INTRAVESICAL PREPARATIONS FOR RECURRENT URINARY TRACT INFECTION PREVENTION (THE VESPER TRIAL): A MULTI-ARM, MULTI-SITE OPEN LABEL RANDOMISED SUPERIORITY TRIAL

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Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust Level 1, Regent Point Regent Farm Road Gosforth Newcastle upon Tyne NE3 3HD
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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 the relevant trial regulations, GCP guidelines, and CTR's SOPs.

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

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General Information This protocol describes the VESPER clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR

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Trial Co-ordination:

The VESPER trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the VESPER Trial Management Group (TMG).

For **all queries,** please contact the VESPER team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigator.

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Randomisation
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Serious Adverse Events:

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to Centre for Trials Research Safety Team within 24 hours of becoming aware of the event (See section 14 for more details).

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Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTIS	Clinical Trials Information System
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DDX	Doctors and Dentists Exemption
DSUR	Development Safety Update Report
EMEA	European Medicines Agency
EUCTD	European Union Clinical Trials Directive
EudraCT	European Clinical Trials Database
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GAG	Glycosaminoglycan

GP	General Practitioner
HB	Healthboard
HE	Health Economics
HTA	Health Technology Assessment
IB	Investigator Brochure
IC	Informed consent
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MSU	Mid-stream urine
MTA	Material Transfer Agreement
NCA	National Competent Authority
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIMP	Non-Investigational Medicinal Product
PCT	Primary Care Trust
PI	Principal Investigator
PIAG	Participant Information Advisory Group
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance

QALY	Quality-adjusted Life Years
QC	Quality control
QL (QoL)	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
rUTI	Recurrent urinary tract infection
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
USM	Urgent Safety Measure
UTI	Urinary tract infection

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. *(specify substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
NSA02	3.0	21.02.25	The dose of Gentamicin has been corrected. Originally the wording was "80mg of Gentamicin diluted to 80ml with normal saline. This has changed to "80mg of Gentamicin diluted to 50ml with normal saline". Clarified the definition of 'women' as 'assigned female at birth'. Clarification of wording to make it clear that if a participant is re-randomised to a different arm, their treatment will start back to time zero ie if a participant gets re-randomised at the end of their 6-months treatment period, they would be on the new treatment for a further 6-months. Update to section 22.6 to "This trial is funded by the National Institute for Health and Care Research".

2 Synopsis

Short title	IntraVESical Preparations for Recurrent Urinary TrAct Infection Prevention (The VESPER Trial): a multi-arm, multi-site open label randomised superiority trial
Acronym	VESPER
Sponsor ref. no.	10774
Clinical phase	Phase IV
Funder and ref.	NIHR HTA (NIHR158130)
Trial design	A pragmatic, multi-arm, multi-site, patient-randomised superiority trial with internal pilot, qualitative and economic evaluations
Trial participants	Women (assigned female at birth) who have failed first-line treatments for recurrent uncomplicated urinary tract infection (UTI) prevention
Planned sample size	412
Planned number of sites	20
Inclusion criteria	• Women (assigned female at birth with recurrent uncomplicated UTI who have failed first-line treatments (at least three episodes of symptomatic antibiotic-treated urinary infection in the previous 12 months or two episodes of UTI in the last 6 months despite the use of first line treatments). • Women aged ≥16 years • Women able to receive intravesical treatments and take second-line oral antibiotic prophylaxis • Women able to give informed consent • Women willing to adhere to a 12-month study protocol
Exclusion criteria	• Women (assigned female at birth unable to receive intravesical treatments or second-line oral antibiotic prophylaxis • Women with structural or functional urinary tract abnormalities considered contributory to rUTI • Pregnancy or intended pregnancy in next 12 months

	• Women who are breast feeding * If a patient has symptoms of a UTI at time of the eligibility assessment and a subsequent urine culture test is positive, they will be treated for the UTI and have a 4-week antibiotic wash-out period before being invited back to clinic to complete eligibility, consent and randomisation. The assessment of participants pregnancy status will be in line with current clinical pathways, this involves asking the patient if there is any possibility of pregnancy at the time of enrolment and follow-up during the trial. Proceeding to pregnancy testing would only occur if the participant volunteers that there may be a chance of pregnancy. If required, the pregnancy test used would be a point-of-care urine test. As all of the treatments within the trial are in widespread clinical use this approach mirrors existing clinical pathways albeit within the context of this comparative clinical trial. Consequently, the routine introduction of pregnancy testing for all participants is not advised.
Treatment duration	6-months
Follow-up duration	12-months post-randomisation (inclusive of 6-months treatment)
Planned trial period	48 months
Primary objective	. The primary objective is to evaluate the clinical and cost-effectiveness of two experimental interventions for women with refractory rUTI: intravesical gentamicin; Intravesical GAG replacement; and compare to the control arm of second-line daily low-dose antibiotic prophylaxis.
Secondary objectives	The secondary objectives are to evaluate the clinical, economic and safety outcomes listed in section 5.4, and to provide a qualitative process evaluation to explore trial processes, intervention mechanisms, and context to inform further implementation.
Tertiary/Exploratory objectives	A SMART design will be used and will allow us to explore the optimal sequence of prophylaxis regimens.
Primary outcomes	Primary Clinical Outcome Symptomatic, antibiotic-treated UTI rate during the 6-month treatment period.

	Primary Economic Outcome Incremental cost per quality-adjusted life year (QALY) gained at 12 months.
Secondary outcomes	Occurrence of UTI in the follow-up period, change in rUTI Impact Questionnaire, antibiotic use, microbiologically-proven UTIs, antimicrobial resistance (AMR) development, prevalence of asymptomatic bacteriuria, adherence with allocated treatment, UTI severity, costs to the NHS, personal social services (PSS) and women, quality-adjusted life years (QALYs), incremental cost per QALY gained at 6 months, incremental net benefit at 12-months, incremental cost per QALY gained over a lifetime horizon, women's marginal willingness-to-pay (WTP) for the interventions and to avoid a UTI, participant satisfaction with treatment and adverse events. Interviews with healthcare practitioners (HCPs) and participants to explore trial processes, intervention mechanisms and context and to inform future implementation. Outcomes will be collected for each participant over the 6-month treatment period following randomisation and also during a follow-up period of 6-months after completion of allocated preventative treatment (making up a total study period of 12-months for each participant) and analysed at trial completion.
Tertiary/Exploratory outcomes	Investigate the main effect of the second-stage treatment for participants who did not respond to their initial treatments and identify the best sequence of prophylaxis regimens that lead to the lowest UTI rate. .
Investigational medicinal products	Gentamicin
Form	80mg of Gentamicin diluted to 50ml using normal saline instilled into the bladder weekly for month 1, fortnightly for Months 2 & 3 and monthly for Months 4,5 & 6* * 11 instillations

Dose	80mg
Route	Intravesical (directly into bladder)
Medical device	Glycosaminoglycan (GAG) replacement compounds (Ialuril, Cystistat, Gepan, etc)
Form	GAG replacement compounds (Ialuril, Cystistat, Gepan, etc) – 1 vial of GAG replacement. compound instilled into the bladder weekly for month 1, fortnightly for Months 2 & 3 and monthly for Months 4,5 & 6* * 11 instillations
Dose	A 6-month regime of instillations will be used. The regime is based on the protocol used at the lead site. The volumes of the chosen GAG replacement options are Cystistat® 50ml, Ialuril® 50ml and Gepan® 40ml.
Route	Intravesical (directly into bladder)
Investigational medicinal products	Oral antibiotics as per NICE antimicrobial prescribing guidelines - Nitrofurantoin, Trimethoprim, Amoxicillin or Cefalexin.
Form	Tablet
Dose	Nitrofurantoin (50/100mg), Trimethoprim (100mg), Amoxicillin (250mg) or Cefalexin (125/250mg once a day)
Route	Oral

3 Trial summary & schema

3.1 See ***Figure 1*** for trial schema and participant flow diagram

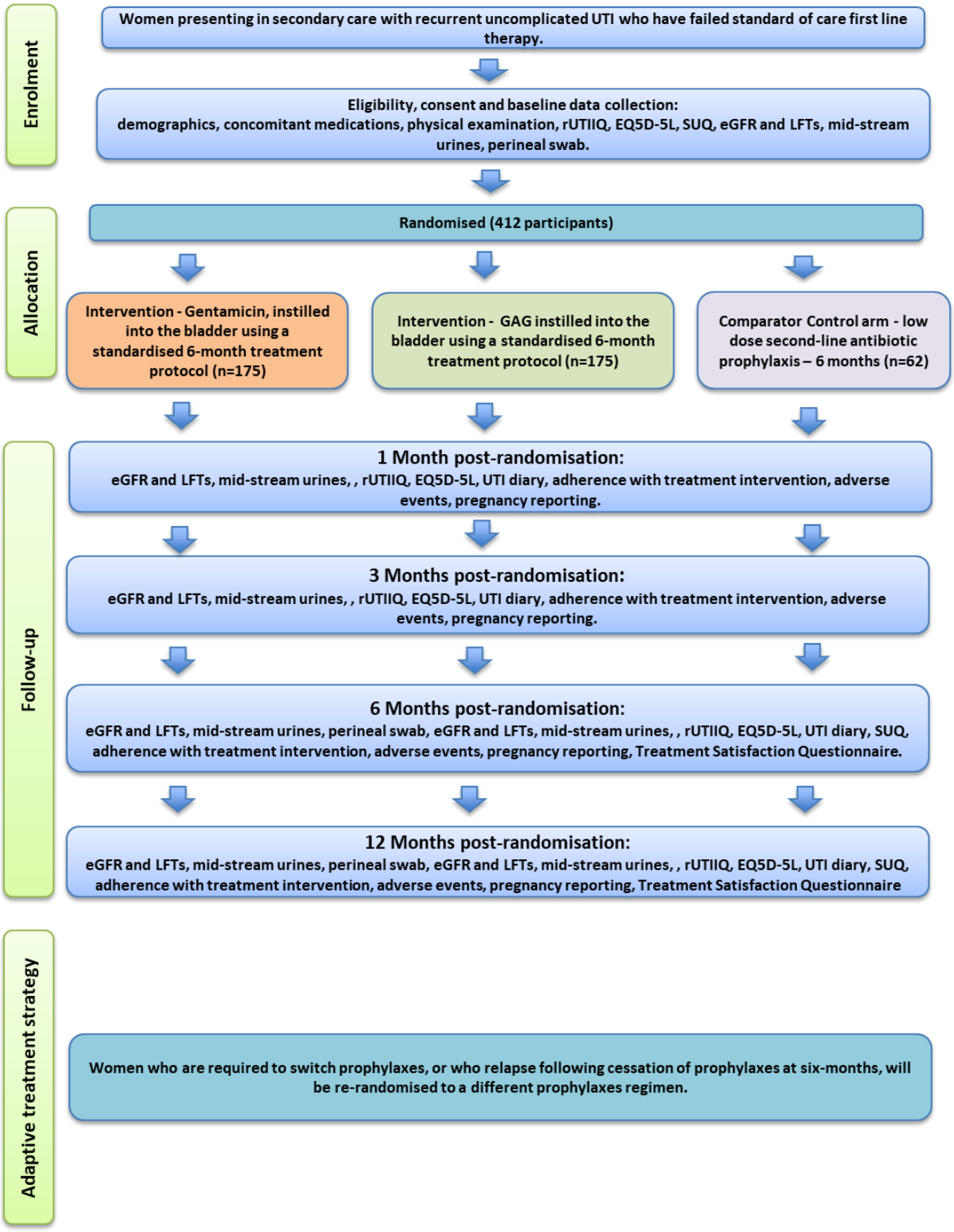

Figure 1: trial schema and participant flow diagram

3.2 Trial lay summary.

Most women experience urine infections during their lifetime, but some get repeated episodes, which considerably reduce quality of life. This is known as recurrent urinary tract infection (rUTI) and is defined as at least two episodes in six months or three in a year. rUTI affects around 600,000 United Kingdom (UK) women and is a very common reason for antibiotic prescription. Overuse and misuse of antibiotics drives increased antimicrobial resistance, which is a critical global health threat. Daily, low-dose, oral antibiotics for up to 6 months is the standard preventative treatment for rUTI however they do not work for some women (about 20%). Patients with infections that are difficult to control may need treatment given directly into the bladder through the urethra (water pipe) using a very thin disposable single use catheter (known as bladder instillations). Patients usually have a series of these treatments over 6-months. Currently, about 75% of surveyed urology specialists report regular use of instillations but the supporting evidence for these treatments is lacking, and current clinical guidelines can only recommend more (second line) daily oral antibiotics.

The VESPER trial compares two treatments given directly into the bladder to prevent UTI against the current recommended treatment of daily oral second-line antibiotics. For this trial, women seen in a hospital urology/urogynaecology clinic with rUTI who have not improved after first-line treatments will be invited to participate. Failed first-line treatments can include antibiotics, methenamine (antiseptic) or vaginal oestrogen. The treatment given to each participant will be decided randomly and will be one of:

1. Gentamicin, an antibiotic, given into the bladder periodically over 6-months (see schedule).

2. Glycosaminoglycan (GAG) replacement preparations given into the bladder periodically over 6 months (see schedule) – these treatments reinforce the inner lining of the bladder and stop bacteria from sticking there.

3. Daily low-dose, second-line antibiotic treatment for 6 months. A range of NICE recommended antibiotics will be permitted, and the antibiotic choice will depend on the type of bacteria causing UTIs and patient tolerance to antibiotics (Standard Care).

Treatments 1 and 2 involve invasive procedures. A trained healthcare professional will do this at the hospital and train patients to be able to self-administer at home if they are able and want to do so.

We will compare the number of UTI episodes occurring in each group during the 6-months of treatment to see which of the three treatments is best at preventing UTI. We will follow-up each woman during and after treatment and record UTI occurrence as well as the benefits, side effects and costs of treatment.

We will also record the types of bacteria found and their resistance to antibiotics. Antibiotic overuse contributes to the global problem of antibiotic resistance which means it is important that researchers continue to explore treatments to reduce use of antibiotics. Although the bladder instillations we will study do include antibiotics, they are given directly into the bladder and do not get into the blood stream like oral antibiotics. This should cause much less impact on antibiotic resistance. All UTI episodes will be treated as per usual care and co-ordinated by local services (GP, walk-in centre, A&E etc.) outwith of the trial team. We will also compare how much each treatment costs and link this to health improvement.

We need 412 women to take part in the study and expect it will take 48 months to complete.

4 Background

Recurrent urinary tract infections (rUTI) affect 2 – 6% of women, equating to at least 600,000 UK women based on current population figures. The vast majority (>90%) are classified as uncomplicated meaning there are no underlying structural or functional urinary tract abnormalities [1 2]. A recent study involving female rUTI patients revealed that they experience around seven UTI episodes/year [3]. Guidelines recommend first-line preventative treatment with long-term (usually 3-6 months), low-dose, daily antibiotics [4-7] but these fail in around 1 in 5 women (equating to over 100,000 women in the UK per year) [8]. NICE currently only recommend second-line daily, low-dose oral antibiotics in these refractory cases, but this guidance is not based on robust evidence of efficacy [4]. Due to this evidence gap, other national/international guidelines are unable to make any recommendations for this refractory patient group. Many clinicians use alternative strategies for refractory rUTI prevention including direct intravesical treatments. The two most commonly used intravesical treatments are antibiotics (gentamicin) or glycosaminoglycan (GAG) replacement compounds and both require patients to be temporarily catheterised for the administration of these treatments. A 2022 meta-

analysis identified no randomised trials (RCTs) of intravesical antibiotics and two small RCTs for intravesical GAG replacement compounds (n=26, n=54) [9]. Despite this paucity of high-level evidence our recent survey conducted via the UK Continence Society found that 76% of specialists regularly use intravesical treatments in their everyday practice. There appears to be a significant disparity between the widespread clinical use of these treatments and the evidence required to justify this. A recent overview in this topic area highlighted the use of intravesical preventative treatments as a potential future therapy and stated that "high local concentrations of antibiotic at the urothelial surface can be achieved by direct instillation into the urinary tract". The authors noted that "only the performance of clinical trials in the appropriate patient populations can properly appraise the potential of intravesical therapy for UTI"[10]. There is clearly an urgent need for a well-designed trial to demonstrate the relative effectiveness of the 2 most commonly used intravesical treatments and compare this to the current guideline-recommended treatment of second line daily oral antibiotics. VESPER, a 3-arm RCT designed to assess the relative effectiveness and cost-effectiveness of two intravesical preventative treatments, Gentamicin and GAG replacement compounds, against guideline-recommended second-line daily oral tablet antibiotic prophylaxis will directly address this evidence gap. Secondary outcomes will include development of antimicrobial resistance (AMR) during treatment, total antibiotic use, patient-reported treatment satisfaction, patient-reported UTI impact[11], adverse events and, using economic analysis, the value of the interventions to women suffering rUTI and to the NHS.

4.1 Rationale for current trial/Justification of Treatment Options

The paucity of evidence and lack of clinical guideline recommendations for women with refractory rUTI illustrates why our study is urgently needed. Clinicians surveyed confirmed the "lack of high-quality evidence" and "absence of guideline recommendation" as major issues in this topic-area but 76% of specialists regularly use intravesical preventive treatments as second line for rUTI indicating that they have become part of routine clinical pathways without robust supporting evidence. Our established UTI patient focus-groups recognised this uncertainty, commenting that "bladder washes were considered last-resort" and "nobody was sure if it would work". VESPER will help address this evidence gap providing guideline writers and policy makers with the evidence to make future robust recommendations.

UTI prevention is a key factor in reducing overall antibiotic consumption which is a major driver of AMR. Tackling AMR is an urgent national and global priority[12]. This trial is timely as it aligns with the Department of Health and Social Care's recently launched 5-year action plan for antimicrobial resistance 2024 to 2029 [13], whose objectives include optimising the use of antimicrobials in humans and are embraced by the NIHR, as demonstrated by their recent AMR Campaign[14], which responds to research recommendations from which responds to research recommendations from NICE guidance for antimicrobial stewardship stewardship[15].

VESPER is directly aimed at infection prevention. The incidence of AMR within post-menopausal rUTI sufferers increases from 25% to >80% following prolonged antibiotics[16]. A systematic review and meta-analysis[17] (searches up to 2009) identified a number of studies that together provide strong evidence of an association at the individual patient level between the prescribing of antibiotics in primary care and antimicrobial resistance in bacteria at different sites, including urinary tract infections, with effects lasting up to 12 months. The UK AMR strategy highlights that "we are heading rapidly towards a world in which antibiotics no longer work" due to "increased and inappropriate use" and advises that "preventing infections is essential"[13]. A recent publication details an estimated 4.95M deaths associated with AMR globally in 2019[18]. Urinary Tract Infections (UTIs) caused by antibiotic-resistant bacteria are difficult to treat and often recur. They also account for a staggering 50% of all known cases of sepsis[13]. For example, unplanned hospital admissions secondary to UTIs cost £434 million in 2013/2014. The frequent UTI sepsis complication is well-recognised and is noted within the NHS Long Term Plan as a key problem to be tackled. The goal is to reduce Gram-negative sepsis by 2024/25 and focus on UTIs as they are a leading cause of bloodstream infections[19]. The key causative organisms of both UTIs and urosepsis are *E. coli* (~50%) and Klebsiella (~15%)[20]. Worryingly, extended-spectrum Beta-Lactamase (ESBL) producing *E. coli* and Klebsiella species are increasingly common, and are included in the World Health Organisation 'priority pathogens' list[21].

VESPER is designed to demonstrate treatment superiority in terms of UTI reduction. The two experimental interventions in our study both have potential to reduce AMR by limiting UTI occurrence and consequent systemic antibiotic exposure which would be a major benefit to public health. Although one experimental arm is an antibiotic, it is unlikely to affect the gut flora as it is administered directly into the bladder and not absorbed systemically due to the low permeability of the urothelium which lines the urinary tract. Previously published work from co-applicants has shown that gentamicin is undetectable in the bloodstream of patients who receive it intravesically. [22, 23].

The existing literature pertaining to intravesical preventive treatments for rUTI supports the urgent need for a well-conducted RCT providing robust evidence of comparative effectiveness of intravesical antibiotics and intravesical GAG replacement compounds. A 2022 systematic review on the subject identified 13 publications (764 patients) but only two were RCTs[9]. Twelve of the 13 studies reported decreases in UTI frequency. The authors recognised the high risk of bias in many studies and concluded that both intravesical gentamicin and intravesical GAG replacement compounds may have efficacy but underlined the "greater need for RCTs". A further systematic review, led by one of our co-applicants, examined the efficacy of intravesical antibiotics[24]. 19 studies were identified but again only two were RCTs. Most patients (80%) were judged to have a successful outcome, but the authors conceded that "most of the data were retrospective, vulnerable to bias and unable to be generalized". They concluded that "future studies with a more robust methodology are required to draw meaningful conclusions". A third systematic review also led by one of our co-applicants specifically examined the efficacy associated with the use of intravesical gentamicin but only included six studies with a total of 166 patients[23]. All six studies reported a decrease in the frequency of UTI to varying degrees. This systematic review concluded that there was "a need for RCTs on intravesical therapy for rUTIs". All contemporary reviews reveal promising results, but all identify the need for well conducted RCTs. VESPER satisfies this objective and will potentially change practice by providing the currently unavailable high-level evidence in this topic area.

We have summarised evidence of the possible clinical utility of intravesical preventative treatments for women suffering with rUTI and the importance of the association between systemic prophylactic antibiotic use for rUTI and AMR. It has convinced us that a robust pragmatically designed trial is required to evaluate the clinical benefit and cost-effectiveness of intravesical treatments for prevention of rUTI. Estimates of prevalence, effectiveness and harms from systematic reviews have allowed us to power the trial conservatively. This is also based on what we, guided by a patient panel, consider to be a minimum threshold difference that would drive patient and clinician acceptability and change practice through inclusion of trial results in future meta-analyses and rUTI management guidance in the NHS and internationally.

5 Trial objectives and outcome measures

VESPER aims to determine the relative clinical and cost-effectiveness of the two most commonly used intravesical preventative treatments for women who fail first-line preventative treatment for rUTI and compare this to standard second line oral antibiotic prophylaxis in a UK NHS setting to demonstrate treatment superiority in terms of UTI reduction rate.

5.1 Primary objectives

The primary objective of VESPER is to evaluate the clinical and cost-effectiveness (using the outcomes listed in 5.3) of two experimental interventions for women with refractory rUTI: intravesical gentamicin; Intravesical GAG replacement; and compare to the control arm of antibiotic prophylaxis (second-line prophylactic daily oral antibiotics [comparator arm]).

5.2 Secondary objectives

The secondary objectives are to evaluate the clinical, economic and safety outcomes listed in 5.4, and to provide a qualitative process evaluation to explore trial processes, intervention mechanisms, and context to inform further implementation

5.3 Primary outcomes measure(s)

The primary clinical effectiveness outcome is the rate of symptomatic, antibiotic-treated UTI, self-reported by participants from randomisation to the 6-month treatment period (verified from medical records).

The primary economic outcome is the incremental cost per quality-adjusted life year (QALY) gained, based on responses to EQ-5D-5L, over 12 months.

5.4 Secondary outcomes measure(s)

Secondary outcome measures include:

- Occurrence of symptomatic UTI in months 6-12 (following treatment completion)
- Psychosocial burden of rUTI using the rUTI Impact Questionnaire[11] at 6 months and 12 months

- Antibiotic use: number of courses of antibiotics prescribed for UTI
- Microbiologically proven UTIs: defined as per the primary outcome plus a concomitant positive urine culture (central laboratory). Participants will be requested to submit urine samples both locally and to the central laboratory when they suspect a UTI based on symptoms. A positive culture will be classified according to UK Health Security Agency (UKHSA) standards for Microbiological Investigations (SMI) B41: Investigation of urine definitions[25].
- AMR in *E. coli* isolated from urine or perineal swabs.
    - Ecological change in terms of bacterial species plus antimicrobial resistance patterns from i) mid-stream urine and ii) faecal reservoir (via optional perineal swabs) during the 6-month treatment period and in the 6 months following completion of treatment. Urine and optional perineal samples will be taken at hospital visits during both treatment and follow-up, plus participants will be requested to submit further urine samples to the central laboratory when they suspect a UTI based on symptoms. GP or hospital records will be checked to confirm any additional urine culture results, including resistance patterns of the bacteria cultured. We are planning to longitudinally monitor development of antimicrobial resistance in the primary uropathogen *E. coli* isolated from urine by collecting specimens sent by participants directly to our central reference laboratory at the time of each UTI and during asymptomatic periods at baseline, 1,3, 6 and 12 months. We will also assess resistance pattern change in *E. coli* within the faecal reservoir by obtaining isolates from perineal swabs sent at baseline, 6 and 12 months.
    - Multi-drug resistance in *E. coli* isolated from urine or perineal swabs, defined as resistance to >=1 antimicrobial agent in >=3 antibiotic categories
- Bacterial species or antibiograms most commonly associated with recurrent UTI.
- Asymptomatic bacteriuria defined as a positive urine culture without symptoms
- Adherence with allocated treatment (patient reported)
- Adverse events
- Hospitalisation due to UTI

- Costs to NHS and personal social services (PSS) at 12 months and modelled over participant lifetime
- QALYs at 12 months based on completion of the EQ-5D-5L at baseline,3 ,6, & 12 months and modelled over participant lifetime.
- Incremental cost per QALY gained at 6 months.
- Incremental cost per QALY gained over a lifetime horizon.
- Willingness-to-pay (WTP) for the interventions' attributes and to avoid a UTI estimated from responses to a discrete choice experiment (DCE) at 13 months
- Participant satisfaction measured using the Treatment Satisfaction Questionnaire for Medication at 6 and 12 months.
- Understanding of contextual factors influencing adherence, acceptability and implementation of intervention.

5.5 Separate exploratory/translational objectives and endpoints

The exploratory outcomes are to investigate the main effect of the second-stage treatment for participants who did not respond to their initial treatments and to identify the best sequence of prophylaxis regimens that lead to the lowest UTI rate.

5.6 Process evaluation

We will carry out a mixed methods process evaluation guided by the new MRC Framework[26] for developing and evaluating complex interventions to:

- understand acceptability and a qualitative understanding of adherence to the intervention, and issues around implementation.
- explore participants' and HCPs/trial recruiter's views on the trial processes including a qualitative overview of local site adaptations and contextual factors influencing trial delivery, and views on trial materials and processes (e.g. recruitment, consent and retention).

6 Trial design and setting

The VESPER Trial is a pragmatic, three-arm, multi-site, open-label, patient-randomised superiority trial with internal pilot, qualitative and economic evaluations comparing two intravesical treatments for the prevention of rUTI in women both directly and to the current guideline-recommended standard of second line daily oral antibiotics, during a 6-month treatment and 6-months post-treatment follow-up period.

The two intravesical treatment arms are intravesical antibiotics – 80mg of Gentamicin diluted to 50ml using normal saline and intravesical GAG replacement compounds (a range of agents are permitted including: Ialuril, Cystistat, Gepan). The daily oral antibiotics arm will use guideline recommended antibiotics which will include, but not be limited to; Nitrofurantoin (50/100mg), Trimethoprim (100mg), Amoxicillin (250mg) or Cefalexin (125/250mg once a day)

We will randomise participants using a 1:3:3 ratio using the covariate-adaptive randomisation procedure following the Pocock and Simon's minimisation method with an 80% random element[27, 28]. Allocations will be minimised by previous UTI frequency (<=4/year; >4/year) and menopausal status (pre; peri/post), both of which have strong prognostic value. We require 412 participants in total (62 in the oral comparator arm and 175 in both intravesical experimental arms) as we are primarily interested in comparisons of each intravesical prophylaxis against standard care and then a head-to-head comparison of intravesical prophylaxes.

We will use a Sequential Multiple Assignment Randomised Trial (SMART) design[29]. This enables women to be re-randomised to a different prophylactic regime if they do not respond to their initially allocated prophylaxis. This will allow us to explore the optimal sequence of prophylaxis regimens. We will define relapse as at least two episodes of UTI occurring in the 6-month treatment period in line with currently accepted definitions of recurrent UTI. All women will have a fixed 12-month post randomisation trial period. If a participant is re-randomised to a different arm, their treatment will start back to time zero ie if a participant gets re-randomised at the end of their 6-months treatment period, they would be on the new treatment for a further 6-months.

Our target population are adult (≥16 years) women with a documented history of recurrent uncomplicated UTI, for whom second-line treatments would be considered e.g. at least three episodes of symptomatic antibiotic-treated urinary infection in the previous 12 months or two episodes of UTI

in the last 6 months despite the use of first line treatments such as intravaginal oestrogen, the oral urinary antiseptic methenamine Hippurate or first-line low dose oral antibiotics.

Whilst the main mode of data capture will be electronic, we will provide alternatives for participants either on paper or by telephone. Urine and optional perineal swab samples will be taken at baseline and at subsequent hospital visits during both treatment and follow-up periods (12 months in total). Participants will also be requested to submit further urine samples to the central laboratory when they suspect a UTI based on their symptoms. Participants will be provided with the central laboratory address together with all sample collection materials that are needed.

Central laboratories contact details:

Dr Mandy Wootton

Specialist Antimicrobial Chemotherapy Unit,

Public Health Wales,

University Hospital of Wales,

Heath Park,

Cardiff, CF14 4XW

The trial is a UK multi-centre trial involving 20 secondary care NHS organisations.

6.1 Adherence data:

We will use quantitative data to explore adherence and to describe differences between different modes of intravesical administration (self vs clinician-delivered) and the timing of this decision in relation to randomisation and whether this is associated with differential response, switching, and outcomes. We will similarly describe the variability (and association with response/outcomes) in prophylaxis implementation more generally.

6.2 Internal pilot phase

We have included a planned internal pilot phase, with progression criteria during the first 8 months of recruitment (study months 8-15). We will review recruitment, including site and participant enrolment, completeness of primary outcome data and treatment adherence. Early qualitative

interviews with participants and HCPs will inform us about trial processes and acceptability. Our recruitment estimates for the pilot have accounted for the fact that the study population are those who have failed first line treatments, considered published reviews and recommendations[30, 31] and acknowledged that recruitment rates are slower when centres initially open. We plan for all sites to be open within the first 8 months with a staggered opening rate. Pooled data of NIHR funded studies show internal pilots typically recruit 15% of their participants within 33% of the total recruiting time[30]. Our progression criteria below are based on these estimates:

Progression criteria	**Red**	**Amber**	**Green**
% Threshold	<60%	61 - 99%	100%
Recruitment rate/site/month	<0.5	0.5-0.99	>1
Number of sites opened	<12	12-18	>18
Total number of participants recruited	37	38 - 61	62

During the 8-month internal pilot phase, we predict the average recruitment rate would be 1 participants/site/month, which accounts for slower recruitment as sites open. The remaining recruitment time after the internal pilot is completed (14 months) estimates a 25% increase in recruitment rate with an average of 1.25 participants/site/month. PI co-applicants and expressions of interest from our 20 sites indicate that they would feasibly recruit 1-2 patients per month. We anticipate opening 18 of our 20 sites by the end of the pilot period. We will review eligibility rates and reasons for exclusions to ensure we are being as inclusive as possible. Also included in the progression criteria is the proportion of participants providing primary outcome data. We would anticipate a completion rate of 90%, rates below this will prompt a review of the process of capturing primary outcome data. The progression criteria have been designed to allow for mitigating strategies to be discussed to allow for some adaptation to recruitment processes. We will constantly be assessing the criteria during the internal pilot phase. We will discuss the results with our Trial Steering Committee, before reporting to the NIHR HTA Programme, for permission to proceed.

6.3 Qualitative evaluation during the internal pilot phase

During the pilot phase we will carry out qualitative engagement via brief interviews with around 5-10 HCPs/research team members and 5-10 trial participants (with option to include carer/supporters) to explore:

- the factors that influence different treatment options for women with rUTI
- attitudes, skills and confidence in recruiting women from under-represented groups onto the trial
- the factors that affect decision to participate in trials
- the participants' experiences of participating in the trial (particularly for women from under-represented groups)

Rapid qualitative analysis will be carried out initially to allow for rapid feedback to the team and for wider reporting. Depending on the results, this data may also be included in a more detailed thematic analysis later in the study.

6.4 Risk assessment

We have made an initial risk assessment of the potential hazards associated with this trial including those occurring and resulting in harm to the participants or researchers. The investigational medicinal products (IMP) to be used in the trial are all in current use in the UK NHS. From this we judge that from an IMP perspective there is low risk to trial participants. Risks associated with the design and methods of the trial including the clinical procedures specified in the protocol, participants' rights related to consent and protection of data and the reliability of trial results have also been assessed. The robust design of the study to mitigate and manage these risks has led to the decision, supported by the sponsor, to apply for 'Type A' status (low risk - notification only) from the Medicines and Healthcare products Regulatory Agency (MHRA) and allow for a risk-proportionate trial management and monitoring approach to the trial. A structured Safety Monitoring Plan will be made to assess risk management by all relevant parties including the sponsor, regulators, pharmacists, and regulatory and governance staff. This will be submitted to the MHRA along with the notification application.

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a TYPE A where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1).

7 Site and Investigator selection

This trial will be carried out at participating sites within the UK. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

Before any Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the VESPER Trial email account (see contact details on page 4):

- Confirmation of Capacity and Capability (C&C) from R&D department following sharing of local information pack.
- Favourable opinion of host care organisation/PI from Main Ethics committee
- MHRA approval
- A signed Trial Agreement
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document

- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- A copy of the most recent approved GP letter on host care organisation headed paper
- A copy of the most recent Pregnancy Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- Returned copy of the Self-Evident Correction Log signed by the PI (if applicable).
- Executed MTA

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the site is now ready to recruit participants into the trial. This 'Green light' letter/email must be filed in each site's Investigator Site File

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiations will be via TEAMS teleconferences.

VESPER will take place in 20 large UK urology/urogynaecology centres each receiving around 15-20 referrals per month of women with uncomplicated rUTI from primary care chiefly through the standard NHS pathways. These centres have well-defined existing clinical pathways in place for the treatment of such patients and will also have experience in treating refractory patients which is our target population. We would estimate that each centre would see 4-6 patients per month with refractory rUTI and would expect each centre to recruit 21 patients for the trial. Any discrepancy in recruitment rate between centres will be monitored and addressed. Recruitment will be carried out by research staff in each of the centres and will involve a clear explanation of the trial including the background, study protocol and aims. If recruitment is not to target in the early phase of the trial, we will identify any common issues and explore the possibility of opening additional centres. We have 5 "reserve" centres already in mind. The embedded qualitative work involving patients and clinicians will also help guide trial processes to maximise recruitment, through exploring barriers and facilitators to participant involvement.

8 Participant selection

In line with the pragmatic nature of this trial we have deliberately minimised the exclusion criteria. We are aware that intravesical treatments currently only apply to those women who are refractory to first-line treatments and as such represent only around 20% of all female patients with rUTI. We felt it necessary to exclude women with structural or functional urinary tract abnormalities as treatment for these patients is usually directed at correction of the underlying abnormality rather than an extended period of prophylaxis. Women who are planning pregnancy or breast feeding have been excluded as antibiotic options in this patient group are limited.

We will exclude patients who have contraindications to any of the three planned trial interventions. Within the oral antibiotic arm there are three possible agents that could be used, and we feel it is unlikely that patients would be sensitive or allergic to all three of those agents. Data from previous trials (ALTAR and ANTIC) have confirmed that no patients were prevented from trial entry due to oral antibiotic sensitivities. With regards to intravesical treatments (GAG replacement and intravesical antibiotics) these are not generally absorbed into the systemic circulation due to the urothelial barrier and therefore sensitivity to these agents is almost unseen. Some patients have in the past shown an inability to retain intravesical treatments due to concomitant issues with continence, but we can usually give advice which enables sufficient retention. For example, we sometimes ask the patients to instil the treatment into the bladder at nighttime prior to going to sleep. For participants who are unable to self-catheterise at home, a clinic appointment will be offered to them to carry out the instillations and to encourage them to retain the instilled substance (Gentamicin or GAG) for as long as they can.

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply:

8.1 Inclusion criteria

- Women (assigned female at birth) with recurrent uncomplicated UTI who have failed first-line treatments (at least three episodes of symptomatic antibiotic-treated urinary infection in the previous

12 months or two episodes of UTI in the last 6 months despite the use of first line treatments). Failed first-line treatments can include antibiotics, methenamine (antiseptic) or vaginal oestrogen.

- Women aged ≥16 years
- Women able to receive intravesical treatments and take second-line oral antibiotic prophylaxis
- Women able to give informed consent
- Women willing to adhere to a 12-month study protocol

8.2 Exclusion criteria

- Women (assigned female at birth) unable to receive intravesical treatments or second-line oral antibiotic prophylaxis
- Women with structural or functional urinary tract abnormalities considered contributory to rUTI
- Pregnancy or intended pregnancy in next 12 months
- Women who are breast feeding

* If a patient has symptoms of a UTI at time of the eligibility assessment and a subsequent urine culture test is positive they will be treated for the UTI and have a 4-week antibiotic wash-out period before being invited back to clinic to complete eligibility, consent and randomisation.

For the purposes of the protocol a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

The assessment of WOCBPs pregnancy status will be in line with current clinical pathways, this involves asking the patient if there is any possibility of pregnancy at the time of enrolment and follow-up during the trial. Proceeding to pregnancy testing would only occur if the participant volunteers that there may be a chance of pregnancy. If required, the pregnancy test used would be a point-of-care urine test. As all of the treatments within the trial are in widespread clinical use this approach mirrors

existing clinical pathways albeit within the context of this comparative clinical trial. Consequently, the routine introduction of pregnancy testing for all participants is not advised.

All queries about participant eligibility should be directed to the Trial Manager (VESPER@cardiff.ac.uk) before randomisation/registration.

9 Recruitment, eligibility and randomisation

9.1 Participant identification

Each research site lead will publicise the trial within their own departments and ensure that colleagues in allied specialities such as infectious diseases and nephrology, who may receive referrals of women with rUTI, are aware of the trial and willing to identify potential participants. We will use established links with Research delivery networks (RDN) and equivalent organisations throughout the UK to ensure that referring General Practitioners (GPs) are aware of the study; can identify potential eligible participants and direct referrals accordingly. All 20 sites have an established clinical research track record and effective infrastructure in place for patient recruitment. For the results from VESPER to be generalisable across the wider NHS then the demographic of patients recruited to the study must reflect that of patients currently being referred to urologists. Furthermore, patients that are being treated by their GPs in primary care will also be identified by liaison of the lead clinician in each site with primary care leads at RDNS. We will publicise VESPER at RDNS events to ensure that referring GPs are aware of the trial and encouraged to refer women eligible for the study. Current clinical classification of UTI categorises these infections as uncomplicated or complicated. A complicated UTI is defined by the presence of a structural or functional abnormality of the urinary tract which contributes to the condition. Treatment of complicated UTI is often focussed on correction of this underlying abnormality. UTI in a male has been classified as complicated therefore this study is restricted to females by definition. Therefore, the presence of an underlying structural or functional abnormality of the urinary tract will be an exclusion criterion. The wide inclusion criteria in VESPER are likely to ensure that a representative range of patients will be eligible and therefore the results obtained will be generalisable to UK NHS practice.

There is evidence that ethnicity, income inequality and deprivation status can increase the risk of suffering from an antibiotic-resistant infection[20]. We will include women and gender non-conforming people assigned female at birth in this study and a wide range of UK centres to ensure ethnic and socio-economic diversity. People who are less affluent, live further away or have work/care

responsibilities may find it harder to visit the site for clinician administered treatment and so we have allowed for self-administered treatment. Whilst we have designed most of our data capture to be electronic, we will provide alternatives for patients either on paper or by telephone. Research visits in addition to those required clinically have been minimised and reimbursement offered when needed. We will use guidance from the INCLUDE framework throughout and monitor equality as part of our trial management group (TMG) meetings. We will follow the INCLUDE recommendations and will select recruiting sites where there is a diverse population including under-represented research areas. We will also produce a recruitment infographic and video with subtitles in multiple languages, and advertise the trial via social media, via the Live UTI Free platform and within local communities. We will monitor our inclusion by ethnicity and aim to maintain a level consistent with the census data by recruiting site, as recommended by the TrialForge STRIDE project[56].

In order to ensure that patients managed in primary care are aware of this trial and get the opportunity to participate we will publicise our trial widely via local primary care networks, specifically those affiliated to study sites. Where appropriate we will look to establish GP practices as Participant Identification Centres (PIC) for the trial and we hope to achieve this via engagement of local PI's at our 20 study sites with their primary care RDNS/Health Board. We will supplement this with the distribution of study information and recruitment posters to GP surgeries local to the trial sites. Although we feel that the majority of patients who have failed initial preventive treatments for recurrent urinary tract infections (rUTIs) would be routinely referred into secondary care we recognise that there may be patients who continue to be managed by their local GPs. We would hope that this will ensure our study results are generalisable and represent the entirety of the population affected with refractory rUTIs.

Where a participant hears about the VESPER trial through social media, Live UTI Free, Bladder Health UK, they will be asked to contact their GP and provide a VESPER information sheet to the GP. If appropriate, the GP will refer the patient to a recruiting secondary care site.

We will aim to ensure that all adult women referred to each site with rUTI are aware of the trial prior to their clinic appointment. We will develop an infographic recruitment video, with sub-titles in different languages to maximise recruitment from under-represented ethnic minorities.

Trial invitation information will include brief details of the need and purpose of the trial and eligibility criteria. It will emphasise the pragmatic nature of the trial and give a realistic indication of the burden to participants. All patients given trial information will be recorded on the screening logs by each participating site. All subjects who agree to consider participation will be seen by local research staff

or the trial coordinator (a staff member who is on the VESPER Trial delegation log) at the respective site to go through the screening, eligibility, consent, baseline and randomisation procedures.

Identification may involve reviewing or screening the identifiable personal information of participants and if so, this will be undertaken by members of the normal clinical team.

9.2 Eligibility, consent and randomisation

A patient who has been identified as being potentially eligible will be invited to an eligibility appointment at a recruiting site. The eligibility assessment will be conducted by a delegated clinician at the recruiting site.

The following processes, see **Figure 2** below, will be undertaken at this appointment:

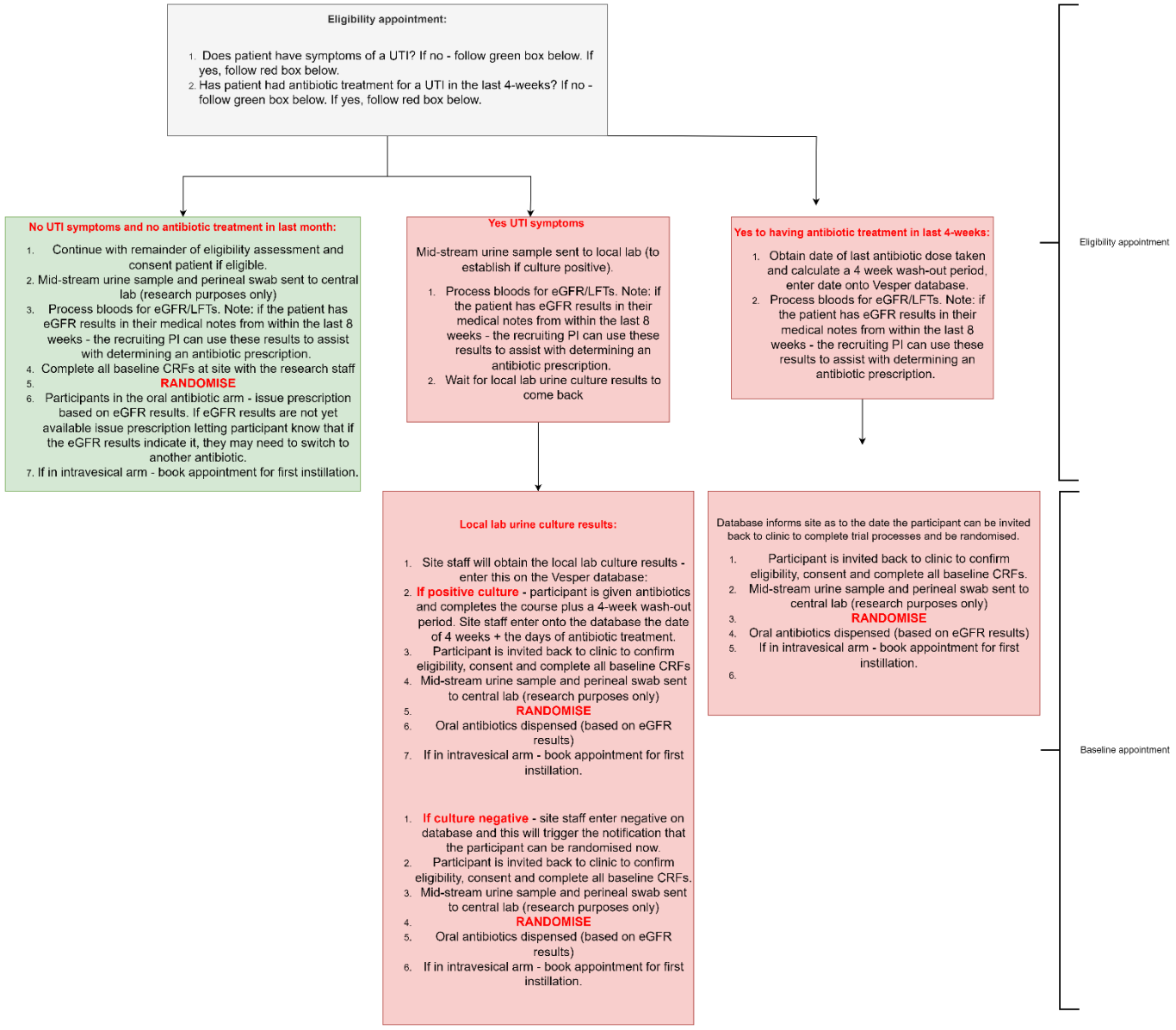

Figure 2 - Eligibility, consent and randomisation flow diagram

The eligibility appointment will include first asking the patient if they currently have any UTI symptoms and if they have had antibiotic treatment for a UTI in the last 4-weeks.

Patients who do not report UTI symptoms or have not taken antibiotics in the last 4-weeks for a UTI will follow the processes in the green box above. Their 'eligibility' and 'baseline' appointment can be within one clinic visit.

Patients who do report either UTI symptoms or having taken antibiotics for a UTI in the last 4-weeks will follow the processes in the red boxes above. These patients will have an 'eligibility' appointment and a separate 'baseline' appointment. The two appointments are required due to the need to obtain urine culture results or due to the need to have a wash-out period before proceeding.

Trial drugs will be dispensed, or arrangements made for attendance for instillations, dependent on the allocated arm. The results from the eGFR tests will inform the antibiotic prescribing decision made for those participants randomised to the oral antibiotic arm. For patients who have eGFR data in their medical records that are within the previous 8 weeks, the clinician can choose to use these results, and not send a sample off for eGFR testing.

For detailed description of conducting the eligibility, consent and randomisation please see section 13.1.1.

Treatment will be prescribed and dispensed following local procedures. Gentamicin and GAG would usually be ordered through inpatient supply route if hospital administered and through outpatient pharmacy if home administered. Oral antibiotics should be ordered through outpatient pharmacy."

This is in line with standard care for patients who fail first-line preventative treatment for recurrent UTIs and therefore will not incur any additional research costs.

9.3 Screening logs

A screening log of all ineligible and eligible but not consented/not approached will be kept at each site so that any biases from differential recruitment will be detected. When at site, logs may contain identifiable information, but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to Vesper@cardiff.ac.uk every month (see section 19 for further detail on data monitoring/quality assurance).

The baseline characteristics of patients who decline participation or are not eligible will be recorded in a screening log and compared with those of participants who enter the trial. We do not anticipate any discrepancy in demographic characteristics (including age, social class and ethnicity) between participants and non-participants and this will serve as confirmatory evidence.

9.4 Recruitment rates

During the 8-month internal pilot phase, we predict the average recruitment rate to be 1 participant/site/month, which accounts for slower recruitment as sites open. The remaining recruitment time after the internal pilot is completed (14 months) estimates an increase in recruitment rate with to average of 1.25 participants/site/month. PI co-applicants and expressions of interest from our 20 sites indicate that they would feasibly recruit 1-2 patients per month.

9.5 Informed consent

Online data capture onto a REDCap bespoke trial database will be the preferred method of data capture, including obtaining informed consent. However, to aide inclusivity, and for situations where the online database is not accessible at the time of taking eConsent, we will provide alternative methods of obtaining consent including on paper copies of the consent form. Where consent forms are completed on paper, the sites will be required to transcribe this data onto the VESPER database as soon as possible.

The potential participant will be fully informed using the VESPER Participant Information sheet, following which the participant's written informed consent must be obtained using the approved VESPER Trial Consent forms. The participant should be given sufficient time after the initial invitation to participate before being asked to sign the Consent Form. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. Consent may be taken by suitably qualified PIs, co-investigators and research nurses, as identified on the VESPER site delegation log.

A copy of the signed consent form should be provided to the participant. For those completing consent on paper a copy should be given to the participant, the original copy should be kept in the investigator site file and a further copy should be kept with participant's hospital notes. A copy will also be sent to the VESPER Trial team via secure Fastfile. For those completing consent online, a copy of the consent form will be downloaded and provided to the participant and to the site research team for inclusion in the investigator site file and the participants medical records.

For qualitative interviews, the informed consent process is detailed in section 13.2.5.

After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of

the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

9.6 Registration and Randomisation

9.6.1 Registration

Suitable participants who have provided written informed consent will be enrolled into the study and will be registered by recording key information including contact details. All baseline data and sample collection will happen prior to randomisation.

9.6.2 Randomisation

Randomisation will be in a 1:3:3 ratio to receive: (1) Oral antibiotic prophylaxis (2) Intravesical Gentamicin (3) Intravesical GAG replacement for 6 months. To reduce the risk of imbalance of key covariates, the Pocock and Simon's minimisation method with an 80% random element will be used for previous UTI frequency (<=4/year; >4/year) and menopausal status (pre; peri/post) (see Section 15.1).

If a participant does not respond to their initially allocated prophylaxis or they experience intolerable side-effects, they can be re-randomised to one of the remaining two prophylactic regimes. Re-randomisation will be based on a 1:1 ratio. Re-randomisation will be based on block randomisation (see Section 15.1). If a participant does not respond to treatment following re-randomisation then they would be permitted to switch to the third treatment arm without the need for any further randomisation. If a participant is re-randomised to a different arm, their treatment will start back to time zero ie if a participant gets re-randomised at the end of their 6-months treatment period, they would be on the new treatment for a further 6-months.

Computerised web-based remote randomisation (available 24 hours a day) will be used. The randomisation system will be built by the in-house CTR information Systems and Technology Solutions team (TMS2). The CTR Trial team will also be notified that a participant has been randomised or re-randomised via an automated e-mail alert mechanism to the VESPER email inbox.

In the event that the online randomisation system is unavailable at site, or the site has problems accessing the online website, then the local investigator may contact the CTR (during office hours). Manual randomisation may be performed by CTR staff on request of the local investigator.

If the online system does not work, a telephone back-up managed by the CTR Trial team will be available for use during office hours Monday to Friday: 08:30-16:00.

For online randomisation: A randomisation/re-randomisation form must be completed on the trial database to randomise the participant.

For telephone randomisation: A randomisation/re-randomisation form must be completed before telephoning the randomisation line.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal of Trial Treatment/ Intervention
2. Withdrawal from questionnaires/data collection
3. Withdrawal from further sample collection (urine and or perineal swab)
4. Withdrawal of samples already collected (these will be destroyed)
5. Withdrawal from follow-up assessments
6. Withdrawal from qualitative interviews
7. Withdrawal of Consent to all of the above

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal.

Participants can stop being part of the trial at any time, without giving a reason, but we will keep data collected prior to the withdrawal.

If a participant wishes to stop taking part in the trial completely, they will need to be seen one last time for an assessment and tests. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, you (the site) will need to continue to collect information about them for as long as the reaction lasts.

A participant may withdraw or be withdrawn from trial treatment for the following reasons:

- Confirmation of pregnancy
- Failure of preventative treatment
- Intolerance to trial medication/intervention
- Withdrawal of consent for treatment by the participant
- Any alteration in the participants condition which justifies the discontinuation of the treatment in the Investigator's opinion

In all instances participants who consent and subsequently withdraw should complete a withdrawal of consent form or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant.

This withdrawal form should be sent via Fastfile to Vesper@cardiff.ac.uk for the attention of the data manager.

In the event a withdrawal form in not completed, it must be assumed that the participant withdraws from all aspects of the trial, and any unprocessed samples retained at the central laboratory must be disposed. However, retained samples can be processed for use in the trial if the participant have signed the optional statement in the consent form that allows the samples to be retained in the event the participant does not complete the withdrawal form.

NB: If a participant is withdrawn for medical reasons by a clinician, the withdrawal form need not be completed. However, confirmation would be needed that the participant agrees to their samples being retained and used as per original consent.

Any queries relating to potential withdrawal of a participant should be forwarded to Vesper@cardiff.ac.uk for the attention of the trial manager.

10.2 Lost to follow up

Participants will be identified as lost to follow-up if it is not possible to contact them for both their 6-month follow-up (6-months + 4 weeks) and 12-month follow-up (12 months + 4 weeks) data collections timepoints.

All outcome data will be collected, and the primary analysis will be performed on an intention to treat basis for protocol non-adherers.

We will make every effort to reduce loss to follow-up rates using the methods listed below:

- We will obtain contact details of all participants at registration. We will also ask participants about times of the day that would be most suitable for the study team to contact them.
- We will emphasise the importance of getting follow-up data to all participants at baseline and the different follow-up assessment points.
- Unless they have explicitly requested otherwise, all participants will be invited to complete follow-up questionnaires and attend follow-up appointments.
- Non-return of participant completed UTI diaries (for those who have opted to complete paper UTI diaries at the time of a UTI or those who are completing the diary online remotely) within a specified timeframe will result in the study team telephoning or texting the participant to remind them to return/complete online their diary. Patient symptom diaries are a necessary component of VESPER considering the primary outcome is “patient-reported antibiotic-treated UTI”.
- We will arrange mutually acceptable dates for the interviews.
- For the telephone interviews, up to three attempts will be made to contact a participant on the scheduled date of their interview. Where contact has been unsuccessful following these attempts, three further attempts will be made to contact the participant.

In respect to sample collection, if the participant is lost to follow up, then they are not subject to the withdrawal processes, and the original consent stands.

11 Trial Intervention

11.1 Treatment(s)

Interventions:

This trial is pragmatic in design and, apart from random allocation of treatment options; participant care will follow standard pathways in participating secondary care NHS sites. We will ensure that all participants have access as desired to the use of other measures to reduce the risk of UTI such as adequate fluid intake, avoidance of constipation and, for post-menopausal women, vaginal oestrogen supplements. We will also give advice concerning use of other potential treatments such as cranberry extract. This is in line with existing clinical practice, for example in a recently published UTI trial it was reported that around 50% of women with recurrent UTI used cranberry supplements in addition to other, prescribed preventative treatments[32]. Participants in all 3 trial groups will receive on demand discrete courses of antibiotics for breakthrough UTIs as decided by their GP or local HCP and these will be recorded on trial CRFs.

Antibiotic prophylaxis

For those women randomised to receive oral antibiotics, a second line once-daily prophylactic low dose will be prescribed for 6 months. The agent to be used will be active against common urinary pathogens and selected by the responsible clinician depending on patient characteristics such as previous use, allergy, renal function, prior urine cultures and local guidance. Current NICE guidelines suggest use of nitrofurantoin 50 mg or 100 mg, trimethoprim 100 mg, or cefalexin 125 mg or 250mg can be used. Renal function will be determined by eGFR at baseline and if this is less than 45 ml/min nitrofurantoin will not be used. Liver function tests will be monitored throughout the trial as some of the antibiotics, particularly nitrofurantoin, require this. Participants will be asked to take the once-daily antibiotic prophylaxis as a single dose at bedtime. If there are specific and/or intolerable adverse effects such as nausea with nitrofurantoin, or candidiasis with cefalexin then changing to an alternative oral antibiotic agent would be advised in consultation with the relevant clinician with the reasons for the change recorded. The aim will be to maintain participants on oral antibiotic prophylaxis for as long as possible during the 6-month treatment period within tolerance and safety constraints. Participants intolerant of prophylactic antibiotics despite trying alternative agents will have the opportunity to discontinue the medication and be offered an alternative treatment which will include intravesical treatments. This information will be recorded, and the participant will continue on in the study. If a participant in the prophylaxis group develops symptoms and signs suggestive of

breakthrough UTI, then they will seek treatment in their usual way predominantly by contacting their GP or local NHS facilities and starting a discrete treatment course of antibiotics. Participants are asked to send a urine sample (and perineal swab at months 6 & 12) to the central laboratory BEFORE taking their discrete course of antibiotics and to complete a UTI diary report form. In this scenario they will stop the prophylactic antibiotic whilst they are taking a treatment course and restart it again the day following the last dose, they take of the treatment course. Clinicians and participants will be advised to use a different agent for treatment than the one they are taking for prophylaxis. Details of all treatment antibiotic courses will be recorded including the agent used and the duration of treatment.

Intravesical Gentamicin

For those women randomised to receive intravesical gentamicin a 6-month regime of instillations will be used. The regime is based on the protocol used at the lead site and participants will receive 80mg of Gentamicin diluted to 50ml with normal saline weekly for month 1, fortnightly for months 2 and 3 and monthly for months 4,5 and 6. We have recently conducted a survey of specialist urologists and urogynaecologists via the United Kingdom Continence Society (UKCS) which indicated that this regime mirrors what is done in clinical practice currently with 71% of clinicians who use intravesical gentamicin recommending a weekly regime initially and only 7% of clinicians use it for more than 6 months. The instillations can be self-administered if the patients are deemed competent in self-catheterisation which is in line with current clinical practice. The patients who self-administer will be instructed to give the intravesical gentamicin before bed to maximise the dwell time within the bladder. Patients unable to self-administer will attend hospital for their intravesical antibiotic treatment and the relative proportion of self vs hospital administration will be recorded. We will sub-analyse results comparing self vs clinician administered treatments. If there are specific and intolerable side effects such as bladder pain, haematuria or inability to hold the intravesical antibiotic then participants will be given the opportunity to discontinue treatment and be offered an alternative treatment which may include oral prophylactic antibiotics or intravesical GAG compounds. This information will be recorded, and the participant will continue on in the study. If a participant in the intravesical Gentamicin group develops symptoms and signs suggestive of breakthrough UTI, then they will seek treatment in their usual way predominantly by contacting their GP or local NHS facilities and starting a discrete treatment course of oral antibiotics. Participants are asked to send a urine sample (and perineal swab at months 6 & 12) to the central laboratory BEFORE taking their discrete course of antibiotics and to complete a UTI diary report form. They will not be instructed to stop

intravesical gentamicin during this treatment course. Details of all oral antibiotic treatment courses will be recorded including the agent used and the duration of treatment.

Intravesical GAG replacement

For those women randomised to receive intravesical GAG replacement a range of agents will be permitted including Cystistat®, Ialuril® and Gepan®. These preparations all aim to replenish the inner lining of the lower urinary tract and prevent bacterial adhesion by reinforcing the urothelial barrier with compounds such as hyaluronic acid and chondroitin. The UKCS survey of clinicians we recently undertook reveals that 45% of clinicians use Ialuril®, 41% use Cystistat® and 14% use Gepan®. In order to maximise recruitment and mirror current clinical practice we will permit the use of any of these 3 compounds. There are no reported efficacy advantages of any of these treatments. The intravesical GAG replacement compound used will be recorded. A 6-month regime of instillations will be used. The regime is based on the protocol used at the lead site and participants will receive one instillation of GAG replacement weekly for month1, fortnightly for months 2 and 3 and monthly for months 4,5 and 6. The volumes of the chosen GAG replacement options are Cystistat® 50ml, Ialuril® 50ml and Gepan® 40ml.

We have recently conducted a survey of specialist urologists and urogynaecologists via the United Kingdom Continence Society (UKCS) which indicated that this regime mirrors what is done in clinical practice currently with 67% of clinicians who use intravesical GAG recommending a weekly regime initially and only 11% of clinicians use it for more than 6 months.

The instillations can be self-administered if the patients are deemed competent in self-catheterisation which is in line with current clinical practices The patients who self-administer will be instructed to give the intravesical GAG preparation before bed to maximise the dwell time within the bladder. Patients unable to self-administer will attend hospital for their intravesical GAG replacement treatment and the relative proportion of self vs hospital administration will be recorded. We will sub-analyse results comparing self vs clinician administered treatments.

If there are specific and intolerable side effects such as bladder pain, haematuria or inability to hold the intravesical compound then participants will be given the opportunity to discontinue treatment and be offered an alternative treatment which may include oral prophylactic antibiotics or intravesical antibiotics. This information will be recorded, and the participant will continue on in the study. If a participant in the intravesical GAG replacement group develops symptoms and signs suggestive of breakthrough UTI, then they will seek treatment in their usual way predominantly by contacting their

GP or local NHS facilities and starting a discrete treatment course of oral antibiotics. Participants are asked to send a urine sample (and perineal swab at months 6 & 12) to the central laboratory BEFORE taking their discrete course of antibiotics and to complete a UTI diary report form. They will not be instructed to stop intravesical GAG replacement during this treatment course. Details of all oral antibiotic treatment courses will be recorded including the agent used and the duration of treatment.

11.2 Treatment supply and storage

The intravesical gentamicin, intravesical GAGs and oral antibiotics will all be sourced from NHS stocks, as all are considered part of usual standard care processes for the second-line preventative treatment for recurrent UTI.

11.3 Treatment prescribing and dispensing

Treatment will be prescribed and dispensed following local procedures. Gentamicin and GAG should be ordered through inpatient supply route and oral antibiotics should be ordered through outpatient pharmacy. Prescriptions for antibiotics are to be prescribed at randomisation, month 1 and month 3.

11.4 Dosing schedule

Intravesical Prophylactic Treatment:

- **Intravesical antibiotics** – 80mg of Gentamicin diluted to 50ml using normal saline instilled into the bladder weekly for month 1, fortnightly for Months 2 & 3 and monthly for Months 4,5 & 6*
- **Intravesical GAG replacement compounds** (Ialuril, Cystistat, Gepan, etc) – 1 vial of GAG replacement. compound instilled into the bladder weekly for month 1, fortnightly for Months 2 & 3 and monthly for Months 4,5 & 6*

*11 instillations

Comparator:

- Second-line prophylactic daily oral antibiotics as per NICE antimicrobial prescribing guidelines - Nitrofurantoin (50/100mg), Trimethoprim (100mg), Amoxicillin (250mg) or Cefalexin ((125/250mg once a day).

11.5 Dose modification for toxicity

Nitrofurantoin – To discontinue immediately if new or worsening symptoms of pulmonary damage occur.

Trimethoprim is contraindicated in blood dyscrasias, and participants who fit this will be prescribed an alternative antibiotic.

Amoxicillin and cefalexin will not be prescribed to any patient with a history of penicillin hypersensitivity.

Renal function will be determined by eGFR at baseline and if this is less than 45 ml/min nitrofurantoin will not be used

If eGFR is less than 30ml/min the dose of oral trimethoprim will be halved.

Liver function tests will be monitored throughout the trial as some of the antibiotics particularly nitrofurantoin require this.

If alterations in any participants liver function tests in the group randomised to prophylactic antibiotics are identified the local PI will be alerted to this and likely will recommend a change in oral antibiotic agent or re-randomisation to one of the intravesical treatment arms.

11.6 Management of toxicity and hypersensitivity reactions

Follow local policies and procedures as per treating clinician.

11.7 Management of overdose

Follow local policies and procedures as per treating clinician.

11.8 Pre-medication

Not applicable.

11.9 Prohibited medications and interaction with other drugs

All treatments are currently in widespread use in the UK NHS, exhibit a low side-effect profile and have little interaction with other common medications which limits absolute contra-indications to either therapy. Examples of drug interactions are given below:

Trimethoprim – Methotrexate / Clozapine

Amoxicillin – Warfarin / Acenocoumarol

11.10 Permitted concomitant medications

Additional over-the-counter preventive adjuncts such as D-mannose, cranberry supplements and vaginal oestrogen will be permitted in line with current standard clinical care[32].

11.11 Trial restrictions

No further restrictions than those already described above.

11.12 Accountability procedures

No medications or associated equipment or consumables are being provided to sites as part of the trial, and therefore, sites are expected to use their own stock. No CTR accountability, recall and disposal procedures are required as described in the VESPER safety Management Plan.

Continuation of the treatments after completion of the 6-month treatment period is not recommended. Following the 6-month treatment period, any additional care, during the 6-month follow up period and beyond is not expected to differ from what is normally expected for patients with recurrent UTIs. It is usual for a period of observation to be undertaken after completion of a period of preventative treatment and the minimum period for this is usually 3 months. Participants will be encouraged to continue without UTI prevention for 6 months following completion of the

intervention but in some cases this may not be possible. If preventative treatment is restarted before the end of the scheduled 6 months post-treatment observation period, then this will be recorded.

11.13 Adherence

We will use quantitative data to explore adherence to the allocated intervention and to describe differences between different modes of intravesical administration (self vs clinician-delivered) and the timing of this decision in relation to randomisation and whether this is associated with differential response, switching, and outcomes. We will similarly describe the variability (and association with response/outcomes) in prophylaxis implementation more generally.

12 Sample Management

See Table 1 for schedule of sample collection.

12.1 Urine and perineal sample collection, transport, processing, analysis and storage:

Following usual care procedures, blood samples will be taken from participants to determine renal function (eGFR) at baseline and each follow-up visit. If this is less than 45 ml/min nitrofurantoin will not be prescribed for the oral antibiotic arm. If eGFR is less than 30ml/min the dose of oral trimethoprim will be halved.

Liver function tests will be monitored throughout the trial as some of the antibiotics particularly nitrofurantoin require this.

Mid-stream urine samples for research purposes will be taken at baseline, at all follow-up visits and when participants suspect a UTI based on symptoms and will be sent to the central microbiology laboratory. The central laboratory will determine microbiologically proven UTIs and any antimicrobial resistance (AMR) in all urinary pathogens isolated from urine samples. The samples sent to the central laboratory WILL NOT be used to inform clinical care. Clinical care will be informed by local processes such as the submission of urine samples to the local microbiology services as per current clinical pathways.

We will also assess resistance pattern change in *E. coli* within the faecal reservoir by obtaining isolates from the optional perineal swabs sent to the central laboratory at baseline, 6 and 12 months.

When participants suspect a UTI based on symptoms at the baseline appointment, a mid-stream urine sample will be sent to the local laboratories by the recruiting site or responsible clinician. During the course of the trial, if a participant suspects a UTI, based on symptoms, they will consult local healthcare services as per usual practice. As part of this a mid-stream urine sample may also be sent to local diagnostic microbiology laboratories (following usual site processes) for identification of microbiologically proven UTIs.

A positive culture will be classified according to UK Health Security Agency (UKHSA) standards for Microbiological Investigations (SMI) B41: Investigation of urine definitions.

Mid-stream urine samples that are being sent to the central laboratory will be collected in appropriately trial labelled sterile 30ml Universal containers containing boric acid. Boric acid will preserve the sample by inhibiting bacterial growth and maintaining the sample's integrity during transport and storage. The urine sample will be transported to the central laboratory in SpeciSafe® transport containers and mailing envelopes which are compliant with UN3373 Regulations for Cat B biological samples.

Urine samples should arrive at the central laboratory as soon as possible.

Perineal swabs (swab with amies transport medium) will be used to collect faecal samples at baseline and at 6 and 12-month follow-up timepoints. Swabs will be returned to the central laboratory in UN3373 regulatory compliant mailing envelopes for Cat B biological samples.

Perineal swabs should arrive at the central laboratory within as soon as possible.

Processing and storage of the urine and perineal samples sent to the central laboratory will be performed according to the VESPER Sample Management and Laboratory Manual.

Processing, analysing and storage of urine and perineal samples will be performed as per section 16.4: Briefly, urine samples will undergo automated microscopy and culture for urinary pathogens according to SMI: B41. Uropathogens will be susceptibility tested using the current standardised EUCAST methods and guidelines.

13 Trial procedures

All participants will be enrolled in the trial for 12-months; 6-months intervention period followed by 6-months follow-up period.

The primary clinical outcome will be assessed at the end of the 6-months intervention period and the primary economic outcome will be assessed over the subsequent 6-months follow-up period.

Secondary outcomes will be measured at the end of the 6-months and 12-month periods.

13.1 Assessments

See Table 1.

Table 1: Schedule of enrolment, interventions and assessments

Procedures							
			Treatment Phase			Follow Up	
	Eligibility	Baseline	Month 1	Month 3	Month 6	Month 12	Month 13
MSU (central lab) *	X	X	X	X	X	X	
MSU (Local lab)		Sent to local lab only if symptoms of a UTI are present					
Eligibility assessment	X	X					
Informed consent	X	X					
Registration/contacts form	X	X					
Demographics	X	X					
Medical history	X	X					
Physical examination	X	X					
rUTI Impact questionnaire*	X	X	X	X	X	X	
UTI diary*			X	X	X	X	
EQ-5D-5L	X	X	X	X	X	X	

Service use questionnaire (SUQ)	X	X			X	X	
Perineal swab (central lab)	X	X			X	X	
eGFR	X	X	X	X	X	X	
LFTs	X	X	X	X	X	X	
Randomisation	X	X					
Dispensing of trial drugs	X	X					
Adverse events			X	X	X	X	
Pregnancy reporting form			X	X	X	X	
Adherence to intervention			X	X	X	X	
Self Vs hospital administration of intravesical treatment			X	X	X	X	
Treatment Satisfaction Questionnaire					X	X	

GP or hospital records search			X	X	X	X	
DCE							X

* Repeated at time of UTI.

X – denotes schedule to follow when a patient presents without symptoms of a UTI and no antibiotic treatment for a UTI in the previous 4-weeks. If this is the case, then the eligibility and baseline appointments can be combined.

13.1.1 Eligibility and baseline appointment

See **Figure 2** for the trial procedures from eligibility assessments through to randomisation.

An initial eligibility check will be conducted where patients are asked whether they currently have symptoms of a UTI or have received antibiotic treatment for a UTI in the previous 4-weeks.

For those who answer 'no' to both the above questions and are eligible, they will be consented at the eligibility appointment. The MSU sample and perineal sample (for the central lab) will be collected. Bloods (local labs as per usual care processes) will be taken to determine eGFR and LFT levels. For patients who have eGFR data in their medical records that are within the previous 8 weeks, the clinician can choose to use these results, and not send a sample off for eGFR testing. The baseline data will then be collected as described in section 13.1.2.

The participant can then be randomised.

For participants randomised to the oral antibiotic arm, a prescription can be issued based on the eGFR results. If participant has eGFR results in their medical notes from within the last 8 weeks, the recruiting clinician can choose to use these results to assist with determining an antibiotic prescription. If eGFR results are not yet available from the bloods taken, the clinician will issue a prescription, letting the participant know that if the eGFR results indicate it, they may need to switch to another antibiotic and they will be contacted if this is the case. If the eGFR results indicate the participant is not suitable for any of the second line oral antibiotics, the participant will need to be withdrawn. If in an intravesical arm the site team will arrange an appointment with the participant for their first instillation at clinic.

For those patients who answer 'yes' to currently having symptoms of a UTI and/or have received antibiotic treatment for a UTI in the previous 4-weeks, the processes indicated in the red boxes of **Figure 2** are to be followed. Those patients with current UTI symptoms will need to wait for the results of the local laboratory urine culture tests to come back to the site team. Patients with a positive culture will need to be prescribed antibiotics and following the antibiotic course wait for a further 4-week wash out period before they can be asked back to clinic to a 'baseline' appointment to re-assess their eligibility, consent, complete sample collection and baseline data collection. Participants can then be randomised. For those in the oral antibiotics arm, the eGFR results will assist in determining

the antibiotic prescription (as described above). For those in the oral antibiotics arm, their prescription can be issued. For those in the intravesical arms, an appointment is booked for their first instillation.

For those patients who answer 'yes' to having antibiotic treatment for a UTI in the previous 4-weeks, they will need to wait a total of 4-weeks for a wash-out period before they can be invited back to clinic to re-assess their eligibility, consent, complete sample collection and baseline data collection. Participants can then be randomised. For those in the oral antibiotics arm, the eGFR results will assist in determining the antibiotic prescription (as described above). For those in the oral antibiotics arm, their prescription can be issued. For those in the intravesical arms, an appointment is booked for their first instillation.

13.1.2 Baseline data collection

Baseline data collection will be undertaken at the participating site by an appropriately delegated member of the VESPER Trial team. Baseline data may be collected at the initial eligibility appointment or at a subsequent 'baseline' appointment (as described above).

- Demographics
- Registration form
- Physical examination
- Medical history
- rUTI Impact questionnaire
- UTI diary
- EQ-5D-5L
- Service use questionnaire
- eGFR & LFTs (Blood samples)
- Mid-steam urine samples
- Perineal swabs

Mid-stream urine samples and perineal swabs will be obtained and sent to the central laboratory.

13.1.3 Follow-up assessments

I. 1-month follow-up visit

One month following randomisation the following data and samples will be collected on CRFs. We will allow a time window of 1-month+3 weeks for this follow-up visit.

- rUTI Impact questionnaire
- UTI diary
- EQ-5D-5L
- Adherence to intervention form
- Adverse events
- GP or hospital records checked to confirm any additional urine culture results (outside of the scheduled hospital visits), including resistance patterns of the bacteria cultured
- eGFR & LFT bloods
- Mid-steam urine samples (central lab)

II. 3-months follow-up visit

Three months following randomisation the following data and samples will be collected on CRFs. We will allow a time window of 3-months +4 weeks for this follow-up visit.

- rUTI Impact questionnaire
- UTI diary
- EQ-5D-5L
- Adherence to intervention form
- Adverse events
- GP or hospital records checked to confirm any additional urine culture results (outside of the scheduled hospital visits), including resistance patterns of the bacteria cultured
- eGFR & LFT bloods
- Mid-steam urine samples (central lab)

III. 6-months follow-up visit

Six months following randomisation the following data and samples will be collected on CRFs. We will allow a time window of 6-months +4 weeks for this follow-up visit.

- rUTI Impact questionnaire

- UTI diary
- EQ-5D-5L
- Service use questionnaire
- Treatment Satisfaction Questionnaire
- Adherence to intervention form
- Adverse events
- GP or hospital records checked to confirm any additional urine culture results (outside of the scheduled hospital visits), including resistance patterns of the bacteria cultured
- eGFR & LFT bloods
- Mid-steam urine samples (central lab)
- Perineal swab (Central lab)

IV. 12-month follow-up visit

Twelve months following randomisation the following data and samples will be collected on CRFs. We will allow a time window of 12-months +4 weeks for this follow-up visit.

- rUTI Impact questionnaire
- UTI diary
- EQ-5D-5L
- Service use questionnaire
- Treatment Satisfaction Questionnaire
- Adherence to intervention form
- Adverse events
- GP or hospital records checked to confirm any additional urine culture results (outside of the scheduled hospital visits), including resistance patterns of the bacteria cultured
- eGFR & LFT bloods
- Mid-steam urine samples (central lab)
- Perineal swab (Central lab)

V. 13-month follow-up

Thirteen months following randomisation the following data will be collected, from all participants, on CRFs. We will allow a time window of 13-months +2 weeks for this follow-up visit.

- Discrete choice experiment

VI GP or hospital records search:

Data relevant to the trial including urine culture results (including resistance patterns of the isolated bacteria), antibiotic prescriptions, and health service utilisation will be extracted from the GP or hospital records for each participant for the 12-month period following randomisation.

13.1.4 Breakthrough UTIs – reporting of UTIs in periods between the follow-up visits

If a participant experiences symptoms of a UTI in the intervening periods between the clinic follow-up visits, they are requested to send a urine (and perineal sample only at months 6 &12) sample to the central laboratory before they take any prescribed discrete antibiotics to treat their UTI. They will also be asked to complete a UTI diary report form and rUTI impact questionnaire,

13.2 Qualitative process evaluation

13.2.1 Process evaluation

We will carry out a mixed methods process evaluation guided by the new MRC Framework[26] for developing and evaluating complex interventions to:

- understand acceptability and adherence to the intervention, and issues around implementation.

- explore participants' views on the trial processes including a qualitative overview of fidelity (e.g. local adaptations, contextual factors) and views on trial materials and processes (e.g. recruitment, consent and retention)

We will also look to identify an appropriate framework(s) to guide our qualitative data interpretation and analysis.

Interviews will be conducted via telephone or video call (depending on the preferences of the participant. We will give each participant a £10 voucher for their time spent participating in an interview.

13.2.2 Patient Interviews

We will carry out semi-structured interviews remotely with around 20 women at two timepoints (total of around 40 interviews).

Interview 1: at the beginning of their involvement in the trial to explore how they have been managing their rUTI, and what their expectations of the trial and intervention are. We will use a purposive sample of women across both intervention trial arms (attempting to include women who have and have not self-administered) and control arm, and across sites. We will also attempt to include diversity across, ethnic groups and age to include experiences of women from under-represented groups.

Interview 2: towards the end of the trial/after follow-up to explore the same (where possible) participants' experiences of the intervention and trial, including the extent to which the intervention has fitted into their everyday lives, contextual factors which may have had an impact on this, and barriers and facilitators to implementation of the intervention. Where we are not able to carry out paired interviews (second interviews with the same women) we will recruit additional participants.

13.2.3 Healthcare Professional/Trial Recruiter (HCP/TR) Interviews

We will also interview around 20 Healthcare Professionals and Trial Recruiters (expected to be around 5-10 from each group) sampled from across the trial sites at one timepoint (towards the middle/end of trial) to understand their perceptions of the intervention (including acceptability and adherence) and experiences of the trial. We will explore contextual factors (e.g. individual, inner setting, outer setting) within sites which may have an impact on implementation and barriers and challenges to implementation, and the way in which these may be overcome[33]. A purposive sample from the trial database to ensure diversity of interviewees including a mixture of low/high recruitment rates of recruiters will be taken by HP and LBH.

13.2.2 Pilot Phase Interviews (to include exploration with Under-represented groups)

In addition, to the interviews described above, we will also explore under-representation within recruited participants, we will also aim to carry out the following:

- During the pilot phase, we will carry out interviews (n = 5-10) with recruiting research team members to explore their attitudes, skills and confidence in recruiting women from under-represented groups onto the trial. The sample will be taken to include diversity within recruiters including a sample of low/high recruiters.

- During the pilot phase and/or main trial, we will carry out interviews with trial participants and their carers/supporters (n = 5-10) to explore their experiences of participating in the trial. We will purposively sample for under-represented groups including older women, women from rural areas, those who are socio-economically disadvantaged and those from ethnic minority groups. The sample will be taken from the study database.

13.2.3 Informed Consent for PE Interviews

Contact details for patients and staff interview participants will be taken from the study database by study team e.g. Data Manager, Qualitative Researcher(s). Interview participants (patients and HCP/Trial Recruiters) will be sent (either by email or post according to their preference) an interview invitation with a PIS and ICF (either for patients or for HCP/Trial Recruiters). A study team member e.g. qualitative researcher(s)will also contact them by telephone or email to decide upon a date and time for the interview. For patient participants, HCPs/Trial Recruiters etc, the qualitative researcher will record oral consent.

Participants are free to withdraw from the research at any time. The withdrawal of consent will not affect data collection already carried out or the use of data collected prior to participant withdrawal. Participant data already collected prior to withdrawal will be retained according to the trial protocol.

13.2.4 Process Evaluation Data Protection

The qualitative researcher will record the interview on a password protected digital voice recorder or directly on to a CU approved platform e.g. Zoom Enterprise Version, Microsoft Teams or Skype for Business. When taking oral consent for HCPs/Trial Recruiters, consent will be recorded as a separate file to the interview. The interview will be transcribed verbatim and uploaded to a shared drive of the secure Cardiff University server as soon as possible. For all interview recordings, a study identification number will be used for the recording filename, which will not include any personal details such as participants' names. All files containing personal data will be password protected and stored in a folder with restricted access. After the recording has been successfully saved to the RDS Drive of the CU server and the recording has been checked, the data from electronic devices will be deleted permanently from digital recorders

Audio recordings will be securely sent to be transcribed verbatim (and anonymized) by an approved transcription company. Returned transcripts will be saved on the shared drive of the secure Cardiff University server. All files containing personal data will be password protected and stored in a folder with restricted access. Interview recordings will be transcribed using the Essential Secretary *Smart Verbatim* option. All interviews will be conducted remotely and captured via a Cardiff University approved platform (e.g. Zoom Enterprise Version, Microsoft Teams or Skype for Business) or a password protected digital recorder (and then transferred to the CU server)

Voice data and anonymised transcripts will be archived for at least 5 years after the project completion in line with Cardiff University policy. Participants can withdraw from the study and request that their data not be included in the analysis up until analysis is completed.

14 Pharmacovigilance

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately on a VESPER trial SAE form (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see section 16.2). This includes SAEs related to IMPs and non-Investigational Medicinal Products (nIMPs), noting however, that the VESPER trial does not have any nIMPs. Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 7 days after the participant completes the trial protocol.

14.1 Definitions

Table 2 -Adverse event definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product

Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

** **Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

*** **Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

14.2 Causality

Causal relationship will be assessed for IMPs and other trial treatments (medical device)::

Table 3 – Causality

IMPs: **Oral antibiotics** as per NICE antimicrobial prescribing guidelines - Nitrofurantoin, Trimethoprim, Amoxicillin or Cefalexin. Gentamicin (intravesical treatment) **Other Trial Treatment (Medical Device):** Glycosaminoglycan (GAG) replacement compounds (Ialuril, Cystistat, Gepan, etc)

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship:

Table 4 -causal relationship

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the IMP?**
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event	Yes

	occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

14.3 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each serious adverse reaction to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening (LT) SARs should not be considered expected (unless explicitly stated in the RSI and approved by the NCA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

The table below lists the RSI's that should be referenced.

Table 5 - RSI Table

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Gentamicin (intravesical treatment)	SmPC for Gentamicin 1 mg/ml solution for infusion	Section 4.8 of SmPC
Amoxicillin (Oral antibiotic)	SmPC for Amoxicillin 250 mg Capsules	Section 4.8 of SmPC
Nitrofurantoin (Oral antibiotic)	SmPC for Nitrofurantoin 100 mg Capsules	Section 4.8 of SmPC
Trimethoprim (Oral antibiotic)	SmPC for Trimethoprim 50 mg/5 ml Suspension	Section 4.8 of SmPC
Cefalexin (Oral antibiotic)	SmPC for Cefalexin 125 mg/ 5 ml Oral Suspension	Section 4.8 of SmPC

Reference Safety Information (RSI) on any CTR trial will be reviewed regularly according to CTR procedures.

Intravesical treatments:

As the intravesical treatments are not absorbed systemically, the expected side-effects associated with the instillation process are listed below in **Error! Reference source not found.** :

Table 6: Expected events in relation to instillation of the intravesical treatments

Common	Less common	Rare
Mild bladder or urethral discomfort after instillation	Urinary tract infection	Blood in urine, severe pain after instillation

14.4 Reporting procedures

14.4.1 Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE form to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, date of birth or year of birth and initials. The participant's name (or any other personal identifiers) should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

SAE Fax number:

0203 0432 376

Serious adverse events and serious adverse reactions should be reported from time of signature of informed consent, throughout the treatment period up to, and including 7 days after the participant completes the trial protocol (ie 7 days after the 12-month follow up timepoint).

SAEs should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

An SAE form should contain at least the minimum information:

- Full participant trial number
- An Adverse Event / Adverse Reaction

- IMP or trial intervention

- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the site will be contacted, and the information must be provided by the site to the CTR within 24 hours.

All other AE's will be captured on CRFs at the time of data collection at the scheduled follow-up appointments.

14.4.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 7days after the participant completes the trial protocol. Serious adverse reactions should continue to be reported until the end of follow up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA, Main Ethics Committee.

14.5 SUSAR reporting

The Newcastle upon Tyne Hospitals NHS Foundation Trust is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (NCAs and relevant ethics committees) as follows:

SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR.

SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR.

If report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life-threatening and non-life threatening.

Any additional, relevant information must be reported within a further 15 days.

14.6 Unblinding for the purposes of SUSAR reporting

VESPER is an unblinded trial, this section, therefore is not applicable.

14.7 Safety Reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA REC, trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs annually throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

Insert details of any specific reporting of SAEs performed by the drug company, and/or production and submission of the trial specific DSUR.

14.8 Contraception and pregnancy

14.8.1 Contraception

The oral antibiotic Trimethoprim, used in this trial has a demonstrated or suspected human teratogenicity/fetotoxicity. The oral antibiotic Nitrofurantoin, used in this trial has demonstrated a risk of neonatal haemolysis when used in late pregnancy. The oral antibiotic Cefalexin is considered safe to use in pregnancy. Intravesical treatments are generally avoided during pregnancy due to the need for repeated bladder catheterisation. WOCBP entering into this trial must agree to use a highly effective method of contraception preferably with low user dependency for at least one month after the last dose of the trial treatment. A highly effective method of contraception is considered as having a failure rate of less than 1% per. Some acceptable contraception methods are listed below;

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable*
- intrauterine device (IUD)*
- intrauterine hormone-releasing system (IUS)*
- bilateral tubal occlusion*
- vasectomised partner*
- sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments.

N.B. periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

**These contraception methods are considered to be low user dependency.*

14.8.2 Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, termination of pregnancy etc. Without follow-up

of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP.

Information on a pregnancy in a VESPER trial participant will be captured by sites on the CTR Pregnancy Report Form (PRF) supplied to sites by the CTR. The PRF should be completed by the trial site within 7 days of becoming aware of the pregnancy and then emailed to the CTR (CTR-Safety@cardiff.ac.uk). Any participant identified as being pregnant whilst on the trial will, under the supervision of the principal investigator at site, have their trial treatment stopped. The site, on becoming aware of the pregnancy, will also complete a withdrawal form. The participant can choose to continue to provide follow-up data and or provide samples even though their trial treatment will be stopped.

VESPER sites must report pregnancy occurring within SAE reporting periods as stipulated in the trial protocol (from time of signature of informed consent, throughout the treatment period up to, and including 7 days after the participant completes the trial protocol). Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC.

14.9 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. The principal investigator or delegated team member at the VESPER recruiting sites must notify the CTR as soon as an USM has been implemented by emailing and marking as urgent: Vesper@cardiff.ac.uk. The trial manager at the CTR will notify the MHRA and Research Ethics Committee of any USMs immediately by telephone, and in any event within 3 days of being made aware of the USM, in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

15 Statistical considerations

15.1 Randomisation

Participants will be individually allocated in a 1:3:3 ratio to one of the three trial arms: (1) intravesical gentamicin, (2) intravesical GAG replacement or (3) oral antibiotic prophylaxis for up to 6 months. The covariate-adaptive randomisation procedure following the Pocock and Simon's range method will be used to minimise the imbalance of key covariates with an 80% random element applied to reduce the risk of subversion. These key minimisation factors are:

- prior frequency of UTI (<= 4 episodes per year or > 4 episodes per year)
- menopausal status (pre-menopausal or menopausal/post-menopausal)

Following randomisation, those in the oral antibiotics arm will be issued with a prescription. For those in the intravesical arms an appointment will be arranged for the participant to come back to clinic for their first instillation.

Participants can be re-randomised to a different prophylactic regime due to lack of efficacy or incidence of predefined adverse events. These include i.) relapse with at least two episodes of UTI occurring in the 6-month treatment period in line with currently accepted definitions of recurrent UTI; ii.) intolerance of side effects of prophylactic antibiotic. In this event, participants will be re-randomised 1:1 between the two remaining allocations. Re-randomisation will be based on block randomisation with no stratification. An individual not otherwise involved with the study will produce the final re-randomisation schedule. The randomisation procedure will be implemented via a web-based remote system (TMS2 - available 24 hours a day) that bult in-house CTR Information Systems and Technology Solutions team with telephone back-up as described in Section 9.5.2. Full details will be provided in a separate randomisation protocol.

15.2 Blinding

The VESPER trial does not use blinding of participants or clinicians. However, the statisticians who perform the primary analysis blind to allocation.

15.3 Sample size

We aim to recruit 412 participants over 21 months and follow them up for a fixed 12-month period (62 in the oral comparator arm and 175 in both intravesical experimental arms). We are primarily interested in comparisons of each intravesical prophylaxis against standard care and then a head-to-head comparison of intravesical prophylaxes.

Two sets of comparisons are powered. The first set compares each intravesical prophylaxis arm to the second-line prophylactic oral antibiotics arm to detect a difference in the UTI rate of 1 (assumed UTI rate of 2 from previous studies[3]). This is calculated based on 90% power, and two-sided alpha of 0.05 (no multiplicity adjustment as comparisons is considered independent). This comparison requires 62 participants in each arm (1:1:1 ratio). The second set is to detect a difference in the UTI rate between the intravesical arms. This is calculated based on 90% power, 5% two-sided alpha (no adjustment as we are making this comparison as part of a fixed sequence. That is, we will only compare the intravesical prophylaxis arms head-to-head if both are superior to the second-line prophylactic oral antibiotics arm), with target effect size of 30% (i.e. a relative difference of 30% between intravesical arms, with an assumed UTI rate of one in one of the intravesical arms). This comparison requires 175 in each intravesical arms and hence 1:3:3 ratio.

Target differences between oral and intravesical treatments are based on PPI work. In line with previous studies[3] the PPI group for VESPER overwhelmingly stated that any intravesical treatment demonstrating a reduction in UTI frequency of 1 episode per year greater than oral antibiotic tablets would be considered superior. Target differences between intravesical treatments are based on our clinician survey administered via UKCS which revealed that the majority of clinicians felt that for one intravesical treatment to be considered superior to another there would need to be a 30% or greater difference in efficacy. This sample size is further inflated to account for a 15% drop-out (as observed in the ALTAR trial[3]).

Although we are proposing a SMART design, our primary interest is the marginal effect of the initial prophylaxis, the comparison of each treatment sequence is considered exploratory and hence the SMART design has no impact on our required sample size.

15.4 Missing, unused & spurious data

Participants with incomplete follow-up will enter the primary analysis following multiple imputation. Further detail will be provided in the Statistical Analysis Plan (SAP).

15.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

15.6 Termination of the trial

Progression criteria for the internal pilot phase are described in Section 6. There is the potential for the trial to terminate early if our funder assesses the trial as not being feasible following the assessment of progress against our targets at the end of the internal pilot with input from our TSC and IDMC.

15.7 Inclusion in analysis

All eligible participants who have been randomised will be included in the primary intention-to-treat analysis regardless of their treatment adherence, discontinuation, and initiation of the subsequent treatment as described in the primary estimand Section 16.1 below. As part of sensitivity analyses, ineligible participants will be excluded from the analysis, and alternative analysis populations (as described in Section 16.1) will be used.

16 Analysis

16.1 Main analysis

Descriptive statistics will be summarised using frequencies and percentages, means and standard deviations, or medians and interquartile ranges as appropriate. Recruitment, retention, and other trial processes (e.g. adherence to allocation) will be reported both overall, by arm, and disaggregated by site, menopausal status, previous UTI frequency, and previous type of failed treatment.

The primary analysis will be an intention to treat, including all randomised participants regardless of adherence or discontinuation of the initial treatment allocation or initiation of the subsequent treatment.

For the clinical-effectiveness primary outcome (rate of symptomatic, antibiotic-treated UTI, self-reported by participants from randomisation to the 6-month treatment period (verified from medical

records)), a Poisson/negative binomial regression model will be fitted to estimate incidence rate ratios, including fixed effects for allocation, covariate factors used in randomisation (prior frequency of UTI and menopausal status) and random effects to model heterogeneity between sites. Regression analysis results will be presented as point estimates with confidence intervals and p-values. The primary estimand for VESPER is below:

Primary clinical question: In women who fail first-line preventative treatment for rUTI, does the strategy to initially prescribe intravesical treatments result in a greater reduction in the rate of symptomatic UTIs over the subsequent 6 months compared to the current guideline-recommended second-line prophylactic antibiotic therapy?

The estimand is described by the following attributes:

- **Population**: women aged ≥16years with recurrent uncomplicated UTI who have failed first-line treatments requiring second-line prophylactic treatment and able to receive intravesical treatments and take second-line oral antibiotic prophylaxis.
- **Endpoint**: rate of symptomatic UTIs from randomisation to 6-months.
- **Treatment condition**: The intravesical treatments and second-line oral antibiotic prophylaxis, regardless of adherence or discontinuation of the initial treatment allocation or initiation of the subsequent treatment (via re-randomisation) (treatment policy strategy);
- **Remaining intercurrent events**: Treatment adherence or discontinuation or initiation of the subsequent treatment are covered by previous attribute.
- **Population-level summary**: Incidence rate ratio from Poisson or negative binomial regression model for intravesical treatments and second-line oral antibiotic prophylaxis arms.

Rationale for estimand: To compare the strategy of initially prescribing intravesical treatments compared to prescribing second-line oral antibiotic prophylaxis as would be observed in routine practice.

Sensitivity analyses around the primary outcome will consider appropriate estimands, accounting for initial allocation and reinstatement/switching of different prophylaxes via the SMART design. Weighted and replicated regression approach will be considered to evaluating adaptive intervention effects[34].

Secondary outcomes will also be analysed based on intention-to-treat using appropriate regression models (e.g. linear regression for continuous outcomes, Poisson/negative binomial for counted outcomes, logistic regression for binary outcomes, as appropriate), adjusting for covariate factors

used in randomisation as per the primary analysis, and are described in the Table below. Mixed-effects models will be considered when participants have multiple data points over time.

As part of our process evaluation, we will describe differences between those who opt for different modes of intravesical administration (i.e. self vs clinician-delivered), including the extent to which it varies across sites. We will also describe the timing of this decision in relation to randomisation and whether this is associated with differential response, switching, and outcomes. We will similarly describe the variability (and association with response/outcomes) in prophylaxis implementation more generally (i.e. which oral antibiotics are used in the oral antibiotic arm, switches and circumstances around switching etc.)

Table 7 - planned outcome analysis

Outcome	Measure	Time frame	Analysis
Occurrence of symptomatic UTI in the 6-month follow-up period	UTI-rate occurred after 6 months of treatment period	At 12 months	Poisson/ negative regression
Change in rUTI Impact Questionnaire	Recurrent UTI impact questionnaire	At 6 months/12 months	Linear regression
Days prescribed antibiotics	Addition antibiotic prescribed	At 6 months/12 months	Poisson/ negative regression
Microbiologically proven UTIs	Per the primary outcome plus a concomitant positive urine culture	At 6 months/12 months	Logistic regression
AMR in *E. coli* isolated from urine or perineal swabs	Resistance to 1 or more antibiotics in the panel tested	At 6 months/12 months	Logistic regression
Multi-drug resistance in *E. coli*	Resistance to >=1 antimicrobial agent in >=3 antibiotic categories	At 6 months/12 months	Logistic regression
Asymptomatic bacteriuria	Positive urine culture without symptoms	At 6 months/12 months	Logistic regression

Adverse events	Type, frequency, and severity of adverse events	At 6 months/12 months	Descriptive statistics
Hospitalisation due to UTI	Number of hospitalisation due to UTI	At 6 months/12 months	Poisson / negative binomial regression
Quality of life	EQ-5D-5L	At baseline/3/6/12 months	Linear regression
Participant satisfaction	Treatment Satisfaction Questionnaire for Medication	At 6 months/12 months	Linear regression

A comprehensive Statistical Analysis Plan will be finalised by the trial statistician, with support from the Management Group (TMG), agreed by the Trial Steering Committee (TSC), and Data Monitoring and Ethics Committee (DMEC) prior to database lock and commencement of analysis. The findings will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement. We will incorporate the estimand framework within our protocol and statistical analysis plan, with the aim of specifying primary and sensitivity estimands and aligning analysis strategies accordingly. Our primary clinical analysis will be based on a "treatment policy" strategy of offering each of these options as second-line prophylaxis and analyse participants in the arm to which they were originally randomised within a multiple imputation framework, regardless of intravesical instillation/prophylactic oral antibiotics receipt (including treatment switching) or outcome availability.

16.1.1 Sub-group & interim analysis

To explore the extent to which there may be a differential intervention effects by the primary outcome, rate of symptomatic UTIs from randomisation to 6-months, the model fitted for the primary analysis will be extended by including a main and treatment group interaction term for menopausal status, previous UTI frequency, and type of failed first-line treatment. For the exploration of differential intervention effects by site, the primary analysis will be extended by allowing for different slopes across sites and compare this to the original model (random intercepts only) using the Likelihood-ratio test. Estimates from the statistical models (main effects and interaction terms) will be presented alongside 95% confidence intervals and p-values.

No formal interim analysis will be conducted.

16.2 Qualitative analysis

Interviews will be recorded (with the consent of participants), transcribed and de-identified. A proportion of the patient and HCP/TR interviews will take place during the pilot phase (around months 8-15). These interviews will be analysed using rapid qualitative analysis to feedback on issues around recruitment and acceptability. The entire dataset of interviews will then be analysed using a thematic approach[35, 36] to identify inductive and deductive themes (including themes relating directly to our interview questions as well as themes which interviewees initiate and had not been pre-empted). The thematic framework will be discussed and refined by experienced qualitative researchers. A proportion of the data will be double-coded, and discrepancies discussed to enhance analysis and vigour. NVivo coding software will be used to manage the data. The qualitative and quantitative data relating to the process evaluation (e.g. acceptability, adherence, implementation) will be brought together during interpretation (data triangulation) with members of the qualitative, quantitative and wider trial team discussing, reflecting upon, and integrating findings (investigator triangulation) to produce an overall mixed methods process evaluation.

As part of our process evaluation, we will describe differences between those who opt for different modes of intravesical administration (i.e. self vs clinician-delivered), including the extent to which it varies across sites. We will also describe the timing of this decision in relation to randomisation and whether this is associated with differential response, switching, and outcomes. We will similarly describe the variability (and association with response/outcomes) in prophylaxis implementation more generally (i.e. which oral antibiotics are used in the oral antibiotic arm, switches and circumstances around switching etc.)

16.3 Cost effectiveness analysis

The economic analysis will consist of both a within-trial and a model-based economic evaluation. A cost-utility analysis will estimate the incremental cost per QALYs gained at 12 months and over a lifetime horizon. A cost-benefit analysis will estimate the incremental net benefits at 12 months. The

within-trial analysis will be conducted on an intention-to-treat principle. Full details of the health economics analyses will be set out in the Health Economics Analysis Plan (HEAP).

16.3.1. Estimation of costs

An NHS and personal social services (PSS) perspective will be adopted in the base case analysis. A further analysis will incorporate costs borne by women and their families. Intervention costs will be estimated using micro-costing and will be based on the costs of the medications and their administration. These resources will be recorded on the eCRFs and costs will be collated from the most up to date routine sources at the time of analysis or directly from sites.[37-39] Additionally, the costs associated with managing rUTIs, mainly the costs associated with antibiotics will be considered.

A bespoke Service Use Questionnaire (SUQ) based on previous studies and PPIE feedback will be used to capture subsequent self-reported resource use [40]. Participants will be asked to complete the SUQ at baseline, 6-, and 12-months post-randomisation. The SUQ will capture information on the frequency of primary and secondary care resource use, direct and indirect costs borne by participants, including time away from usual activities, and any additional healthcare resources used by participants. These resources will be combined with unit costs to estimate the total subsequent treatment costs for each individual participant.[37, 38]

The direct and indirect costs borne by participants will be estimated in an analysis which adopts a wider perspective beyond the NHS and PSS. Time away from work and usual activities will be collected via the SUQ, in addition to any out-of-pocket payments made by trial participants to manage their rUTI (e.g., over-the-counter medications). Direct and indirect costs incurred by participants to access care will be taken from a previous NIHR HTA study and inflated to the price year of the economic evaluation to reduce participant burden[41, 42].

In the base case analysis intervention costs, costs associated with managing rUTIs including primary and secondary care resource use will be combined to estimate the total NHS and PSS cost per participant. Participant costs will be combined with these costs in subsequent analysis. For each randomised arm an average total cost per participant will be estimated.

16.3.2 Outcomes

EQ-5D-5L

The EQ-5D-5L will be administered at baseline, 3-, 6- and 12-months post-randomisation. Responses will be converted into utility values using the UK recommended tariff[43]. QALYs will be estimated using the area under the curve approach[44]. In a sensitivity analysis the disutility associated with a UTI episode, estimated in a previous NIHR HTA study, will be considered in the QALY calculation[3].

Willingness-to-pay to avoid a UTI

Despite considering the disutility associated with a UTI in a sensitivity analysis, given the short duration of UTIs, potential differences in quality of life associated with a reduction in UTIs may not be captured by QALYs. In a previous NIHR HTA study women were asked to value, in monetary terms, how much they would be willing-to-pay to avoid a UTI[41]. The average willingness-to-pay value estimated will be inflated to the current price year and combined with the number of UTIs reported by participants in VESPER[42]. This will be presented as the burden of UTIs reported in VESPER on women, in monetary terms, for each of the randomised arms.

Discrete choice experiment

To estimate women's preferences for the trial interventions and their associated outcomes, a discrete choice experiment (DCE) will be administered, to all participants, at month 13, so as to not affect the response rate for other trial outcomes. A DCE involves presenting individuals with a series of hypothetical alternative choice sets, usually pairwise, differing in their attributes and levels, and asking them to indicate their preferred alternative in each set[45]. The key attributes and associated levels reflecting the features and outcomes of the interventions, and a cost attribute will be derived using a literature review, and consultations (likely in the form of interviews and focus groups) with both women and clinicians. Once the attributes and levels have been identified, the DCE will be designed in NGene[46]. The responses to the DCE will be analysed using appropriate regression models, such as conditional logit models and mixed logit models. These regression models will allow us to predict the value and relative importance that participants place on the different attributes of each intervention[47]. The inclusion of a cost attribute will allow us to estimate women's marginal willingness-to-pay for each of the interventions' attributes and the net benefit of the treatments can also be estimated[48].

16.3.3 Within-trial analysis

For the within-trial analysis, costs and outcomes will not be discounted as the time horizon is 12-months. The economic analysis will compare the interventions in terms of mean costs and effects to estimate cost-effectiveness. Differences in costs and effects will be estimated simultaneously using seemingly unrelated regression, which controls for observed (e.g., age, baseline costs and utilities) and unobserved individual characteristics[49]. If one treatment is not dominant (i.e., less costly and more effective) then, for the cost-utility analysis the incremental cost per QALY gained at 12-months will be estimated; and the cost-benefit analysis will estimate the incremental net benefit.

Sensitivity analysis

To replicate the primary outcome, time horizon, a sensitivity analysis will be undertaken to estimate the incremental cost per QALY gained over the treatment phase (6-months). Only costs and utilities reported between baseline and the 6-month follow-up will be considered in this analysis.

Both deterministic (e.g., variation in unit costs) and stochastic, in the form of the bootstrapping technique, will be used to explore potential uncertainties in costs, effects and cost-effectiveness[50]. This statistical impression will be presented as both cost-effectiveness acceptability curves (CEACs) and cost-effectiveness planes[51, 52]. For the cost-benefit analysis statistical imprecision will be displayed as cost and willingness-to-pay planes and as the probability of an intervention being efficient (i.e., the probability that the benefit of the intervention is greater than the cost).

16.3.4 Model-based analysis

An economic model will extrapolate the costs and outcomes from the within-trial analysis to estimate the longer-term impact of interventions using a NHS and PSS perspective. The model-based analysis will estimate cost-effectiveness for both a patient-lifetime time horizon and a 12-month follow-up. The latter time horizon would form part of the internal validation of the model as we can compare estimates provided by the model with those provided by the within-trial analysis. The structure and parameters of the model will be informed by the trial, previous models, the literature, clinical advice and PPIE input[8]. The model will be developed in accordance with NICE's reference case and guidelines for good practice[53, 54].

Sensitivity analysis

Similar to the within-trial analysis deterministic sensitivity analysis will be used to explore potential uncertainty in key assumptions, such as the model structure or individual model parameters. All of the model-based analyses will be combined with probabilistic sensitivity analysis (PSA)[55]. The PSA will likely be a Monte Carlo simulation which requires all model parameters to be assigned a distribution, which represents the uncertainty surrounding them. The PSA results will also be presented on CEACs which display the probability of each intervention being considered cost-effective over a range of possible threshold values for an additional QALY.

16.4 – Microbiology analysis

Urines:

In the trial laboratory, the urine samples will undergo automated microscopy analysis (Sysmex UF 5000) for detection of Red Blood Cells (RBC), White Blood Cells (WBC), bacteria, and Squamous Epithelial Cells (SEC). 50µL urine will be cultured using a spiral plater (Don Whitley Scientific) onto blood and chromogenic agar, with quantitative counts for all clinically relevant uropathogenic bacterial isolates determined after overnight incubation at 35±1°C. Initial identification using the chromogenic media of all isolates will be followed by Matrix Assisted Laser Desorption/Ionisation - Time of Flight (MALDI-ToF) mass spectroscopy (Bruker BioTyper Sirius) for those cultures deemed significant.

For trial purposes urines will be considered as indicative of UTI if they fulfil SMI B41 definitions[56] for "Probable UTI" or "Possible UTI" (see below) based on combinations of host, sample type, symptoms, WBC and CFUs. Presence of WBC where relevant to the definition will be considered as significant at a threshold of >100 WBCs/µL. The definitions are as follows:

Probable UTI is defined as $\geq 10^5$ CFU/ml of pure culture, irrespective of WBC levels.

Possible UTI is defined using the following criteria: re culture at ≥105 with predominant growth (where the second or third organisms are at least $3x\log_2$ CFU/ml below the predominant organism) irrespective of WBC (dual culture: where both are $\geq 10^5$ or one is $\geq 10^5$ and the other is $\geq 10^4$) accompanied by WBC, pure or predominant culture at 104 - 105 accompanied WBC, predominant culture at 10^4 - 10^5 of a UTI pathogen species accompanied

by WBC OR pure or dual culture (where both present are known urinary pathogens at 10^3 – 10^4 accompanied by WBC.

Urines with culture results of pure/predominant growth of Coagulase Negative Staphylococci at ≥10^4 CFU/mL but counts of WBC<100 and SEC>100 may be excluded as likely contaminated.

Antimicrobial susceptibility testing will be performed on all significant isolates using the EUCAST Disk Diffusion method and breakpoints. For Gram-negative uropathogens the following antimicrobials will be tested: ampicillin/amoxicillin, co-amoxiclav, piperacillin/tazobactam, nitrofurantoin, trimethoprim, mecillinam, fosfomycin, cephalexin, cefixime, cefuroxime, cefpodoxime, cefotaxime, ceftazidime, ciprofloxacin, ertapenem, meropenem, temocillin, gentamicin, amikacin & co-trimoxazole. For Gram-positive uropathogens, Staphylococcus aureus/saprophyticus will be tested against cefoxitin, co-trimoxazole, erythromycin, clindamycin, tetracycline, mupirocin, penicillin, gentamicin, fusidic acid, linezolid, ciprofloxacin, rifampicin, vancomycin and teicoplanin. For Enterococci, ampicillin, ciprofloxacin, nitrofurantoin, vancomycin and teicoplanin will be tested whilst penicillin, clindamycin, nitrofurantoin, vancomycin and teicoplanin susceptibility will be determined for Streptococci.

All Probable and Possible UTI pathogen isolates will be stored for future analysis at -80°C on protect beads.

Perineal swabs:

Perineal swabs will be cultured directly onto blood and chromogenic agar, streaking for single colonies. After overnight incubation, any presumptive or the dominant *E.coli* isolate will be confirmed using the Bruker MALDI ToF. Storage and susceptibility testing will be performed as per the urinary pathogens above. Antibiotic susceptibility results will be compared to those obtained from the *E. coli* (if any isolated) from the corresponding urine sample to identify similar patterns.

17 Data Management

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

Source data for the VESPER trial will be from a variety of sources. Data will be collected using an electronic system with paper CRF back up. There will also be data collected from participants' medical notes and patient reported questionnaires. Patients will be asked to complete UTI diaries at home which may be in paper format but preferably emailed directly via the REDCAP database, at given timepoints, to prompt completion.

Training for completion of study CRFs will be provided to the appropriate trial staff prior to trial commencement at site initiation.

17.1 Data collection

17.2 Completion of CRFs

Paper CRFs

If the electronic database is not available, paper CRFs will be used, and data will be entered onto the database at a later point. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.

CRF pages and data received by the CTR from participating trial sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised. Where a data query is required, this will be per site and include the relevant PIDs, CRF/timepoints and the nature of the query, and be sent to the relevant site staff using either a data query form/spreadsheet or including the query details in an email. All queries should be logged and tracked within the REDCap database, which has an in-built query system that allows logging of raised and responded to data queries with a full audit trail.

Received query replies must be received along with a signature (wet or electronic) from the relevant delegated staff member. If a signature is missing for a completed data query, then this will be re-queried. Query responses should be logged on the query log and database by the data manager and can be closed off if the reply answers the query satisfactorily and the database has been corrected. For any queries that are not answered satisfactorily, these will be re-raised.

Completed data queries should be printed and stapled to the back of the paper CRF to ensure a clear audit trail.

Electronic CRFs

The preferred method of data collection will be via electronic data entry directly onto the trial online database. This web-based system is a secure and encrypted system accessed by an institutional password and complies with the General Data Protection Regulation 2016 standards. The system can be accessed on:

https://redcap.ctr.cardiff.ac.uk/redcap/

A user password will be supplied to investigators upon completion of all processes required prior to opening. This will include a site initiation to complete a database walkthrough to ensure the trial teams are comfortable with data entry prior to site opening. Trial teams will also have to be approved for data entry on the delegation log by the PI.

The database will flag missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised. Where a data query is required, this should be per site and include the relevant PIDs, CRF/timepoints and the nature of the query, and be sent to the relevant site staff using either a data query form/spreadsheet or including the query details in an email. All queries should be logged and tracked within the REDCap database, which has an in-built query system that allows logging of raised and responded to data queries with a full audit trail.

Received query replies must be received along with a signature (wet or electronic) from the relevant delegated staff member. If a signature is missing for a completed data query, then this needs to be re-queried. Query responses should be logged on the query log and database by the DM and can be closed off if the reply answers the query satisfactorily and the database has been corrected. For any queries that are not answered satisfactorily, these must be re-raised.

Web-based data collection forms (eCRFs) should be completed following the Schedule of assessments (see Table 1).

All aspects of data management for VESPER can be found in the VESPER Data Management Plan.

A VESPER data collection manual will be provided to sites providing detailed instructions on how to complete both paper and electronic CRFs.

18 Translational research or sub trial

N/A

19 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

20 End of Trial definition

The intervention period is for 6-months following randomisation. This is followed by a 6-month follow-up period.

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as the date of final data capture of the last participant to meet the trial endpoints.

Sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

21 Archiving

The TMF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF (including the sites full dataset) at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

22 Regulatory Considerations

22.1 CTA

This trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority (CA): MHRA. Classification of whether any changes to the protocol is defined as a substantial amendment or not will be based on HRA guidance and sponsor assessment. All amendments will be reviewed by the TMG, and if necessary, sponsor representative, for approval prior to being submitted, via IRAS and email, to REC, HRA, and if necessary, the MHRA. The central trial team will alert all site trial teams and R&D departments once approval has been received for the amendment. The amendment history will be listed in the protocol and in the amendment log which is filed in the VESPER TMF.

22.2 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review dependant on the location of the lead site ie. HRA for an England led trial.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

22.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian and the translational sample custodian for this trial is the Chief Investigator.

This includes collection of NHS number (or equivalent e.g. CHI number in Scotland), name, date of birth, address (incl postcode), telephone number, email address to register participants.

22.4 Indemnity

Non-negligent harm:

Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

Negligent harm:

The Sponsor will provide indemnity for claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial in the event that trial participants suffer negligent harm due to the management of the trial provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS organisations this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts will provide their own professional indemnity.

22.5 Trial sponsorship

The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as Sponsor for the VESPER trial. Delegated responsibilities will be assigned to the sites taking part in this trial and will be documented in the site agreements (mNCA).

The sponsor will delegate responsibilities to the CTR, as documented in the Delegation of Duties Agreement. The CTR shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)

- UK Policy Framework for Health and Social Care Research.
- The General Data Protection Regulation 2016.
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

The trial will be conducted in compliance with the protocol, the EU regulation and Good Clinical Practice as required by the regulations.

22.6 Funding

This trial is funded by the National Institute for Health and Care Research (project number: NIHR158130). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The study is adopted on the NIHR portfolio.

23 Trial management

The Centre for Trials Research at Cardiff University will manage the trial. The trial will be conducted in accordance with the above-mentioned regulations. The trial manager will be responsible for running the trial and will be accountable to the Sponsor.

23.1 Project Team meetings

The project team will meet weekly and will include the TL, TM, DM, TS, TA, PV and other research staff directly employed to the trial. The CI will attend one PT meeting per month. The project team will discuss all day-to-day management issues and will refer any key management decisions to the TMG.

23.2 TMG (Trial Management Group)

The TMG will consist of the CI, Co-Applicants, Collaborators, TL, TM, DM, TS, PV, research partners/ PPI and TA. The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents (information sheets, Protocol, etc.). They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will

normally meet monthly throughout the course of the trial. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter which will be filed in the TMF.

23.3 TSC (Trial Steering Committee)

A TSC, consisting of an independent chair, and two/three other independent members including a patient representative/PPI, will meet at least annually. The first meeting will be before the trial commences to review the Protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The TM and TS will attend as observers. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

23.4 IDMC (Data Monitoring Committee)

To monitor accumulating data on safety and any trial intervention benefit, an IDMC will be established. The Committee will consist of an independent chair and two/three other independent members. The first meeting will take place before the trial commences to review the Protocol. The main role of the IDMC is to review the data periodically and make recommendations to the TSC. IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter which will be filed in the TMF.

24 Quality Control and Assurance

24.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the VESPER trial.

Low monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Where electronic health records (EHR) are being used, trial teams and monitors should check EHR process early in trial and periodically thereafter.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

24.2 Audits & inspections

The trial is participant to inspection by the MHRA as the regulatory body. The trial may also be participant to inspection and audit by The Newcastle upon Tyne Hospitals NHS Foundation Trust, under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data / documents.

The site must inform the CTR of any MHRA inspections.

25 Public Involvement and Engagement

Preparatory PPI exercises during the grant submission stage included a series of focus groups comprising patients with rUTI and discussion with national patient organisations such as Bladder Health UK and Live UTI-free. Patients stressed the significant impact of each UTI episode and stated that any new treatments that could reduce UTI frequency, even by 1 episode per year, would be welcome. Patients informed us that rUTI were impactful enough for them to consider invasive procedures such as the catheterisation required for intravesical instillations. Most patients demonstrated an awareness of AMR and the need to restrict antibiotic consumption. Some were able to detail their own problems with resistant bacteria and felt this underlined the need for our planned trial.

Two senior members of Bladder Health UK helped formulate this application, along with a patient with lived experience and they will join the TMG providing PPI input throughout the entire study Our PPI members have contributed to the development of the VESPER protocol.

Through PPI strategy meetings, chaired by the VESPER PPI lead, the group have identified and recruited four women with lived experience of recurrent UTI from a diverse background to form the VESPER Patient Advisory Group (PAG) alongside the current PPI members. PPI meetings will be held approximately 6 times a year and will be attended by the PPI lead, CI, TM and our PPI members from the TMG.

PPI partners and the PAG members have contributed to the development of the participant facing documents (participant information sheets, consent forms, recruitment posters) and will contribute to the development of an infographic recruitment video. Our TMG PPI partners and PAG members will also contribute to the development of our participant recruitment strategies and recruitment materials

Our PPI partners and the PAG members will be involved in writing lay summaries of the trials results and assist with public engagement via the dissemination of the trial results to participants and relevant patient groups via different platforms.

26 Publication policy

The trial results will be published in a general medical journal with the monograph published in the NIHR Journals Library. We will disseminate research findings to those involved in the care of women with rUTI via social media, topic-specific meetings/conferences and peer-reviewed general medical journals as numerous specialities are involved in the treatment of rUTI. The trial will provide high-level evidence to use in new or updates of existing systematic reviews. To facilitate inclusion in relevant guidance documents, two of the co-applicants sit on European guidelines committees including the chief investigator (CH) who is Chair of the Female Guideline Committee of the European Association of Urology and co-applicant Somani is the editor of the Journal of Clinical Urology, the official journal of British Association of Urological Surgeons. Policy makers will be targeted via national commissioning bodies, aiming to reduce rates of systemic antibiotic prescription through the provision of alternative prophylactic options. Participants will be provided with a lay summary of results and have access to journal articles through the trial website. PPI co-applicants will review results and write lay summaries for dissemination to relevant patient groups such as Bladder Health UK. These will be in accessible formats in keeping with Equality legislation.

27 Milestones

M1-7 set-up, M8-15 internal RCT pilot, M16 stop/go assessment, M8-28 recruitment, M14-41 follow-up completion; M42-48 analysis and write-up.

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