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The importance of overcoming the challenges in delivering the Proper Understanding of Recurrent Stress Urinary Incontinence Treatment (PURSUIT) study

Caroline Pope [a,b], Nikki Cotterill [c,d], Marcus J. Drake [d,e,*], Beth Fitzgerald [a], Tamsin Greenwell [f], Swati Jha [g], J. Athene Lane [a,b], Stephanie J. MacNeill [a,b], Sangeetha Paramasivan [a,b], Wael Agur [h,i], Alison White [j]

[a] Department of Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[b] Bristol Trials Centre, University of Bristol, Bristol, UK
[c] Faculty of Health and Applied Sciences, School of Health and Social Wellbeing, University of the West of England, Bristol, UK
[d] Bristol Urological Institute, Southmead Hospital, Bristol, UK
[e] Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[f] Department of Urology, University College London Hospital, London, UK
[g] Sheffield Teaching Hospitals, NHS Foundation Trust, UK
[h] School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK
[i] University Hospital Crosshouse, NHS Ayrshire and Arran, Kilmarnock, UK
[j] Patient and Public Involvement (PPI) Representative, University of Bristol, Bristol, UK

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ABSTRACT

There is insufficient data to assess the effects of any of the different management strategies for recurrent or persistent stress urinary incontinence in women after failed interventional treatment. The evidence base lacks well-designed randomised trials with sufficient power to answer this hugely important issue. PURSUIT is the Proper Understanding of Recurrent Stress Urinary Incontinence Treatment study, assessing through randomisation whether endoscopic or surgical interventions achieve better cure and/or quality of life outcomes at 1 year, and will follow up to 3 years to see if responses are sustained. The manuscript provides an outline of the study, describes the challenges it has faced, and advocates the importance of ensuring its successful delivery.

1. Introduction

Stress urinary incontinence (SUI) in women may seem an easy symptom to treat, but the challenge of improving quality of life (QoL) can easily be under-estimated. Interventional surgery may transform a woman's life for the better, whilst for others only a partial or minimal improvement may be seen. This disappointing outcome is exacerbated by risks of adverse effects, such as urinary retention, dyspareunia or prolapse, which can be severe enough to outweigh the presenting symptom. To this can be added the risk of serious complications where vaginal mesh has been used [1,2]. Mesh complications can need several operations and still leave those affected with ongoing symptoms [3]. Around one third of women who were initially continent develop significant SUI within a year after mesh removal and proceed to further anti-incontinence surgery [4]. Psychologically, an unsatisfactory outcome can have high impact, as it is often detrimental to relationships, work life and health. Furthermore, it follows a protracted time course of symptoms since childbirth, including referrals to several healthcare professionals and multiple treatments. For many women there may be a sense of frustration, feelings of anger, and anxiety when faced by the prospect of yet another intervention.

The experiences of a woman who had hopes of SUI cure from an intervention, but actually never saw improvement (persistent SUI) or developed recurrent SUI, add up to make a very challenging situation. By this stage, the symptoms and wider challenges to relationships and work life have been chronic, and faith in the medical profession may have been shaken. Hence, making appropriate recommendations based on robust evidence is vital. Yet, there is very little evidence to offer these patients as they decide what to do about their next treatment. A systematic review found insufficient data to assess the effects of any of the different management strategies for recurrent or persistent stress incontinence in women after failed midurethral tape surgery [5]. The wide variation in reported outcomes for all SUI and

* Corresponding author at: Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.
E-mail address: marcus.drake@bui.ac.uk (M.J. Drake).

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recurrent SUI procedures is noteworthy [6]. The evidence base entirely lacks well-designed and properly executed randomised trials with sufficient power to answer the hugely important issue of how to treat this situation. Healthcare professionals seeing women with ongoing incontinence despite treatment are in an invidious position, since the medical profession has manifestly failed to identify best practice.

PURSUIT is the Proper Understanding of Recurrent Stress Urinary Incontinence Treatment (ISRCTN 12201059) trial. This randomised study will assess whether endoscopic or surgical interventions achieve better cure and/ or quality of life outcomes at 1 year, and will follow up to 3 years to see if responses are sustained. Here we provide an outline of the study, describe the challenges it has faced, and advocate the importance of ensuring its successful delivery.

2. Study design

PURSUIT is a two-arm randomised controlled trial in adult women diagnosed with recurrent or persistent SUI, comparing urethral bulking injections ("Endoscopic arm") with a surgical operation ("Surgical arm") [Fig. 1]. In the surgery arm, the type of surgical intervention provided will depend on two factors: the operations currently available in the UK National Health Service (NHS), as well as joint decision making involving the woman and her clinician after the participant has reviewed the patient information leaflet. Operations currently available in the NHS include colposuspension, autologous urethral sling or artificial urinary sphincter; midurethral tapes (MUT) are not available. Any licensed or guideline-supported urethral bulking agent can be used in the endoscopic arm, and single or repeat injections are permitted.

PURSUIT was designed with a very active contribution from people affected by recurrent or persistent SUI. The study will take place in around 30 urology or gynaecology departments in the UK, with specific expertise in urogynaecology or functional urology. The only inclusion criterion is recurrent or persistent SUI which is bothersome, and the patient is willing to consider interventional therapy. The exclusion criteria are the presence of predominant urgency incontinence, significant pelvic organ prolapse, urethral diverticulum or neurological disease. Pregnant women and those currently being treated for gynaecological or bladder cancer are also excluded. Any exposed vaginal mesh, for example exposed MUT, needs to be dealt with and resolved before consideration. Recent pelvic surgery, current participation in another relevant study and inability to give informed consent are also exclusion criteria.

The primary outcome is a patient-reported outcome of incontinence, the International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF) captured at 1 year after randomisation. Secondary outcomes include ICIQ-UI-SF at 6 months, 2 years and 3 years, and Patient Global Impression of Improvement (PGI-I) and POP/Incontinence Sexual Function Questionnaire (PISQ-IR) at 1, 2 and 3 years. Operative criteria, such as hospital stay and return to usual activity, and adverse events of treatment/ re-treatment will be captured. Cost-effectiveness will be measured in a health economic component. A QuinteT Recruitment Intervention (QRI) [7] has been integrated within the pilot phase of the trial to identify recruitment challenges and to collaboratively develop strategies to overcome them, disseminated through recruiter training sessions in the pilot and main phase of the trial. A qualitative study will evaluate patient experiences of the intervention, and clinicians' views, using semi-structured interviews during feasibility, baseline and after the intervention package.

250 women will be recruited in order to detect a difference in mean ICIQ-UI-SF at 1 year of 1.9 (assuming a standard deviation of 4.1) with 90% power and a significance level of 5%, allowing for 20% loss to follow-up. Patients will undergo evaluation and urodynamic testing as per UK National Institute of Health and Care Excellence guidance. Due to the timescales, any crossover cases will generally receive retreatment after 1 year, and so are unlikely to affect the primary outcome.

3. The current challenges

PURSUIT addresses a condition which is not life threatening, and this has meant the Covid-19 pandemic brought delivery of the study to an abrupt halt in March 2020. Even as the restrictions brought about by the pandemic gradually lift, the healthcare system in the UK has to deal with several issues. Access to primary healthcare is currently difficult in some areas due to heavy demand, meaning that women find it hard to obtain specialist referral. Hospital services are still dealing with changes in practice, prioritisation of urgent care and staffing issues. Many hospitals have limited capacity for admitting patients, so that surgical procedures now face substantial waiting-lists. As things stand, women may delay seeking treatment for recurrent or persistent SUI. In light of these challenges, adaptations were made to the design and conduct of the study to allow recruiters to screen, identify, approach, and take consent from patients but delay their randomisation and collection of baseline data until study interventions can proceed. The introduction of remote processes such as electronic consent (eConsent) facilitated the continuation of recruitment when few face-to-face consultations were being held.

A key recruitment challenge that has been identified in PURSUIT is centred on clinical equipoise [8]. The trial was designed in collaboration with women affected by recurrent or persistent SUI, after establishing that there was genuine collective uncertainty [9] in the clinical community about whether surgery or bulking agents best suits this population group. In order to ensure the study design was acceptable to the study population, a carefully designed patient information leaflet about the interventions and participation in the study went through multiple levels of scrutiny, including input from patient representatives. This helped ensure that the written information presented a neutral and balanced position, so that the women could make this very personal decision on an individual basis. The study encourages clinicians to describe the need for evidence for treatment choice in this situation, and to provide the patient information leaflet as an early step in the clinical pathway — ideally using the leaflet to describe the intervention, guide verbal discussions and thereby minimise risk of bias and influence. The rationale behind this suggestion was that when patients have had sufficient time to read, understand and reflect on the written information provided in advance, they will be familiar with the potential interventions and the basis of randomisation in research. This then provides a good grounding for discussions to answer questions about interventions and whether to participate in the study – a task that can be further guided by the written information. However, much of this depends on women being offered the study and being made fully aware of it – a role that rests with the clinicians.

It is acknowledged that individual clinicians who have treatment preferences (sometimes based on specific patient characteristics) may find it challenging to put the trial forward to potentially eligible patients, even when the eligibility criteria are clear. Hence, they may face intellectual and emotional challenges in arriving at a position of equipoise that facilitates good recruitment practices [8–10]. This may lead them to override or undermine an initial statement of equipoise. Potentially it may give rise to biased terminology or unbalanced information, or may prompt the clinician to make treatment recommendations. It has been shown that these challenges can be overcome with training and support for clinicians [11], which is the primary aim of the QRI training integrated in the PURSUIT study. Clinicians recruiting to PURSUIT are encouraged to undergo the training, which is grounded in qualitative data collected from the trial. The support of the extended clinical community in ensuring every eligible patient is offered the trial in a balanced manner is crucial to ensure the success of the PURSUIT trial.

The robust patient contribution in PURSUIT was key to designing the patient information leaflet about the interventions and participation in the study. The leaflet went through multiple levels of scrutiny to ensure it presented a neutral position, so that the women could make

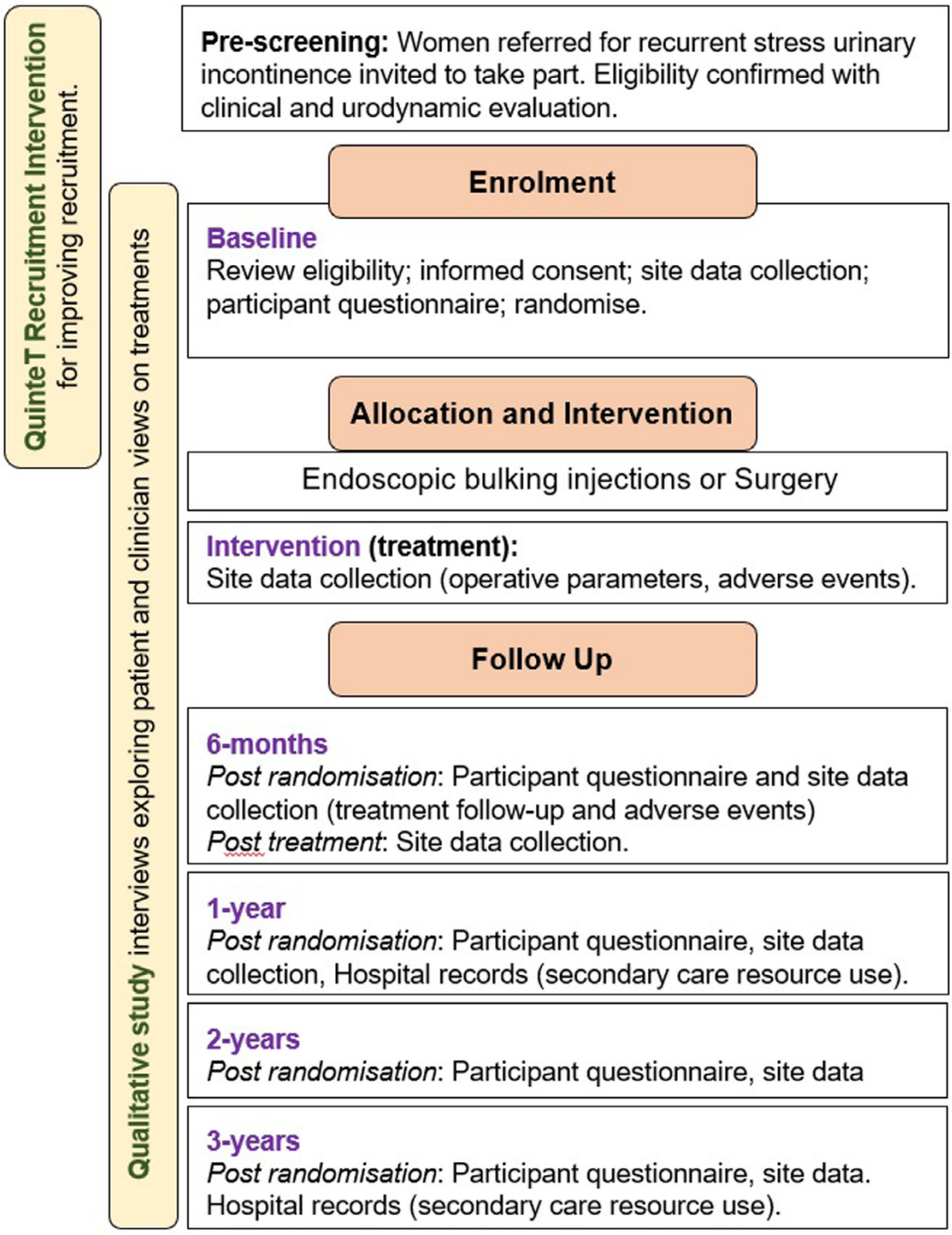

Fig. 1. Study flow chart for PURSUIT.

this very personal decision on an individual basis. The study encourages clinicians to describe the need for evidence for treatment choice in this situation, and to provide the patient information leaflet as an early step in the clinical pathway — with the leaflet used to describe the interventions neutrally, and thus reducing risk of bias and influential coaching. Once the woman concerned has had the chance to study the information leaflet, she will be familiar with the potential interventions and the basis of randomisation in research. That then provides a good grounding for discussions to answer questions about interventions and whether to participate in the study.

4. Discussion

The 2021 UK national report on pelvic floor disorders identified that urgent action is needed to address inequalities in care and improve outcomes, and this includes a focus on research [12]. The NHS constitution for England states a commitment to innovation and to the promotion, conduct and use of research to improve the current and future health and care of the population. This includes an openly-stated pledge "*to inform you of research studies in which you may be eligible to participate*" [13]. Benign urology and urogynaecology appear to lag behind the

oncological setting, where equity of access to research trials is better established. In that setting, the clinical team more often facilitates patient access to studies, rather than acting as a gatekeeper.

The current evidence base for management of recurrent or persistent SUI is insufficient in terms of both quantity and quality, and does not permit firm recommendations to be made on the most effective treatment. PURSUIT provides a major opportunity, with a pragmatic design resulting from active engagement with patient and public input. However, there are major challenges in delivering the study in the current healthcare climate in the UK. The exclusion criteria are kept as limited as possible, principally covering risk factors which place a woman at increased risk of adverse outcome from surgery [14], for example neurological disease [15]. Hence, a strong focus on making every potential recruit aware of the study is essential, such that it needs to be supported throughout the functional urology and urogynaecology professions [16]. This means that the anachronistic view of studies as bringing additional burden to patients must be replaced by an attitude that they have the right to participate in research should they choose, as is increasingly the case in oncological settings.

Crucially, the women who could participate in the study should be presented with unbiased information, and be free to make a decision according to their own individual view. They will have had some difficult experiences during the protracted course of their incontinence management, and this could influence their attitude towards effectiveness and adverse effects. While clinicians tend to look towards effectiveness as the key driver of treatment selection, the person directly affected by the outcome may well balance the potential outcomes differently. Professionals, with adequate support and training, can become skilled at good recruitment practices. This includes offering the trial to all eligible patients, providing unbiased information on the trial and treatments, and avoiding interpolating their own opinions into their trial discussions with patients. This enables the patient to make an informed decision regarding participation in research, which needs to be respected primarily. The use of the patient information leaflet is invaluable in providing clear and unbiased information, introducing the study in an appropriate way, and functioning as a clear guide for verbal discussions.

5. Conclusion

PURSUIT has the potential to provide the first adequate study for assessing interventional treatment of recurrent or persistent SUI, provided substantial pandemic-related and equipoise-based challenges can be overcome (with training and support for the latter), enabling the medical professions to fully engage with the study.

CRediT authorship contribution statement

Caroline Pope: Design of research, Execution of studies, Analysis and manuscript drafting, Analysis and writing of the results. **Nikki Cotterill:** Design of research, Execution of studies, Analysis and manuscript drafting. **Marcus J. Drake:** Design of research, Execution of studies, Analysis and manuscript drafting, Analysis and writing of the results. **Beth Fitzgerald:** Design of research, Execution of studies, Analysis and manuscript drafting. **Tamsin Greenwell:** Design of research, Execution of studies, Analysis and manuscript drafting. **Swati Jha:** Design of research, Execution of studies, Analysis and manuscript drafting. **J. Athene Lane:** Design of research, Execution of studies, Analysis and manuscript drafting. **Stephanie J. MacNeill:** Design of research, Execution of studies, Analysis and manuscript drafting. **Sangeetha Paramasivan:** Design of research, Execution of studies, Analysis and manuscript drafting. **Wael Agur:** Design of research, Execution of studies, Analysis and manuscript drafting. **Alison White:** Design of research, Execution of studies, Analysis and manuscript drafting.

Declaration of competing interest

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.cont.2022.100020.

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