment.[5-7] Some people with stones can develop more serious problems including uncontrolled pain, infection, visible blood in the urine (haematuria), impaired kidney function and kidney failure. Despite successful removal of the initial stone, many treated patients will develop a further stone, with a lifetime recurrence risk of 50%.[8] Renal stones are a major burden on the National Health Service (NHS) in the UK resulting in over 82,000 in-patient hospital stays and over 25,000 procedures carried out to remove stones in England in 2013 - 2014.[9] Kidney pain from stones (renal colic) is the most common cause of emergency admission to urology departments in the UK, and given the age group most commonly affected it results in time off work and loss of economic activity.[3] The on-going need for pain killers and the detriment to family, social and work activity reduces quality of life and incurs additional costs.

Stones most commonly develop in the lower part (pole) of the kidney accounting for up to 35% of cases.[10] There are currently three technologies available within the NHS to remove lower pole kidney stones: extracorporeal shockwave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), and flexible ureterorenoscopy with laser lithotripsy (FURS). The choice of treatment can be guided by stone size, likely stone composition, the anatomy of the drainage system of the affected kidney, clinician and patient preference and availability of equipment and expertise.[11] Current evidence indicates that the success rate in terms of stone clearance differs between these technologies which may partly relate to stone size. They are also distinct in terms of degree of invasiveness, anaesthetic requirement, treatment setting, number of procedures required to clear the stone, and type and rate of complications.[11, 12]

Extracorporeal shockwave lithotripsy is non-invasive, has a low risk of complications, and does not require anaesthesia. Current evidence suggests it has reasonable efficacy in terms of stone clearance for smaller lower pole stones at 3 months (63-74% clearance rate for stones ≤10 mm).[10] However, 3-month efficacy rates for lower pole stones >10 mm appear to be lower, (23-56% for 11-20 mm stones, and 14-33% for 21-30 mm stones).[13, 14] If the stone is not cleared additional treatments may be required using either repeated ESWL or more invasive options. Following ESWL small residual stone fragments can be left in the kidney and may result in recurrent stone formation over time (20% at 5 years).[7, 15]

Having considered this evidence, guidance issued by the European Association of Urology (EAU) and widely followed in UK clinical practice recommends ESWL as an option for lower pole stones ≤10mm whereas for larger stones recommended options are FURS or PCNL.[11] However the guidance adds that ESWL may be used for larger stones if stone factors and patient preference are favourable. Flexible ureteroscopy and laser fragmentation and PCNL are more invasive than ESWL, require a general anaesthetic, and carry a greater risk of complications.[16, 17] A single FURS treatment appears to result in good clearance rate for stones up to 15 mm with repeat procedures or combined procedures required for larger stones. Percutaneous nephrolithotomy is the most invasive treatment option and is associated with a higher risk of complications, but it also appears to result in the highest stone clearance rates which are close to 100% for stones ≤10 mm, 93% for stones 11-20 mm, and 86% for stones 21-30 mm.[18] Stone clearance rates for FURS appear to lie between those of

ESWL and PCNL.[19-25] The EAU guidance also comments that there remains considerable uncertainty regarding the management of lower pole stones, with each treatment option having advantages and disadvantages.

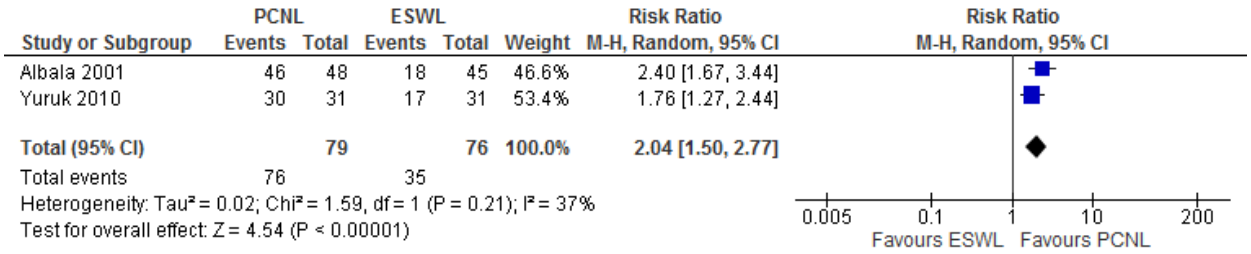
1.2 Rationale for the trial

A Cochrane review and meta-analysis (2014) of randomized controlled trials (RCT) compared ESWL with either FURS or PCNL for the treatment of renal stones.[12] The review concluded that PCNL had a better stone-free rate than ESWL at 3 months [relative risk (RR) 0.39, 95% confidence interval (CI) 0.27-0.56], whereas FURS appeared to have similar stone-free rates to ESWL (RR 0.91, 95% CI 0.64-1.30). They included five RCTs (n =338) however only three focused on lower pole stones. Of these three RCTs (160 participants), two compared ESWL against PCNL, one for stones up to 30 mm[13] and one for stones up to 20 mm.[26] The third compared ESWL with FURS for lower pole stones ≤10 mm.[27] The review concluded that the included trials were small and of low methodological quality. The authors had planned to undertake subgroup analyses by size and location of stone, but this was not done "because of insufficient data".

A systematic review performed by some of the PUrE investigators,[28] focusing solely on stones located in the lower pole of the kidney, and included trials comparing PCNL with FURS (a comparison not considered in the Cochrane review). Our review identified four additional relevant trials involving 408 participants [29-32] and we undertook subgroup analyses by stone size (<10mm and 10-20mm). Taking the seven trials involving participants with lower pole kidney stones as a whole, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality of evidence scores for the outcome of stone free rates indicated they were of 'moderate' quality. Our meta-analyses found PCNL and FURS produce significantly higher stone free rates than ESWL for lower pole stones ≤ 20 mm at 3 months. Combining two RCTs (n = 155), stone free rates for those participants with stones ≤20 mm were higher following PCNL than ESWL (RR 2.04; 95% CI 1.50-2.77; Figure 1). Combining five RCTs (n = 508) showed that FURS resulted in higher stone clearance rate compared to ESWL (RR 1.31; 95% CI 1.08 to 1.59; Figure 2). However, in a subgroup meta-analysis combining three studies (n = 300) for stones ≤10 mm the advantage of FURS over ESWL was less although still statistically significant (RR 1.11; 95%CI 1.03 to 1.19; Figure 2). One RCT (n = 93) which reported stone free rate categorised by stone size for PCNL versus ESWL found that the degree of superiority of PCNL was lower for stones sized ≤10 mm compared to those sized >10 mm to ≤20 mm (RR 1.56 95% CI 1.11 to 2.21; compared to RR 2.40 95% CI 1.67 to 3.44; Figure 2). Although stone free rates were higher when treated with PCNL compared to FURS there was considerable uncertainty around this estimate as the data come from only one small RCT (n = 28)[30]

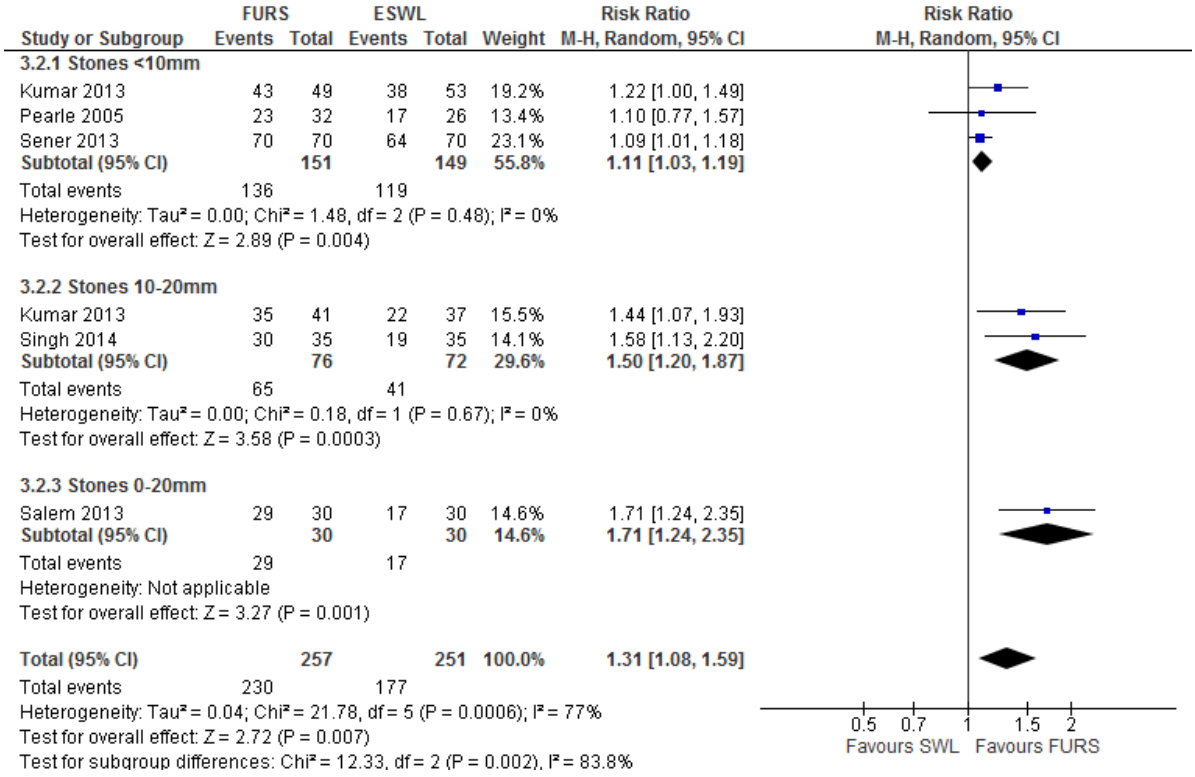
The included trials reported few data on patient outcomes (such as quality of life) or on resource use and none on cost effectiveness. Pearle[27] suggested that ESWL gave better quality of life, shorter convalescence (days to 100% recovered), and had fewer analgesic requirements than FURS (participants had lower pole stones ≤10 mm). Conversely, Singh[33] reported significantly higher participant satisfaction with FURS and comparable convalescence (time to return to routine activity) after having three or fewer ESWL sessions (participants had stones sizes of 10 – 20 mm). Convalescence was shorter after just a single ESWL session. There were conflicting data on patients' willingness to undergo the procedure again. In one trial the participants[27] favoured ESWL whereas in another[33] FURS was preferred. ESWL (one session) was associated with a shorter hospital stay than either PCNL[13] or FURS.[27] One trial also suggested shorter treatment duration for ESWL (one session) compared to FURS.[27]

Figure 1: Forest plot demonstrating meta-analysis of PCNL vs. ESWL for outcome of stone free rate at 3 months for lower pole stones ≤ 20mm.



Albala 2001[13] and Yuruk 2010[26] reported outcomes for <20mm LPS. Albala 2001[13] also reported outcomes for ≤10mm and 11-20mm LPS (see Table 1 in Donaldson 2015)[28]

Figure 2: Forest plot demonstrating meta-analysis of FURS vs. ESWL for stone free rate for lower pole stones at 3 months *[Singh 2014 = 1 month].



* Sener 2014[32] & Pearle 2005[27] included ≤10mm stones. Singh 2014[33] included 10-20mm stones. Kumar 2013[29] and Salem 2013[31] included ≤20mm LPS. Kumar 2013[29] reported results for 0-9.99mm and 10-20mm stones individually whilst Salem 2013[31] only reported results for ≤20mm stones. All studies reported SFR at 3m except Singh 2014[33] which reported SFR at 1m.

In summary, there is some evidence to inform estimates of the relative clinical effectiveness (based upon stone free rate) of ESWL, FURS and PCNL in the treatment of lower pole stones and to guide clinical practice. However there is sparse evidence, on the impact of these treatments upon patient reported health status and quality of life outcomes (such as severity and duration of pain after intervention), their care pathway (such as the need for additional treatments) and resource use. The PUrE trial aims to provide robust evidence on health status, quality of life, clinical outcomes and resource use to both the NHS and society to close this gap in evidence. This can directly inform choice and NHS provision of the three treatment options. The results will benefit patients, clinicians and the NHS as

it will inform guidance and decision making in regard to which of the competing interventions ESWL, FURS, or PCNL is the most suitable (clinically effective and cost effective) for the treatment of people with lower pole kidney stones of varying sizes.

2. TRIAL OBJECTIVES

The aim of the study is to determine which of FURS, PCNL and ESWL offer the best treatment outcomes in terms of clinical effectiveness and cost effectiveness for people with lower pole kidney stones seeking treatment within the UK NHS. An initial pilot phase will be built in to the trial to assess feasibility of recruitment and check appropriateness of eligibility criteria and outcome measures. The research question to be addressed is: In people requiring treatment for lower pole stones of the kidney does flexible ureterorenoscopy with laser lithotripsy result in better quality of life than standard treatment with ESWL or PCNL according to stone size, and is it cost-effective for the UK NHS?

The clinical effectiveness and cost-effectiveness of FURS as the first treatment option in comparison to ESWL for stones ≤ 10mm in maximum dimension or PCNL for stones >10mm and ≤25mm in maximum dimension will be determined with respect to:

i) patient reported health status measured as area under the curve of the EQ-5D-5L questionnaire completed at multiple time points up to 12 weeks post-intervention;
ii) incremental cost per quality adjusted life years (QALYs) at 12 months post-randomisation
iii) successful stone clearance at 12 weeks,
iv) further interventions required to treat stones within 12 months of randomisation and
v) treatment-related harms experienced up to 12 months after randomisation.

The null hypotheses being tested are:

1) The use of FURS to treat lower pole kidney stones ≤ 10mm will not be different to ESWL as assessed by the EQ-5D AUC up to 12 weeks post treatment.
2) The use of FURS to treat lower pole stones of the kidney >10mm and ≤ 25mm will not be different to PCNL as assessed by the EQ-5D AUC up to 12 weeks post treatment.

3. TRIAL DESIGN

Two separate pragmatic multicentre patient-randomised open label superiority RCTs with an initial internal pilot phase. A summary of the trial design is shown in Figure 3.

RCT 1: Flexible ureterorenoscopy with laser lithotripsy (FURS) versus extracorporeal shockwave lithotripsy (ESWL) recruiting patients with stones of maximum dimension ≤ 10 mm

RCT 2: Flexible ureterorenoscopy with laser lithotripsy (FURS) versus percutaneous nephrolithotomy (PCNL) recruiting patients with stones of maximum dimension > 10 mm and ≤ 25 mm

3.1 Interventions to be evaluated

Experimental

- Flexible ureterorenoscopy with laser lithotripsy (FURS)

Standard

- Extracorporeal shockwave lithotripsy (ESWL)
- Percutaneous nephrolithotomy (PCNL)

All three interventions are currently in general use by Urology departments throughout the UK NHS. This trial aims to test the interventions in a standard NHS setting in order for the results to be generalisable to current routine care in the UK. In line with this aim, all procedures will be delivered in NHS facilities and supervised by NHS staff trained and competent in the procedures. All participants will be under the care of a named consultant urologist who, as in standard NHS practice, will be responsible for planning and carrying out the allocated procedure and arranging follow up. The surgical interventions, FURS and PCNL, will be carried out by a trained urologist, or by a trainee urologist under the supervision of a senior urologist. They will be supported by the standard team of ward and theatre staff and radiographers. In some centres a specialist uro-radiologist will also assist with the procedures, particularly with access to the stone. The ESWL intervention can be delivered using any device approved for this purpose including both fixed site and mobile lithotriptors. Delivery of the treatment will be according to local practice by staff trained in the procedure; typically radiographer and nurse, and supervised by a urologist. The techniques and equipment used for FURS, PCNL and ESWL continue to evolve and hence will differ in detail between different surgeons and departments. The trial protocol will not mandate the use of any specific detailed technical method for each intervention under study but as part of trial initiation of each site the standard procedure including equipment used for FURS, PCNL and ESWL for that site will be recorded on a trial proforma and updated with changes as necessary. It is anticipated that at 8 to 12 weeks post-intervention participants will receive imaging to assess stone clearance in accordance with usual standard of care.

For flexible ureterorenoscopy (FURS), a thin (3mm diameter) flexible endoscope (ureteroscope) is passed into the kidney via the natural urinary passages (urethra, bladder and ureter) and is used to directly see the stone. A laser fibre (typically 200 or 273 µm holmium laser fibre) is then passed through the working channel of the ureteroscope and laser energy used to fragment the stone within the kidney. Larger fragments can be retrieved with a wire basket device passed through the working channel whilst smaller fragments (<2 mm) maybe left to pass spontaneously. Generally the patient will pass remaining fragments in the urine during the week following the procedure. The procedure is performed as a day-case or with an overnight stay (2014 NHS average = 1.7 days) and usually requires general anaesthesia. A single dose of antibiotic to prevent infection is often given at the start of the procedure. The duration of the operation depends on size of stone but is typically 1.0 – 1.5 hours. A temporary ureteral stent may be placed at the end of the procedure to protect against blockage of the ureter caused by swelling of its lining cells. The operating surgeon will monitor progress and degree of stone clearance during the procedure and this may be checked with a plain kidney X-ray afterwards. Possible harms of the procedure are urinary tract infection, bleeding and damage to the urinary system which may require a more prolonged period of stenting. The stent itself can cause pain and urinary symptoms such as increased urinary frequency and haematuria. For the purposes of the PUrE trial FURS treatment is expected to be a single procedure in the great majority of cases. However an additional procedure will be considered as part of the FURS treatment strategy in cases of technical complexity or larger stones as long as it takes place with six weeks of the initial FURS procedure. Any additional procedures will be recorded separately for trial purposes. Once stone clearance has been confirmed the ureteric stent will be removed as an out-patient procedure with local anaesthetic. Placement and removal of the stent will be considered part of the FURS treatment strategy in the PUrE trial.

Extracorporeal shockwave lithotripsy (ESWL) involves the generation of an external acoustic (sound) pulse, called a shock-wave, outside the body which is then focused onto the kidney stone through the patients flank skin, causing it to fragment. Stone fragments pass down the urinary tract spontaneously which may take a few weeks. It is routinely performed in an outpatient setting with analgesia, with or without sedation as required. A single dose of antibiotic may be given at the start of the procedure if there is thought to be

a higher than normal risk of getting an infection afterwards. Each session lasts 1.0 – 1.5 hours and stone fragmentation is monitored during the procedure and then by a plain X-Ray (or other imaging as standard) taken at a follow up appointment at approximately three weeks. For the PUrE trial two separate ESWL treatments will be considered as part of the initial ESWL intervention strategy. These should take place within an eight week period and each episode will be recorded separately for trial purposes. The treating urologist may however decide that further ESWL is not appropriate if stone fragmentation is insufficient following the first or second session. The first session of ESWL will be taken as the initial treatment point for the purposes of timing of outcome assessments. Possible harms of ESWL include urinary tract infection, visible bleeding in the urine and blockage of the ureter by the stone fragments. There is also a small risk of bruising surrounding the kidney.

Percutaneous nephrolithotomy (PCNL) is a surgical procedure to remove stones from the kidney by a direct approach. A small (10mm) incision is made on the skin overlying the kidney, through which a needle is passed into the urine collecting tube system of the kidney. This can be guided either by simultaneous ultrasound imaging of the kidney or by preliminary telescopic placement of a tube through the urethra, bladder and ureter. Contrast fluid can then be injected into the collecting system to guide the needle passage through the skin and into the kidney. Placement of the needle is planned using the available imaging (typically a CTKUB) in order to give the best access to successfully remove the stone. For a stone in the lower pole of the kidney this is usually into the lowermost part of the collecting system. Once the needle is satisfactorily placed, a flexible guide wire is then passed into the collecting system of the kidney and used to guide stretching (dilatation) of the needle track to make it wide enough for a hollow rigid access sheath to be passed creating a 10 mm wide channel between the skin and the urine collecting system of the kidney. A rigid metal telescope (nephroscope) can then be inserted down this channel into the kidney's collecting system in order to see the stone and either retrieve it whole using graspers or to fragment the stone using a variety of energy delivery devices; most commonly an ultrasonic probe or pneumatic device. After the operation the kidney is drained for a period by a tube placed either through the access channel or as a stent down the ureter into the bladder. In addition a urinary catheter may be inserted to drain the bladder for a short period after the procedure. The operation is performed under general anaesthesia with a typical duration of 1-3 hours depending on complexity, and patients usually stay in hospital for a few days (2014 NHS average stay= 4.6 days). Antibiotic treatment is frequently given at the start of the procedure and may be continued for a few days after if there is active infection. The drainage tubes are usually removed after 24 - 48 hours without need for further anaesthesia. Stone clearance is monitored during the procedure and if necessary by a plain X-ray (or other imaging) before discharge from hospital. Possible harms include urinary infection, bleeding (which may be severe), and inadvertent puncture of other organs. For the PUrE trial a single PCNL treatment is expected to be required to completely remove stones up to 25 mm.

Apart from randomised allocation of the initial intervention and participant completion of questionnaires the PUrE trial does not seek to change or impose any specific protocol regarding the clinical management of participants recruited at each trial site. The trial will however record relevant aspects of the participant care during their involvement in the trial up to 12 months after randomisation and obtain patient-reported outcome measures. In particular trial participants undergoing any of the stone treatments under test may require further interventions either to correct harms arising from the initial intervention or because of inadequate stone clearance by the initial intervention. The circumstances, nature and outcome of these additional procedures will be recorded and patient reported outcome measures obtained where possible before and after each additional intervention to assess effect on health status

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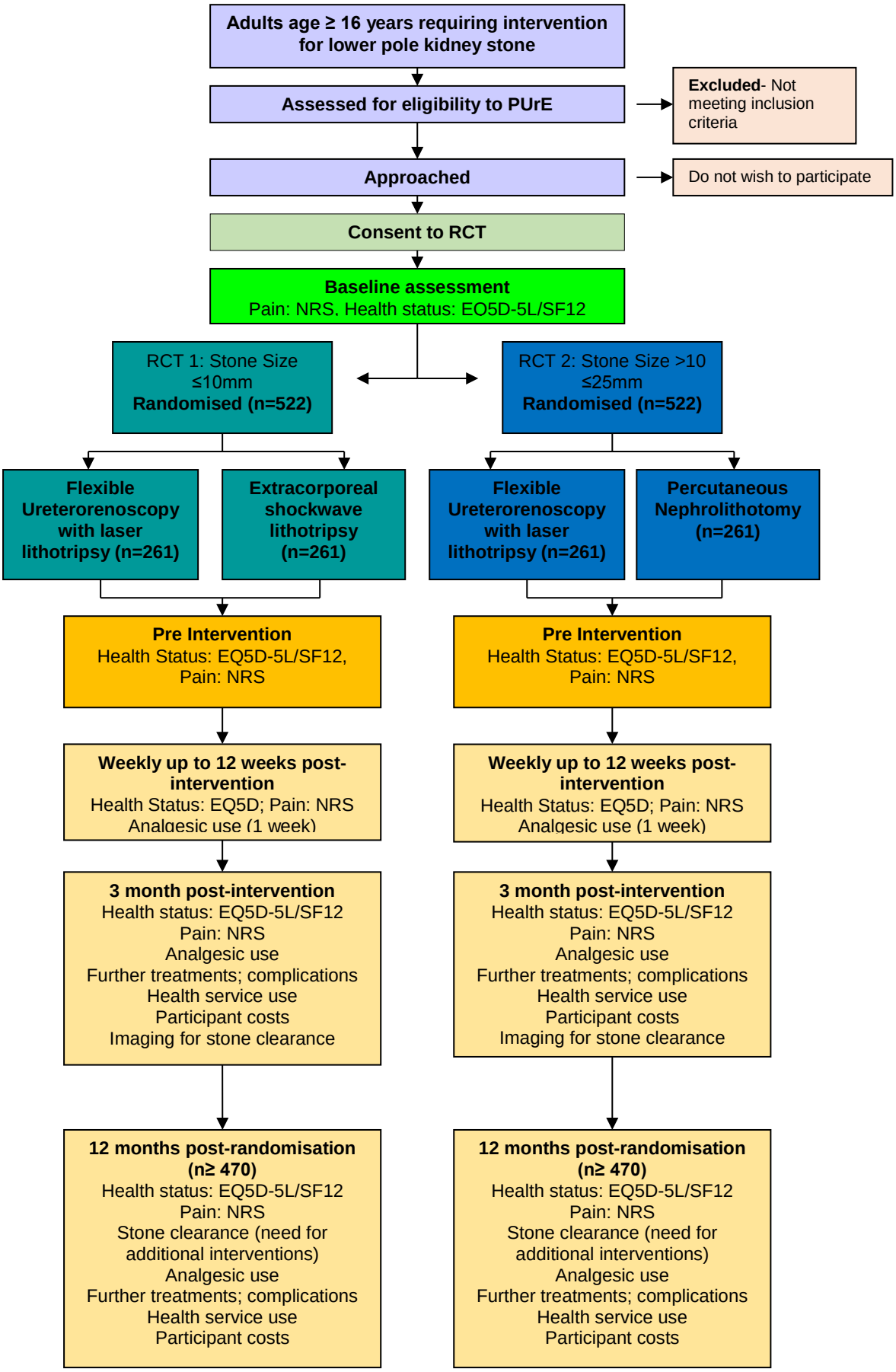
Figure 3: The clinical and cost effectiveness of interventions for stones in the lower pole of the kidney: The PUrE RCT



3.2 Trial population

Adults (≥ 16 years old), presenting to NHS urology departments with a stone ≤25 mm in the lower pole of the kidney confirmed by non-contrast computed tomography scan of the kidneys, ureters and bladder (CTKUB). Patient and clinician must agree that active intervention is appropriate to remove the lower pole stone, and patients must be able to undergo either treatment for the specific stone size, and be capable of giving informed consent which includes adherence with the requirement of the trial. Patients with multiple stones will be eligible provided all stones in the lower pole measure ≤25 mm in maximum dimension and, if there are stones, of any size, elsewhere in the urinary system, that the lower pole stone is the priority for treatment.

3.2.1 Selection of participants

Clinicians will assess patients presenting with lower pole kidney stone. This will be aided by patient and clinician trial publicity material. A screening log documenting brief details of potentially eligible patients but without personal identifiers will be kept at each site to provide a summary of reasons for non-inclusion in the study to inform the CONSORT diagram and assess generalisability of trial findings.

3.2.2 Planned inclusion and exclusion criteria

Inclusion criteria:

- Adults ≥16 years of age
- Lower pole stone ≤25 mm in maximum dimension with decision to treat that stone
- Presence of stone previously confirmed by CTKUB
- Able and willing to undergo either treatment for specified stone size
- Capacity to give informed consent to participate in trial which includes adherence to trial requirements

Exclusion criteria:

- Pregnancy
- Patients with co-existing stone that takes precedence in deciding treatment modality (such as obstructing ureteric stone or large upper pole stone)
- Patients with health or other factors that are absolute contraindications to an intervention that they may be allocated
- Patients unable to understand or complete trial documentation

3.3 Recruitment and Trial Procedures

3.3.1 Identifying participants

Patients with lower pole stones eligible for PUrE may be referred electively to urology departments having had a stone identified opportunistically by abdominal imaging or during investigation of urinary tract symptoms. Alternatively they may present as an emergency with loin pain or infection. We will therefore inform clinical teams at each trial site of the target population backed up by trial publicity and trial summaries. At an appropriate point during their initial assessment patients will be informed about the trial and given a trial patient information leaflet (PIL) with the contact details of the local research team. Patients will be given adequate time to consider participating in the study. They will have the

opportunity to take study information away with them if desired in which case the local research team will contact the patient after at least 24 hours to determine their interest. If the patient is interested the research team will confirm eligibility and discuss the individual's possible participation with the clinical team. If both patient and clinical team agree regarding participation, arrangements will be made for consent to study, randomisation and clinical discussion and timing of allocated treatment. Wherever possible these processes will be arranged to take place together during one visit. Patients who decline, those who are ineligible or those for whom one of the possible allocated treatments is unsuitable will be recorded without identifiers on a screening log.

3.3.2 Informed consent

The PIL explains that the trial is investigating the effectiveness of active interventions for stones in the lower pole of the kidney. Patients will be informed that depending on stone size the trial will investigate whether the use of FURS will be superior to ESWL (stones ≤ 10 mm) and whether use of FURS will be superior to PNL (stones >10 mm ≤ 25 mm). Signed informed consent forms will be obtained from the participants in all centres. Participants who cannot give informed consent (e.g. due to incapacity) will be not be eligible for participation. The participant's permission will be sought to inform their general practitioner that they are taking part in this trial. We will also take optional consent for agreement to be approached for further studies on kidney stones, and for long-term follow up through their local and central NHS clinical records after their active trial participation has finished.

3.3.3 Randomisation and allocation

Eligible and consenting participants, who have previously had a CTKUB to confirm the presence and size of stone will be randomised dependent upon the stone size using the telephone Interactive Voice Response (IVR) randomisation application or via the web based application - both hosted by the fully registered UK Clinical Research Collaboration (UKCRC), Clinical Trials Unit (CTU) at the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU) in Aberdeen. Randomisation will be stratified by centre within each RCT. Participants with a stone ≤10 mm will be entered into RCT 1 and randomised to either FURS or ESWL. Participants with a stone >10 mm and ≤25 mm will be entered into RCT 2 and randomised to either FURS or PCNL. Participants will then follow the standard care pathway for the allocated treatment. All the treatments allocated by randomisation in the study are used in routine clinical practice and in this pragmatic trial patients are expected to be treated using normal local clinical pathways and guidelines. The only trial-specific interventions apart from randomised treatment allocation will be participant completion of outcome questionnaires.

3.3.4 Follow-up procedures

Eligible patients who have given signed informed consent to participate in the study will be asked to complete the EQ-5D-5L, SF-12, pain score (NRS) and use of analgesics at baseline prior to randomisation. A baseline clinical CRF will also be completed which will include stone size measured as maximum dimension on a CTKUB. They will then be randomised to either one of the interventions dependent upon the size of the lower pole stone and placed upon the appropriate waiting list. Waiting time duration for the trial interventions will be recorded and monitored. Participants will be asked to complete the pain score (numeric rating scale: NRS), EQ-5D, and use of analgesic questions at a number of fixed and variable time points during their trial participation. Fixed points will be baseline, just prior to initial intervention, weekly up to12 weeks after initial intervention (FURS, PCNL and first ESWL session) and at 12 months post-randomisation. Variable points after 12

weeks will be just prior and one week after any additional intervention (including planned additional sessions of ESWL and removal of stent) and during any other hospital admissions related to treatment of their lower pole kidney stone (such as admissions for pain control or infection). At 12 weeks post initial intervention, and at 12 months post-randomisation, participants will be asked to complete questions relating to their primary and secondary care use and their associated travel. At 12 months post-randomisation participants will be asked to additionally complete the SF-12. Participants will also be given the opportunity to complete an EQ-5D at their discretion throughout the duration of the trial.

Reminders may be used. For the earlier timepoints this may be a text message or e-mail on the day that the questionnaire is due. For the later timepoints (e.g. 12 weeks and 12 months) this reminder will be sent approximately two weeks and four weeks after the questionnaire is due.

We will offer and use all methods of delivery and collection of questionnaires and reminders including use of research teams for time points associated with hospitalisation, postal mail, e-mail, web-based and SMS text, taking into account each participant's stated preferred means of receiving and completing the measures. Participants will be sent a voucher (of modest value) as a token of appreciation for completion and return of the questionnaires.

Case report forms collecting information on care process and outcome will be completed by site research teams at baseline, following each initial and subsequent additional intervention (including planned additional ESWL sessions and stent removal), at 12 weeks post-intervention, after any additional stone-related treatments (e.g. admissions due to pain or infection) and 12 months post-randomisation. These will be entered at site onto the web-based trial management platform.

To measure the secondary clinical outcome of stone clearance participants will have kidney imaging at between 8 and 12 weeks according to clinical need and participant convenience. We will state preference for imaging by CTKUB during site initiation but renal ultrasound and plain X-Ray will be acceptable according to patient preference, safety and local practice. We will ask local site clinical teams (radiologist/urologist) to state whether there is complete clearance of the target stone from the urinary tract defined as no further action or observation required for that stone; acceptable clearance where observation is required but no intervention planned; and unacceptable clearance where further intervention will be required. The maximum dimension of the largest fragment in millimeters will also be recorded at baseline.

3.3.5 Withdrawal procedures

Participants are free to withdraw consent to participate at any time. Outcome data derived from medical records will be collected for those that withdraw unless the participant specifically withdraws their consent for this. All data collected up to the point of withdrawal will be retained and used in the analysis. Failure to undergo allocated treatment either because of participant preference or change of circumstance will not result in withdrawal and the participant will continue to participate in trial procedures unless consent to the trial is withdrawn.

3.3.6 Subsequent arrangements

Informing key people

Following formal trial entry the Study Office will inform the participant's general practitioner of their involvement in the trial if the participant consents to this. This will be by letter and information about PUrE and the Study Office contact details will be enclosed. GPs are

asked to contact the Study Office if the participant moves, becomes too ill to continue or dies, or any other notifiable event or possible serious adverse event occurs. Alternatively, staff at the Study Office may contact the GP for study-related follow up.

4. SAFETY

The PUrE trial involves procedures for treating lower pole stones which are all well established in current NHS clinical practice. Adverse effects may occur during or after any type of surgery. We will monitor serious adverse events and the local PI or their delegate at the site will categorise these as expected or unexpected. Only serious unexpected adverse events related to the trial interventions or death of a participant will be notified to the Sponsor and Ethics Committee.

4.1 Definitions

4.1.1 Adverse events

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant, not necessarily having a causal relationship.

Adverse events are not:

- continuous and persistent disease or symptom, present before the trial, which fails to progress;
- signs or symptoms of the disease being studied (in this case renal stones); or
- Treatment failure.

A **serious adverse event** (SAE), is any AE that;

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect,
- is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs or SAEs as appropriate.

4.1.2 Expected adverse events:

In this study the following events are potentially expected for each intervention:

FURS
Common (greater than 1 in 10)
Mild burning pain passing urine
Visible bleeding on passing urine
If a ureteric stent is placed it may cause pain and having to pass urine frequently

Occasional (between 1 in 10 and 1 in 50)
Kidney pain
Urinary tract infection needing antibiotic treatment

Rare (less than 1 in 50)
Damage to the ureter
Leakage of urine into the body
Scarring or stricture of the ureter

ESWL
Common (greater than 1 in 10)
Visible blood in urine
Pain in the kidney
Urinary tract infection
Bruising of the skin.

Occasional (between 1 in 10 and 1 in 50)
Stone fragments stuck in the tube (ureter) between the kidney and the bladder.

Rare (less than 1 in 50)
Kidney bruising
Damage to the pancreas or lungs by the shockwaves requiring further treatment

PCNL
Common (greater than 1 in 10)
Visible blood in the urine
Fever (high body temperature)
If a ureteric stent is placed it may cause pain and having to pass urine more frequently

Occasional (between 1 in 10 and 1 in 50)
Urinary tract infection

Rare (less than 1 in 50)
Severe kidney bleeding requiring transfusion or emergency treatment
Damage to adjacent organs such as lung, bowel, spleen, or liver
Damage to kidney or infection needing further treatment
Leakage of urine into the body
Leakage of irrigating fluids into the body

4.2 Procedures for detecting, recording, evaluating & reporting AEs, SAEs

4.2.1 Detecting AEs and SAEs

Hospital visits (planned or unplanned) associated with further interventions or complications of treatment (e.g. expected AEs listed in section 4.1.2) due to the lower pole stone will be recorded as an outcome measure, but will not be reported as serious adverse events. Other SAEs related to the intervention will not be reported an SAE, but will be recorded in the case report forms (CRFs). Planned primary care or hospital visits for conditions other than those associated with the lower pole stone will not be collected or reported.

All deaths for any cause (related or otherwise) will be recorded on the serious adverse event form.

4.2.2 Recording AEs and SAEs

Depending on severity, when an AE/SAE occurs, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes and diagnostic reports)

related to the event. The Investigator (or delegate) should then record all relevant information in the CRF and on the SAE form when appropriate.

Information to be collected includes type of event, onset date, PI assessment and outcome of event.

4.2.3 Evaluating AEs and SAEs

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 4.1.1.

Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- **Related**: resulted from administration of any of the research procedures
- **Unrelated**: where an event is not considered to any of the research procedures.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Within PUrE, 'related' is defined as an event that occurs as a result of a procedure required by the protocol, whether or not it is either a) the specific intervention allocated at randomisation or b) it is administered as an additional intervention as part of normal care.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 4.1.2).

4.2.4 Reporting AEs and SAEs

Reporting responsibilities of the CI

When an SAE form is uploaded onto the trial website, the Trial Manager will be automatically notified. If, in the opinion of the local PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the sponsor within 24 hours of receiving the signed SAE notification. The sponsor will provide an assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity will be resolved by further discussion between these parties.

The CI or delegate will report any related and unexpected SAEs to the REC within 15 days of the CI becoming aware of it. All related SAEs will be summarised and reported to the Ethics Committee, the Funder and the Trial Steering Committee in their regular progress reports.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

4.2.5 Regulatory reporting requirements

The Chief Investigator is responsible for submitting annual reports to the REC on the anniversary of the approval.

All adverse events will be assessed in respect of seriousness, relationship to trial intervention, whether expected or unexpected, and therefore, whether constituting a Serious Adverse Event (SAE) by the local PI, CI or their deputies.

5. OUTCOME MEASURES

5.1 Primary outcome measure

Patient reported Health status (EQ-5D-5L) area under the curve (AUC) to 12 weeks post-intervention, based upon EQ-5D completion at fixed time points; at baseline (recruitment), just prior to initial intervention (FURS, PCNL or first session of ESWL), weekly up to 12 weeks after initial intervention, and at variable time points; just prior to any additional intervention (including planned additional ESWL sessions and removal of stent) and once during hospitalisation for adverse events related to treatment (e.g. pain and infection).

Economic Incremental cost per quality adjusted life year (QALYS) gained at 12 months post-randomisation based on the estimated NHS costs and participant responses to the EQ-5D (including additional time point at 12 months).

5.2 Secondary outcome measures

Patient-reported Severity of pain as measured by the Numeric Rating scale (NRS; completed with EQ-5D-5L), Generic health profile as measured by the SF-12 (completed at baseline and 12 months), use of analgesia (completed with NRS and EQ-5D).

Clinical Stone clearance measured at between 8 and 12 weeks post initial intervention using renal imaging (CTKUB preferred but plain X-Ray and ultrasound acceptable). Measured by local trial staff and categorized as complete, acceptable, or unacceptable. Also maximum dimension of the largest fragment of the treated stone in mm. Need for additional treatment (carried out or planned) at 12 weeks post-initial treatment and 12 months post-randomisation. Complications during initial intervention. Intervention-related complications at 12 weeks (categorised by Clavien-Dindo classification) post treatment and up to 12 months post-randomisation. All measured by site staff and entered on CRF.

Economic NHS primary and secondary care resources used and their costs. Patient costs (out of pocket), time off work up to 12 months post-randomisation. Data gathered from completion of CRFs by site staff and participant questionnaire at 12 weeks post initial treatment and 12 months post-randomisation.

6. DATA COLLECTION AND PROCESSING

6.1 Measuring outcomes

Outcome data will be collected throughout the trial for each participant from consent until 12 months following randomisation. See Table 1 for schedule of events.

6.2 Schedule of data collection

Table 1: Source and timing of measures

		Timing					
			Intervention (PCNL or first session ESWL/FURS)				
				Weeks post intervention		Additional intervention (pre and post if >12 weeks) or treatment-related hospitalisation	Post-randomisation 12 months
Outcome measure	**Source**	Baseline*	Pre	1 to 11	12		
Health status EQ-5D-5L	PQ	✓	✓	✓	✓	✓	✓
Pain	PQ	✓	✓	✓	✓	✓	✓
Health profile SF12	PQ	✓	✓		✓		✓
Use of analgesics	PQ	✓	✓	✓	✓	✓	✓
Stone clearance (imaging)	CRF				✓**		✓
Additional interventions received	CRF&PQ				✓	✓	✓
Complications	CRF&PQ				✓	✓	✓
NHS primary and secondary healthcare use	CRF, PQ		✓		✓	✓	✓
Participant costs	PQ		✓		✓		✓

CRF = case report form, PQ = participant completed questionnaire
*Baseline is after informed consent has been given but prior to randomisation
** stone imaging performed at 8-12 weeks post treatment.

6.3 Data processing

Data collected locally will be input at sites by the local research team. Staff in the Trial Office will work closely with the local research teams to ensure data are as complete and accurate as possible. Participant questionnaires will be sent from and returned to the Trial Office in Aberdeen with the exception of the one and two-week questionnaires which may be distributed by the local research teams. Extensive range and consistency checks will further enhance the quality of the data.

7. SAMPLE SIZE, PROPOSED RECRUITMENT RATE AND MILESTONES

7.1 Sample size

The primary outcome is the AUC measured from multiple completion of the EQ-5D by each participant up to 3 months post initial intervention (FURS, PCNL or first session of ESWL). In order to detect a 0.3 SD difference, with 90% power, and alpha set at 5%, 235 participants per group (470 total) are required. Such a difference in generic health status is considered clinically relevant and in terms of treatment effect size, in the small to medium range as observed in other clinical studies. To allow for the anticipated approximately 10%

of participants for whom outcome data is completely missing, and therefore the AUC cannot be calculated, it is proposed to randomise 522 participants in both RCT 1 and 2 giving a total trial population of 1044 participants.

7.2 Recruitment rates

We plan to recruit the trial population from approximately 50 NHS centres across the UK each recruiting an average of one participant per month to either RCT 1 or RCT2. Our plan is to achieve the target of 1044 participants (522 to each RCT) over a 34 month recruitment window. The projected participant recruitment and centre start up schedule is given in Appendix 1.

7.2 Milestones

The project timetable and milestones can be found in Appendix 1.

7.3 Feasibility phase

We will use the early part of the trial as an internal pilot phase to assess the credibility of our recruitment assumptions, to test the appropriateness of trial information and to ensure efficient running of trial processes and outcome data collection. We will assess feasibility once we have at least 9 calendar months of recruitment to RCT1 and RCT2; which allowing for a 6 month start up, should be reached by calendar month 15. By this time we would expect to have recruited from about half of the anticipated 50 recruitment sites (at a staggered rate of 3 per month) and accumulated around 110 randomised participants to the 2 trials combined. This will allow us to assess the recruitment status both as a whole and for each RCT along the following lines:

1. We are recruiting to within 75% of our target within our “steady state” recruiting sites, in which case we conclude that there is sufficient reassurance to continue unchanged to the main study;
2. We are recruiting to between 50% and 75% of target rate, in which case we will report to the monitoring committees and funder that the RCT(s) are feasible with appropriate modifications such as opening more sites, modifying any barriers to recruitment, or allowing for more recruitment time at a site by setting up sites more quickly and/or adding some extra months to lengthen the recruitment at the best recruiting sites;
3. We are recruiting to less than 50% of the anticipated rate and we would enter discussions with the funder to determine whether the RCTs are feasible. This may require extra research work to determine whether barriers to recruitment are surmountable by modifications to trial design and recruitment process.

8. STATISTICAL ANALYSIS

The primary outcome, health status AUC, will be generated for each participant using the trapezoidal rule. Data for participants who have missed a scheduled time point will be estimated using a multiple imputation approach to make use of partial outcome data. Sensitivity analyses will be conducted to assess the robustness of the treatment effect estimate to these approaches. The primary outcome measure will be analysed using linear regression with adjustment for design variables. Secondary outcomes will be analysed using generalised linear models with adjustment for design and baseline variables as appropriate. Subgroup analyses will explore the possible modification of treatment effect by important factors; [centre, participant body mass index, stone size (maximum dimension and volume), stone density on CTKUB (Hounsfield units), stone mineral composition, skin to stone distance). We will also explore within each allocated group whether technical

factors modify the treatment effect [access sheath versus no access sheath and digital versus non digital instrument (FURS); fixed site versus mobile device (ESWL); calibre of access track (PCNL)]. This will be done by including treatment-by-factor interactions in the model and they will be classified as exploratory analyses. All analyses will initially be performed on an intention-to-treat basis, although we will consider additional analysis groups such as per-protocol if indicated. The main statistical analyses will be based on all participants as randomised, irrespective of subsequent compliance with the treatment allocation. All treatment effects sizes will be summarised by estimates and 95% confidence intervals from the appropriate models. From the feasibility phase we will report estimates of recruitment rates and potential participant availability, together with appropriate confidence intervals. There are no planned interim outcome analyses; all analyses will occur following completion of trial follow-up. Interim analyses will be performed if requested by the Data Monitoring Committee (DMC).

All analyses will follow a carefully documented Statistical Analysis Plan. RCT 1 and RCT 2 will be analysed entirely separately. The Trial Steering Committee and the Independent DMC will be asked to review and comment on the statistical analysis plan prior to analysis. We propose that progress and monitoring of the two RCTs will be undertaken within the same DMC and TSC. The team propose that each study will be analysed once completed. The DMC and TSC will meet before recruitment begins to agree its terms of reference and other procedures.

9. ECONOMIC EVALUATION

An economic evaluation to assess the relative efficiency of trial care pathways will be an integral part of the study. A within trial analysis[34, 35] as well as a simple Markov Model[36, 37] to extrapolate the analysis beyond the RCT follow up period will be considered. The perspective of the analysis will be that of the NHS and personal social services.[38] The analysis will rely on participant responses to the EQ-5D to estimate quality adjusted life years (QALYs) at 12 months. Resource use and costs will be estimated for each participant. The evaluation will consider the costs of the care pathways that patients receive. This will include costs of the interventions, ESWL, FURS, and PCNL and the cost of simultaneous and consequent use of primary and secondary NHS services (including additional interventions received) by participants. Personal costs such as purchase of medications, particularly analgesics, will be estimated. As the clinical condition commonly affects people of working age time off work will be also retrieved to estimate indirect costs (e.g. human capital approach). The incorporation of indirect costs into the economic evaluation is debatable; however, the collection of these data will open the possibility to include these costs into the analysis or report them separately following reporting practice at the time of analysis.

9.1 Collection of data

Participant level resource use data will be captured for the initial intervention and any subsequent admissions/treatments required through to 12 months post-randomisation using case report forms (CRF). Patient primary care services resource use as well as medications will be collected using a patient questionnaire delivered at 12 weeks post-intervention and at 12 months post-randomisation. Special attention will be taken on questionnaire question wording in order to minimise recall time overlapping (and hence avoid double counting). In addition, the patient questionnaires will collect data on time off work. Each resource use event will be valued using appropriate unit prices obtained from national sources, including NHS reference costs,[39] and the Unit cost of health and social care.[40] British National Formulary[41] will be used to obtain unit costs to value medications,

and published wage categories to value time off work. Total NHS costs will be summed for each patient to 12 months post-randomisation.

9.2 Participant costs

Participant costs will comprise self-purchased healthcare (e.g. prescription and over the counter medication). Information will be collected using the 12 week post-intervention and 12 month post-randomisation questionnaires. Participants will be asked for information on travel costs incurred by visits to GP, hospital doctor or other health care provider.

9.3 NHS health service resource use

Use of secondary care services following the treatment period will be collected using participant questionnaires (PQ) and CRF. Information on outpatient visits (PQ at 12 weeks post-intervention and 12 months post-randomisation), readmissions and additional interventions relating to the use and consequences of the interventions being compared will be recorded (CRF). 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 post-intervention and 12 months post-randomisation.

9.4 Cost effectiveness

Cost effectiveness will be measured in terms of costs of the treatment care pathways and quality adjusted life years (QALYs) at 12 months post-randomisation for the within trial analysis. Mean NHS costs, patient costs and QALYs will be compared between randomised groups at 12 months. Incremental costs and QALYs will be estimated for FURs versus ESWL (participants with stones ≤10 mm) and for FURs versus PCNL (participants with stones >10 mm and ≤ 25mm stones) using linear regression with adjustment for design variables and baseline values as appropriate. Final decision on what regression model to use is data dependent. However, as the RCT is planned to involve 50 recruitment sites from the UK the use of multilevel regression models will be considered.[42] Uncertainty surrounding joint estimates of incremental cost and effects will be characterised and presented graphically using cost-effectiveness acceptability curves.[43, 44] Guidelines for economic evaluation advocate for a long enough time horizon to consider all cost and consequences relevant for the analysis.[38] In order to assess longer term cost-effectiveness, a simple Markov model will be developed using available data on recurrence rates and extrapolation of costs and effects out to five years post-randomisation.

10. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

10.1 Trial office in Aberdeen

The trial office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the local recruitment sites. The Trial Manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of trial activities. The Data Co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal).

The PUrE trial office team will aim to meet formally at least monthly during the course of the trial to ensure smooth running and trouble-shooting.

10.2 Local organisation in sites

Lead Urologist (Local Principal Investigator)
Each collaborating centre will identify a Lead Urologist who will be the point of contact for that centre. The responsibilities of this person will be to:

- establish the study locally (for example, by getting agreement from clinical colleagues; facilitate local regulatory approvals; identify clinical research team support; and inform all relevant local staff about the study (e.g. other consultant urologists, junior medical staff, secretaries, ward staff)
- take responsibility for clinical aspects of the study locally (e.g. if any particular concerns are raised)
- identify and/or support colleagues to identify potential participants
- notify the Study Office of any unexpected clinical events which might be related to study participation
- provide support, training and supervision for the local Research Team
- Represent the centre at the collaborators' meetings.

Local Team
Each collaborating centre will identify a member of the local Research Team to be responsible for day to day recruitment and follow up of participants to the study. The responsibilities of this person will be to:

- keep regular contact with the local Lead Urologist, with notification of any problem or unexpected development
- maintain regular contact with the PUrE Study Office
- keep local staff informed of progress in the study
- identify any eligible patients at clinics or on the ward while they are in hospital; explain the study and the potential for participation in PUrE if they are eligible
- obtain patient's written consent
- keep a log of whether patients are recruited or not (with reasons for non-participation)
- collect baseline data describing the participant, log this information in the web-based PUrE database and send paper copies to the Study Office along with a copy of the signed consent forms
- use this information to randomise the participant
- file the hospital copy of the consent form in the hospital notes along with information about PUrE.
- ensure randomisation, treatment and post-treatment data are collected and recorded in the web-based PUrE database, and send paper copies (as requested) to the Study Office
- file relevant study documentation (e.g. consent forms) in the participant's medical records
- organise alternative recruiters in case of holiday or absence
- represent the centre at the collaborators' meetings.
- maintain a study site file in line with local and national standard operating procedures

10.3 Project Management Group (PMG)

The trial is supervised by its Project management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. The PMG will meet in person or by teleconference every six months on average. The research team has the expertise to cover the clinical and surgical aspects of the research.

10.4 Trial Steering Committee (TSC)

The trial is overseen by a Trial Steering Committee (TSC). The membership of this Committee is comprised of three independent members along with the Chief Investigator (Prof. Samuel McClinton) or a nominated delegate. The trial sponsor(s) other PUrE grant-holders and key members of the central office (e.g. the trial manager) can participate in TSC meetings but are not members. The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate. Details of the membership of the TSC can be found at the start of this protocol. CHaRT has adopted the TSC Charter adapted from the DAMOCLES Charter for DMCs and suggests to the independent TSC members that they adopt the Terms of Reference contained within. The TSC will meet approximately yearly.

10.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be convened. The DMC will be made up of three 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.

11. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

11.1 Research Governance

The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. This will ensure compliance with Research Governance, and provide centralised trial administration, database support and economic and statistical analyses. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.
The CI will ensure, through the PUrE TSC that adequate systems are in place for monitoring the quality of the trial including compliance with appropriate governance and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial.

11.2 Data protection

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 1998 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The senior IT manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Participants will be allocated an individual specific trial number and their details will be anonymised on the secure database. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses. 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.

11.3 Sponsorship

The University of Aberdeen and NHS Grampian are the co-sponsors for the trial.

12. ETHICS AND REGULATORY APPROVALS

The North of Scotland Research Ethics Committee has reviewed this trial. The trial will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. Annual progress reports and a final report at the conclusion of the trial will be submitted to the North of Scotland REC within the timelines defined in the regulations.

13. QUALITY ASSURANCE

The trial will be monitored to ensure that the trial is being conducted according to the protocol, adhering to the requirements of Research Governance, and the appropriate regulations. 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.

13.1 Risk assessment

An independent risk assessment has been carried out by the sponsor. The trial will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations.

14. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the Health Technology Assessment programme of the National Institute for Health research (NIHR HTA).
The necessary trial insurance is provided by the University of Aberdeen.

15. END OF TRIAL

The end of participation in the trial for each participant is defined as the final data capture to answer the research question; the 12 month post-randomisation questionnaire and case report form. The end of the trial is defined as the end of funding.

The end of trial will be reported to the Research Ethics Committee (REC) within 90 days, or 15 days if the trial is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the trial will be provided to the REC within one year of the end of the trial. An end of trial report is also required by the NIHR HTA at the end of funding.

16. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data will be entered into the database by the local investigator and members of the local research team working in each 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 teams to ensure that data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

The co-sponsors are responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least 10 years following close of trial.

17. SATELLITE STUDIES

It is recognised, that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advanced with the Project Management Group. REC approval will be sought for any new proposal, if appropriate.

18. AUTHORSHIP PUBLICATION

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 or scientific journal. If all grant-holders and researcher staff fulfil authorship rules, group authorship may be appropriate for some publications under the collective title of 'the PUrE 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 may be attributed to the named individual(s) and the PUrE Trial Group.

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

We intend to maintain interest in the trial by publication of PUrE 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 PUrE Newsletter to all involved in the trial. Further details on the publication policy can be found in the Appendix 2.

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Appendix 1: Project Schedule and Recruitment Plan

Project schedule

The study duration will be 60 months including an internal pilot phase:

Study Milestones (see Figure 4: Gantt chart of trial progress)

Months: 1-5: study initiation, NHS approvals; start site set up;
Months: 6-24: staggered site start up; establish study in 50 sites;
Months: 6-40: identify and recruit participants;
Months: 41-54: complete 12 months follow up;
Months: 55-60: close down, analysis, report writing.

Figure 4: Gantt chart of trial progress

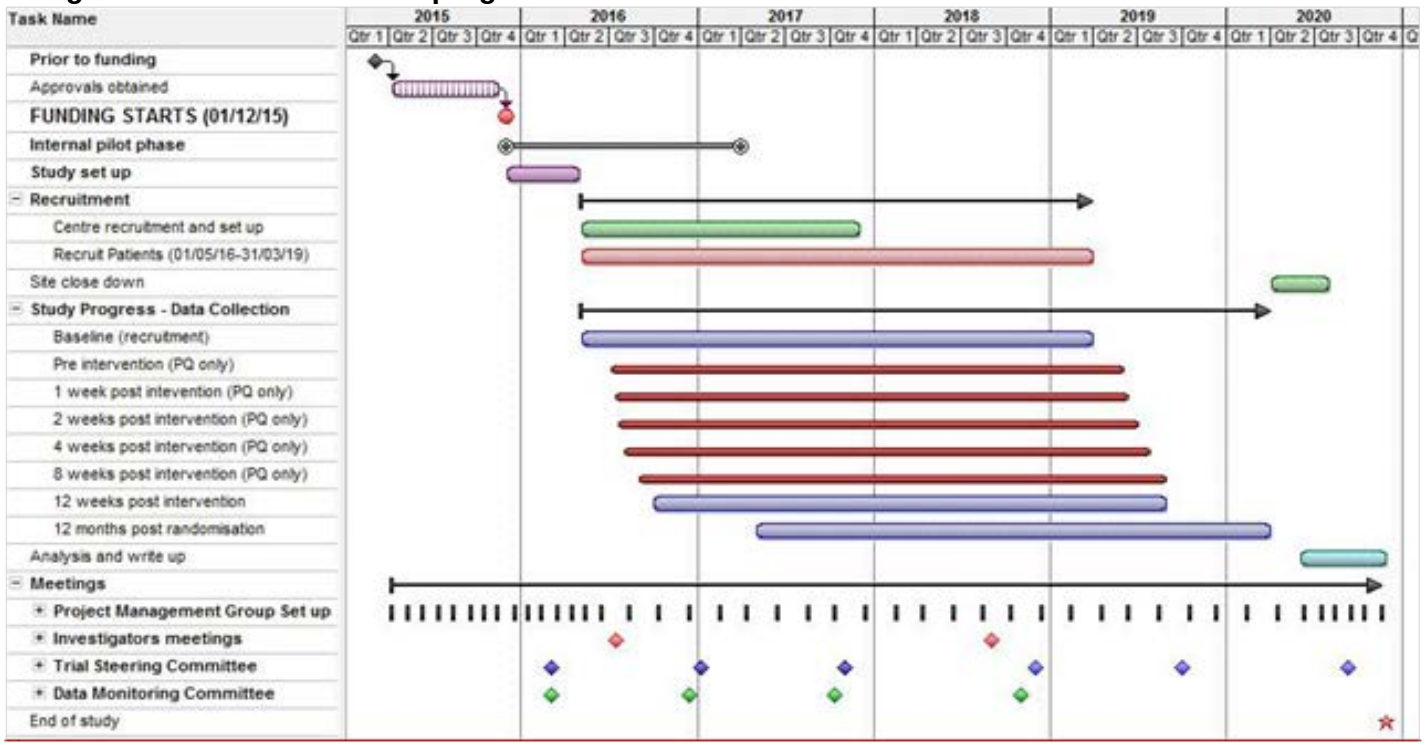
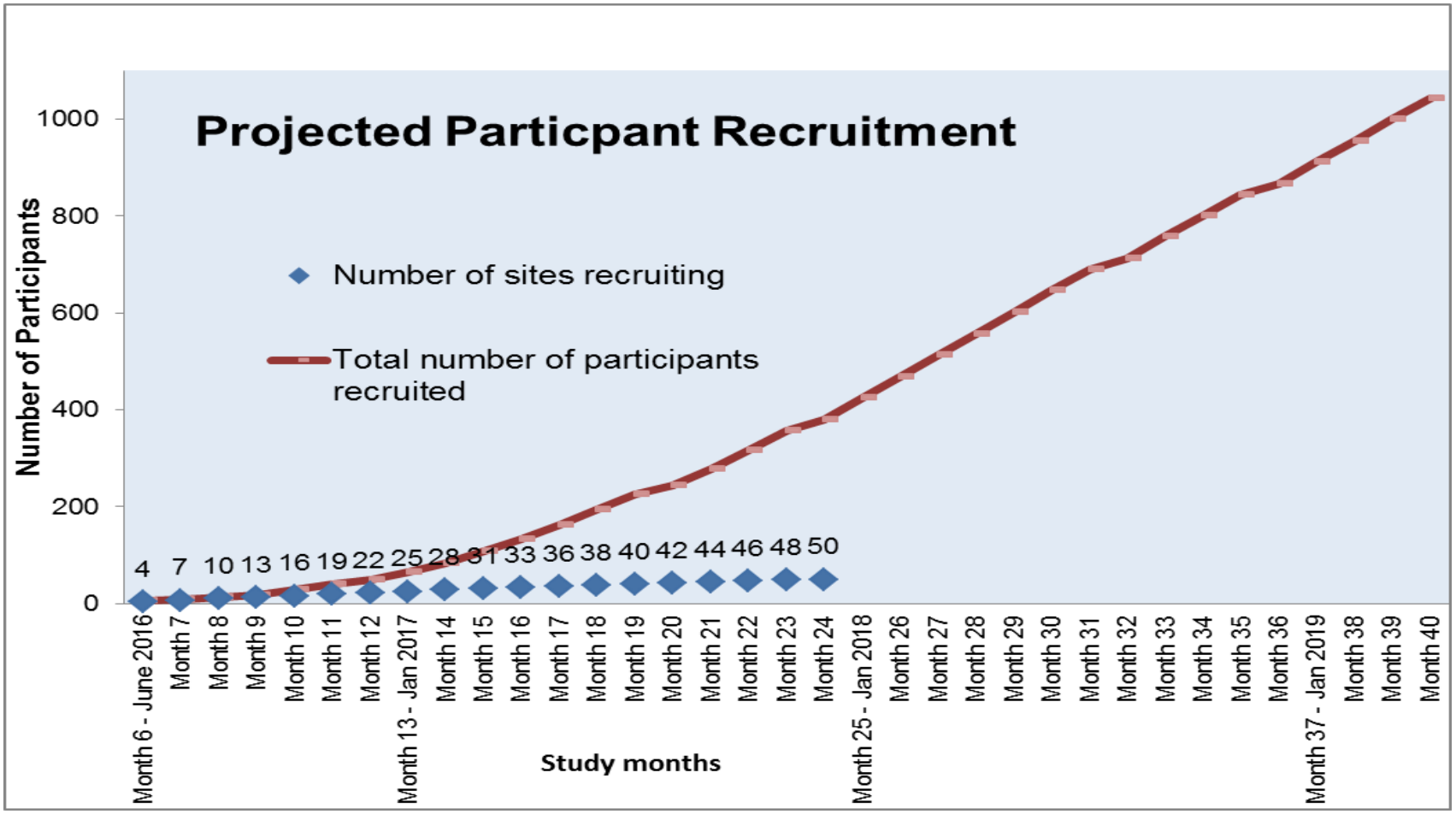


Figure 5: **Projected participant recruitment and centre start up graph for the whole project (RCT 1 and RCT 2).**



Appendix 2: Authorship 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 PUrE 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 by-line 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 PUrE

a. Operationalising authorship rules

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

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

If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The PUrE 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 PUrE Trial Group'.

ii. *Reports of satellite studies and subsidiary projects*

Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders 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 PUrE 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 PUrE 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 PUrE 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 PUrE trial including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the PUrE 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 undertakes 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).

3. REFERENCES

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