Proper Understanding of Recurrent Stress Urinary Incontinence Treatment in women (PURSUIT): A Randomised Controlled Trial of Endoscopic and Surgical Treatment

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AUS	Artificial Urinary Sphincter
BRTC	Bristol Randomised Trials Collaboration
BSUG	British Society of Urogynaecology
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DPA	Data Protection Act
EQ-5D-5L	EuroQol 5-dimension 5-level
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to treat
MHRA	Medicines and Healthcare products Regulatory Agency
MUT	Midurethеral Tape
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PIL	Participant Information Leaflet
PISQ-IR	Pelvic Organ Prolapse/Incontinence Sexual Questionnaire-IUGA
PGI-I	Patient Global Impression of Improvement
POP	Pelvic Organ Prolapse
PROM	Patient Reported Outcome Measure
QALY	Quality adjusted life year
QoL	Quality of Life
QRI	Quintet Recruitment Intervention
QuinteT	Qualitative Research Integrated within Trials
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
SUI	Stress urinary incontinence
TMF	Trial Master File
TMG	Trial Management Group
TOT	Transobturator Tape
TSC	Trial Steering Committee
TVT	Transvaginal Tape
UoB	University of Bristol

TRIAL SUMMARY

Trial Title	Proper Understanding of Recurrent Stress Urinary Incontinence Treatment in women: A Randomised Controlled Trial of Endoscopic or Surgical Treatment	
Short title	PURSUIT	
Trial Design	A two-arm randomised controlled trial in women with recurrent stress urinary incontinence (recurrent SUI) comparing endoscopic intervention (urethral bulking injections) with a surgical intervention (such as colposuspension, autologous urethral sling, midurethral tape (MUT) or artificial urinary sphincter (AUS)).	
Trial Participants	Adult women diagnosed as having recurrent and persistent SUI by their urologist or gynaecologist.	
Planned Sample Size	250 people from (at least) 20 NHS urological and urogynaecological referral units, across the United Kingdom (UK).	
Treatment and recruitment duration	2 years	
Follow up duration	3 years in total with primary outcome at 1-year post randomisation	
Planned Trial Period	• April 2019 to March 2025 – 6 years total • Recruitment October 2019 - October 2021 (2 years) • Follow-up until October 2024	
	Objectives	**Outcome Measures**
Primary	To explore whether surgical or endoscopic bulking interventions improve continence at 1-year post randomisation.	Patient reported outcome of continence (ICIQ-UI-SF) at 1-year post-randomisation.
Secondary	To explore:	
	• Clinical subjective measure of continence (longer term).	• ICIQ-UI-SF at 6-months, 2- and 3-years post randomisation, to measure longer term impact.
	• Improvement of symptoms post-intervention.	• PGI-I: Patient Global Impression of Improvement at 1-, 2- & 3-years post-randomisation.
	• Procedure/Operative assessment measures.	• Assessment of procedure/operation time, estimated blood loss, hospital stay, return to normal activity. Collected at time of intervention and 6 months post-intervention.
	• Incontinence sexual function questionnaire.	• PISQ-IR at 1-, 2- and 3-years post-randomisation.
	• The safety of each intervention and the likelihood of re-treatment.	• Evaluation of treatment and re-treatment and adverse events for each intervention, assessed at intervention, 6-months post intervention, and 6-months, 1-, 2- and 3-years post-randomisation.
	• Cost-effectiveness from an NHS and societal perspective in terms of Quality Adjusted Life Years	• EQ-5D-5L at baseline, 6-months, 1-, 2- and 3-years post-randomisation.

	(QALYs) and ICIQ-UI-SF at 1-year, and from an NHS secondary care perspective in terms of QALYs at 3-years.	• Resource use collected from questionnaires at 6-months and 1-year post randomisation. • Secondary care resource use abstracted from hospital electronic systems at 1- and 3-years post randomisation. *(Hospital Episode Statistics (HES) to be used if electronic records are unavailable).*
	• Women's experiences of interventions and associated quality of life.	• Qualitative interviews to evaluate women's experiences of interventions at baseline, 6-months, 1- and 3-years post intervention.
	• Clinician's views of interventions.	• Qualitative interviews to evaluate clinicians' experiences of interventions around baseline.

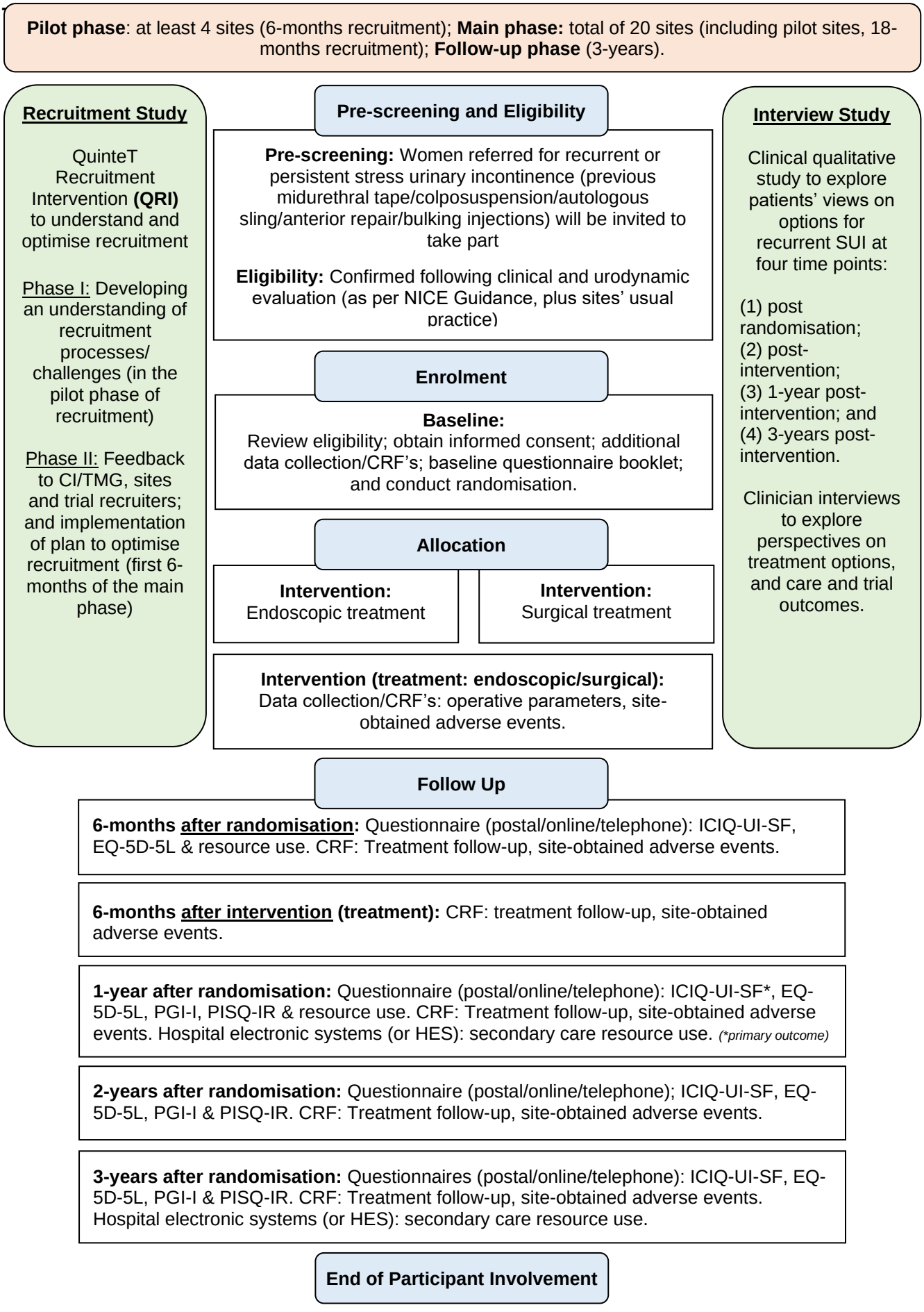

Figure 1 Trial Flowchart

TRIAL PROTOCOL TITLE

Proper Understanding of Recurrent Stress Urinary Incontinence Treatment in Women (PURSUIT): A Randomised Controlled Trial of Endoscopic or Surgical Treatment.

1 BACKGROUND AND RATIONALE

Urinary leakage with physical activity is known as stress urinary incontinence (SUI), and primary SUI affects a quarter (16-35%) of women after pregnancy. Until recently, the most common surgical treatment was a “midurethral tape”, an operation which helps to support the bladder exit (urethra). Alternative surgical options include colposuspension, fascial sling, artificial urinary sphincter or endoscopic bladder neck injections. In many cases symptoms may come back after surgical treatment. This situation is called recurrent SUI.

Little is known about the chance of cure or potential treatment-related problems for women. There is also no consensus on how to treat women with failed primary continence surgery. A study by Tincello *et al*. (funded by Wellbeing of Women) surveyed patients and clinicians about this question (1). “No consensus on what is the correct treatment” was achieved by a clinician survey and patient views were highly individual. There is a problematic lack of high quality evidence for the best treatment for recurrent SUI (2, 3).

The fundamental mechanism of SUI may be either;

1. Urethral hypermobility, where the sphincter muscle is fundamentally normal, but is prevented from functioning due to impairment of its ligamentous support.

2. Intrinsic sphincter deficiency, where the sphincter muscle is not normal, because the nerves to the muscle, or the muscle itself, are damaged. Consequently, there is weakened resistance by the sphincter.

NICE NG123 on Urinary Incontinence in Women (4) suggests that women whose primary surgical procedure for SUI has failed (including women whose symptoms have returned) should be referred to tertiary care for assessment (such as repeat urodynamic testing, including additional tests such as imaging and urethral function studies), and discussion of treatment options by the multidisciplinary team.

In primary SUI, NICE recommends pelvic floor muscle training (PFMT) and, if this fails, surgery is an option. Surgical failure rates after midurethral sling procedures are variable and range from approximately 8-57% at five years of follow-up (5). The problem may reflect persistent hypermobility or emergence of sphincter deficiency. This affects quality of life (QoL), ability to work and has substantial cost impact. Up to 17% of women undergo a second operation for SUI within 10 years. The James Lind Alliance, a group of healthcare professionals and patients, identified this topic as a top 10 research priority in urinary incontinence. Women with recurrent SUI commonly express desire to return to normal life, but they also wish to minimise the severity of surgery or complications.

This study ‘Proper Understanding of Recurrent Stress Urinary Incontinence Treatment in women’ (PURSUIT) is designed to help patients and doctors work out how to treat this common problem. It aims to establish whether surgical treatment is superior to endoscopic injections in terms of symptom severity at one year after randomisation in women with recurrent SUI. PURSUIT will randomise participants between surgical and endoscopic interventions and is powered to ascertain clinically meaningful differences in symptom outcomes at one year. PURSUIT addresses the research question “What is the best treatment for women with recurrent SUI after failed primary surgery?”.

Available options to treat women with failed primary continence surgery include further physiotherapy, repeat midurethral tape/sling insertion, colposuspension, autologous fascial

sling, artificial urinary sphincter or endoscopic bladder neck injections (bulking agents). The descriptions for each current procedure/operation are:

- Autologous fascial sling: where a strip of the patient's own tissue (fascia) is used to compress the urethra.

- Colposuspension: where the anterior vaginal wall is repositioned to support the urethra

- Midurethral tape (MUT): where a medical mesh tape to support the urethra is placed retropubically (Transvaginal tape, TVT) or through the obturator canal of the pelvis (Transobturator tape, TOT).

- Artificial urinary sphincter (AUS): where an implanted cuff is used to compress the urethra to keep the woman continent. The compression can be released by pressing on a component in the vaginal labium so the woman can pass urine when she wants to.

- Endoscopic bulking injections: where a cystoscope is used to guide injection of bulking agents to the urethra, to enhance its ability to close effectively.

The choice of surgical approach partly depends on the mechanism of the recurrent SUI, whether it is hypermobility or intrinsic sphincter deficiency. Thus, colposuspension, autologous fascial sling or midurethral tape are preferred by some surgeons for hypermobility, as these restore support for the urethra and bladder exit. Autologous fascial sling or AUS are believed to be more successful for women with recurrent SUI due to intrinsic sphincter deficiency, as they compress the urethra and thereby restore some resistance. For both mechanisms, endoscopy is a less invasive procedure than surgery. For SUI treatment with endoscopy, urethral bulking agents are injected into the urethra wall to reduce the size of the channel (also known as bladder neck injections). Examples of urethral bulking agents are Bulkamid®, Deflux® and Macroplastique®. There are a few substances marketed for urethral bulking, and a Cochrane review states that no clear-cut conclusions could be drawn from trials comparing alternative agents (6). This review also suggested greater symptomatic improvement was observed with surgical treatments but set against likely higher risks.

2 AIMS AND OBJECTIVES

2.1 Aim

To determine whether surgical treatment is superior to endoscopic bulking injections in terms of symptom severity at 1-year after randomisation, in women with recurrent SUI.

2.2 Primary objective

To identify whether surgery achieves superior symptomatic outcome compared to endoscopic bulking injections (treatment), at 1-year after randomisation.

2.3 Secondary objectives

i. Longer term impact of the interventions on continence (self-reported)
ii. The improvement of symptoms post-intervention
iii. Operative assessment
iv. Sexual function
v. The safety of each intervention and the likelihood of re-treatment
vi. Cost-effectiveness from an NHS and societal perspective in terms of Quality Adjusted Life Years (QALYs) and ICIQ-UI-SF at 1-year, and from a secondary care NHS perspective in terms of QALYs at 3-years
vii. Women's experiences of interventions and associated QoL. Qualitative component to optimise recruitment outcomes and to evaluate women's experiences of interventions
viii. Clinician's views of interventions

2.4 Primary endpoint/outcome

The primary outcome is the patient reported outcome measure (PROM) of continence using the International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF) at 1-year after randomisation.

2.5 Secondary endpoints/outcomes

Secondary outcomes are detailed in Table 1, below.

Table 1. Secondary outcomes and measures (tools)

Outcome	Tool/method
Clinical subjective measure of continence (longer term)	ICIQ-UI-SF questionnaire at 6-months, 2- & 3-years post randomisation
Improvement of symptoms	Patient Global Impression of Improvement (PGI-I) questionnaire at 1-, 2- & 3-years post randomisation
Procedure/Operative assessment measures	Assessment of procedure/operation time, estimated blood loss, hospital stay, return to normal activity, at time of intervention and at 6-months post intervention
Incontinence Sexual Function Questionnaire	POP/PISQ-IR questionnaire at 1-, 2- & 3-years post randomisation
Adverse Events	Evaluation of treatment and retreatment, adverse events of each intervention at intervention, 6-months post intervention, and 6-months, 1-, 2- & 3-years post randomisation
Cost Effectiveness from an NHS and societal perspective in terms of QALYs and ICIQ-UI-SF at 1-year, and from a secondary care NHS perspective in terms of QALYs at 3-years	EQ-5D-5L (used to calculate QALYs) questionnaire at 6-months, 1-, 2- & 3-years post randomisation Secondary care resource use from Trust electronic systems (or HES) at 1- and 3- years post randomisation. Community based and patient resource use questionnaire at 6-months and 1-year post randomisation
Patient experiences of the intervention	Qualitative interviews with patients at 6-months, 1-year and 3-years post intervention
Clinician views of the intervention	Qualitative interviews with clinicians around baseline

3 TRIAL DESIGN

A definitive two-arm randomised controlled trial (RCT) in women with recurrent stress urinary incontinence (SUI) comparing endoscopic intervention (urethral bulking injections) with a surgical intervention (such as colposuspension, autologous urethral sling, midurethral tape (MUT) or artificial urinary sphincter (AUS)).

3.1 Internal pilot

Participants will be recruited over a 2-year period. Participant and site recruitment will be reviewed 6-months after the first site is given the green light to begin recruiting. This 6-month pilot phase incorporates the QuniteT Recruitment Intervention (QRI) as described in Section 9.

The aim of the pilot phase is to test that our assumptions about recruitment and delivery of the interventions are achievable. At least four sites will recruit during the pilot phase. Up to an additional six sites will be set up during the pilot phase to maintain the rate of recruitment in anticipation of continuing to the full trial.

We developed recruitment projections allowing for the staggered opening of sites, start up and seasonal effects. Based on our projections, we expect to have recruited 24 women by the end of the 6-month pilot phase.

In the internal pilot, the Trial Management Group (TMG) will meet monthly to review recruitment rates and whether further actions can be taken to improve them, if required. Stop/Go progression criteria are described in the table below.

Table 2 Internal pilot 'Stop/Amend/Go' criteria

	Participants	Anticipated action
GO (green)	19-23 participants recruited (>75% of expected) if all 4 sites are recruiting from the first day of the recruitment period at the expected rate	Continue -TMG will monitor recruitment rates closely
AMEND (amber)	13-18 participants recruited (54-75% of expected) if all 4 sites are recruiting from the first day of the recruitment period at the expected rate	Identify remediable factors, discuss with TMG and TSC. Submit recovery plan to HTA with new targets for the following 6 months
STOP (red)	1-12 participants recruited (≤50% of expected) if all 4 sites are recruiting from the first day of the recruitment period at the expected rate	Stop the trial, unless there is a strong case that unanticipated remediable factors have been identified and can be addressed after further discussion with the funder

3.2 Planned recruitment rate

The planned recruitment for PURSUIT is 250 participants from (at least) 20 sites. A 24-month recruitment period is deemed sufficient to identify, contact and consent 250 eligible women. In our recruitment progression estimates (
Figure 2) we assumed that at least four sites would be recruiting in the 6-month internal pilot phase (i.e. October 2019 to end of March 2020) with up to six more open to recruitment in the seventh month of recruitment (April 2020). By the 13th month (October 2020) all 20 sites will be open.

[a] *Recruitment starts in month 7 of the overall trial (i.e. October 2019) for a period of 24-months (i.e. to end of September 2021).*

[b] *A large number of site openings are proposed in months 7 and 12 of the recruitment period, although monthly site openings may vary according to the needs of the trial and available resources. The target of all 20 sites open by the 13th month (October 2020), however, remains.*

Figure 2 Participant and site recruitment projections

4 TRIAL SETTING

This trial will be delivered in a secondary care setting across (at least) 20 urology and urogynaecology units in UK hospitals. Sites will be selected based on their referral populations, research capacity and capability.

5 ELIGIBILITY CRITERIA

5.1 Subject population

Women with recurrent or persistent stress urinary incontinence (SUI).

5.2 Inclusion criteria

- Adult women (≥18-years) with bothersome SUI symptoms after primary SUI surgery (including bulking injections)
- Urodynamics to confirm recurrent or persistent SUI
- Patient willing to consider interventional therapy
- Patient willing to be randomised and willing to give consent

5.3 Exclusion criteria

- Predominant urgency incontinence
- Pelvic organ prolapse (POP) more than or equal to stage II
- Relevant neurological disease, disease, such as a stroke, multiple sclerosis, Parkinson's disease, or spina bifida (diabetes mellitus is not an exclusion criterion unless it is causing diabetic neuropathy)
- Being treated for gynaecological or bladder cancer
- Unresolved mesh exposure from previous MUT
- Current pregnancy
- Urethral diverticulum
- Recent pelvic surgery (e.g. POP repair, stress incontinence surgery, and hysterectomy within the last 6-months)
- Participation in another study that might influence results or increase patient burden
- Unable to give informed consent/complete assessments
- Previous artificial urinary sphincter (AUS) surgery

5.4 Co-enrolment in other research studies

Co-enrolment in the PURSUIT study and another competing study will not be permitted due to potential impact on the study objectives. If participants enrolled in the PURSUIT study express interest in enrolling in other (non-competing) clinical studies, the participant's site team must contact the central trial team to discuss co-enrolment before the participant enrols in the additional study. Due care will be paid to the burdens of co-enrolment in this trial. Co-enrolment will be considered on a case-by-case basis taking into consideration factors such as comorbidities, social support and distances necessary to travel.

6 RECRUITMENT

***IMPORTANT NOTE:* Due to the variation in patient pathways at each hospital (site), arrangements should be individualised according to local practice (set-up).** *Where feasible, potentially eligible women should be provided with the study Participant Information Leaflet(s) (PIL(s)), have any questions answered, provide written informed consent and be randomised prior to discussing treatment (as per their randomised allocation) with their surgeon. This approach aims to minimise the number of hospital attendances, or remote consultations, for the patient and avoids discussing (potentially) irrelevant treatment options in detail (e.g. surgery options when randomised to receive bulking injections).*

6.1 Pre-screening and eligibility

Previous assessment results of women attending urology clinics will be reviewed to determine eligibility. Patient notes and urodynamic unit clinical reports for women with previous midurethral tape/colposuspension/autologous sling/anterior repair/bulking injections referred for recurrent or persistent stress urinary incontinence, will be assessed at sites by the clinical research team.

When a woman presents with symptoms suggestive of recurrent SUI, diagnostic testing to confirm urodynamic stress incontinence using standard approaches according to NICE (4) will be considered. This testing will be done as part of their routine NHS clinical care. If a woman's previous SUI surgery was midurethral tape, it will be considered whether it is possible that she might have a tape exposure (for example by physical examination, and consideration of whether cystoscopy is appropriate). If SUI is confirmed and there is no perceived risk of midurethral tape exposure being present, then the patient will be invited to participate in the PURSUIT study.

Sites may also recognise other opportunities and methods for identifying potentially eligible women (and inviting them to take part), which should be utilised to minimise disruption to routine practice and involvement for the patient (e.g. during a routine clinical appointment/physiotherapy appointment/urodynamic assessment/multidisciplinary team (MDT) meetings).

6.2 Invitation to participate

Site staff should complete trial-specific screening logs for all potentially eligible women and provide confirmation of the patient's outcome for the study; this will be one of three main outcomes: 1) patient confirmed as ineligible; 2) patient was eligible but declined to take part; 3) patient was eligible and consented to take part. Where possible, screening logs will include reason(s) for non-participation. This will ensure that participants are not approached more than once, as well as highlight patients who are willing to be contacted in the future (e.g. if they were not able to participate when first approached due to an acute intercurrent illness at that time). Sites will provide the central trial team (at University of Bristol) with a copy of their screening logs on a monthly basis, for monitoring.

Hospital staff will also be informed about the study by the Principal Investigator and the research nurse, so that they can answer queries from participants and their relatives.

6.2.1 Patients identified from pre-screening/referrals/lists

Those patients identified from pre-screening or from referral letters (as described in Section 6.1) will be provided with the main study PIL, and the Qualitative Studies PIL if appropriate,

(accompanied with a study-approved covering letter if sent by post or electronically). Site staff should then follow-up these patients, either face-to-face or remotely, to answer any questions the patient may have and to see if they would like to take part in the study; this follow up should be after at least 24-hours and (ideally) within 8 weeks of the initial invitation. If the patient is eligible and would like to take part, then written informed consent should be obtained (see 6.3, below).

6.2.2 Patients identified during an appointment

If a potential participant is identified during a clinical appointment, whether being conducted face-to-face or remotely, the research nurse (or trained delegate) may discuss the study with the patient there and then and provide the study PIL(s) (either given directly, via post or electronically). Following provision of the study PIL, patients will be given the chance to ask questions and should ideally have at least 24-hours to think about taking part before a follow-up is conducted where they can provide written consent (see 6.3, below).

If, however, the patient is happy to take part in the study *without* having at least 24-hours to review the PIL and study details, and requests to provide written consent at that time, then this is possible and should be done as detailed in 6.3, below. However, the patient *must not be randomised* until at least 24-hours has passed **and** only when all study interventions (which would normally be available at that site) can proceed according to routine clinical pathways and timings (see 6.4.1, below).

6.2.3 Study poster

An approved study-specific poster may also be displayed in suitable clinic rooms, which provides the contact details of trial related staff who interested women can contact for further information. Site staff should then proceed as described above.

6.2.4 Women who decline participation

Women who are eligible but decline to take part in the study (e.g. not willing to be randomised, or any other reason), may be asked to consent to being contacted for a qualitative research interview to explore reasons for non-participation (i.e. the “Recruitment Study”). Sites are expected to update patient medical notes indicating that the patient declined to take part in this study, providing study details (title), date, and any reason(s) if provided.

6.3 Consent

Written informed consent will be obtained from all patients who are deemed eligible and agree to take part in the study. The consent form(s) will also refer to the possibility of long-term follow-up and being contacted about other research if the woman is willing/invited. When a patient provides informed consent to enter the study, they will be given a unique 6-digit participant identification number, which is recorded on the consent form(s) and subsequent trial documentation.

Consent to take part in the study may be obtained face-to-face (e.g. during a clinical appointment or at a study-specific baseline visit), or remotely during a clinical, or study-specific, consultation which is being conducted via any method of contact employed/supported by the local NHS trust at the time.

Written informed consent may be obtained in the following ways:

a) written consent form – a study-approved paper (wet ink) consent form signed by the patient during a face-to-face consultation
b) eConsent form – a study-approved (Health Regulatory Agency (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA)-compliant) online eConsent form signed (electronically) by the patient during a remote or face-to-face consultation. eConsent does not need to be followed up with a paper (wet ink) written consent form as an electronic signature constitutes documented informed written consent
c) verbal consent form, followed by written consent form or eConsent form – a study-approved verbal consent form completed by the researcher during a telephone or video consultation with the patient. This must be followed up with written consent (using either the paper (wet ink), or online eConsent, form) which can be completed via post (paper form only), online, or during the patient's next face-to-face appointment. To obtain written consent via post (*only* after verbal consent has been given) the site staff should sign two copies of the written consent form and post both copies, along with a copy of the completed verbal consent form, to the participant. The participant should complete and sign both copies of the written consent form. The participant must then send one copy of the completed written consent form back to the site staff and keep the other copy of the written consent form and the completed verbal consent form for their records.

Four copies of completed consent form(s) are required (*for each type used*):

1) a copy must be filed in the Investigator Site File (ISF) together with a copy of the PIL in recruitment order*
2) a copy should be provided to the patient*
3) a copy should be placed in the patient's medical notes with a supporting record of the discussion and a copy of the PIL**
4) a copy should be provided to the PURSUIT central trial team (University of Bristol).

**If a written or verbal consent form is completed, the 'original' form should be filed in the ISF. If an eConsent form is completed, a copy is automatically emailed to the patient once processed, and additional copies can be obtained via the eConsent (database) system.*

***Besides completing the consent form (which includes the study title and date of consent), sites should record key details of the informed consent process in the patient's medical notes. Patients are not required to provide reasons for taking part in the study, or not, but if reasons are given, then they should also be documented in their notes.*

6.4 Randomisation and baseline data collection

***IMPORTANT NOTE:* The timing of randomisation and baseline data collection will depend on the permitted local processes regarding study interventions (surgical and endoscopic treatments) which are in place at the time.** Randomisation and baseline data collection (participant questionnaire and baseline CRF) should not be completed until it has been confirmed at a site level that all study interventions (which would normally be available at that site) can proceed according to routine clinical pathways and timings.

If study interventions have been paused (e.g. due to COVID-19 restrictions), patients may provide informed consent to take part, but randomisation and baseline data collection should

not be undertaken until all treatment interventions can proceed. As soon as treatment interventions can proceed, arrangements should be made to complete randomisation and baseline data collection (either face-to-face or, wherever possible, remotely via telephone or video-call). In this situation, where a delayed randomisation approach has been taken, site staff should ensure eligibility and consent of each participant are still applicable and valid before proceeding with randomisation and data collection. Previous urodynamic results (used for initial confirmation of study eligibility) can be used providing that the doctor considers that they are still relevant, i.e. the tests were conducted since the woman's last procedure and her symptoms have not changed since then. If the patient has changed her mind and no longer wishes to be randomised, or is no longer eligible, the site should complete the 'PURSUIT participant change of permissions/withdrawal form' and follow essential reporting procedures specified on the form. For clarity, a copy of the consent form(s) and completed change of permissions/withdrawal form should be kept at site, as well as forwarded to the central trial team for their study records.

If study interventions are proceeding as usual (according to routine clinical pathways and timings), randomisation and data collection may be done at the same time at which consent is obtained* (either face-to-face or remotely) or be completed during separate consultations.

**If participants have not had 24-hours to consider study information then randomisation must be delayed; see 6.4.1 below or details.*

6.4.1 Randomisation

A local research nurse or trained delegate (including a member of the central trial team if needed) should only randomise patients after eligibility has been confirmed, written consent obtained and the patient has had at least 24-hours to consider the study information and had any questions answered. The randomisation sequence will be generated by the Bristol Randomised Trials Collaboration (BRTC) Clinical Trials Unit (CTU) using their established (proven) online randomisation system or automated telephone system. Patients will be randomised on a 1:1 basis to the "endoscopic" or "surgical" intervention (treatment) arm. The individual randomisation will be stratified by site.

Randomisation can be conducted during a face-to-face consultation (clinical appointment or study-specific visit) or be completed remotely. Remote randomisation does not need to be done *during* a consultation (although it can be); e.g. if randomisation is conducted using the automated telephone system, site staff may choose to complete the randomisation procedure and inform participants of their allocated intervention later (after the consultation).

If a patient was happy to take part without having at least 24-hours to decide, the site should re-contact the patient to confirm they are still willing to proceed with the study; if the patient is willing, the site can proceed with the randomisation and inform the patient of her intervention allocation. The research site should record that the patient opted for this consent and randomisation approach in their medical notes, and in the PURSUIT Baseline CRF. If the patient has changed her mind and no longer wishes to be randomised, the site should complete the 'PURSUIT participant change of permissions/withdrawal form' as described above (6.4).

Once a participant has been randomised, they are 'enrolled' in the study and treatment (intervention delivery) can proceed. Hospital staff should complete and send a study approved letter to the participant's General Practitioner (GP) informing them that their patient has entered the trial.

6.4.2 Baseline data collection

Baseline data (participant baseline questionnaire booklet and baseline CRF) can be collected at a face-to-face consultation or be completed remotely, in accordance with the timings described above (section 6.4).

Ideally, wherever possible, participants should complete their baseline questionnaire *during* their appointment. The site staff complete the baseline CRF and then the randomisation process. Following completion and return of the baseline questionnaire, participants can then be informed of their randomised treatment allocation. If participants request to complete their questionnaire remotely at another time (i.e. online or via post and not during the baseline appointment), staff may complete the randomisation process during (or after) the baseline appointment but should delay informing the participant of their treatment allocation until after the baseline questionnaire has been completed and returned. Ensuring that the baseline questionnaire has been returned before informing the participant of their allocation ensures that questionnaire responses are not biased in any way by the patient's knowledge of their randomised treatment allocation.

Baseline data may be collected from a participant who has given written informed consent *before* having 24-hours to consider study information (although only when interventions are proceedable). In this situation, if the participant later decides they do not want to be randomised, the baseline data already collected should be suitably discarded by the research site; this data does not need to be retained for trial purposes as the patient decided not to enrol (be randomised) into the study.

7 INTERVENTION

7.1 Overview of trial allocation

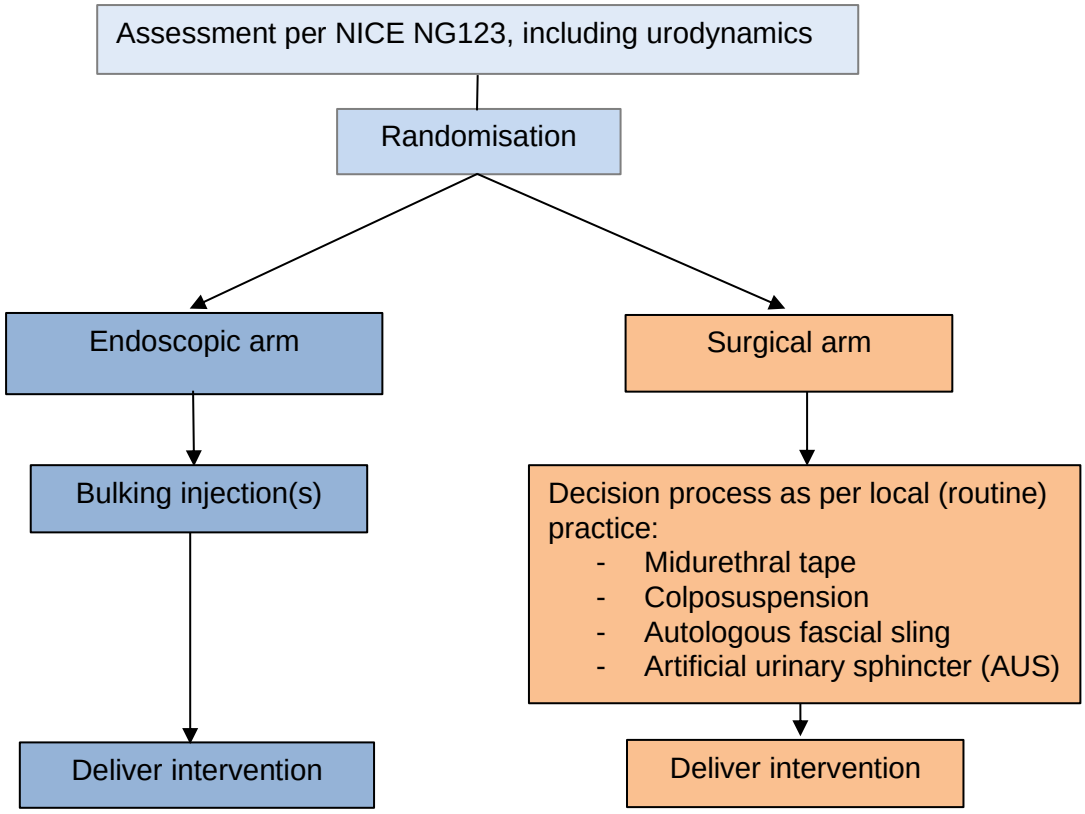

Figure 3 Overview of trial allocation

7.2 Assessment procedure

After women with a history of recurrent SUI have been identified, standard assessments as per NICE NG123 guidance (4) will be undertaken, including urodynamic testing, to confirm diagnosis. These assessments will also help to ascertain what type of surgery would be suitable for the patient, should she be randomised to the "surgical" treatment arm. Following these assessments, the patient is then randomised (allocated) to either the "endoscopic" (bulking injections) or the "surgical" treatment arm.

If the participant is randomised to the "surgical" treatment arm: The type of surgical intervention should be decided using the study PIL (previously provided) and a detailed discussion between the patient and surgeon (clinician), as per usual local practice. If necessary, either as part of usual local practice, or if requested by the patient, the discussion with the surgeon (clinician) *may* include the use of additional local/national information leaflets or decision aids; if the 'NICE Patient Decision Aid for surgery for stress urinary incontinence in women' is used (see NICE NG123 (4)), the surgeon (clinician) should explain to patients that this is not written for patients with *recurrent* SUI. The clinical team will use the assessment to identify the presence of recurrent SUI, and the underlying mechanism(s). This assessment will be used to predetermine which type(s) of operation could be offered to the patient if randomised to surgery. Cystoscopy may be undertaken if the clinical team considers it is medically indicated, however it is not mandatory within the assessment for the PURSUIT trial.

7.3 Endoscopic (bulking injections) arm

Endoscopic urethral bulking agents to reduce the size of the channel (also known as bladder neck injections) are injected into the urethra wall under direct vision, using a cystoscope. Examples of urethral bulking agents are Bulkamid®, Deflux® and Macroplastique®. In the endoscopic arm, repeat injections will be permitted. *(**NB:** Sites should use their usual urethral bulking agent(s). The PURSUIT trial is not imposing 'which' urethral bulking agent(s) should be used; this information will be requested in the Peri-Operative Case Report Form (CRF)).*

7.4 Surgical arm

The different surgery options for recurrent SUI are:

- Autologous fascial sling; where a strip of the patient's own tissue (fascia) is used to compress the urethra.
- Colposuspension; an operation to support the urethra by repositioning the anterior vaginal wall.
- Midurethral tape (MUT); where a mesh tape to support the urethra is placed retropubically (TVT) or through the obturator canal of the pelvis (TOT).
- Artificial urinary sphincter (AUS); an implanted cuff, which compresses the urethra to keep the woman continent, and the compression can be released by pressing on a component in the vaginal labium so the woman can pass urine when she wants to.

Important to note: *there are specific rules from the NHS which regulate the use of mesh in vaginal surgery, including midurethral tapes. The rules relevant at the time will be used for anyone wishing to consider this type of surgery.*

7.5 Cross-over of intervention arms

There should be no cross-over of patients from their randomised treatment allocation to the alternative treatment until after the primary outcome is recorded (1-year post randomisation). However, this is guidance only and cannot be imposed. As detailed in Section 8 (Trial Procedures, below), sites will be asked to monitor and record all treatments that a participant receives; if cross-over does occur then details, including reason(s) why should be recorded in study CRFs.

7.6 Ensuring standardisation of intervention and outcome measurement (performance bias)

Intervention; all professionals involved in delivery of the interventions will already be fully trained in the procedures, as these are specialist units recognised by subspecialist professional bodies (BSUG, BAUS Section of Female, Neurological and Urodynamic Urology). We will rely on quality of service delivery as scrutinised by the local continence MDT (or equivalent) process'.

Outcome measurement; standardisation relies on the use of validated PROMS.

8 TRIAL PROCEDURES

8.1 Schedule of assessments and outcomes

Table 3 Measurement of clinical and resource use outcomes: components and timings

		INTERVENTION/ POST		POST-RANDOMISATION			
Time of data collection (⟶)	**Baseline**	**Treatment (Intervention)**	**6-months post-treatment (intervention)**	**6-months post-randomisation**	**1-year post-randomisation**	**2-years post-randomisation**	**3 -years post-randomisation**
Outcome Measures (↓)							
Case Report Form(s) (CRFs)	●	●	●	●	●	●	●
Adverse events		●	●	●	●	●	●
ICIQ-UI-SF[a]	●/○			○	○	○	○
PISQ-IR	●/○				○	○	○
EQ-5D-5L	●/○			○	○	○	○
PGI-I					○	○	○
Non secondary care resource use *(questionnaire)*				○	○		
Secondary care resource use *(electronic medical records abstraction)*					●		●

[a] *Primary outcome (ICIQ-UI-SF) at 1-year post-randomisation*

Key: ● *Completed at study site* ○ *Completed remotely (e.g. via post/online/telephone)*

Table 4 Measurement of qualitative (interview) outcomes: components and timings

Time of data collection (⟶)	**Baseline**	**3 to 6-months post-treatment**	**1-year post-treatment**	**3 -years post-treatment**
Outcome Measures (↓)				
Qualitative interview selected patients (verbal consent)	◊	◊	◊	◊
Qualitative interview selected staff (verbal consent)	◊			

Key: ◊ *Interviews may be conducted face-to-face or via telephone.*

8.2 Baseline

Baseline data collection should only be conducted after the patient has provided written informed consent and when their treatment intervention can proceed. Wherever feasible, data collection should be carried out **during** a face-to-face or remote consultation* and should occur as close to randomisation as possible (see 6.4.2).

Questionnaire (participants): Participants will complete the "Baseline" study questionnaire booklet which contains the following PROMs:

- International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF). The ICIQ-UI-SF is a questionnaire for evaluating the frequency, severity and impact on QoL of urinary incontinence in men and women across the world. This questionnaire is also used to screen for incontinence, to obtain a brief yet comprehensive summary of the level, impact and perceived cause of symptoms of incontinence and to facilitate patient-clinician discussions;
- Short form of the Pelvic Organ Prolapse (POP)/Urinary Incontinence Sexual Function Questionnaire (PISQ-IR); and
- EuroQol Group EQ-5D-5L. A standardised instrument to measure generic health and calculate QALYs.

***In some circumstances the patient may request to complete the questionnaire booklet at a separate time from the consultation e.g. complete a paper copy at home and return it via pre-post envelope, or complete it online in their own time. Sites and/or the central trial team (Bristol) will monitor the return of any questionnaires not completed during the baseline consultation.*

CRF (site staff): A research nurse, or other delegated site staff member, will complete the "Baseline CRF". CRF contents are derived from outcome measures and demographic information to include (as a minimum):

- Patient contact details, including email address
- NHS/CHI number
- Patient demographics, including date of birth and ethnicity
- GP contact details
- Charlson Comorbidity Index data
- Record of other diagnostic assessments (e.g. flow rate test/urodynamics/cystoscopy)
- Current medications (including whether on topical oestrogen therapy)
- Parity
- Previous pelvic surgery and dates
- Anticipated cause of SUI (hypermobility/intrinsic sphincter deficiency/both/not diagnosed)

Qualitative interviews: Purposely selected patients and staff (timing flexible from baseline to 6-months) will be interviewed for qualitative analysis by the trial qualitative researchers (as detailed in Section 9.2).

8.3 Treatment (Intervention)

Section 7 provides an overview of the possible treatments (interventions). There will be a waiting period until the patients are invited for the relevant procedure by the hospital (site); the PURSUIT trial does not impose treatment time periods, rather local site waiting times (lists) will apply. Research staff at each site will record procedure/operative data in the study "Peri-operative CRF"; this refers to the period from when the participant is admitted to hospital to undergo treatment (intervention) for their SUI (surgery or endoscopic urethral bulking injection), through to when they are discharged for their primary treatment (intervention). Data collection will include (as a minimum):

- Date of admission
- Height, weight and body mass index (BMI) (likely measured at pre-op visit)
- American Society of Anaesthesiologists (ASA) physical status classification
- Date of procedure (if different from admission)
- Hospital where procedure took place
- Name of surgeon
- Treatment/Operative procedures
    - Endoscopic arm: type of urethral bulking agent(s) used
- Complications
- Details of catheterisation
- Transfusion
- Post void residual volume (PVR) (if recorded)
- Adverse events (from patient notes) *(Section 10 details Safety Reporting)*
- Date of discharge

8.4 6 months after treatment (intervention)

CRF (site staff): Participants are not required to return to site for any study-specific assessments at this timepoint. Site staff, however, will be asked to complete the "6-months after treatment CRF" via medical note review. Data capture will include (as a minimum):

- Adverse events
- Endoscopic arm only: re-intervention (i.e. was a repeat injection needed?)

Qualitative interviews with selected patients will be conducted by trial qualitative researchers (as detailed in Section 9.2).

8.5 6 months after randomisation

Questionnaire (participants): the central trial team (at University of Bristol) will ask participants to complete a study questionnaire booklet, which can be completed via post, online, or telephone; a range of methods are offered to suit participant needs and increase response rates. The "6-month" questionnaire booklet will contain the following PROMs:

- ICIQ-UI-SF
- EQ-5D-5L; and
- Questions relating to community-based NHS resource use; patient costs e.g. incontinence pads; time off work and return to normal activities.

CRF (site staff): Participants are not required to return to site for any study-specific assessments at this timepoint. Site staff, however, will be asked to complete the "6-months after randomisation CRF". Data capture will include (as a minimum):

- Complications of treatment (if applicable)
- Details of catheterisation (status/duration/other details)
- Have any other treatment procedures (interventions) taken place since initial treatment? If so, relevant (what/when) details of what and when.
- Adverse events
- Endoscopic arm only: re-intervention (i.e. was a repeat injection needed?)

8.6 1 year after randomisation

Questionnaire (participants): the central trial team (at University of Bristol) will ask participants to complete a study questionnaire booklet, which can be completed via post, online, or telephone; a range of methods are offered to suit participant needs and increase response rates. The "1-year" questionnaire booklet will contain the following PROMs:

- ICIQ-UI-SF
- PISQ-IR
- EQ-5D-5L
- PGI-I; and
- Questions relating to community-based NHS resource use (patient costs e.g. incontinence pads; time off work and return to normal activities).

CRF (site staff): Participants are not required to return to site for any study-specific assessments at this timepoint. Site staff, however, will be asked to complete the "1-year CRF". Data capture will include (as a minimum):

- Complications of treatment (if applicable)
- Details of catheterisation (status/duration/other details)
- Have any other treatment procedures (interventions) taken place since initial treatment? If so, relevant (what/when) details of what and when.
- Adverse events
- Endoscopic arm only: re-intervention (i.e. was a repeat injection needed?)

Secondary care resource use data (sites): Secondary care resource use data will also be collected. Inpatient and day case admissions; outpatient visits and procedures; and accident and emergency attendances will be obtained from hospital (site) electronic systems*. The information from the hospital systems will be requested in the form of HRG codes for inpatient stays, day cases and outpatient procedures. For outpatient visits currency codes will be requested to designate the type of outpatient appointment (e.g. consultant face-to-face) and a service code to identify the clinical speciality. For accident and emergency visits a currency code will be requested to indicate the intensity of treatment and a service code to indicate whether the patient was subsequently admitted to hospital.

**If it is not possible to obtain this information from the hospital trusts (due to exceptional circumstances) then an application to Hospital Episode Statistics (HES) database will be made.*

8.7 1 year after treatment

Qualitative interviews will be conducted, by the trial qualitative researchers, with the same patient cohort as previous interviews where possible (as detailed in Section 9.2).

8.8 2 years after randomisation

Questionnaire (participants): The central trial team will ask participants to complete the "2-year" questionnaire booklet (either via post, online or via phone). The booklet will contain the following PROMs:

- ICIQ-UI-SF
- PISQ-IR
- EQ-5D-5L; and
- PGI-I.

CRF (site staff): Participants are not required to return to site for any study-specific clinical procedures at this timepoint. Site staff, however, will complete a "2-year CRF" via medical note review. Data capture will include (as a minimum):

- Complications of treatment (if applicable)
- Details of catheterisation (status/duration/other details)
- Have any other treatment procedures (interventions) taken place since initial treatment? If so, relevant (what/when) details of what and when.
- Adverse events
- Endoscopic arm only: re-intervention (i.e. was a repeat injection needed?)

8.9 3 years after randomisation

Questionnaire (participants): The central trial team will ask participants to complete a "3-year" questionnaire booklet (either via post, online or via phone). This final questionnaire booklet will contain the following PROMs:

- ICIQ-UI-SF
- PISQ-IR
- EQ-5D-5L; and
- PGI-I.

CRF (site staff): Participants are not required to return to site for any study-specific clinical procedures at this timepoint. Site staff, however, will complete a "3-year CRF". Data capture will include (as a minimum):

- Complications of treatment (if applicable)
- Details of catheterisation (status/duration/other details)
- Have any other treatment procedures (interventions) taken place since initial treatment? If so, relevant (what/when) details of what and when.
- Adverse events
- Endoscopic arm only: re-intervention (i.e. was a repeat injection needed?)

Secondary care resource use data (sites): Secondary care resource use will also be obtained from hospital electronic systems (or HES), as described above, at 1-year.

8.10 3 years after treatment

Qualitative interviews will be conducted, by the trial qualitative researchers, with the same patient cohort as previous interviews where possible (as detailed in Section 9.2).

8.11 Thanking participants for their involvement

Upon completion of the 1- and 3-year questionnaire booklets, the central trial team will offer women a £10.00 gift voucher (i.e. £10.00 per questionnaire, up to £20.00 in total). In addition, for women who take part in the nested 'Interview Study', the central trial team will offer women a £10.00 gift voucher following each completed interview; women will be invited for four interviews, therefore up to £40.00 in total. Women will also be sent participant newsletters telling them about the study, including progress and results once available, which is expected to be in 2025 (or as soon as possible thereafter). Section 16 provides further details about dissemination.

8.12 Methods/procedures to protect against other sources of bias

8.12.1 Loss to follow up (attrition bias)

We will take active measures to minimise loss of women from the trial in line with REC approval. This may include, for example:

- reminders to women via various methods (e.g. telephone/post/email)
- ability to complete questionnaires via multiple methods (e.g. post/online/telephone)
- obtaining back-up 'best contact' addresses
- contacting their GP (practice) to check their contact details on record are still valid (7)
- using vouchers as retention incentives (8)

In addition, we may access centrally held NHS data, for example via the NHS Strategic Tracing Service in England and Wales, to find new addresses.

We have extensive experience of using the above strategies and measures and have received Ethics approval to do so in previous studies.

8.12.2 Measurement bias

Validated questionnaires for PROMs will be used to minimise measurement bias.

8.13 Blinding

Due to the nature of the intervention, participants and those administering the intervention will not be blinded to group allocation. Nor will the supporting clinical and site staff, to ensure relevant data collection. Two statisticians based at the University of Bristol will support this trial. The senior statistician co-applicant will be blinded throughout the trial. The second trial statistician will perform all disaggregated analyses according to a pre-specified statistical analysis plan and will attend closed DMC meetings as required. The health economist(s) will be blinded when cleaning data, but unblinded when conducting the analysis. Other members of the study team will remain blinded to aggregate data. The Study Manager and administrative staff will likely be unblinded to individual level data to enable appropriate data collection.

8.14 Withdrawal from trial

Participants can choose to withdraw for any reason at any time during their involvement in the trial. Participants can withdraw from (a) complying with the allocated trial treatment or (b) providing data to the trial, at any time for any reason without affecting their usual care. In both cases efforts will be made to report the reason for withdrawal as thoroughly as possible in a study-specific “Change of permissions/Withdrawal” form. If a participant wishes to withdraw from receiving the allocated trial treatment, efforts will be made to continue to obtain follow-up data, with the permission of the patient or family as appropriate (including access to medical notes/databases).

In the event the clinician feels it is unsafe for the participant to continue in the study, he/she can withdraw the participant from the study.

In all cases, the study would retain, confidentially, any data collected up to the point of withdrawal for analysis. As advised in the PIL, we would continue to collect data from their electronic records unless they request otherwise.

8.15 End of trial

The end of trial for PURSUIT will be when the last patient has completed their 3-year follow-up and all data has been finalised (all data queries have been resolved and the study database has been locked).

9 NESTED STUDIES

9.1 Recruitment Study - QuinteT Recruitment Intervention (QRI)

The PURSUIT trial will employ an integrated study aimed at optimising recruitment and informed consent (9, 10). Recruitment challenges may arise in relation to identifying potentially eligible women, differences in levels of equipoise among clinicians and women's preferences for surgery or endoscopy. There may also be organisational challenges in relation to how the treatments are operationalised within the trial context and with the integration of the trial into existing clinical practice across sites. The QRI is aimed at identifying and addressing such recruitment difficulties promptly (9, 11, 12). The need for surgeons to be trained to recruit is known from trials where recruitment was optimised in a pilot phase and further support provided to maintain it (13, 14). The QRI will be carried out intensively in the internal pilot phase (months 7-12; October 2019 – March 2020), with lessons learnt used to sustain recruitment during the transition to the main phase (months 13-18, April 2020 – September 2020).

The QRI uses novel qualitative and mixed-method approaches pioneered during the NIHR HTA-funded ProtecT (Prostate testing for cancer and Treatment) study, later refined and applied to several other RCTs, leading to insights about recruitment issues and the development of recruitment strategies (15, 16).The QRI will proceed in two iterative phases: sources of recruitment difficulties are rapidly investigated in Phase I, informing a mix of generic and tailored interventions to improve recruitment in Phase II.

9.1.1 Phase I: Understanding recruitment

Phase I aims to understand the recruitment process and how it operates in clinical sites. A multi-faceted approach will be used to investigate site-specific or wider recruitment obstacles. These will comprise:

a) Mapping of eligibility and recruitment pathways:

Detailed eligibility and recruitment pathways will be compiled for clinical sites, noting the point at which women receive information about the trial, which members of the clinical team they talk to, and the timing and frequency of appointments. These will be compared with details specified in the trial protocol and pathways from other sites to identify those that are potentially more/less efficient. The QRI researcher will also work closely with the clinical trials unit (CTU) to compose detailed logs of potential RCT participants, documenting the numbers of screened, eligible, approached and randomised patients (SEAR approach) (17). Adherence to treatment allocation amongst those randomised and reasons for non-participation amongst decliners will also be noted. These will help identify points at which women do not continue with recruitment and be considered in relation to estimates specified in the grant application/study protocol.

b) Audio-recording and observations of recruitment discussions:

Scheduled face-to-face appointments or remote consultations (e.g. telephone or video-call) during which the trial is discussed with the patient will be routinely audio-recorded (and if necessary, also observed) with written consent. Audio-recordings will be made using an encrypted device. The audio-recordings will be used to explore information provision in relation to key study concepts and treatment options, recruitment techniques, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Audio-recordings will be collected by trial staff across

sites and transferred to/from the University of Bristol (UoB) through UoB-approved secure data transfer facilities or encrypted flash drives/memory cards that adhere to NHS Trust policies.

c) In-depth interviews:

Semi-structured interviews will be undertaken with three groups:

- Members of the Trial Management Group (TMG), including the Chief Investigator (CI) and those involved in the design, management and leadership of the trial (*n*=4-5)
- Clinicians or researchers who are involved in the patient pathway and trial recruitment (*n*=20-25)
- Eligible women who have been approached to take part in the trial (*n*=5-10)

Interviews with members of the TMG and clinicians or researchers (recruiters) will explore their perspectives on the RCT, and where relevant, their experiences of recruitment. Interviews with eligible women will explore views on the presentation of study information, understanding of trial processes (e.g. randomisation), and reasons underlying decisions to accept or decline the trial. Professionals as well as women will be purposefully sampled, to build a sample of variation on the basis of characteristics such as professional expertise, trial recruitment experience and study site or age and the final decision about trial participation (i.e. accept or decline), respectively.

The numbers specified above are estimates based on previous QRIs and the precise numbers will be guided by data saturation (when no new information is forthcoming) and other considerations (e.g. timing of interviews).

Interviews will take place at a mutually convenient location, in a suitably private and quiet setting or participants will be offered the option to be interviewed over the telephone or via a video-call. Interviews will be audio-recorded using an encrypted device (as described above). UoB's 'lone researcher' safety policies will be adhered to for any interviews taking place in non-public settings (e.g. participants' homes).

d) Observation of TMG and investigator meetings:

The QRI researcher will regularly observe and make detailed notes of study meetings to gain an overview of trial conduct and overarching challenges (logistical issues, etc.). These meetings may be audio-recorded with informed consent.

e) Study documentation:

The Participant Information Leaflet (PIL) and consent form will be contrasted with the interviews and recorded appointments, to identify any disparities or improvements that could be made.

9.1.2 Phase II: Development and implementation of recruitment intervention strategies

The QRI team, with the CI and TMG, will formulate a 'plan of action' to improve recruitment and information provision, grounded in the findings from Phase I.

Generic forms of intervention may include 'tips' documents that provide suggestions on how to explain the trial design and processes. Supportive and responsive feedback will be a core component of the plan of action, with the exact nature and timing of feedback dependent on the issues that arise. Site-specific feedback may cover institutional barriers, while multi-site group feedback sessions may address widespread challenges that would benefit from discussion.

All group feedback sessions will be aided by displaying anonymised data extracts from interviews and audio-recorded consultations. Individual confidential feedback will also be offered, particularly where recruiters experience specific difficulties, or where there is a need to discuss potentially sensitive issues.

Investigator meetings/teleconferences and site visits from the CI/TMG members may also be employed to discuss technical or clinical challenges (e.g. discomfort surrounding eligibility criteria).

9.1.3 Iterative nature of Phases I and II

Although the QRI has been presented as two distinct phases for clarity, in reality these are likely to overlap. New avenues of enquiry will emerge throughout the conduct of the QRI (e.g. in feedback meetings), and rigorous monitoring of screening logs before/after interventions may indicate a need for further investigations (Phase I) or intervention (Phase II).

9.1.4 Evaluating changes in recruitment figures and practice

Recruitment figures (numbers of screened, eligible, approached and randomised women) will be assessed before and after the 'plan of action' is implemented, and regularly monitored thereafter to assess changes. Continued targeted investigation of recruitment issues and delivery of feedback/training will be undertaken as necessary, with particular focus on changes in recruitment practice before and after the intervention.

9.1.5 Consent processes for the QuinteT Recruitment Intervention (QRI)

Healthcare professional consent:

Recruiting staff and TMG member consent will be obtained through a 'master' consent form that covers all aspects of the QRI. Research nurses or the QuinteT researcher will obtain written consent from all staff (wet ink paper consent form or eConsent online). This will be a one-off process to cover consent for all future recordings of appointments, interviews, and observations of TMG/investigator meetings throughout the study.

Patient consent:

(i) Audio-recording/observing recruitment appointments:

Patients will be provided with a copy of the Qualitative Studies PIL prior to or during their first PURSUIT trial discussion. Patients will be given sufficient time to read the information, ask any questions, and consider their participation in the Recruitment Study. Sites may potentially have different ways of identifying patients for the PURSUIT study, thereby requiring different consent processes. One of the approaches below would be adopted as necessary.

a) Single-step consent: During a consultation (face-to-face or remote) which involves a discussion about PURSUIT study participation, research nurses will check that patients have received, read and understood the Qualitative Studies PIL (provided previously).

Patients' written consent (wet ink paper consent form or eConsent online) will then be obtained if they agree to participate.

b) Two-step consent:
   - If patients were not provided with/did not receive the Qualitative Studies PIL in advance of their consultation, a two-step consent process will be adopted. Research nurses (or clinical collaborator) will briefly explain the purpose of audio-recording and ask patients to provide verbal consent for the discussion to be audio-recorded. The Qualitative Studies PIL will be provided to patients at the end of the consultation (directly, via post or electronically).
   - Similarly, if a patient's initial discussion about potential participation in the PURSUIT study is being conducted remotely, and the online eConsent cannot be used, research nurses will check to make sure the patient has read and understood the Qualitative Studies PIL provided prior to the discussion. Patients will then be asked to provide verbal consent for the discussion to be audio-recorded.

     In both instances above, verbal consent from patients will be documented by the research team on the 'Verbal Consent to Audio-recording' form. Patients who provide verbal consent will subsequently be asked to provide written informed consent for the audio-recording process. Written consent may be obtained using either the wet ink paper written consent form or online eConsent form which can be completed via post (paper form only), online, or during the patient's next face-to-face appointment. To obtain written consent via post (*only* after verbal consent has been given) the site staff should sign two copies of the written consent form and post both copies to the participant. The participant should complete and sign both copies of the written consent form and send one copy of the completed written consent form back to the site staff, keeping the other copy for their records. Future discussions about potential PURSUIT participation will be audio-recorded subject to receiving this written consent; if patients choose not to provide written consent, the recording made from their initial discussion will be deleted, and no further recordings made.

(ii) Interviews:

The QRI consent form will include a clause that asks patients if they would be willing to be take part in a future research interview. Patients may then be approached by the qualitative researcher.

9.1.6 Analysis of QRI data

Audio-recordings of interviews and appointments will be transcribed verbatim in full or in parts (targeted) by a UoB-approved transcription service/transcriber that has signed the necessary confidentiality agreements. Transcripts will be edited to ensure anonymity of respondents and stored securely, adhering to the university's data storage policies.

Interview data will be managed using NVivo software (QRS International), and analysed thematically using constant comparative approaches derived from Grounded Theory methodology (18). Audio-recorded recruitment appointments and follow-up discussions will be subjected to content, thematic, and novel analytical approaches, including aspects of targeted

conversation analysis and appointment timing (the 'Q-QAT method') (19, 20). There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Analysis of QRI data will be led by the qualitative research associate (RA) with the guidance of the QRI lead, with a sample of transcripts independently coded by both researchers.

Key issues identified from the observation notes of appointments and TMG/investigator meetings will be considered alongside other qualitative findings. Findings from all sources will be drawn together in a descriptive account that will be presented to the CI/TMG and will form the basis for the 'plan of action' (Phase II above).

9.2 Interview Study - Qualitative research to understand women's and clinicians' attitudes

Patient interviews will focus on attitudes to, and experiences of, endoscopic and surgical interventions. HCP views on the interventions will be explored, along with facets of trial participation.

9.2.1 Objectives

To explore through patient (participant) interviews:

i. At baseline (following randomisation): Health-seeking drivers; previous treatment experience and perceptions of effectiveness; product usage; perspectives on both endoscopic and surgical treatment options – what would they like/expect to be offered; expectations regarding outcomes; determinants of satisfaction.
ii. At follow-up (3 to 6-months following delivery of the treatment): Perspective on treatment received; positive and negative aspects of the treatment, including pain, post-procedure recovery, associated symptoms, symptom improvement or deterioration, new onset symptoms; return to activities and daily life impact, product usage.
iii. At long term follow-up (12- and 36-months following delivery of the treatment): Long term perspective on treatment received; symptom status; comparison with expectations, positive and negative aspects of the treatment; product usage; desire for further treatment; requirement for coping strategies; would they advocate the procedure; satisfaction with symptom status.

To explore through Clinician (Urologist/Urogynaecologist) interviews:

i. Perspectives on the different methods of treatment and available options within those groups; treatment preferences; reasons for endoscopic vs. surgical treatment decisions; technical aspects of the procedures;
ii. Perspectives on care outcomes – symptom status, length of recovery, long term results, complication rates;
iii. Perspectives on trial outcomes – women may receive different treatments than the clinician would usually advocate.

9.2.2 Overview

We will conduct qualitative interviews with study participants and clinicians involved in the trial to explore recurrent SUI generally, the acceptability and attitudes to the proposed treatments and to improve understanding of the shorter- and longer-term outcomes. To our knowledge

no studies to date have explored patient or clinician views on endoscopic/surgical treatment options for recurrent SUI.

9.2.3 Interviews

A standardised approach will be employed to explore the above areas in accordance with published qualitative research methods. Interviews will be carried out by an experienced qualitative researcher and will be conducted either face-to-face or over the telephone. Interviews will be semi-structured and follow a topic guide informed by literature review and discussion between study researchers and encourage participants to discuss their perspectives with regard to the aims above. Interview transcripts will be handled as above, using NVivo10 (or updated version if applicable). Analyses will be conducted by the qualitative researcher on an ongoing basis in an iterative manner, according to principles of thematic content analysis. Recordings will be listened to and transcripts read and re-read for familiarisation. Segments of text will be 'coded' by assigning descriptive labels. Codes will be grouped on the basis of shared properties to create themes and coded transcripts will then be examined and compared to inductively refine and delineate themes (constant comparison). A subset of interviews will be independently analysed by a second study researcher and coding discrepancies discussed to maximise rigour and reliability. Plausibility of data interpretation will be further discussed between the study team throughout the analyses. Descriptive accounts of the audio-recordings and interviews will be prepared.

9.2.4 Participant sampling and recruitment

Theoretical purposive (non-probability) sampling will be used to ensure the diverse characteristics of the population are sampled (e.g. participant's varying in age, clinical history, intervention arm, duration of symptoms). Geographical distribution will also be factored to ensure representation of varied populations. Sampling and analyses will continue in iterative cycles until no new themes are emerging and established themes cease evolving (data saturation). It is anticipated all recruiting clinicians will be required for the feasibility stage to evaluate QRI components, followed by approximately 40 patient interviews (20 in each intervention arm) for both baseline and each follow-up evaluation during the main trial (post-procedure, one year and three-year follow-up). It will be important to follow-up as many of the same women as possible for the interviews at the four time points to explore the intervention trajectory. We plan to interview approximately ten clinicians again at participating sites in order to capture sufficient viewpoints to evaluate the clinical perspective on both intervention arms involved.

9.3 Interview conduct

Informed consent for qualitative interviews will be sought at the time of main study consent, alluding to interviews at a number of time points. After discussing concerns or questions, verbal informed consent will be requested, and audio-recorded. Participants will be informed that non-participation or withdrawal from the Interview Study will not affect their involvement in the main study.

10 SAFETY

Serious and other adverse events (S/AEs) will be recorded and reported in accordance with the Good Clinical Practice (GCP) guidelines and the Sponsor's Research Related Adverse Event Reporting Policy.

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, medical device or intervention and which does not necessarily have a causal relationship with this treatment. In all instances, it will be up to the Principal Investigator of each participating site (or appropriate delegate, e.g. clinician) to determine whether the person's change in health is related to the trial. AEs are not continuous and persistent disease or symptoms, present before the trial, which fail to progress; signs or symptoms of the disease being studied (in this case recurrent SUI); or treatment failure.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening[a] • requires inpatient hospitalisation or prolongation of existing hospitalisation[b] • results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect. **NB:** Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious. Medical judgment will be exercised in deciding whether an AE is serious in other situations.

[a] *The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.*

[b] *The definition of hospitalisation is an unplanned overnight stay. Note, however, that the patient must be formally admitted – waiting in outpatients or an Accident & Emergency Department (A&E) would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g. respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting unless complications occur.*

10.2 Severity classifications

Mild event	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event	An event that prevents normal everyday activities.

10.3 Relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

10.4 Identification of AEs

Due to the nature of surgical treatment as employed for recurrent SUI, AEs are expected to occur throughout the course of the trial. Research sites are responsible for reporting AEs for their trial participants during the trial; see Section 10.6 for reporting details. Participants may also self-report any inpatient stays or events in their follow-up questionnaires or hospital appointments, which will prompt a hospital/GP note review if an unreported AE is indicated. The AE information will then be completed and verified.

10.5 Classification of S/AEs

The Principal Investigator (PI) of each participating site (or appropriate delegate, e.g. clinician) is responsible for categorising whether AEs are serious, expected, and related. A list of events that can be expected during/after any surgery, or within this patient population can be found below; other factors such participant history should not be taken into account.

Expectedness is not related to what is an anticipated event within a particular disease. AEs which add significant information on specificity or severity of a known, already documented AE constitute unexpected events. For example, an event more specific or more severe than that described below is considered unexpected.

For the PURSUIT Trial:

- pre-planned hospitalisation or elective procedures e.g. for pre-existing conditions which have not worsened do not constitute an AE. However, any hospitalisation of a pre-existing condition resulting from worsening, or elective procedures booked after the patient has signed the consent form would constitute an AE; and

- an AE is defined as 'related' if it occurs as a result of a procedure required by the protocol, whether or not this procedure is the specific intervention under investigation or whether or not it would have been administered outside the study as normal care.

The following events can be expected during/after any procedure/surgery or within this patient population:

- Anaesthetic complications, e.g. stroke or cardiac events such as myocardial infarction
- Operative injury to adjacent structure
- Fistula
- Return to theatre
- ITU admission
- New urinary tract symptoms
- Urinary tract infection
- Wound infection
- Pelvic organ prolapse (POP)
- Urinary retention/catheterisation (intermittent self-catherisation (ISC) and indwelling)
- Pain
- Implant exposure (tape, AUS)
- Incisional hernia
- Deep vein thrombosis (DVT)/Pulmonary embolism (PE)
- Bleeding/haematoma/blood transfusion
- Chest infection
- New sexual problems e.g. dyspareunia
- Other infections (sepsis, septicaemia, abscess, respiratory)
- Inflammation e.g. osteitis pubis
- Death

10.6 Recording and reporting procedures for all AEs

All adverse events (serious and non-serious) should be recorded in the participant's medical (patient) notes, and appropriate study CRF(s).

10.6.1 Reporting procedures for non-serious AEs

All adverse events (serious and non-serious) should be recorded in the participant's medical (patient) notes, and appropriate study CRF(s).

CRF AE data capture will include (as a minimum):

- a description of the event
- the date/time that it started and stopped

- the severity of the event
- details of any actions taken in response to the event.

The participant should be followed up by the hospital (site) research team until the event subsides.

If the event is defined as 'serious' (a SAE), the hospital (site) research team should proceed to follow reporting procedures for SAEs, outlined in Section 10.6.2, below.

10.6.2 Reporting procedures for SAEs

Sites will record all SAEs in the study SAE log in the investigator site file (ISF). A copy of this should be securely transferred to the central trial team/CTU on a monthly basis for monitoring and reporting purposes.

The central trial team/CTU will provide a summary report of all SAEs to the Data Monitoring Committee (DMC) on a regular basis (as agreed and described in their written charter). A copy of the SAE logs will be provided to the sponsor at routine sponsor meetings by the central trial team.

- **Expected SAEs** will *NOT* be reported to the Sponsor *unless* they are fatal. **Expected SAEs which *are* fatal** will be reported to the Sponsor within 24 hours of staff becoming aware of the event.

- **Unexpected SAEs which are *not* causally related to the research procedures** will not be reported to the Sponsor.

- **Unexpected SAEs which *are* causally related to the research procedures** (i.e. Serious Adverse Reactions (SARs)) will be reported to the Sponsor within 24 hours of staff becoming aware of the event. These will also be reported to the REC immediately (and must be within 15 days) by the central trial team.

All SAEs reportable to the Sponsor must be documented on the full "SAE/SAR Initial Report Form", which is provided by the central trial team.

- **Sites** should scan and email the form, with high importance, to the central trial team immediately after becoming aware of the event.
  Email: pursuit-trial@bristol.ac.uk, cc Marcus Drake (Chief Investigator) marcus.drake@bristol.ac.uk. *(Please note: typical working hours: Monday to Friday, 09:00-17:00. In the event of University closure dates, an out of office automatic response will notify the site of alternative contact details/arrangements).*
- **The central trial team** will confirm receipt with the site and forward the completed form to the Sponsor (and REC, if required) within the reporting periods noted above.

For each SAE reported to the Sponsor, the following information (as a minimum) will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to research procedures), in the opinion of the PI
- Whether the event would be considered expected or unexpected.

Each SAE must be reported to the Sponsor separately and not combined on one SAE form.

Any change of condition or other follow-up information relating to a previously reported SAE should be documented on the separate “SAE/SAR Follow Up Report Form” provided by the central trial team.

As above, sites should scan and email the form to the central trial team who will confirm receipt and forward it to the Sponsor (and REC, if required) within the necessary timeframes, i.e. as soon as it is available or within at least 15-days of the information becoming available to the research team.

Events will be followed up until the event has resolved or a final outcome has been reached.

Figure 4 below summarises the safety reporting requirements.

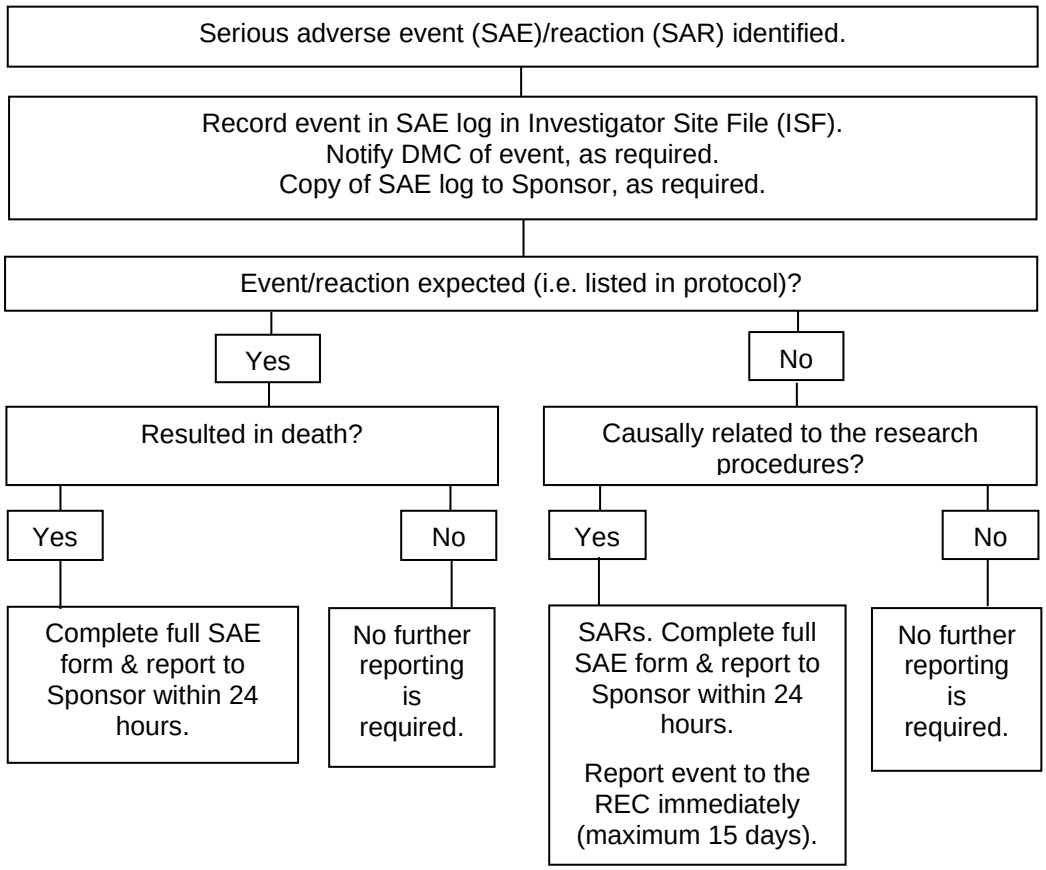

Figure 4 Overview of safety reporting requirements

10.7 Responsibilities

All adverse events will be documented and reported in accordance with North Bristol NHS Trust's Safety Reporting Standard Operating Procedure (SOP).

10.7.1 Principal Investigator (PI)/research nurse

PIs and research nurses (or suitably trained delegates) at each site will be checking for AEs when participants attend for treatment/follow-up, and at specified data collection points (see Section 8). They will be responsible for:

- Using medical judgement in assigning seriousness, causality and expectedness.
- Ensuring that all SAEs are documented.
- Ensuring that all expected SAEs resulting in death and all unexpected SAEs which are causally related to the research procedures are reported as per the procedures noted above, including the provision of further follow-up information as soon as available.
- Ensuring that SAEs are chased with the central trial team if a record of receipt is not received within 2-working days of initial reporting.

10.7.2 Chief Investigator (CI)

The CI will be responsible for:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all reportable SAEs.
- Ensuring safety reports are prepared in collaboration with appropriate members of the TMG group for the main REC and DMC.
- Reporting safety information to the independent oversight committees identified for the trial (DMC and TSC).
- Expedited reporting of SAEs to the REC within required timelines.
- Notifying PIs of SAEs that occur within the trial.
- Central data collection of SAEs.

11 STATISTICS AND HEALTH ECONOMIC ANALYSIS

11.1 Sample size calculation

To inform our calculations we reviewed the literature using the ICIQ-UI-SF. A recent study of women with SUI suggested that the minimum clinically important difference was –5 when using anchor-based methods, and –2 with distribution-based methods (21). We felt that the conservative estimate of –2 (equivalent to a difference of 0.5 standard deviation (SD)) was an important difference. To allow for the possibility that 5% of women randomised to surgery instead receive endoscopic therapy before 1 year, we reduced difference to detect to –1.9. Thus we estimate that we need to recruit 250 women (125 in each group) to detect a difference in mean ICIQ-UI-SF at 1 year of 1.9 (assuming common standard deviation of 4.1; in line with the assumptions made in the study by Sirls *et al*.(21)) with 90% power and a significance level of 5%. This includes an inflation factor accounting for 20% loss to follow-up, as we are using a PROM as the primary outcome.

11.2 Analysis

All analyses and reporting will be in line with CONSORT guidelines. Primary analyses will be based on the intention-to-treat (ITT) basis, analysing women in the groups to which they were randomised. A full statistical analysis plan (SAP) will be developed and agreed by the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) prior to undertaking analyses for the main trial.

Summary of baseline data and flow of participants
Descriptive statistics will be used to summarise characteristics of patients and compare baseline characteristics between groups. Means and SDs will be used for continuous outcomes or medians and interquartile ranges if required for skewed data. Categorical variables will be summarised using frequencies and proportions. Baseline variables to be explored include those described in Section 8.2. Patient reported outcome scores based on standardised questionnaires will be calculated based on the developers' scoring manuals and missing erroneous items will be handled according to these manuals.

Secondary analyses will adjust for any prognostic variables showing a marked imbalance at baseline (ascertained using descriptive statistics).

11.2.1 Primary outcome analysis

The PROM, ICIQ-UI-SF at 1-year post-randomisation is the primary outcome. Comparisons between treatment arms will be made using a multivariable linear model with random effect for site to account for within-site correlation. The model will adjust for baseline ICIQ-UI-SF scores. The underlying assumptions of the model will be checked, and analyses adjusted accordingly.

11.2.2 Secondary outcome analysis

The secondary outcomes in this study are outlined in Section 2.5 and these explore the longer-term impacts of the intervention on self-reported and objective improvements in continence and sexual function. Continuous measures will be studied in the same manner as the primary outcome and ordered categorical variables will be studied using ordinal logistic regression. Where outcomes are measured at multiple time points post-randomisation repeated measures analyses will be used to examine whether treatment effects are sustained, diminished or emerged later. These will be investigated formally by introducing an interaction term between treatment arm and time. All models will adjust for the outcome at baseline.

Surgical outcomes will be described using descriptive statistics for those women allocated to the surgical arm and no formal comparisons will be made between surgeries.

11.2.3 Subgroup analyses

We will conduct a small number of pre-defined subgroup analyses to assess whether the difference in ICIQ-UI-SF at 1-year between the two treatment arms differed according to baseline characteristics including age. Effect modification will be assessed by including an interaction term in the regression model and formal tests of interaction will be performed. These analyses will be outlined in detail in the SAP which will be agreed in advance by the TSC and DMC.

11.2.4 Adjusted analysis

All primary analyses will adjust for the outcome as measured at baseline. Secondary analyses will adjust for any prognostic variables demonstrating marked imbalance at baseline as determined using descriptive statistics.

11.2.5 Proposed frequency of analyses

Women will complete outcome measures at 6-months and 1-, 2- and 3-years after randomisation. They will be asked to consent to longer term follow-up, although this is not funded in this application. Analyses of the 6-month to 3-year follow-up data will be completed at the same time as the 2- and 3-year follow-up data provides context for the primary outcome data at 1-year. An independent DMC will review confidential accumulating data at its discretion, but at least annually. No interim statistical analyses by study arm are planned.

11.2.6 Procedure(s) to account for missing or spurious data

The primary analyses will be based on the observed data and a sensitivity analysis will be conducted where missing data are imputed using appropriate methods based on patterns of missingness.

Data will be entered promptly, and data validation and cleaning will be carried out throughout the trial. Where spurious data are observed, values will be checked against available records.

11.3 Economic evaluation

The base case cost-effectiveness analyses will be from an NHS perspective, comparing costs in relation to QALYs at 1-year follow-up. A societal perspective analysis at 1 year and a further NHS secondary care perspective analysis at 3 years, comparing costs in relation to QALYs will also be conducted. Discounting for the 3-year analysis will be based on NICE recommended rates at the time, currently 3.5% for both costs and benefits. The relevant most up-to-date NHS reference costs will be used to value the information obtained from either the Hospitals' costing systems or HES. Community-based NHS resource use, time off work and normal activities will be valued using routine data e.g. Unit Costs of Health and Social Care; ONS Annual Survey of Hours and Earnings. Participant car travel will be valued using HMRC advisory fuel rates. All other travel costs and out of pocket expenditure will be valued as reported by the participants.

The EQ-5D-5L will be administered at baseline, 6-months, 1-, 2- and 3-years after randomisation. These values will be transformed into utility scores and individual QALYs will be calculated using the area under the curve approach.

At both 1-year and 3-year time points and for all perspectives, differences in mean costs and QALYs between the trial arms will be evaluated using appropriate regression techniques, adjusting for site; whether women have hypermobility or intrinsic sphincter deficiency as ascertained at baseline and in the case of QALYs, baseline utility.

Incremental cost-effectiveness ratios will be calculated if no arm is dominant i.e. more effective and less costly than the other arm. Incremental net monetary benefit statistics will also be produced over a range of willingness to pay thresholds for a QALY.

Additionally, at 1 year a cost consequence analysis from an NHS perspective, will be used to compare the differences in costs and the differences in ICIQ-UI-SF.

Uncertainty for all analyses will be addressed using cost-effectiveness acceptability curves and sensitivity analyses. A health economics analysis plan (HEAP) will be produced prior to analysis, in which sensitivity analyses will be outlined. These are likely to include different approaches to dealing with missing data, based on reasons why the data might be missing.

12 DATA MANAGEMENT

12.1 Source data and documentation

Source data is the first place the data is recorded. Source data for this trial will consist of paper or electronic (where eConsent has been taken) copies of the consent form, participant completed questionnaires (paper or electronic), paper CRFs designed specifically for the study and audio-recordings of consultations and interviews. Where data is recorded first in the patient's medical records that is, and will remain, the primary source data. Any specifically designed CRFs would be considered supplementary source data.

When a participant consents to enter the trial, they will have a unique participant identification number allocated. Personal data entered directly into the password protected database and maintained on a SQL Server database system within the University of Bristol will only be accessible to members of the research team. Any data stored on laptops will be encrypted. Any information that is analysed or transferred outside the European Economic Area (EEA) will be anonymised.

Participants will be informed via the PIL that personal information such as their name, email address and phone number will be stored on the secure database with the central trial team.

Data obtained by paper will also be entered onto the password protected database (by trained members of staff). Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to PURSUIT trial staff. Information capable of identifying participants will not be removed from clinical sites apart from when sending data to the trial team at the University of Bristol. This data will not be made available in any form to those outside the trial, with the exception of NHS digital for linkage or for inspection purposes by the sponsor or other regulatory authorities. Consent forms and clinical letters with personal identifiable data will be stored in a locked filing cabinet. Participant details will be anonymised in any publications that result from the trial.

12.2 QRI and qualitative research data

Where applicable, site staff will be asked to set up an audio-recorder during recruitment discussions with potential participants. The audio-recorder must be stored securely at sites in a locked drawer/cabinet when not in use and returned to the central trial team securely at the end of the study. Audio-recordings of appointments in which the trial is discussed will be held on the encrypted digital audio-recorder and regularly transferred to the University of Bristol through approved secure data transfer facilities and/or encrypted flash drives/memory cards that adhere to NHS Trust policies. Interview data captured on an audio-recorder will be uploaded to a secure, password protected University of Bristol server as soon as possible after each interview.

All audio-recorded data will be stored on a password protected computer maintained by the University of Bristol. Audio-recordings will be transcribed by University of Bristol employees or University-approved transcription services. Audio-recordings and transcripts will be labelled with a unique identification number, edited to ensure anonymity of respondents, and stored securely adhering to the University's data storage policies.

Anonymised quotations and parts of voice-modified recordings may be used for training, teaching, research and publication purposes for this and future studies. Anonymised transcripts may be made available to other researchers who secure the necessary approvals

for purposes not related to this study, subject to individual written informed consent from participants. At the end of the study, anonymised data (including transcripts of audio-recordings) will be stored in a secure research data storage facility, alongside the other study data; see Section 12.8 below, for further details.

12.3 Data collection

Baseline data will be collected face-to-face or remotely, entered directly into paper CRFs and either entered at site by clinical site staff into a trial specific database or sent securely (by post or electronically) to the central trial team for entry into the trial specific database. Participant questionnaires at 6-months, 1-, 2- and 3-years after randomisation will be sent to the participants by the central trial team and, depending on the patient's preference, they will be able to complete the questionnaires electronically or return paper copies to the central trial team (or by telephone if requested to reduce loss to follow-up).

Sections 2 and 8.1 outline the standardised data collection tools being used. A central administrative database will be set up by the BRTC that prompts the trial team when participant questionnaires are due. PIs (or delegated member of staff) must keep records of all participating patients (sufficient to link records e.g. CRFs and hospital records), all original signed informed consent forms and copies of the CRFs.

Questionnaire return from the participants will be followed up. If a participant fails to return a questionnaire, a total of up to four contacts per timepoint (either phone, email or post) can be made by the site/central trial team. In case of a missing questionnaire, the response to the questionnaire can be collected over the phone by the central trial team, or site.

12.4 Data handling and record keeping

Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018 and General Data Protection Regulation (GDPR).

For this trial, research data will be kept for at least 5 years after the end of the trial. Personal data (e.g. name and address, or any data from which a participant might be identified) will not be kept for longer than is required for the purpose for which it has been acquired.

All electronic data files will be saved in a secured computer and to a password protected University of Bristol network space, in accordance with the University of Bristol's data security policies.

12.5 Database platforms

All administrative and clinical study data will be stored in separate REDCap instances. REDCap is a secure, web-based electronic data capture (EDC) system designed for the collection of research data. The system has been developed and supported by Vanderbilt University. BRTC at the University of Bristol (UoB) has set up its own infrastructure so that all systems are hosted at and supported by UoB.

A Relational Database Management System will be used to provide integration services between administrative and clinical databases. These data will be stored here, to support the workflow of the study team. These data will be not made available for analysis. These data are stored in a SQL Server system maintained by UoB.

12.5.1 Administrative Data

The Administrative data will be kept in a secure database that is only accessible from within the UoB firewall. All users will require (at least honorary) contracts with UoB in order to access it.

12.5.2 Clinical Data

The clinical data will be stored on a separate server to the administrative data. Anonymised clinical data is linked by a study participant ID. Email addresses are collected as they are essential for the correct functioning of the survey feature. The 'Email Address' field is flagged as an identifier and not included in the export for the statistician, so the data set can be considered pseudonymised at export and doesn't need further processing.

12.5.3 Storage

North Bristol NHS Trust and the Bristol Randomised Trials Collaboration (University of Bristol) are joint data controllers for the PURSUIT Trial. Data will be held at the University of Bristol and will conform to the University of Bristol Data Security Policy and in Compliance with the GDPR as it applies in the UK, tailored by the Data Protection Act 2018.

12.6 Access to Data

For monitoring purposes, the CI will allow monitors from the sponsor (or delegate), persons responsible for the audit, representatives of the Research Ethics Committee and other Regulatory Authorities to have direct access to source data/documents.

The Data Manager (in collaboration with the CI) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released.

12.7 Archiving and destruction of trial materials

An archiving plan will be developed for all trial materials. Data will be held in compliance with the sponsor's standard procedures. All research data will be retained in a secure location during the conduct of the trial and for at least 5 years after the end of the trial. Data will be kept at the University of Bristol for this time and, at the end of the archiving period, will be destroyed by confidential means with the exception of a final trial dataset which will be made available for data-sharing purposes (see section 12.8 below). Where electronic records are in use, University of Bristol and/or North Bristol NHS Trust's policy will be followed. The approval of NBT as owner of data and Study Sponsor, as well as the CI, will be sought prior to destruction of the data.

Participating sites will be responsible for ensuring that all study records held at site are archived appropriately when notified by the Sponsor/BRTC (central trial team).

12.8 Access to the final trial dataset

Anonymous research data, including QRI audio-recordings and associated data, will be stored securely and kept for future analysis with participant consent. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses. Members of the TMG will develop a data sharing policy consistent with UoB policy. Data will be kept anonymous on research data storage facility (RDSF). Requests for access to data must be via a written confidentiality and data sharing

agreement (DSA) available from the RDSF website which will be confirmed by the CI (or appointed nominee).

The DSA should cover limitations of use, transfer to third parties, data storage and acknowledgements. The person applying for use of the data will be scrutinised for appropriate eligibility by members of the research team.

13 TRIAL MANAGEMENT

The Chief Investigator (CI) will take overall responsibility for managing the various components of the trial and will meet at least monthly with the leads for each component. In years 1-2 the CI will be establishing the trial, supported by the trial manager and lead research nurse. The BRTC, a UK Clinical Research Collaboration (UKCRC) registered trials unit, as part of the Bristol Trials Centre, will support the delivery and conduct of the trial.

13.1 Trial Management Group (TMG)

A TMG will meet at least once each quarter in the first 2 years, then 6-monthly to review progress, with potential for additional ad hoc meetings, as required/indicated. The TMG will have responsibility for the day-to-day management of the trial and will report to the TSC. It will be chaired by Professor Marcus Drake (CI) and will consist of relevant co-applicants, including Patient and Public Involvement (PPI) co-applicants, sponsor as well as representatives from the BRTC. Meetings will be in person and by teleconference to maximise attendance.

13.2 Trial Steering Committee (TSC)

Membership, responsibilities and reporting mechanisms of the TSC will be formalised in a TSC charter. The TSC will make recommendations/key decisions during the trial to the TMG and minutes will be sent to the funder.

The TSC will comprise of an independent chair Cathryn Glazener plus three additional independent members (Suzie Venn (clinician), Andrew Elders (statistician) and an independently nominated PPI representative (PPI member) ^. The independent members will cover expertise in statistics, trials, urology and urogynecology. Marcus Drake (CI) will also be a formal (not-voting) member of the TSC. Observers may also attend (including other members of the TMG or members of other professional bodies) at the invitation of the Chair. The TSC will meet for the first time by month 6 of the trial and then 6-monthly thereafter.

13.3 Data Monitoring Committee (DMC)

The DMC will meet once prior to recruitment of the first participant and convene at years 2, 3, 4 and 5 prior to the TSC meeting to review the AE data and any other ethical aspects that arise and report to the TSC. Responsibilities and reporting mechanisms of the DMC will be formalised in a DMC charter.

It will comprise an independent chair, Graeme MacLennan, and two other independent members, Stelios Doumouchtsis and Charlotte Foley with expertise in trials and statistics, and gynaecology and urology ^. In addition, Marcus Drake (CI) and Trial Manager will attend the open session only. The Senior Statistician will attend the open session only and Trial Statistician will attend both open and closed sessions.

^ *if for any reason named members of the TSC and/or DMC are unable to continue as a member of the committee, then a suitable replacement will be sourced.*

13.4 Patient and Public Involvement (PPI)

People with recurrent SUI will be involved in every phase of the research trial. This will involve design of recruitment process, review of the protocol, participant information, consent and data collection forms and informing dissemination of the research findings to participants. A Patient Advisory Group (PAG) will be formed, it will meet biannually in year 1 and 6 and

annually in years 2, 3, 4 and 5. This group will be co-chaired by the PPI head who is also a co-applicant.

13.5 Sponsor

This trial will be sponsored by North Bristol NHS Trust. The sponsor will be responsible for overall oversight of the trial.

13.6 Funding

This project was funded by the National Institute for Health Research HTA programme (project number 17/95/03).

14 MONITORING, AUDIT AND INSPECTION

The study will be monitored in accordance with the sponsor's (North Bristol NHS Trust) Monitoring SOP, which is consistent with the UK Policy Framework for Health and Social Care Research. All trial related documents will be made available on request for monitoring and audit by North Bristol NHS Trust, the Research Ethics Committee (REC) and available for inspection by other licensed bodies.

A trial monitoring plan will be developed by the sponsor and agreed by the TMG and CI based on the trial risk assessment which may include on site monitoring.

The sponsor usually delegates some of the monitoring to the central trial team. The following checks would be typical:

- That consent is taken by an appropriately authorised person
- That written informed consent has been properly documented
- That data collected are consistent with adherence to the trial protocol
- That CRFs are only being completed by authorised persons
- That SAE recording, recording of protocol deviations and reporting procedures are being followed correctly
- That no key data are missing
- That data is valid
- Review of recruitment rates, withdrawals and losses to follow-up.

14.1 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented on the relevant forms and reported to the CI and sponsor. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, DMC and the TMG.

A serious protocol breach will be reported to the Sponsor as soon as possible. The sponsor will determine the seriousness of the breach and whether onward reporting to the REC is necessary.

14.2 Notification of Serious Breaches to GCP and/or the protocol and Poor-Quality Data

A "serious breach" is a breach which is likely to affect to a significant degree:
a) the safety or physical or mental integrity of the subjects of the trial; or
b) the scientific value of the trial.

The sponsor must be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per appropriate sponsor SOP. Repeated major breaches may be considered serious breaches and notified to the REC and HRA.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Governance and legislation

This trial will be conducted in accordance with:

- International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines
- UK Policy Framework for Health and Social Care Research
- Data Protection Act (DPA) 2018
- General Data Protection Regulation (GDPR)

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC.

Before any site can enrol participants into the trial, the CI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes along with other documentation required for the sponsor to grant sites with a greenlight letter.

For all amendments the CI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' R&D departments that permissions are ongoing.

This research trial will be run in accordance with ICH GCP. ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible.

15.2 Research Ethics Committee (REC) review and reports

Ethics review of the trial protocol and other trial related participant facing documents will be carried out by a UK REC. HRA approval will be sought alongside REC. Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.

All correspondence with the REC will be retained in the Trial Master File (TMF)/Investigator Site File (ISF).

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI (or designee) will notify the REC of the end of the study and if the study is ended prematurely (including the reasons for the premature termination). Within one year after the end of the study, the CI (or designee) will submit a final report with the results, including any publications/abstracts, to the REC.

ICH GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to ICH GCP guidelines.

15.3 Peer Review

The proposal for this trial has been peer-reviewed through the NIHR HTA peer-review process, which includes independent expert and lay reviewers.

15.4 Poor quality data

The quality of the trial data will be monitored throughout the trial and data completeness will be reported to the DMC and TSC, and any cause for concern over data quality will be highlighted and an action plan put in place.

15.5 Financial and other competing interests

This applies to the chief investigator, PIs at each site and committee members for the overall trial management. Research team, trial committee members and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

15.6 Risks and benefits

Given the routine use of the proposed surgical and endoscopic procedures for the treatment of recurrent SUI, the study team (as supported by the TSC and DMC) believe this study does not pose any specific risks to individual participants, nor does it raise any serious ethical issues.

As with all trials the main benefit of participating is an altruistic one to improve care for subsequent women requiring these interventions. As detailed in Section 8.11 (above), we will offer women gift vouchers upon completion of specified trial procedures, at specified timepoints.

The PIL will provide clear details of the anticipated risks and benefits of taking part in the study. The risk and benefits of the study will be discussed with the participating sites as part of the process of inviting women to take part and providing written informed consent.

15.7 Indemnity

The necessary trial insurance is provided by the Sponsor. North Bristol NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this trial. The PIL provides a statement regarding indemnity for negligent and non-negligent harm.

16 DISSEMINATION POLICY

The results of the study will be published in the academic press and provided to the sponsor for publishing on the sponsor's research website. We will also publish results on the UoB study website. We will work with our PPI partners to prepare lay summaries to enhance broader dissemination and engagement. All participants will be offered a lay summary of the main findings of the study. The trial will also be presented at national and international conferences such as the International Continence Society (ICS). This will in turn be used by the national and international community to inform practice, with incorporation into NICE Guidelines and other international Guidelines such as those of the European Association of Urology.

The findings of the trial will be disseminated nationally through BAUS and BSUG, part of the Royal College of Obstetrics and Gynaecology, as these are the specialist bodies with the responsibility for guiding clinical practice, policy matters, research priorities, governance and training in matters related to incontinence. BAUS and BSUG are well placed to implement the findings by informing NHS policy (NICE) and by dissemination of evidence-based clinical practice to its members. The trial registration will be reviewed at least annually, and results will be uploaded within 1-year of the last patient last visit.

Besides disseminating the main findings, we anticipate providing participants and sites with newsletters at suitable intervals during the study, to help keep them informed of progress and help maintain interest.

17 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in UK Policy Framework for Health and Social Care Research, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the **Study Sponsor**:

Signature: Date:

..../...../.....

Name (please print):

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

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Statistician:

Signature: Date:

..../...../.....

Name: (please print):

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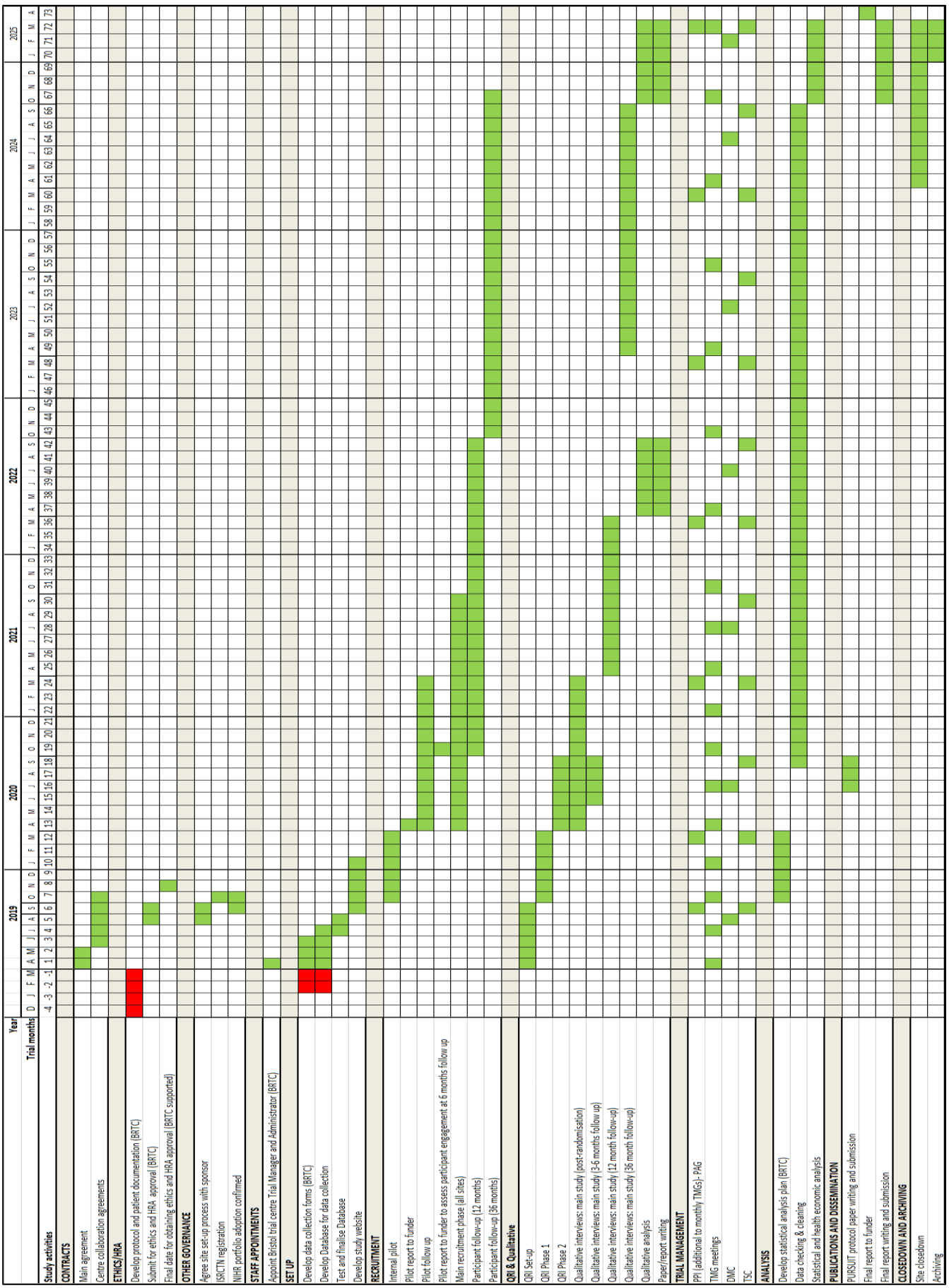
18 APPENDIX 1: PURSUIT Gantt Chart



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