# CLINICAL TRIAL PROTOCOL


## Dequalinium versus usual care antibiotics for the treatment of bacterial vaginosis (DEVA): a multicentre randomised, open label, non-inferiority trial

Protocol Version 2.0

26 March 2021

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| **Amendment number** | **Protocol version number** | **Type of amendment** | **Summary of amendment** |
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| 01 | 2.0 | Substantial | Adaptations to recruitment and sub-study have been made in response to Covid-19 pandemic along with minor administrative changes throughout the protocol. |

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## Trial Summary

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| **Full title** | Dequalinium versus usual care antibiotics for the treatment of bacterial vaginosis (DEVA): a multicentre, randomised, open label, non-inferiority trial. |
| **Trial design** | Phase IV, multicentre, open-label, two-arm, parallel, randomised, non-inferiority trial. |
| **Objectives** | **Primary objective**<br>To determine if the proportion of women reporting resolution of BV symptoms 4 weeks after treatment is not worse in women treated with dequalinium chloride compared to usual care antibiotics without the need for additional treatment**.**<br><br>**Secondary objectives**<br>To determine:<br>• The proportion of women reporting resolution of BV symptoms 4 weeks after treatment (with or without the need for additional treatment)<br>• The effect of dequalinium chloride on number of days to resolution of BV symptoms without the need for additional treatment<br>• The effect of dequalinium chloride on microscopic resolution of BV at week 4 without the need for additional treatment<br>• The adherence to dequalinium chloride and usual care antibiotics<br>• The side effects of dequalinium chloride and usual care antibiotics<br>• The satisfaction with BV treatment<br>• The effect of dequalinium chloride on recurrence of BV symptoms within 12 weeks<br>• The effect of dequalinium chloride on number of days to recurrence of BV symptoms<br>• The cost of treating BV with dequalinium chloride compared with usual care antibiotics |
| **Eligibility criteria** | **Inclusion Criteria**<br>• Cis-Women aged 16 years and over<br>• Diagnosis of BV confirmed by microscopy with symptoms of vaginal odour plus or minus vaginal discharge requiring treatment with usual care (BV guideline recommended) antibiotics<br>• Willing to use either intravaginal dequalinium chloride tablets (pessaries) or the clinician selected usual care antibiotic BV treatment<br>• Willing to avoid vaginal sex whilst taking/using trial treatment<br>• Willing to avoid vaginal douching whilst taking/using trial treatment<br>• Willing to complete follow up questionnaires in English<br>• Written informed consent<br><br>**Exclusion Criteria**<br>• Contra-indications or allergy to dequalinium chloride or clinician selected usual care antibiotic BV treatment |

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| | • Use of oral antibiotics concurrently, within the 14 days prior to randomisation or planned use over the 14 days from randomisation<br>• Use of intravaginal therapies (including vaginal douching) concurrently, within the past 14 days prior to randomisation or planned use over the next 14 days from randomisation<br>• Pregnant women who are seeking a termination<br>• Unwilling to provide GP information (only to be used for pregnant women or women who become pregnant in the first 4 weeks of the trial)<br>• Previous participation in this trial<br>• Resident outside the UK (for shipment of trial medication and sample kits only) |
| **Description of interventions** | **Intervention**<br>The intervention group will receive dequalinium chloride 10 mg vaginal tablet for 6 nights.<br><br>**Control (usual care antibiotics)**<br>The control group will receive clinician-chosen usual care antibiotics selected from UK guideline recommended or alternative oral or topical antibiotic BV treatments.<br><br>Clinicians will choose the control treatment prior to randomisation. If the patient is randomised to the control arm they will receive this predetermined BV treatment. |
| **Outcome measures** | **Primary**<br>Participant-reported resolution of BV symptoms 4 weeks post-treatment start date without the need for additional treatment.<br><br>**Secondary**<br>• Participant-reported resolution of BV symptoms 4-weeks post-treatment start date (with or without the need for additional treatment)<br>• Time to participant-reported resolution of BV symptoms without the need for additional treatment<br>• Microscopic resolution of BV on microscopy at week 4 (without the need for additional treatment) as assessed by central laboratory analysis of participant taken vaginal smears (in a subgroup of participants)<br>• Participant reported proportion of prescribed trial BV treatment taken<br>• Participant-reports of vaginal irritation (itching, pain and/or burning), vaginal discharge, unpleasant vaginal smell, nausea, vomiting, diarrhoea, abdominal pain, unpleasant taste and candida infection<br>• Participant-reported satisfaction with treatment |

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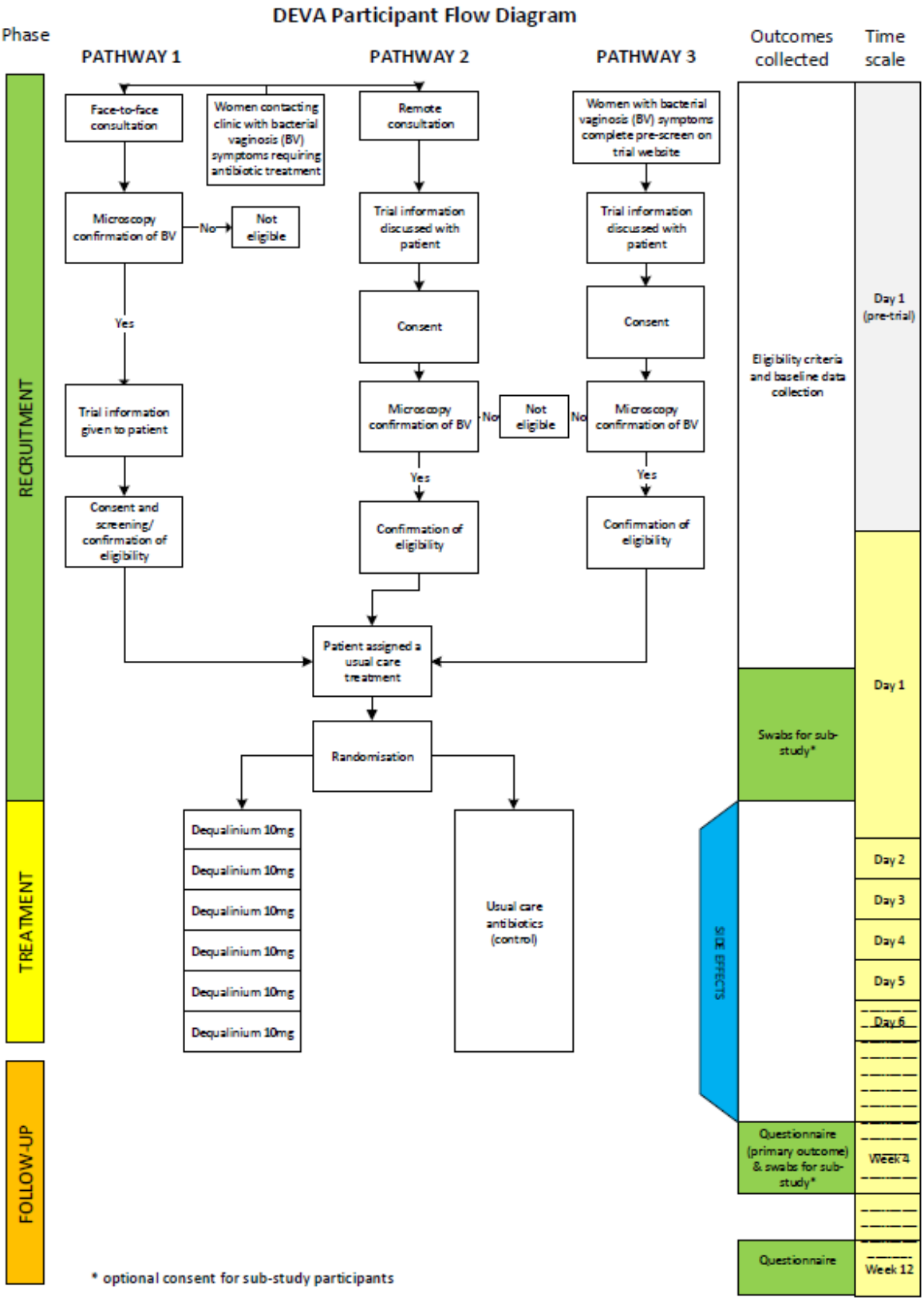
| | • Participant-reported recurrence of BV symptoms within 12 weeks of treatment start date, for those who resolved within 4 weeks without additional treatment<br>• Time to participant reported recurrence of BV symptoms<br>• Cost of BV treatment, including additional medication and healthcare usage relating to BV |
| **Sample Size** | The trial will recruit 904 participants.<br><br>Assuming 78% of participants have bacterial vaginosis symptom resolution at week 4 in both the control and intervention groups, a total sample size of 722 for analysis (361 in each group) will achieve 90% power to conclude non-inferiority with a lower confidence limit for the absolute risk difference of 10%, with a 1 sided significance level of 0.025. This margin was acceptable to 68% of a sample of women attending 2 GUM clinics and 81% of clinicians experienced in treating BV. To allow a loss of primary outcome data of up to 20% the trial will recruit 904 women.<br><br>Participants will be invited to take part in a sub-study collecting extra samples for vaginal microbiota analysis, at baseline and at Week-4, until 150 pairs of baseline and week-4 samples have been received by the central laboratory. The inclusion of 150 participants in the sub-study is not based on a specific sample size calculation. |
| **Expected recruitment duration** | 18 months |

## Trial Flow Diagram



## Abbreviations and Definitions

| Term | Description |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.<br>Comment:<br>An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. |
| **Adverse Reaction (AR)** | All untoward and unintended responses to an IMP related to any dose administered.<br>Comment:<br>An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship. |
| **BV** | Bacterial Vaginosis |
| **DEVA** | Dequalinium versus usual care antibiotics for the treatment of bacterial Vaginosis |
| **DMC** | Data Monitoring Committee |
| **DMP** | Data Management Plan |
| **GUM** | Genitourinary Medicine |
| **ICF** | Informed Consent Form |
| **IMP** | Investigational Medicinal Product |
| **ISF** | Investigator Site File |
| **NAAT** | Nucleic Acid Amplification Test |
| **NIHR** | National Institute for Health Research |
| **NCTU** | Nottingham Clinical Trials Unit |
| **PIS** | Participant Information Sheet |
| **RCT** | Randomised Controlled Trial |
| **SAP** | Statistical Analysis Plan |
| **Serious Adverse Event (SAE)** | Any untoward medical occurrence or effect that:<br>**1.** Results in death<br>**2.** Is life-threatening*<br>**3.** Requires hospitalisation or prolongation of existing hospitalisation<br>**4.** Results in persistent or significant disability or incapacity<br>**5.** Is a congenital anomaly/birth defect<br>**6.** Or is otherwise considered medically significant by the Investigator** |

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| | Comments:<br>The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria.<br>* Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.<br>** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious. |
| **Serious Adverse Reaction (SAR)** | An Adverse Reaction which also meets the definition of a Serious Adverse Event |
| **Source data** | 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 |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.<br>A SUSAR should meet the definition of an AR, UAR and SAR. |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |
| **Unexpected Adverse Reaction (UAR)** | An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for a licensed product).<br>When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected. |

# 1 Background and Rationale

## 1.1 Background

Bacterial vaginosis (BV) is the most common cause of vaginal discharge in women of reproductive age. In 2018, 86,870 women were diagnosed with BV in English Genitourinary Medicine (GUM) clinics[1] and 90 cases per month were diagnosed at the Leeds GUM clinic. In the UK, 9% of women having cervical cytology smears taken in primary care[2] and 15% of pregnant women attending an antenatal clinic were found to have BV.[3] It is estimated that up to a third of women will get it at some time in their lives.

BV produces an offensive vaginal odour and it is associated with serious sequelae.[4] It increases the acquisition of sexually transmitted infections (STI)[5] and HIV[6] and the transmission of HIV.[7] It is associated with miscarriage, preterm birth[8] and pelvic inflammatory disease which causes infertility.[9]

The most frequently used treatment for BV in the UK is 7-days oral metronidazole.[4] This has microbiological resolution rates of 61-94% one month after treatment.[10] Recurrences are common, occurring in 23%, 43% and 52% of women at 1, 3 and 6-months after metronidazole[11], necessitating repeated or long term antibiotics.[12] There are other antibiotic treatment regimens recommended in national guidelines using intravaginal metronidazole, intravaginal or oral clindamycin or oral tinidazole, but the failure rates are the same.[13] Recurrent BV has a severe impact on quality of life[14] and vulvovaginal candidiasis often occurs following antibiotic treatment for BV.[12]

Dequalinium chloride (currently available under the brand name Fluomizin®) is an anti-infective and antiseptic agent belonging to the class of quaternary ammonium compounds. It is a surface-active substance and the primary mechanism of action is an increase in bacterial cell permeability and the subsequent loss of enzyme activity, finally resulting in cell death. Dequalinium chloride exhibits a rapid bactericidal activity and in the form of vaginal tablets exerts its action locally within the vagina. It is administered in the form of 10mg vaginal tablets for a treatment course of six days. Advantages of dequalinium chloride in comparison to the antibiotics used to treat bacterial vaginosis include: it has a broad antimicrobial spectrum, it is less vulnerable to resistance, it achieves a high concentration of the substance at the infection site, while systemic exposure is negligible.[15] Dequalinium chloride was licensed for use in the UK in June 2015 and is currently the only antiseptic licensed for treatment for BV in the UK.[16]

A descriptive review identified 8 published studies testing dequalinium chloride (n=577 women).[15] However, only two were controlled trials and only one compared dequalinium chloride with antibiotic therapy.[17] These randomised controlled trials (RCTs), plus a number of case series, suggest that dequalinium chloride is well tolerated with very little absorption from the vagina, and hence few systemic side-effects and no serious adverse events.[15] Other studies have compared dequalinium chloride with povidone-iodine or other therapies which are not prescribed in the UK.[18]

There is only one published RCT to date comparing dequalinium chloride with a guideline recommended treatment, vaginal clindamycin cream.[17] This was a single-blinded, randomised trial in 15 sites, and included 321 women. Women were randomised to either vaginal dequalinium chloride tablets or vaginal clindamycin cream. Follow-up visits were 1 week and 1 month after treatment. The trial showed a dequalinium chloride clinical cure based on Amsel's criteria of 79.5% at 30 days but it did not include patient-centred outcomes and there was no longer-term follow up to assess recurrences.[17] In the RCT comparing dequalinium chloride to povidone-iodine, 78.3% of women

treated with dequalinium chloride had BV resolution at 30 days.[18] However, no previous RCT has compared dequalinium chloride to the most commonly used antibiotics prescribed to treat BV.

The aetiology of BV is unclear but *Gardnerella vaginalis* may produce a biofilm on the vaginal walls to which the many other BV associated bacteria (BVAB) adhere.[19] BV represents a low-lactobacillus polymicrobial dysbiosis and women with BV have complex, diverse, and heterogeneous vaginal bacterial communities.[20] In contrast, women with normal vaginal flora are colonised principally with lactobacillus species with either *Lactobacillus crispatus, L. gasseri, or L. jensenii.*[21] The diversity of BV bacteria[21] may explain the poor efficacy, and high recurrence rate, following antibiotic treatments because the bacteria may not all be sensitive to the antibiotic used. A broad-spectrum antiseptic such as vaginal dequalinium chloride may have better activity against the wide variety of bacteria which are present. Also, dequalinium chloride has some antifungal activity so vulvovaginal candidiasis may occur less frequently than occurs following the use of antibiotics. However, an advantage of a narrower-spectrum antibiotic, such as metronidazole, is that it does not damage lactobacilli which are essential for the restoration to the normal lactobacilli-dominant microbiota.[22] Without the return to lactobacilli-dominance there is a high risk of recurrence.[23] It is not known what effect dequalinium chloride might have on the lactobacilli as this has not been studied.

The DEVA trial will compare dequalinium chloride to usual care antibiotics for the treatment of BV. It will add to our knowledge on the clinical effectiveness and side-effects of dequalinium chloride and will evaluate its cost compared to the usual antibiotics used to treat BV. If dequalinium chloride is effective in treating BV it will result in reduced antibiotic use for this common condition. Whilst there is little evidence of increasing metronidazole resistance amongst the BVAB, reduced use of metronidazole will help to prevent the emergence of resistance in common potential pathogens, (e.g. *Helicobacter pylori*[24]) and avoids disruption of the normal microbiome (e.g. in the bowel).

## 1.2 Trial Rationale

BV has been identified recently as an area that represents a particular challenge in STI treatment and control, being described as neither rare nor benign, it is a condition of high global burden in women of reproductive age and is associated with serious and costly sequelae.[25]

Alternative treatments for BV are clearly needed. In a qualitative study of women who had experienced BV, most were dissatisfied with current treatments.[26] Although 7-day antibiotic treatment is effective at the time of treatment, many women felt frustrated and distressed at having BV recur, often quite quickly after treatment. Most women disliked taking antibiotics, especially on a regular basis, and felt frustrated at the lack of alternative effective treatments.[26] The poor long-term efficacy of BV treatments and high rates of recurrence are also areas of concern for women who attend for their BV care in the UK; they often ask if better treatments are available. Identifying better treatments will improve the care and wellbeing of women experiencing BV and reduce their complications from it. Fewer return visits, and reduced complications, due to less recurrent BV, also has the potential to reduce health service costs.

### 1.2.1 Justification for participant population

The target population is women with symptoms of BV confirmed on microscopy examination of a sample of vaginal discharge, including either first or recurrent episodes. The trial will be as inclusive as possible with only safety issues (e.g. allergies to dequalinium chloride or usual care antibiotics) or clinical requirement for antibiotic therapy being exclusion criteria. The UK guideline for the management of bacterial vaginosis recommends that symptomatic pregnant women should be

treated in the usual way to non-pregnant women.[4] The Summary of Product Characteristics (SmPC) of Fluomizin 10mg vaginal tablets states that limited data from clinical studies in pregnant women did not suggest adverse effects on the pregnancy or on the foetus/neonate, and that no reproductive toxicity studies have been conducted in animals because of the expected low systemic exposure to dequalinium chloride after vaginal administration. Consequently, pregnant women with an ongoing pregnancy are eligible for inclusion but pregnant women seeking termination of pregnancy will be excluded from the trial because the national guidelines recommend that they are all given metronidazole prophylaxis against anaerobes to reduce post-abortal infections.[27]

### 1.2.2 Justification for trial design

The trial design is pragmatic and reflective of a 'large simple trial' to make the trial attractive and convenient to both patients and clinicians.

Follow-up will be until 12 weeks to assess longer term efficacy than the previous trials of dequalinium. A non-inferiority trial design is being used in view of the similar resolution rates for dequalinium chloride compared to antibiotic therapy in previous studies. A literature search, and search of registered clinical trials, identified only two similar non-inferiority trials. Both used different non-inferiority margins. A comparison of dequalinium chloride with intravaginal clindamycin cream used a 15% margin[17], a comparison of oral metronidazole with intravaginal boric acid is using 10%[28]. Considering oral metronidazole, a randomised comparison of 7 day and 14 day regimes was powered to detect a minimum difference of 20%[29], whilst another trial comparing oral metronidazole and intravaginal lactic acid gel aimed to detect a difference of 6% between treatments (VITA trial, HTA Project:15/110/02) [29].

In the absence of a conventionally accepted or clinically justified non-inferiority margin, 60 female patients in two Genitourinary Medicine (GUM) clinics completed a questionnaire which asked them to consider the pros and cons of an oral antibiotic and a new treatment (referred to as an "antiseptic") and whether they would accept the antiseptic over the antibiotic if the antiseptic was 'worse' than the antibiotic. They were told that 80% of patients had their symptoms cleared on antibiotics and were asked if they would use the antiseptic if 65%, 70% and 75% of patients had their symptoms cleared. The results were that 33% would accept dequalinium chloride if 65% had symptom clearance, 68% would accept it if 70% had symptom clearance and 95% would accept dequalinium chloride if 75% had symptom clearance. An on-line survey was undertaken of 21 consultants who treat BV in the UK. They were asked to choose what would be the lowest margin of difference with dequalinium chloride compared to standard treatment that would be acceptable and clinically useful. The results were that 19% would accept 65% symptom clearance, 81% would accept 70% symptom clearance and all would accept 75% symptom clearance. We therefore chose a 10% non-inferiority margin, which is acceptable to the majority of patients and clinicians and which gives a sample size that is feasible to recruit.

**Recruitment in response to Covid-19 pandemic**

The Covid-19 pandemic has resulted in a number of changes to the provision and operation of NHS sexual health services. The introduction of social distancing has reduced face to face consultations with many adopting a mixed approach of face-to-face and remote consultations (either video or telephone). To ensure the trial remains pragmatic and in line with sexual health services provided, patients can now enter the trial via one of three recruitment pathways (please see Trial Flow diagram) either through a recruitment centre (in person or remote) or through patient self-referral via the trial website.

To account for the reduction in BV patients identified through the Genitourinary Medicine (GUM) clinics, to protect recruitment during any further redeployment of clinic and research staff from recruiting centres and to expand recruitment potential throughout the UK, a self-referral recruitment pathway that allows patients to express interest via the trial website has been included. Leeds Sexual Health (LSH) will act as the recruitment centre for patients identified via this pathway, undertaking screening, eligibility assessments and the management of care for these patients during their participation on the trial.

**Heath Economics**

The health economics component is a simplified cost comparison. This is important to include as dequalinium chloride is more expensive than oral metronidazole, but it is important to understand whether these initial treatment cost differences would be offset by differences in NHS resource use and other costs. This element will indicate whether dequalinium chloride treatment will be deliverable within the NHS, given current budgets. Such cost considerations are a core concern for clinicians and providers as with increasing pressures on NHS funds, alternative treatments are unlikely to be adopted unless there is evidence about their costs compared to usual care. Evidence on costs is also used by NICE as part of the Guidelines development process.

**Patient Vaginal Samples**

For inclusion in the trial, all participants are required to have microscopic confirmation of BV. BV microscopy is used for diagnostic purposes in most GUM clinics as part of standard care. To assess eligibility for the trial, all patients screened will be asked to take a vaginal smear to confirm the presence of their BV and for those recruited during a face-to-face consultation this will be done prior to consent but form part of their baseline visit data collection. In-clinic BV microscopy will be performed following local clinic procedure. As microscopic BV testing is not currently offered as part of standard care for patients treated for BV remotely, a trial-specific BV sample testing kit will be sent from Leeds Sexual Health (LSH) to patients at their home address to take their own vaginal samples. The patient will take their own sample and return it by post to LSH who will coordinate the analysis of these with Leeds Teaching Hospitals NHS Trust central laboratory. Results will be reported back to the recruiting site via the trial randomisation system; those patients with confirmed BV on microscopy will then undergo a final eligibility check and be randomised by the recruiting site.

In addition, baseline sexually transmitted infection (STI) swabs to test for *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis* (TV) will be analysed for all women randomised onto the trial.

Participants recruited remotely will be also be required to provide a BV smear at 4 weeks post-treatment start date to confirm microscopic presence of their BV. BV microscopy slides for patients recruited remotely will be read at the central laboratory by two, of a group of six, assessors. It is important to keep interpretation within the same group of assessors to reduce the inter-observer variability of BV diagnosis on microscopy that has been reported: in a study of thirteen international experts, complete agreement occurred in only 63% of the microscopy slides.[30] BV is associated with all of the above STIs, and the inflammatory responses to them alters the vaginal microbiota.[5] Women with these infections at baseline will not be excluded from the study but, as potential confounders, adjustments may be made in a sensitivity analysis of the primary outcome.

Performing these laboratory investigations complies with the recommended guidelines for undertaking BV treatment trials[31], and for inclusion in BV treatment meta-analyses[13]. The standard

criteria for studies to be included in BV treatment meta-analyses are women with Gram-stain proven BV in whom other causes of vaginal discharge have been excluded and where treatment failure has been confirmed by Gram-stained slide[13].

Pathway 1 (face-to-face) participants, in keeping with standard clinical practice, will not be asked to provide a week 4 vaginal smear. In standard clinical practice retreatment would be based on patient self-reported symptoms and this information will be collected in the 4 and 12 week questionnaires.

As participants in the remote pathways will be required to provide self-taken vaginal samples at home as part of their study activity, a subgroup will be invited to participate in the sub-study which involves consenting to and providing an additional self-taken vaginal microbiota swab at baseline and 4 weeks post-treatment start date. The consent for this will be optional, and participants who do not give their consent will not be precluded from participating in the trial. By specifically asking for additional consent we expect to maximise the sample return rate. Recruitment of participants into the sub-study will continue until 150 participant sample pairs (both baseline and week 4 samples) have been received by the central lab. Once received, no further patients will be asked to participate in the sub-study.

The Covid-19 design adaptations, introducing the two remote recruitment pathways, allows us to potentially engage with a much larger patient pool than traditional in-clinic recruitment which will make the results of this trial more generalisable while retaining an efficient study design.

### 1.2.3 Choice of treatment

Oral metronidazole is the medication most likely to be used to treat BV, but other antibiotics and alternative routes of administration are also recommended in UK guidelines. The control group will therefore include any UK guideline recommended/alternative oral or topical antibiotic treatment for BV (at the time of writing this protocol this is oral metronidazole, intra-vaginal metronidazole, oral clindamycin, intra-vaginal clindamycin, oral tinidazole).[4] This makes the trial more generalisable as it will allow a greater population of patients to be included (e.g. those with contraindications to metronidazole and those who do not wish to take oral antibiotics) and be responsive to sporadic shortages of particular antibiotics.

Clinicians will select the control treatment prior to randomisation, after discussion of the options with the woman. If the patient is randomised to the control arm, they will receive this predetermined BV treatment.

# 2 Aims, Objectives and Outcome Measures

## 2.1 Aim

To determine if dequalinium chloride is effective in the management of BV compared to usual care antibiotics.

## 2.2 Objectives and outcome measures

### 2.2.1 Primary

| Objective | Outcome Measure | Assessment time point/method |
|---|---|---|
| To determine if the proportion of women reporting resolution of BV symptoms 4 weeks after treatment (without the need for additional treatment) is not worse in women treated with dequalinium chloride compared to usual care antibiotics | Participant-reported resolution of BV symptoms 4 weeks post-treatment start date without the need for additional treatment | Week 4 questionnaire* |

### 2.2.2 Secondary

| Objective | Outcome Measure | Assessment time point/method |
|---|---|---|
| To determine the proportion of women reporting resolution of BV symptoms 4 weeks after treatment (with or without the need for additional treatment) | Participant-reported resolution of BV symptoms 4 weeks post-treatment start date with or without the need for additional treatment | Week 4 questionnaire* |
| To determine the effect of dequalinium chloride on number of days to resolution of BV symptoms without the need for additional treatment | Time to participant-reported resolution of BV symptoms without the need for additional treatment | Week 4 questionnaire |
| To determine the effect of dequalinium chloride on microscopic resolution of BV at week 4 without the need for additional treatment | Microscopic resolution of BV on microscopy at week 4 (without the need for additional treatment) as assessed by central laboratory analysis of participant taken vaginal smears (in a subgroup of participants) | Week 4 self-taken smear |

| Objective | Outcome Measure | Assessment time point/method |
|---|---|---|
| To determine adherence to dequalinium chloride and usual care antibiotics | Participant reported approximate proportion of prescribed trial BV treatment taken | Response to text message at Day 14 or Week 4 questionnaire |
| To determine the side effects of dequalinium chloride and usual care antibiotics | Participant-reports of:<br>Vaginal irritation (itching, pain and/or burning), vaginal discharge, unpleasant vaginal smell, nausea, vomiting, diarrhoea, abdominal pain, unpleasant taste and candida infection | Week 4 questionnaire |
| To determine the satisfaction with BV treatment | Participant-reported satisfaction with treatment | Week 4 questionnaire |
| To determine the effect of dequalinium chloride on recurrence of BV symptoms within 12 weeks | Participant-reported recurrence of BV symptoms within 12 weeks of treatment start date | Week 12 questionnaire |
| To determine the effect of dequalinium chloride on number of days to recurrence of BV symptoms | Time to participant reported recurrence of BV symptoms from time of symptom resolution without additional treatment. | Week 4 and week 12 questionnaire |
| To determine the cost of treating BV with dequalinium chloride | Cost of BV treatment, including additional medication and healthcare usage relating to BV | Week 4 and week 12 questionnaire |

* this information may be collected by text message or phone call if the week 4 questionnaire is not completed

# 3 Trial Design and Setting

## 3.1 Trial Design

Phase IV, multi-centre, randomised, open-label, parallel group, non-inferiority trial with equal allocation (1:1) to receive either dequalinium chloride (intervention) or usual care antibiotics (control). Recruitment of 904 women is required to achieve 90% power to conclude non-inferiority. Further information on sample size and randomisation can be found in section 13.

## 3.2 Trial Setting and Participant Identification

The trial allows for patients to be identified and recruited into the trial via one of three recruitment pathways, taking into consideration changes that have been made to clinical services in response to the Covid-19 pandemic.

**Pathway 1 – face-to-face recruitment via a GUM clinic**
Patients attending clinic appointments and being seen in person at a clinic consultation will be identified and recruited by a participating GUM clinic. Participants in this pathway will be screened, consented and randomised during their clinical consultation by a member of the site DEVA research team. Participants will be issued their study medication during their consultation and will not be required to provide additional vaginal samples or attend further clinic visits as part of their trial participation.

If during a clinical consultation the patient requests more time to consider the trial they are able to book a further consultation or recruit via one of the remote pathways, in this instance they should not be prescribed treatment as this would make them ineligible for the trial should they decided to take part. If a patient decided to do this, eligibility would need to be reassessed at a further consultation (in person or remote) to ensure that they still meet all eligibility criteria.

**Pathway 2 – remote recruitment via a GUM clinic**
In light of the Covid-19 pandemic, face-to-face appointments may not always be conducted. It is expected that routine clinic appointments may be carried out remotely via telephone/video call in place of an in-clinic visit. Patients with suspected BV will be identified and recruited by the participating GUM clinic, however the trial will be discussed during a remote consultation (telephone or video) with a member of the site DEVA research team and the Participant Information Sheet (PIS) and Informed Consent Form (ICF) will be provided electronically.

In order to confirm eligibility for the trial, consented patients will be required to take a self-taken vaginal swab to confirm a BV diagnosis. Patients will be posted a trial sample kit containing two swabs; one to confirm their BV diagnosis and the other for STI screening (this is for the purpose of the trial only and will only be tested if it is confirmed that they have BV and are randomised onto the trial). Samples will be posted back to LSH who will coordinate analysis with the central laboratory. BV microscopy results will be reported back to the recruiting site (via the trial randomisation system) to share with the patient, whether positive or negative. Patients with a positive BV microscopy result, who remain interested in participating will complete final eligibility and be randomised onto the trial. Trial medication will be prescribed and dispensed directly from the recruiting site to participants in accordance with local policy. Those who do not have BV on microscopy will be informed that they are ineligible for the trial because their symptoms are not due to BV so BV treatment will not be of benefit to them. They will be advised to contact their GP or local sexual health clinic if their symptoms persist. The method of patient contact for negative results will be dictated by local Trust policy.

**Pathway 3 – self-referral via the DEVA trial website**
Patients can express their interest in joining the trial via a self-referral (pre-screen) form on the trial website. Those patients who meet the pre-screen criteria will complete a webform with their personal details and on submission of this the LSH DEVA research team, who will manage the care of all participants who are recruited via this pathway, will be notified to contact them to discuss the trial. Those who remain interested in participating will be sent a link with their PIS and ICF electronically.

In order to confirm eligibility for the trial, consented patients will be required to take a self-taken swab to confirm a BV diagnosis. Patients will be posted a trial sample kit containing two swabs; one to confirm their BV diagnosis and the other for STI screening (this is for the purpose of the trial only and will only be tested if it is confirmed that they have BV and are randomised onto the trial).

Samples will be posted back to LSH who will coordinate analysis with the central laboratory. BV microscopy results will be shared with the patient, whether positive or negative. Patients with a positive BV microscopy result, who remain interested in participating will complete final eligibility and be randomised onto the trial. Study medication will be prescribed and dispensed to participants by LSH in accordance with local policy. Those who do not have BV on microscopy will be informed by text that they are ineligible for the trial because their symptoms are not due to BV so BV treatment will not be of benefit to them. The text will inform them to contact their GP or local sexual health clinic if their symptoms persist.

Potentially eligible patients will generally be identified in the following ways:

<u>Pathways 1 and 2: GUM clinic recruitment</u>

1 Patients attending "walk-in" clinics or those triaged for telephone consultations will be recruited opportunistically by the local site research team upon presentation to clinic. A trained member of the site research team will approach the patient about participating in the trial.

2 Patients with a pre-bookable appointment at a GUM clinic may be identified in advance by the local site research team following a review of their clinic booking system. A member of the site research team will approach the patient about participating in the trial during their appointment.

3 Patients that have previously attended a clinic appointment for the treatment of bacterial vaginosis (and consented to further contact by the clinic) may be identified from clinic systems and sent brief details (using pre-approved wording) of the DEVA trial (by post, text or email) advising them that the trial is being conducted and how to find out further information should their symptoms recur.

4 Patients who contact the local clinic as a result of trial advertising and promotional material.

<u>Pathway 3: Website recruitment</u>

5 Patients with BV symptoms who self-refer via the DEVA trial website as a result of trial advertising, promotional material or information from their local GUM clinic.

6 Patients who contact the Nottingham Clinical Trials Unit (NCTU) as a result of trial advertising and promotional material.

Advertising materials will be produced which may include trial posters, electronic advertising (e.g. on NHS Trust clinic booking systems, websites etc.), social media and search engines. All wording used for advertising material will be approved by the Research Ethics Committee (REC) prior to use.

# 4 Eligibility

## 4.1 Inclusion Criteria

- Cis-women aged 16 years and over
- Diagnosis of BV confirmed by microscopy with symptoms of vaginal odour plus or minus vaginal discharge requiring treatment with usual care (BV guideline recommended) antibiotics
- Willing to use either intravaginal dequalinium chloride tablets (pessaries) or the clinician selected usual care antibiotic BV treatment
- Willing to avoid vaginal sex whilst taking/using trial treatment
- Willing to avoid vaginal douching whilst taking/using trial treatment
- Willing to complete follow up questionnaires in English
- Written informed consent

## 4.2 Exclusion Criteria

- Contra-indications or allergy to dequalinium chloride or clinician selected usual care antibiotic BV treatment
- Use of oral antibiotics concurrently, within the 14 days prior to randomisation or planned use over the 14 days from randomisation
- Use of intravaginal therapies (including vaginal douching) concurrently, within the 14 days prior to randomisation or planned use over the 14 days from randomisation
- Pregnant women who are seeking a termination
- Unwilling to provide GP information (only to be used for pregnant women or women who become pregnant in the first 4 weeks of the trial)
- Previous participation in this trial
- Resident outside the UK (for shipment of trial medication and sample kits only)

# 5 Screening and Consent

## 5.1 Screening

All trial activity must be recorded in the patient's NHS medical notes in each of the pathways. It is important that a record of the consultation, trial information and eligibility reviews (including eligibility BV smear results and confirmation of consent for those remotely recruited) are documented in the patient medical notes and each entry dated and signed by the individual completing the activity. A copy of the signed consent form (paper or electronic) must be filed with the patient medical notes.

**Pathway 1: GUM face-to-face screening**
Cis-women either pre-identified by, or presenting to, recruiting GUM clinics with symptoms of BV, locally confirmed by microscopy will be approached by a member of the local site research team to determine whether they are interested in participating in the trial. If they are interested, they will be given the opportunity to learn more about the trial from a member of the site DEVA research team and given a PIS.

**Pathway 2: GUM remote screening**
Cis-women either pre-identified by, or contacting recruiting GUM clinics with symptoms of BV will be triaged by telephone by a member of the local site research team to determine whether they are interested in participating in the trial. If they are interested, they will be given the opportunity to learn more about the trial and those who confirm their interest will be sent a link with their PIS and ICF. On completion of this by both parties (the patient and the site personnel), an eligibility sample kit (BV microscopy and STI screen) will be sent to their home address for them to complete and return to LSH to confirm their BV diagnosis and eligibility for the trial.

**Pathway 3: Website self-referral screening**
Cis-women with symptoms of BV will self-refer via the trial website, by completing a short pre-screening form to assess their initial eligibility. Those who complete this and meet the criteria will complete their personal details within the webform, which will notify the research team at LSH, who will telephone them to give them the opportunity to learn more about the trial and determine whether they would be interested in participating. If they are interested, they will be sent a link with their PIS and ICF. On completion of this by both parties (the patient and the site personnel), an eligibility sample kit (BV microscopy and STI screen) will be sent to their home address for them to complete and return to the central laboratory at LSH to confirm their BV diagnosis and eligibility for the trial.

### 5.1.1 Use of Screening data

Pathways 1 and 2

Details of all patients approached about the trial will be recorded within the trial randomisation system. Patients that decline trial participation are not obliged to give a reason, however this will be recorded where this is known. Sites will be required to provide a summary of screening data on an ongoing basis throughout the recruitment period.

Pathway 3

Details of all pre-screen forms completed via the trial website will be recorded within the trial randomisation system. Details of all participants who are pre-screen successes will be recorded and all information regarding their potential participation (ICF completed, eligibility sampling kit returned etc) will be recorded. Information on where the participant found out about the trial (social media advertising, search engine etc) will also be recorded as part of the randomisation system screening data.

All screening information provided for all three pathways will be reviewed regularly by the trial management group (TMG) and oversight committees.

## 5.2 Consent

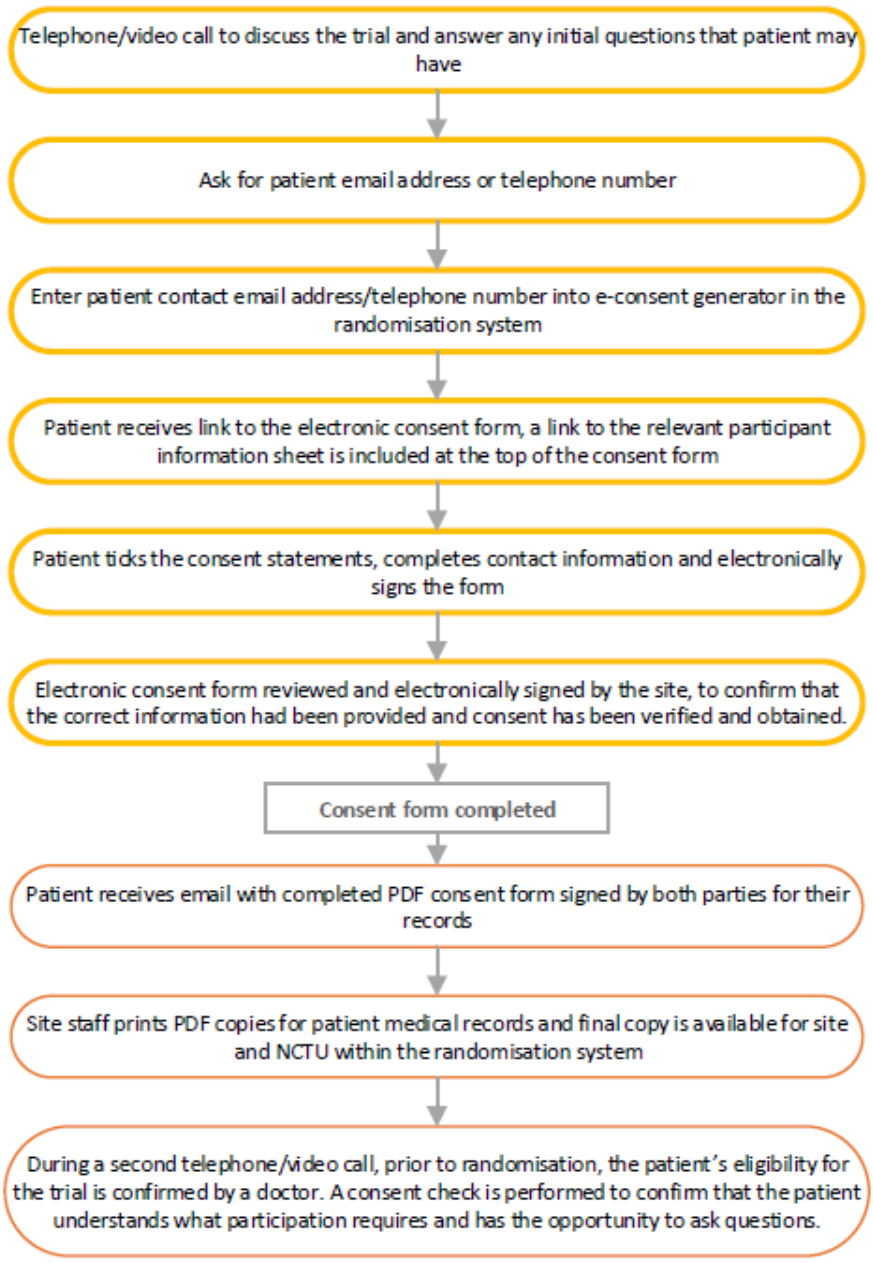
Written/electronic informed consent for each participant must be obtained prior to performing any trial related activities.

The potential participant will be given the opportunity to ask questions prior to completing their consent form and prior to randomisation. Consent will be obtained by a member of the research team (at the local recruiting clinic or LSH) in accordance with the delegation of responsibilities authorised by the Principal Investigator on the site delegation log. This will usually be by a medically

qualified doctor, or where local Trust policy allows this may be by a research nurse. **Eligibility for the trial must always be confirmed by a medically qualified doctor via the eligibility checklist and a copy of the checklist must be uploaded onto the trial randomisation system.**

Consent for the trial will be taken in writing. Electronic consent may be used where a baseline face-to-face visit is not undertaken (see e-consent process flow diagram below). For site recruitment (pathways 1 and 2) local NHS policy will dictate the method of consultation which will be in accordance with usual care for that site (face-to-face, video or telephone). Patients screened via the trial website (pathway 3) will exclusively complete electronic consent. All consent taking will be in accordance with trial approvals, applicable regulatory policies and NHS guidelines.

**Figure 1: E-consent process**



The ICF will include consent for the collection of contact details for the purpose of sending sampling kits (remote pathways only), obtaining follow-up information and receiving trial communications. Where participants have given their consent to receive a summary of the trial results at the end of the trial their contact details will also be used for this purpose.

To be eligible to enter the trial patients must provide consent for their GP's contact details to be collected. GPs will only be contacted for the purpose of obtaining pregnancy outcome information for patients who are pregnant when recruited onto the trial or become pregnant within the four weeks after starting treatment. This information is collected for the purpose of safety monitoring. Where a participant is found to be pregnant post-randomisation via information given in their follow-up questionnaires at 4 or 12 weeks, the recruiting site will be contacted to obtain information relating to the outcome of the pregnancy from the participant's GP. GP details are routinely recorded within clinic systems, however, site staff will be asked to confirm up-to-date GP contact details are held within their local systems prior to enrolment.

### 5.2.1 Responsibilities

It is the responsibility of the Principal Investigator to ensure informed consent is obtained appropriately for all patients recruited at their site. A PIS will be provided to facilitate this process. Investigators or delegates will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. They will also stress that participation is voluntary so the patient is free to decline participation and may withdraw from the trial at any time. Patients attending GUM clinics would ordinarily receive treatment during their clinic visit and thus for those recruited via pathway 1, consent for participation in the trial will be sought during the same clinic visit as diagnosis of BV. Patients recruited via pathways 2 and 3 will be sent a ICF link during their trial information discussion with the research team, patients will have 30 days to review the documentation and complete consent for the trial. Patients will have two opportunities to discuss the trial and ask questions, once with a researcher prior to completing consent and again prior to randomisation. Every discussion must be documented in detail, signed, and dated in the patient medical notes. Where possible consent forms will be signed by the researcher who had the initial discussion with the patient and shared the consent form. Due to the nature of the electronic consent process this may not always be possible. In these instances, a different delegated researcher can verify and countersign the consent form, following review of the patient medical notes. During the call to confirm eligibility the researcher conducting the consultation will undertake a consent check to confirm the patient understands what trial participation entails and that they are happy to randomise onto the trial. The researcher will document the details of this consent check in the patient medical notes. DEVA is a low-risk, pragmatic trial comparing licensed BV treatments so the patient will be given adequate time to read the PIS and ask any questions they may have.

### 5.2.2 Documentation of consent

If a patient expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the relevant ICF, this will either be a paper or electronic. For patients who do not give their consent during a face to face visit, this will be obtained electronically. Details of the initial trial discussion, when the ICF was issued and countersigned, eligibility confirmation and the consent check (remote pathways only) must be recorded in full in the patient medical records. All details recorded in the medical notes must be signed and dated by the person completing the record.

The patient must give explicit consent for the regulatory authorities, members of the research team and representatives of the Sponsor to be given direct access to the participant's medical records and for a copy of the signed ICF to be shared with the NCTU. The NCTU will review patient consent forms to ensure they have been completed correctly by both parties and that electronic ICFs have been completed within a reasonable timeframe.

**Paper ICFs**

Paper ICFs will be completed by the patient and the research team member during the clinical consultation, prior to any trial specific activity taking place. Patients must initial each consent point and sign and date the consent form. The researcher who is taking consent must verify and countersign the form during that same clinical visit. The patient must be given a copy of the paper consent form and a copy must be filed in their medical notes and ISF. The paper ICF must be uploaded to the DEVA randomisation system for NCTU review.

**Electronic ICFs**

Electronic ICFs will be emailed to the patient by the research team member after the initial trial discussion. Patients have 30 days from sending the e-consent link to complete their form. Patients must tick the consent points, complete their contact information and sign the form. The date will be generated when they submit their signature. Returned electronic ICFs should be verified and countersigned by a member of the research team on the day that the patient returns the form, or when returned out of hours, the next working day (where possible).

A PDF copy of the completed electronic ICF will be emailed to the patient and a copy will be filed in the medical notes. As electronic consent forms are captured as part of the DEVA randomisation system there is no need for sites to upload these forms. The trial does not require the forms to be printed and filed as part of the ISF but can be printed and filed if required by local Trust procedures. Patients who present for a second time (after initially failing screening or who tried to complete consent outside of the 30 day window) will have their eligibility assessed and new e-consent form issued following the same process as new patients presenting to the trial.

For those patients who consent electronically, a second consent check should be performed at the second consultation (where BV smear result is confirmed and final eligibility assessed) to confirm they are happy to participate. The researcher will ask the patient whether they have any questions, that they understand the trial prior to randomisation and document the discussion in the patient medical notes.

Patients screened and consented via pathway 3 will need to have a new entry in their medical record to allow for complete and accurate documentation of the consent process.

### 5.2.3 GP Notification

General Practitioners (GPs) of patients attending GUM clinics are not routinely notified of their GUM clinic visit or of any BV treatment received by the patient during their visit to ensure full confidentiality for the patient. Since both dequalinium chloride and any usual care antibiotics dispensed to DEVA trial participants will be used within their licensed indications and prescribed in accordance with usual clinical practice, GPs will not be informed of a patient's participation in the trial, with the exception of participants who are pregnant.

All participants are required to consent to their GP being informed of their trial participation. GP's will only be contacted if patients are pregnant when joining the trial or in the event they become pregnant in the 4 weeks following start of study treatment. GPs of pregnant participants will be notified in order to allow collection of outcome information relating to the pregnancy and safety monitoring purposes. The research team of the recruiting centre (this will be LSH for those recruited via pathway 3) will be responsible for notifying participant's GPs where appropriate (either at baseline clinic visit or via follow-up questionnaires/additional contact made with clinic), informing them of their patient's participation in the trial. Pregnancy outcome information will be obtained from the participant's GP by research staff at the recruiting site. All outcome data will be collected on the trial pregnancy outcome form and entered into the electronic case report form (eCRF).

# 6 Enrolment and Randomisation

## 6.1 Enrolment

Prior to enrolment patients must provide their informed consent (written or electronic) and BV diagnosis must be microscopically confirmed. Baseline data will then be collected by a member of the recruiting research team and the participant will be enrolled using the online trial randomisation system. See section 8.2.3 for further information on baseline data collection requirements.

During enrolment and prior to randomisation, the usual care antibiotic treatment that the participant will receive if they are randomised to the usual care treatment arm, must be recorded in the randomisation system. Randomisation will not be possible until a usual care treatment has been selected. For those recruited remotely, this will be completed during the follow-up phone call when final trial eligibility is assessed.

An authorised member of the site research team will then log into the secure randomisation system and randomise the participant.

## 6.2 Randomisation

Participants will be assigned to treatment groups using a remote internet-based randomisation system developed and maintained by the NCTU. Access to the system will be granted by the NCTU in accordance with the roles delegated by the Principal Investigator on the Site Delegation Log.

Treatment will be assigned using a minimisation algorithm balancing on the following factors:

- first episode or isolated recurrence of BV (no previous episodes in the past year) or recurrence (previous episode in the past year)
- a female sexual partner in the previous year, or not[32]
- method of contraception (none, barrier, intrauterine, hormonal; if more than one method is used, they will be prioritised as intrauterine, hormonal then barrier)[32-35]
- whether they consent to provide self-taken samples for the sub-study at baseline and week 4, or not
- recruitment site
- pathway (1, 2 or 3)

The randomisation algorithm will include a probabilistic element to allocation making prediction of the allocated group virtually impossible.

## 6.3 Concealment and blinding

Allocation will be concealed to all trial staff using an automated web system operated by the NCTU. The control treatment will be determined and recorded by the clinician for each participant prior to randomisation.

Blinding of the participant and site research team is not possible due to the nature of the intervention; a number of different usual care antibiotics with different routes, formulations and duration are used in the control arm.

Central laboratory staff performing BV microscopy and STI testing will be blinded to the participant's treatment allocation. The trial and senior trial statisticians will be blinded to participants' treatment allocation, including other data with the potential to lead to unblinding, until after the statistical analysis plan (SAP) is finalised and approved and the trial database (including randomisation system) is locked. Any data summaries and analyses which require knowledge of the treatment allocation (e.g. within the closed report for the DMC) will be conducted by a statistician who is independent of the trial. Such summaries and analyses will be held in an area which is accessible only to the statistician(s) who are independent of the trial.

Table 1 provides an overview of the blinding status of all individuals involved in the management and delivery of the trial.

**Table 1: The blinding status of individuals involved in the trial**

| Trial role | Blinding status | Comments |
|---|---|---|
| Participant | Not blinded | Not possible due to the nature of the intervention. Participants will be informed which arm of the trial they have been randomised to immediately after randomisation. |
| Principal investigator and site research staff | Not blinded | Not possible due to the nature of the intervention. Following randomisation, an email will be sent to the PI (unblinded for participants they randomise only) and/or member of the site research team performing the randomisation (as delegated) confirming treatment allocation. |

| Trial role | Blinding status | Comments |
|---|---|---|
| Chief Investigators | Blinded | The Chief investigator and Deputy Chief investigator will remain blinded to treatment allocation overall (knowledge of treatment allocation is limited to participants at their own site). In instances where serious adverse events are reported, the CIs will become unblinded to complete the full causality assessment. |
| Software programmer | Not blinded | The software programmer is responsible for the management of the randomisation system and database and will have access to all unblinded datasets within both systems. |
| DEVA Trial Management staff within NCTU | Blinded | Trial Management staff within NCTU will remain blinded to treatment allocations as far as possible; there may be situations where site staff require support for randomisation and in these situations it is acknowledged that trial management staff may become aware of treatment allocation but efforts will be made to ensure the blind where possible. Serious Adverse Event reports will be handled by the trial management team who may become unblinded to a participant's treatment allocation. |
| Data management | Not blinded | Data management staff will have access to the unblinded datasets within the trial randomisation system and database to ensure data quality and undertake central monitoring activities. |
| Trial statistician and Senior Trial Statistician | Blinded | The trial and senior trial statisticians will not have access to treatment allocations or data which has the potential |

| Trial role | Blinding status | Comments |
|---|---|---|
| | | to unblind until after the final database lock. |
| Independent statistician | Not blinded | A statistician independent of the trial management team will be responsible for generating the Data Monitoring committee (DMC) closed reports and other potentially unblinding data, (e.g. treatment adherence) and will therefore be unblinded to trial interventions. |
| Health Economist | Blinded | The health economist will not have access to treatment allocations or data which has the potential to unblind until after the final database lock. |
| Central laboratory staff (STI) | Blinded | Laboratory staff who will process the STI samples will be blinded to the treatment allocation. |
| Central slide assessors (BV) | Blinded | The central assessors who will review the week 4 participant slides for microbiological evidence of BV will remain blinded to the participant treatment allocation. |

# 7 Trial treatment / intervention

## 7.1 Treatment

Patients will be randomised to one of the following treatment arms:

| ARM | TREATMENT | FORMULATION AND DOSE |
|---|---|---|
| INTERVENTION | Dequalinium Chloride | 10mg vaginal tablet for 6 nights.<br>This is the formulation and course that is licensed for use in the UK. |
| CONTROL | Usual care antibiotics | Clinician-chosen usual care antibiotic treatment selected from UK guideline recommended or alternative oral or topical antibiotic BV treatments which (at the time of writing this protocol) will be one of the following treatments:<br>• Metronidazole 400 mg orally twice daily for 5-7 days<br>• Metronidazole 2 g single dose orally<br>• Intravaginal metronidazole gel (0.75%) once daily for 5 days<br>• Intravaginal clindamycin cream (2%) once daily for 7 days<br>• Tinidazole 2 g single dose orally<br>• Clindamycin 300 mg orally twice daily for 7 days. |

The treating clinician will choose the control treatment prior to randomisation, following discussion with the patient. If the patient is randomised to the control arm of the trial, they will receive this predetermined BV treatment. For those recruited during a face-to-face consultation, treatment will be prescribed and dispensed to the participant during their baseline clinic visit, for those recruited remotely, treatment will be prescribed on the day of randomisation. Shipment of treatment to participants will be performed in accordance with local pharmacy policy and agreed by the Trial Management Group as appropriate. All prescribed trial treatments will be recorded on the electronic Case Report Form (eCRF) and will be monitored against the pre-selected treatment choice prior to randomisation recorded in the eCRF. Any issues of non-adherence to the pre-specified control group antibiotic will be reviewed by the Trial Management Group and identified as protocol non-compliances. Any systematic issues of non-compliance will be investigated with the sites.

### 7.1.1 Investigational Medicinal Products (IMPs)

The following treatments will be considered IMPs in the trial:

| IMP Category | Product Name | Formulation | Route of administration | Dose | Duration |
|---|---|---|---|---|---|
| Test IMP | Dequalinium Chloride | Tablet | Vaginal | 10 mg daily | 6 days |

| IMP Category | Product Name | Formulation | Route of administration | Dose | Duration |
|---|---|---|---|---|---|
| **UK guideline recommended antibiotic BV treatment as follows:** | | | | | |
| Comparator | Metronidazole | Tablet | Oral | 400 mg twice daily | 5-7 days, (clinician prescribing preference) |
| Comparator | Metronidazole | Tablet | Oral | 2 g | Single dose |
| Comparator | Metronidazole | Gel 0.75% | Intravaginal | One application (5g) daily | 5 days |
| Comparator | Clindamycin | Cream 2% | Intravaginal | One applicator daily | 7 days |
| Comparator | Tinidazole | Tablet | Oral | 2 g | Single dose |
| Comparator | Clindamycin | Capsule | Oral | 300 mg twice daily | 7 days |

**Non-Investigational Medicinal Products (NIMPs)**

There are no Non-Investigational Medicinal Products in the trial.

## 7.2 Treatment Supply and Storage

### 7.2.1 Treatment Supplies

Following randomisation and treatment allocation, trial treatment will be dispensed to participants from standard clinic stocks in accordance with the usual site supply procedures. Patients randomised to the control arm (usual care antibiotics) should receive the antibiotic treatment chosen by their clinician prior to randomisation. Patients attending GUM clinics receive treatment free of charge so all treatment prescribed as part of the trial will also be free, regardless of recruitment pathway.

### 7.2.2 Packaging and Labelling

Trial specific labelling will not be required as all IMPs have a marketing authorisation in the UK and are being used within their licensed indication.

The IMP will be dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional and labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/31 94) (Marketing Authorisations Etc.) Regulations 1994 that apply in relation to relevant dispensed medicinal products.

### 7.2.3 Storage of Treatment

There are no trial-specific requirements for the storage of any of the IMPs used in this trial. All treatment prescribed and dispensed for the purpose of the trial will originate from standard clinic

stock which will be stored in accordance with the manufacturer's storage instructions as detailed in the applicable Summary of Product Characteristics (SmPC). Sites will follow their own local policies for storage of medication.

## 7.3 Dosing Schedule

In accordance with standard practice, participants will be instructed to start their allocated treatment on the day they receive their treatment, this will be the date of randomisation for those recruited in clinic, and the date treatment is delivered for those recruited remotely. The date treatment was actually started (or taken if single dose) will be collected directly from the participant on the follow-up questionnaire.

## 7.4 Treatment Interaction(s) or Contraindications

### 7.4.1 Dequalinium Chloride

Patients with any known hypersensitivity to dequalinium chloride and young girls who have not yet had their first menstruation, and have thus not reach sexual maturity are not eligible to take part in the trial (see section 4). Please refer to the Summary of Product Characteristics (SmPC) for dequalinium chloride.

### 7.4.2 Usual care antibiotic BV treatments

Patients with known hypersensitivity to their prescribed usual care antibiotic BV treatments are not eligible to take part in the trial. Use of intravaginal soaps, intravaginal spermicides, vaginal douches, vaginal steaming (yoni steaming) and jade eggs is not recommended during any of the IMP treatments. Please refer to the SmPC for each IMP treatment for further details.

## 7.5 Accountability Procedures

Sites will follow their own local procedures for recording medication dispensed to trial participants. There are no additional trial-specific accountability requirements.

## 7.6 Treatment Modification

Participants who are prescribed intravaginal therapies will be advised that they may delay or pause treatment during menstruation. The date treatment was actually started will be collected directly from the participant on the follow-up questionnaire.

### 7.6.1 Missed Doses

In the case of any missed doses, participants will be advised to continue their treatment course until it is completed. Information on compliance with allocated treatment will be collected as part of the follow-up questionnaire.

# 8 Trial procedures and assessments

## 8.1 Summary of trial procedures

A summary of trial procedures is shown in figure 2. A detailed description of each procedure can be found in section 8.2.

**Figure 2: Summary of trial procedures by time point**

| | BASELINE ASSESMENTS (Pre-randomisation) | | RANDOMISATION | FOLLOW-UP (time from randomisation) | | |
|---|---|---|---|---|---|---|
| | **Pathway 1** | **Pathway 2 and 3** | **Day 1** | **Day 14** | **Week 4** | **Week 12** |
| **PROCEDURE:** | | | | | | |
| **a** – Eligibility screen | **X** | **X** | | | | |
| **b** – Informed consent | **X** (paper) | **X** (electronic) | | | | |
| **c** – Baseline data collection | **X** | **X** | | | | |
| **d** – Randomisation | | | **X** | | | |
| **e** – Prescribe usual care treatment | **X** | **X** | | | | |
| **f** – Issue randomised trial treatment | | | **X** For remote pathways 'issue' refers to the shipment of treatment to the participant | | | |
| **g** – Vaginal swab for STI testing | **X** | **X~** Self-taken, posted by participant | | | | |
| **h** – Vaginal smear for microscopy | **X** (following local procedures) | **X** Self-taken, posted by participant | | | **X** REMOTE ONLY Self-taken, posted by participant | |
| **i** – Vaginal swab for future study of vaginal microbiota* | | **X*** Self-taken, posted by participant | | | **X*** REMOTE ONLY Self-taken, posted by participant | |
| **INTERVENTIONS:** | | | | | | |
| **j** – Dequalinium Chloride (intervention group) | | | **X** (days 1-6) | | | |
| **k** – Usual care antibiotics (control group) | | | **X** (duration of treatment in accordance with usual care) | | | |
| **FOLLOW UP:** | | | | | | |
| **l** –Treatment adherence text message | | | | **X** | | |

| | BASELINE ASSESMENTS (Pre-randomisation) | | RANDOMISATION | FOLLOW-UP (time from randomisation) | | |
|---|---|---|---|---|---|---|
| | **Pathway 1** | **Pathway 2 and 3** | **Day 1** | **Day 14** | **Week 4** | **Week 12** |
| **PROCEDURE:** | | | | | | |
| **m** – Participant questionnaire (online or postal based on preference) | | | | | **X** | **X** |
| **n – Pregnancy outcome[#]** | | | The outcome of participants pregnant at the time of randomisation or found to have conceived between randomisation and Week 4 follow up will be collected throughout the duration of the trial. | | | |

~only to be analysed for those patients who randomise onto the trial
*sub study participants only (optional consent)
[#] where applicable. Refer to section 8.4

## 8.2 Baseline procedures

### 8.2.1 Eligibility screen including BV microscopy

Screening data for patients entering the trial via all three pathways will be collected by each site and recorded within the trial database. The screening information collected may differ slightly between the recruitment pathways.

Microscopic confirmation of BV is required for entry into the trial;

**Pathway 1**
BV microscopy and STI screening should be performed in accordance with local practice (prior to consent) during the patient's clinical consultation. As part of the baseline data collection the results of both the microscopy testing and STI screen should be recorded in the trial eCRF from the patient's medical notes.

**Pathways 2 and 3**
Patients who complete consent remotely will be required to take their vaginal sample for BV diagnosis and confirmation of trial eligibility prior to randomisation. During their trial information session, the research team member will explain why the sample is required, when to expect receipt of the sample kit and information on how to take vaginal samples. Patients will be posted the eligibility sample kit at the point the ICF is countersigned. This kit will contain everything they need to take their BV eligibility sample and a swab for STI screening, including detailed instructions on sample taking and kit postage. Once the sample has been taken and packaged, the participant will post the completed kit (in the pre-paid envelope provided) to LSH. Upon receipt, the BV eligibility sample will be checked and tracked to the central laboratory by a member of the research team for analysis. Results will be recorded within the trial randomisation system and the patient's medical notes. The results of the BV microscopy will be shared with each patient, regardless of whether they are eligible for the trial or not. Analysis of STI samples will only be performed on patients who are randomised onto the trial. If a participant is found to have a positive STI screen (gonorrhoea, chlamydia or TV) this will be reported;

- To the site Principal Investigator for participants recruited via pathway 2

- Directly to the participants in pathway 3 where the LSH team will refer them to their nearest sexual health clinic (if they wish) or written information will be provided about their infection which can be taken to their GP.

For those who do not randomise (not eligible or choose not to participate for any other reason), these samples will be discarded following standard central laboratory procedures and confirmation of this will be recorded. Those who do not have confirmed BV on microscopy will be advised to contact their GP or local sexual health clinic if they are concerned about their symptoms or if their symptoms persist. More information on trial samples is detailed in section 8.2.6.

Eligibility will be confirmed and signed off by the principal investigator (or delegated trial clinician) on the eligibility checklist form once informed consent and baseline data have been obtained. This must be completed prior to randomisation.

### 8.2.2 Informed Consent

Informed Consent will be obtained as described in section 5.2.

### 8.2.3 Baseline data collection

After informed consent and confirmation of BV have been obtained, baseline visit data will be collected. Where the baseline visit is not conducted as a face to face visit (e.g. in response to changed procedures resulting from the Covid-19 pandemic) the baseline 'visit' will be conducted remotely (telephone or video) to allow all baseline data to be collected accurately. Patients screened via the remote pathways will have a minimum of two remote visits (to allow for trial information to be provided and baseline information and eligibility to be confirmed) prior to being randomised onto the trial.

- Demographic information
- Intended usual care antibiotic treatment
- BV history
- BV symptoms
- Sexual history
- Contraception use
- BV microscopy
- Pregnancy status
- GP contact details
- Participant's preferred contact details for receiving trial communications including follow-up questionnaires

### 8.2.4 Randomisation

Participants will be randomised to receive either dequalinium chloride (intervention) or doctor-chosen usual care antibiotic treatment (control treatment) using a remote internet-based randomisation system maintained by NCTU. A delegated member of the research team will log in to the secure randomisation system and enrol and randomise the participant to the treatment allocation (see section 6.2).

### 8.2.5 Prescribe/issue trial treatment

Dequalinium chloride or pre-defined usual care antibiotics should be prescribed according to local practice following randomisation. The actual treatment dispensed to the patient will be recorded in the eCRF post-randomisation. Where the choice of usual care antibiotics specified prior to randomisation is not prescribed to the participant post-randomisation, a reason for this will be entered onto the eCRF and details of the actual treatment prescribed entered.

### 8.2.6 Participant sampling

#### 8.2.6.1 Main trial sampling

##### 8.2.6.1.1 Pathway 1

In addition to local BV microscopy, sites should complete a baseline STI screening test as per local GUM clinic procedure. No additional self-taken at home sampling is required for participants recruited via pathway 1.

##### 8.2.6.1.2 Pathway 2 and 3

Patients screened and recruited remotely will be required to take samples as follows;

###### *8.2.6.1.2.1 Baseline*

At baseline, in addition to the smear taken for BV microscopy to assess trial eligibility (see section 8.2.6.2), a further vaginal swab will be taken for STI testing to determine the presence of any concurrent sexually transmitted infections (gonorrhoea, chlamydia and trichomonas. See section 8.2.6.3). Analysis of the STI swab sample will only take place if the patient randomises onto the trial. STI samples for patients who cannot randomise for any reason will be discarded following the local procedures at the central laboratory.

###### *8.2.6.1.2.2 Week 4*

At the week 4 time point participants will take and return one vaginal smear for microscopy.

The results of the above tests are not intended to inform the clinical management of the patient and results of the week 4 swab will not be reported back to the patient. Clinicians will ensure all tests for the clinical management of a patient are taken in accordance with their local policy to inform immediate patient care as indicated by the participant's clinical presentation and must not rely on the results of any swabs taken for the purpose of the trial for this purpose.

*8.2.6.1.2.2.1 Vaginal Smear for microscopy*

Patients that have consented to take part in the trial will be asked to take a vaginal swab to produce a vaginal smear for microscopy at baseline as part of their eligibility screen (after written consent has been obtained) and four weeks post-treatment start date.

The site research team will advise the patients on how to take their own vaginal smear and ensure they understand what they need to do prior to sending their sample kits. An instruction leaflet will also be provided as part of the sampling kit with an instructional video available to the participant on the trial website.

*8.2.6.1.2.2.2 Vaginal swab for STI testing at baseline*

Patients that have consented to take part in the trial will be asked to take a vaginal swab for STI testing at baseline (after written consent has been obtained).

The local site research team will instruct the participant on how to take their own vaginal swabs prior to sending the sample kit. Self-taken genital swabs are widely used in clinical practice and have good sensitivity and specificity.[35-37]

Baseline STI samples will only be analysed for patients who randomise onto the trial. Results and any positive STI screening results will be reported back to the Principal Investigator at the recruiting site. However, it is acknowledged that the time taken for the laboratory to receive, analyse and report STI sample results may be up to 2 weeks and therefore the results of these tests will not be relied upon for the clinical management of participants. All participants will be managed according to local site treatment protocols should an STI be suspected.

All samples will be posted to the research team at LSH who will track the samples and forward to the central laboratory (Leeds Teaching Hospitals NHS Trust) for analysis.

#### 8.2.6.2 Sub-study vaginal microbiota at samples at baseline and week 4 (pathways 2 and 3 ONLY)

For those who consent to participating in the optional sub-study, two additional swabs (one at baseline and one at week 4) will be taken for a future study of microbiota. These will be sent as part of the baseline eligibility and week 4 sample testing kits and once completed will be posted by the participant to the central laboratory. On receipt these samples will be frozen at -70◦C and stored at Leeds Teaching Hospital NHS Trust. These samples will be used for future analysis of the vaginal microbiota to assess any changes between baseline and week 4. The analysis of these will be the subject of a future grant application and further ethical approval and only the research team will have access to the samples whilst in storage.

#### 8.2.6.3 Replacement sample kits (pathways 2 and 3 ONLY)

There may be instances where participants require additional kits to be sent to them to complete their eligibility or week 4 samples. Information on ordering replacement kits can be found in section 8.5.1 and is present in the sample kit instruction leaflet.

## 8.3 Interventions

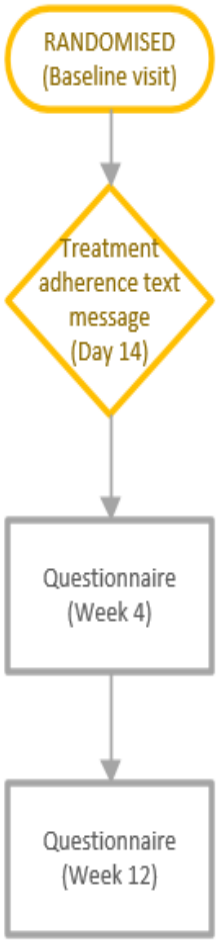
Participants will be prescribed dequalinium chloride or usual care antibiotics in accordance with the manufacturer's instructions and local policy. See section 7.4.

## 8.4 Follow-up procedures

In accordance with normal clinical practice, participants will not be required to re-attend or contact the GUM clinic for their BV as part of their participation in the trial.

Following randomisation, all follow-up information for non-pregnant participants will be obtained directly from the participant and coordinated by NCTU without further involvement from the recruiting site. If a site recruits a pregnant participant or one of their participants discovers they are pregnant between randomisation and week 4 they will be required to obtain the pregnancy outcome from the participant's GP. Figure 2 shows the follow up time points in the trial.

**Figure: 3 Flow diagram for DEVA participant follow-up**




Follow-up of participants will start at day 14 via text message and will continue at week 4 and week 12 via self-completed questionnaires. Participants will be required to give their consent for collection of contact details for the purpose of issuing follow-up questionnaires and important trial communications (e.g. reminder messages) as part of the eligibility assessment and informed consent process.

A text message will be sent to all participants 14 days post-randomisation asking whether the participant has completed their prescribed treatment course to minimise recall bias and loss of data. For those participants who confirm they did not complete their treatment, a second text message will be sent asking how much of their treatment was taken and to provide this information by text message. Valid text responses (pre-programmed within the text message survey system) will be automatically entered into the relevant field on the participant questionnaire, locking the answer field for those completing it online. For those completing paper questionnaires this question will be removed prior to sending the questionnaire to the participant to ensure these questions will then not be asked again as part of the week 4 questionnaire.

### 8.4.1 Vaginal swab for BV microscopy (Week 4)

Where participants are required to take samples for the study they will be sent additional text messages reminding them to take their vaginal smear and prepare a microscopy slide, and where additional consent has been given, the swab for vaginal microbiota, using the kits posted to them by LSH. These will then be returned by the participant using the pre-paid packaging provided. The research team at LSH will track receipt of all returned sample kits and facilitate the sending of these to the central laboratory within the same trust (Leeds NHS Teaching Hospitals NHS Trust). LSH will oversee the tracking, reporting and recording of samples within the trial randomisation system. This will allow for accurate reminders to be sent to participants who have not completed their samples.

### 8.4.2 Details of participant questionnaires (Week 4 and Week 12)

**Week 4 Follow-up**

Participants will complete an online or postal questionnaire (depending on patient preference stated at baseline) four weeks after their treatment start date which will collect information on the following:

- Participant reporting of BV symptoms
- Trial treatment adherence & satisfaction
- Participant reporting of symptoms and known treatment side effects including vaginal irritation (itching, pain and/or burning), vaginal discharge, unpleasant vaginal odour, nausea, vomiting, diarrhoea, abdominal pain, unpleasant taste and vaginal candidiasis.
- Additional medications for BV

- If they are pregnant
- Douching
- Sexual contact and condom use
- Use of additional health service resources for BV and additional BV trial treatment

**Week 12 Follow-up**

Participants will complete an online or postal questionnaire (depending on patient preference) twelve weeks after their treatment start date which will collect information on the following:

- Whether they have had a recurrence of BV
- Additional medications for BV
- Douching
- Sexual contact
- Health service use for BV and additional BV treatments
- Condom use
- If they are pregnant

### 8.4.3 Use of participant prompts and reminders

Participant contact details will be collected prior to or at baseline. Strategies to minimise loss to follow-up will include using text, email and phone reminders. Text messages will be sent and phone calls made to participants (prompts to complete questionnaires and one to obtain the primary endpoint data) between baseline and 14 weeks following randomisation (week 12 plus two weeks). Participants may also be contacted by telephone by a member of the trial team in order to collect follow up data if no responses are received.

## 8.5 Analysis and Reporting of Trial Samples

All participant self-taken samples (baseline and week 4) will be sent by post to the research team at LSH, who will be responsible for logging receipt of all samples, ensuring safe transportation to the relevant testing laboratory, and reporting all results back to the recruitment sites and NCTU (from the laboratory), via the trial randomisation system. The LSH research team will undertake this task to ensure full oversight of samples is maintained throughout the duration of remote pathway recruitment and the sub-study. All samples will be posted directly to Leeds Sexual Health by the participant.

STI vulvovaginal swabs for participants randomised remotely will be analysed by the central lab at Department of Clinical Microbiology at Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* using the Aptima Combo 2 (with confirmation of N. gonorrhoeae positives using the Aptima GC) and Aptima TV. All results from these tests will be recorded onto the trial randomisation system and the site notified of the results. It is at the discretion of the Principal Investigator at the recruiting site to report these back to the patient where relevant, however it is acknowledged that the time taken for the laboratory to receive, analyse and report sample results may be up to 2 weeks; the results of these tests will not be relied upon for the clinical management of participants.

Vaginal smears returned by those patients in the remote pathways will be verified centrally using Nugent's scoring (main method used in research).[38] Two readers from a team of six independent experts, blinded to the treatment allocation, will read these. Discrepant results will be reread and

reviewed by a third reader (where required) until consensus is reached to ensure a robust, objective and blinded method of diagnosing BV or lack of BV. Any evidence of Candida infection will also be recorded. The presence of Candida at baseline will not exclude entry into the trial unless the treatment given is an intravaginal antifungal agent. The presence of Candida at week 4, if negative at baseline, will be categorised as a side effect of the treatment.

Eligibility smears taken more than 30 days after countersigning of consent will not be read or used as an assessment of patient eligibility. Samples will be discarded, and potential patients will be asked to repeat their initial screening to ensure that they continue to have untreated symptoms and remain eligible for the trial. Week 4 samples returned before or after the week 4 timepoint will be read and recorded within the trial randomisation system (date sample taken and Nugent score). Deviations are not required to be completed for samples received before or after the week 4 timepoint and information on how sample data will be used in the final analysis is detailed in the current version of the trial Statistical Analysis Plan (SAP).

The additional sub-study swabs will be frozen and stored for future analysis of the vaginal microbiota to assess any changes between baseline and week 4 in the subgroup of the participants who consented to this. The analysis of these will be the subject of a future grant application and further ethical approval.

Results from the samples taken for the purpose of the trial will not form the basis for patient management at the trial baseline visit; clinicians will take additional tests processed locally to inform immediate patient care as indicated by the patient's clinical presentation. Full details on the taking, analysing and reporting of samples is documented in the current version of the DEVA Sample Processing Protocol.

### 8.5.1 Replacement sample kits

Participants will be advised that additional sample kits can be requested by emailing the trial inbox and information on how to collect study samples can be obtained from their trial research team (recruiting centre or LSH) or the trial website. Information on the kits sent and their kit numbers will be recorded within the randomisation system.

## 8.6 Study Within A Trial (SWAT)

### 8.6.1 Background

Failure to collect outcome data in randomised trials is inefficient and can result in bias and loss of statistical power[39]. A great deal of effort is often expended in recruiting participants to trials. Ensuring that as many of these participants as possible are retained and provide outcome data can greatly improve research efficiency and minimise the risk of bias resulting from incomplete data.

In this trial, participants do not return to clinic after receiving their treatment. Outcome data is collected at 4 weeks and 12 weeks after treatment start date through questionnaires (online or postal) which participants are alerted to via text message(s) and/or e-mail. It is not known whether the timing of these text messages may have an effect on the return of questionnaires but informal evidence from a previous trial found that the timing may be important.[40] This was also felt to be an investigation of importance by the trial PPI group.

A SWAT will therefore investigate the effects of the timing of text message communication with participants during the trial on questionnaire return rates. Participants will be randomised to receive all trial reminder text messages in the morning (approx. 8am) or in the evening (approx. 7pm).

If the questionnaire return rate is 80% in one group, this study could detect a difference between groups of 8% to 9% at the 5% significance level with 90% power. Data from this SWAT may be combined with data from other similar SWATs in a future meta-analysis which would allow detection of smaller differences.

### 8.6.2 Interventions

*Intervention Group 1:* Reminder emails and text messages sent in the morning (approx. 8am)
*Intervention Group 2:* Reminder emails and text messages sent in the evening (approx. 7pm)

### 8.6.3 Method of allocation

Participants will be randomised to receive communications in the morning or evening after they have been randomised into the main trial. Timing will be assigned using a minimisation algorithm balancing on the treatment group (dequalinium chloride or usual care) just assigned. The minimisation will be an internal process which is triggered by allocation to treatment and there will be no communication to sites of the timing allocation. See section 13.3.1 for further details on randomisation methodology.

### 8.6.4 Outcome measures

The primary outcome will be the proportion of participants returning their week 4 questionnaire.

### 8.6.5 Secondary outcomes

- The proportion of participants returning their week 12 questionnaires
- The time to return of the week 4 and week 12 questionnaires from randomisation
- The number of primary outcomes (in main trial) obtained by questionnaire, text message and phone call.

### 8.6.6 Analysis

The analysis of this SWAT will be documented in the DEVA SWAT statistical analysis plan. Analyses will not include between treatment group comparisons but will include treatment as a co-variate. One interim analysis is planned 12 months after the first participant has been randomised examining the week 4 questionnaire return rates only. If the difference between return rates is such that the lower limit of the 95% CI for the difference in return rates between the two groups has an absolute value of 3% or more the strategy showing the greatest return rate will then be implemented for all future participants. Otherwise the SWAT will continue until the end of the trial. Analyses will include appropriate descriptive statistics and between-group comparisons for each strategy using multivariate regression models, with site and treatment group as covariates.

### 8.6.7 Dissemination

The SWAT will be registered on the Northern Ireland MRC Trials Hub for Methodology Research SWAT registry. The findings will be made publicly available as soon as possible after the end of the SWAT and will be made available to researchers conducting meta-analysis in this field.

## 8.7 Non-compliance with allocated treatment

Following randomisation, any participants that do not adhere to their allocated treatment (for whatever the reason e.g. participant changes their mind, is unable to tolerate treatment, is found to be ineligible post-randomisation) will remain part of the trial and will be followed-up according to the trial schedule. Participants will be advised to complete follow-up questionnaires and will be sent reminder messages in accordance with the agreed schedule, unless they specifically request to discontinue their involvement in follow-up activities.

## 8.8 Withdrawal

Participants who do not adhere to allocated trial treatment are not required to withdraw, please see section 8.9.

### 8.8.1 Withdrawal prior to randomisation

Any patients that request to withdraw their consent **prior to randomisation** will be withdrawn completely; they will not be randomised, follow-up questionnaires will not be issued and their contact details will be removed from the trial randomisation system and database (two systems linked).

## 8.9 Discontinuation from trial follow-up/other trial-related activities post randomisation.

Participants may withdraw their consent for follow-up and/or other trial-related activities /receiving trial-related communications. The NCTU must be informed of all requests by participants to stop their involvement in the trial; appropriate action will be taken to ensure that the participant's wishes are followed.

Sites will be trained to determine which activities participants may wish to withdraw from.

Patients may withdraw from one or all of the following activities:

| **Withdrawal type** | **Withdrawal procedure** | **Use of data** |
|---|---|---|
| Discontinue follow-up questionnaires | Any participant that requests to discontinue from trial follow-up procedures will be marked as withdrawn on the trial database and no further contact will be made with the participant for the purpose of obtaining follow-up data. | Any data collected prior to participant withdrawal will be retained and used. |
| Discontinue from collection of week 4 vaginal samples | Any patient that requests to no longer collect vaginal samples (main trial and/or sub-study) will be marked as withdrawn from sample collection on the trial database. | Any samples taken prior to withdrawal will be analysed and reported. |

| Withdrawal type | Withdrawal procedure | Use of data |
|---|---|---|
| | No further reminders to take or post vaginal samples will be issued. | |
| Discontinue from other trial communications | Any patient who requests to be withdrawn from other trial communications will be removed from all mailing lists for ongoing trial contact (e.g. newsletters and reminders) but will still receive trial questionnaires. | N/A communications only |
| Withdraw from trial findings | Trial results will be sent to all participants who agreed to receive these at randomisation unless a specific request is received to withdraw them from receiving trial results. | N/A trial results only |

**Data which has already been collected for these participants will be included in trial summaries and analyses.**

### 8.10 Protocol Non-compliances

Protocol compliance will be assessed via central monitoring of eCRF data in accordance with the trial monitoring and data management plans. If a member of site staff is made aware of a non-compliance, they are advised to report this to the trials unit who can assess and record where appropriate.

## 9 Adverse Event Reporting

### 9.1 Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 (and subsequent amendments/regulations). Definitions of different types of AEs are listed in the table of abbreviations and definitions. AEs will be reported by the participants on the week 4 questionnaire. The Principal Investigator will assess the seriousness and causality (relatedness) of all SAEs reported by the participant with reference to the allocated treatment) Reference Safety Information (RSI) (Listed as Undesirable Effects in section 4.8 of the current SmPC), which will be documented on the participant SAE form, eCRF and medical notes.

### 9.2 Adverse Events

All IMPs used in the trial are UK-licensed drugs being used within their licensed indications with well characterised safety profiles. In order to provide secondary outcome data about the adverse events associated with the use of dequalinium chloride or any of the usual care antibiotics, only specified

Adverse Reactions (ARs) experienced during treatment with dequalinium chloride and usual care antibiotic treatments will be collected.

The following are regarded as expected for the purpose of this trial and will be collected on the 4-week follow-up questionnaire completed by the participant:

- Vulvovaginal irritation (itching, pain and/or burning)
- Vaginal discharge
- Unpleasant vaginal smell
- Nausea
- Vomiting
- Diarrhoea
- Abdominal pain
- Taste disturbance
- Candida infection/ yeast infection/ thrush

Only the presence (and severity) or absence of the above will be collected for this trial.

## 9.3 Serious Adverse Events (SAEs)

SAEs are not anticipated in this low risk trial, however, we will endeavour to collect details of any SAEs experienced by a participant in relation to their BV or BV treatment via the Week 4 questionnaire. All participants who indicate that they have been to hospital for an overnight stay in relation to their bacterial vaginosis or trial treatment will be contacted by the recruiting site research team to assess against the SAE criteria.

### 9.3.1 Identification of SAEs via Week 4 questionnaire

The Week 4 participant follow-up questionnaire includes questions to ascertain whether a participant has had any BV or BV treatment related hospital admissions since they consented to take part in the trial.

Where participants have confirmed that they have had a hospital admission, a review of the participant's completed questionnaire will be conducted by the trial management team at NCTU within 1 working day of receipt and the recruiting site may be asked to contact the participant to obtain further information to determine whether an event has occurred that fulfils the SAE criteria. Where a SAE has been experienced, the Principal Investigator (or delegate) must report the SAE on an SAE form to the NCTU. The reporting procedure for an SAE is outlined in section 9.5.

Planned hospital admissions will not be reported as SAEs.

### 9.3.2 Identification of SAEs by recruiting sexual health clinic

Participants will not return to the recruiting GUM clinic for the purpose of follow-up for the trial, however if a participant makes further contact with the recruiting site and gives information relating to a potential serious adverse event that has occurred within the Reporting Period (see section 9.4), an SAE form must be completed and submitted to the NCTU within 1 working day of becoming aware of the event.

### 9.3.3 Monitoring pregnancies for potential Serious Adverse Events

All women participating in the trial will be asked to provide details of their GP in the event they are pregnant at baseline or become pregnant in the first 4 weeks of participation. For those already pregnant at baseline they will be required to provide their due date. For those who report a new pregnancy on their Week 4 or Week 12 follow-up questionnaire, the site team will be notified by NCTU and a pregnancy notification form should be completed. Recruiting centres will contact the participant's GP to advise that they are participating and to notify them that as part of trial safety reporting they will be contacted to provide information on the outcome of the pregnancy.

Details on the outcome of the pregnancy will be collected on a pregnancy outcome form. All women who confirm that they are or have become pregnant up to 4 weeks post-treatment start date will be followed up for outcomes. If the outcome of the pregnancy constitutes an SAE in accordance with the definition, an SAE Form must be completed by the Principal Investigator.

## 9.4 Reporting period

Details of ARs (as detailed above) will be documented and reported from the date of randomisation until 4 weeks after treatment start date except in the case of pregnancy outcomes that fulfil the SAE criteria.

## 9.5 Reporting Procedure

### 9.5.1 Adverse Events

Adverse events are collected on the participant questionnaires. The participant will be advised to record any adverse reactions as specified in their trial questionnaire. In cases where participants cannot be contacted to obtain further information, details of the adverse event recorded in the questionnaire will be sent to the CI for assessment. All SAEs reported to or identified by the NCTU will be sent to the CI for assessment.

### 9.5.2 Serious Adverse Events

The Week 4 participant follow-up questionnaire includes questions to ascertain whether a participant has had any BV or BV treatment related hospital admissions since they consented to take part in the trial.

Where participants have confirmed that they have had a hospital admission, a review of the participant's completed questionnaire will be conducted by the trial management team at NCTU within 1 working day of receipt and the recruiting site will be asked to contact the participant for more information.

Where an SAE has been experienced, the Principal Investigator (or delegate) must report the SAE on an SAE form to the NCTU within 24 hours of obtaining the information from the participant. When completing the form, the Principal Investigator will be asked to define the causality and the severity of the SAE.

The form should be sent to the NCTU using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the information:

**To report an SAE, email the SAE Form to:**

**nctu-SAE@nottingham.ac.uk**

On receipt of a completed form, NCTU will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt. If confirmation of receipt is not received within 1 working day, please contact the NCTU trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the Site File.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the NCTU trial Office and a copy kept in the Site File. Investigators should also report SAEs to their own Trust if required by local practice.

The NCTU safety handling team will forward all SAE reports to the CI for assessment.

#### 9.5.3 Provision of follow-up information

Participants should be followed up by the local site research team until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form.

### 9.6 Reporting Procedure – NCTU trial Office

On receipt NCTU will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the trial master file (TMF). If a response is not received within 1 working day, the site should contact NCTU to ensure the SAE has been received.

Seriousness and causality will be reviewed independently by the Chief Investigator (or deputy Chief-Investigator where agreed). An SAE judged by the Investigator or Chief Investigator (CI) to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The CI will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Reference Safety Information (RSI)) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

In instances where a suspected SAE has been reported on the participant questionnaire but the recruiting site has been unsuccessful in contacting the participant to obtain further details, the NCTU will be notified and the research team will provide all available information to the CI to assess whether the hospital admission meets the trial SAE criteria. Where the CI confirms an SAE has taken place, the recruiting site will be required to complete an SAE form and report this to the NCTU within 24 hours of notification from the CI.

## 9.7 Reporting to the Competent Authority and Research Ethics Committee

### 9.7.1 Suspected Unexpected Serious Adverse Reactions

NCTU (on behalf of the Sponsor) will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported to the MHRA within 15 days.

### 9.7.2 Serious Adverse Reactions

NCTU (on behalf of the Sponsor) will report details of all SAEs and SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

### 9.7.3 Adverse Events

Details of all ARs will be reported to the MHRA on request.

### 9.7.1 Other safety issues identified during the course of the trial

The MHRA and REC will be notified immediately if a significant safety issue is identified during the course of the trial.

## 9.8 Investigators

Details of all SUSARs and any other safety issues which arise during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence will be filed in the Investigator Site File.

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## 9.9 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all ARs and SAEs.

## 9.10 Reporting to third parties

No reporting of adverse events to third parties is expected. Any safety issues identified during the course of the trial will be notified to the MHRA.

# 10 Data Handling and Record Keeping

## 10.1 Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained.

Source data is kept as part of the participant's medical notes generated and maintained at site. Each site will record the location of source data at their site using a source data location log prior to commencing recruitment. Data that are not routinely collected elsewhere may be entered directly onto the eCRF; in such instances the eCRF will act as source data and this will be clearly defined in the source data location log and recorded. Some recruiting centres may initially record trial information into a source data worksheet, where this has been used this will be noted within the eCRF for that participant.

For this trial, source data refers to, though is not limited to, the participant's medical notes at the GUM clinic, laboratory results for tests recorded as part of the baseline visit data collection, data recorded directly into the eCRF, source data worksheets (when direct entry to the eCRF is not possible) and follow-up questionnaires.

All data collected directly from participants (via online questionnaires or text message) will be considered as source data within the eCRF. Where paper questionnaires are issued to participants these will be returned to the NCTU for data entry and will be considered source data. Where questionnaire data is obtained via telephone, this data will be entered directly into the eCRF or collected on paper proforma (where direct eCRF is not possible) by a member of the NCTU and will be considered source data.

For the participants recruited remotely, results for BV eligibility and week 4 vaginal smear readings will be captured within the trial randomisation system and this will be considered source data. Results from analysed STI samples will be reported to LSH who will enter them into the trial randomisation system. Recruiting sites will be notified to review all patient eligibility sample results within the randomisation system. Week 4 samples are not required to be reported back to recruiting centres or participants.

Day 14 text message responses will be captured and collected as part of the eCRF and considered source data.

Participant use of aide memoires is permitted but these will not be collected by NCTU and will not be considered source data.

## 10.2 Electronic Case Report Form (eCRF) Completion

Data reported on the eCRF will be consistent with the source data and any discrepancies will be investigated. Staff delegated to complete eCRFs will be trained to adhere to ICH-GCP guidelines and trial-specific guidance on the completion of the eCRF.

Site staff are only required to complete the eCRF for the baseline data collection. This must be done within 7 days of the randomisation date.

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the eCRF has been completed correctly and that the data are accurate. This will be evidenced by the electronic signature of the site's Principal Investigator on the eCRF. It is the responsibility of the Principal Investigator to ensure there are site staff in place locally to complete data entry into the eCRF in a timely manner.

To assist with data completion, sites will be provided with source data worksheets, data will then be entered into the eCRF by a member of the site research team (as authorised by the PI on the site delegation log). Where data are collected first onto a source data worksheet, they should be transferred onto the eCRF within 7 days of the date they were initially recorded.

### 10.3 Data Management

All trial data will be entered onto the trial specific randomisation system and database through the eCRF with participants identified only by their unique trial number and initials. Both the randomisation system and database will be developed and maintained by NCTU. Access to the both systems will be restricted and secure. Any missing or ambiguous data will be queried with the site via the eCRF, sites should respond to the data queries in a timely manner, ideally within 2 weeks of the query being raised. All access and data transactions will be logged in a full audit trail.

Participant's eCRF data will be reviewed and frozen on an ongoing basis once they are deemed to have a complete set of data that has passed data validation checks (i.e. there are no data queries outstanding). Once all participant data have been frozen and the statistical analysis plan has been finalised, the trial database will be locked (set to read only). This will be done prior to the final data analysis.

Data should be entered directly into the eCRF where possible. Source data worksheets will be provided to sites to assist with the collection of data where entry directly into the eCRF is not possible. Data recorded on the source data worksheets will be entered into the eCRF by the site research team and any completed source data worksheet will be classed as source data and therefore will be retained within the participant's medical notes.

For samples and questionnaire follow-up of participants, identifiable information about participants (i.e. contact details) will be entered by the sites into the online randomisation system. This information will be held in a separate database to the trial anonymised data. Access to this information will be restricted to those involved in the follow-up phase, as authorised by the CI.

For questionnaires sent electronically, a secure link to an online questionnaire will be sent to each participant. Where paper copies of questionnaires are used, a paper version of the questionnaire will be sent by NCTU to the contact address provided by the participant at their baseline visit, with a pre-paid return envelope.

Questionnaires returned to NCTU will be entered by a member of NCTU and reviewed by a separate member of the data team. Data obtained from these participant reported outcomes will not be subject to data queries. Decisions on how to treat anomalous data will be made by members of the

TMG blinded to allocations and documented in the Data Management Plan and/or Statistical Analysis Plan (where required).

### 10.4 Archiving

It is the responsibility of the Sponsor to ensure that all documents in the Sponsor file are retained for 25 years after the end of trial. It is the responsibility of the NCTU to ensure that all documents in the TMF are retained for at least 25 years after the end of trial and that Principal Investigators ensure all essential trial documentation contained within the Investigator Site Files and participant source data worksheets at their site are securely retained for at least 25 years after the end of the trial. The end of trial is defined in section 12. No documents will be destroyed without prior approval from the Sponsor.

### 10.5 Data Sharing

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Participants' contact details, including name, address, telephone/mobile number and email will be shared between participating sites and NCTU for the purposes of issuing sample kits, questionnaires and electronic reminders (text/email) for the trial.

Minimal linked anonymised data (participation identification code, initials and date of birth), used for labelling of laboratory samples, will also be shared with Leeds Teaching Hospitals NHS Trust.

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team and NCTU research team will have access to these data.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in computer files.

Data generated as a result of this trial will be available for inspection on request by Leeds Teaching Hospitals NHS Trust, NCTU, the REC, local R&D departments and the regulatory authorities.

Anonymised participant data may be shared with researchers external to the trial research team in accordance with the NCTU's data sharing procedure. All requests for data should be sent to the Nottingham Clinical Trials Unit.

## 11 Quality control and quality assurance

### 11.1 Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current signed CV to the NCTU. All members of the site research team will also be required to sign a site delegation log and training log. Prior to commencing recruitment all sites will undergo a process of initiation and site staff will have completed GCP training. Key members of the site research team will be required to attend a meeting (this could be face-to-face or a video conference) covering

aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The NCTU must be informed immediately of any change in the site research team.

## 11.2 Monitoring

### 11.2.1 On-site Monitoring

Monitoring will be carried out as required following a trial risk assessment and as documented in the trial monitoring plan. Any monitoring activities will be reported to the Sponsor in accordance with the delegation of responsibilities between the NCTU and Sponsor and any issues noted will be followed up to resolution. On-site monitoring visits may also be triggered with the monitoring triggers specified in the trial monitoring plan. If a monitoring visit is required, the NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the DEVA trial staff access to source documents as requested.

### 11.2.2 Central Monitoring

The NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. The trial team will check incoming eCRF data against the criteria for monitoring outlines in the monitoring plan. Sites will be requested to send in copies of signed ICFs and other documentation for in-house review for all participants. This will be detailed in the monitoring plan and the Participant Information Sheet.

## 11.3 Audit and Inspection

The Principal Investigator will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. Sites are also requested to notify NCTU of any MHRA inspections.

## 11.4 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and its amendments) the Sponsor of the trial is responsible for the oversight of notification to the licensing authority of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. It is the responsibility of NCTU to notify the licensing authority, in writing within 7 days of becoming aware of a breach and confirm this has been communicated with the Sponsor.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial. Sites are therefore requested to notify the NCTU of any suspected trial-related serious breach of GCP and/or the trial protocol. Where NCTU is investigating whether or not a serious breach has occurred, sites are also requested to cooperate in providing sufficient information to report the breach to the MHRA and REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the trial oversight committees (Trial Management Group, Trial Steering Committee, DMC), the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

# 12 End of Trial Definition

The end of trial will be the final database lock. NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, NCTU will inform the MHRA and REC within 15 days of the end of trial. NCTU will provide them with a summary of the clinical trial report within 12 months of the end of trial.

# 13 Statistical Considerations

## 13.1 Power Calculations / sample size calculation

Assuming 78% of participants have BV symptom resolution at 4 weeks post treatment start date in both the control and intervention groups[10,17,18], a total sample size of 722 for analysis (361 in each group) will achieve 90% power to conclude non-inferiority with a lower confidence limit for the absolute risk difference of 10%, using a 1 sided significance level of 0.025. To allow a loss of primary outcome data of up to 20% the trial will recruit a total of 904 women. The 10% non-inferiority margin was acceptable to 68% of a sample of women attending two GUM clinics and 81% of clinicians experienced in treating BV.

## 13.2 Definition of Outcome Measures

### 13.2.1 Outcome measures

| Outcome Measure | Description/Derivation |
|---|---|
| **Primary Outcome** | |
| Participant-reported resolution of BV symptoms 4 weeks post-treatment start date without the need for additional treatment. | Resolution of BV symptoms 4 weeks post-treatment start date, as reported by the participant on their week 4 questionnaire or via a follow-up phone call without the need for additional treatment. The proportion of participants will be calculated as the number resolved without additional treatment out of the total providing resolution data. |
| **Secondary Outcomes** | |
| Participant-reported resolution of BV symptoms 4 weeks post-treatment start date with or without the need for additional treatment. | Resolution of BV symptoms 4 weeks post-treatment start date, as reported by the participant on their week 4 questionnaire or via a follow-up phone call with or without the need for additional treatment. Participants with resolution data who do not provide details of whether they have used additional treatment will be |

| | |
|---|---|
| | included. The proportion of participants will be calculated as the number resolved out of the total providing resolution data. |
| Time to participant-reported resolution of BV symptoms without the need for additional treatment | Time in days from date of starting treatment to date of resolution of BV symptoms for participants who had resolution without the need for additional treatment. The data are provided by participants on their week 4 questionnaire, with the date starting treatment on the 14 day survey (if responded). |
| Microscopic resolution of BV on microscopy at week 4 (without the need for additional treatment) as assessed by central laboratory analysis of participant taken vaginal smears (in remote pathways only) | Resolution is defined as being negative for BV (Nugent score 0-6) 4 weeks post treatment start date without the need for additional treatment. All participants should be positive for BV at baseline (inclusion criteria).<br>Data are from the microscopy results on the samples taken at 4 weeks (post-treatment start date) and the additional treatment data on the week 4 questionnaire. |
| Participant reported approximate amount of prescribed trial BV treatment taken | Adherence will be measured using the categories of adherence used in the text messages and week 4 questionnaire and summarised as:<br>• All treatment taken/used<br>• Most treatment taken/used (approximately 75% to 99%)<br>• Half to three quarters of the treatment taken/used (approximately 50% to 74%)<br>• Some treatment taken/used but less than half (approximately 1% to 49%)<br>• No treatment taken/used<br>Reasons for not taking/using the full course of trial treatment will be measured in the week 4 questionnaire using the following categories accidentally missed taking doses, didn't like taking treatment, side effects of the treatment, other.<br>Proportions in each category will be calculated. |
| Participant-reports of: vaginal irritation (itching, pain and/or burning), vaginal discharge, unpleasant vaginal smell, nausea, vomiting, diarrhoea, abdominal pain, unpleasant taste and candida infection | The presence or absence, and severity (mild, moderate or severe) for these side effects, are collected on the Week 4 questionnaire. The proportion with symptoms will be calculated; proportions in severity categories will be out of those with side effect present. |
| Participant-reported satisfaction with treatment | The level of satisfaction with trial treatment is collected on the Week 4 questionnaire as very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied, and proportions in each category will be calculated. |
| Participant reported recurrence of BV symptoms | The Week 12 questionnaire collects whether participants have experienced a new episode of BV. For analysis, only participants who |

| | |
|---|---|
| within 12 weeks of treatment start date | have recorded resolution of BV by 4 weeks without the use of additional treatment can be judged to have had a recurrence, hence proportion recurring will be those with a new episode out of those resolving without additional treatment, whether or not they took additional treatment after 4 weeks. |
| Time to participant reported recurrence of BV symptoms | The date of resolution of BV and additional treatment are recorded on the week 4 questionnaire. The date of first BV recurrence (new episode) is recorded on the week 12 questionnaire. The time to participant reported recurrence is the time in days between resolution without additional treatment and recurrence. Those who resolved without additional treatment but had not yet recurred by week 12 are censored at the 12 week date. |
| Cost of BV treatment, including additional medication and healthcare usage relating to BV | Healthcare resource use associated with BV and BV treatments are collected on the week 4 and week 12 questionnaires. Details of alignment with associated costs are provided in Section 13.4. |

## 13.3 Analysis of Outcome Measures

The analysis and reporting of the trial will be in accordance with CONSORT guidelines. A full statistical analysis plan (SAP) will be developed by a blinded statistician (usually the trial statistician) and agreed prior to database lock and release of treatment allocations.

For primary and secondary outcomes, with the exception of side effects, participants will be analysed according to randomised group regardless of adherence with the allocated intervention. Side effect data will be summarised according to the treatment the participant received. If a participant received dequalinium chloride when randomised to usual care, side effect data would be summarised as dequalinium chloride. If a participant received usual care when randomised to dequalinium chloride, the side effect data would be summarised as usual care. The data for 'usual care' will be pooled and analysed as one treatment group.

The primary approach to the primary comparative analysis will be to analyse as randomised without imputation of missing data unless the proportion of missing data is greater than anticipated (i.e. greater than 20%) with due emphasis being placed on the confidence intervals for the between arm comparisons. It is expected that adherence with trial treatment will be high. However, if it is lower than expected, a CACE (complier average causal effect) analysis will be performed to check the stability of the conclusions. Compliers will be those reporting use of at least 75% of the treatment. The SAP will provide details of circumstances where a CACE analysis should be performed.

Continuous variables will be summarised, dependent on distribution, in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables will be summarised in terms of frequency counts and percentages. Descriptive statistics of demographic and clinical measures will be used to assess balance between the randomised arms at baseline, but no formal statistical comparisons will be made.

The evaluation of the primary outcome will be performed using a mixed effects model for binary outcome that includes factors used in the minimisation (first/isolated episode or recurrent BV, female sexual partner in the previous year, method of contraception, , pathway; site may or may not be included). If this model does not converge a generalised estimation model with siteas a panel variable may be used instead. The primary effectiveness parameter comparing dequalinium chloride with the usual care arm will be the risk difference in the proportion of participants who report resolution of symptoms 4 weeks after treatment for BV, along with the 2-sided 95% confidence interval. Dequalinium chloride will be regarded as non-inferior to usual care antibiotics if the lower bound of this 2-sided 95% confidence interval for the risk difference (dequalinium chloride minus usual care antibiotics) is -10% or greater (e.g. a lower bound of 9% would be considered non-inferior) i.e. Dequalinium chloride is not likely to be worse than usual care antibiotics by more than 10%.

The VITA trial[40] was similar in design to this trial and had a questionnaire return rate of just under 80%. Experiences from VITA and discussion with PPI members and site staff, have allowed strategies to be developed to improve questionnaire return including simplification of questionnaires, schedules of reminders by text message, refinement of the technology used, additional training of sites, and a backup of telephone collection of primary outcome data. These strategies are being implemented into the DEVA trial but there is still the potential for missing data. Therefore, it is planned that several strategies to investigate the effect of missing primary outcome data will be undertaken as sensitivity analyses, including the use of multiple imputation with chained equations and minimisation variables as covariates. Where the proportion of missing primary outcome data is greater than 20%, the primary analysis will use multiple imputation. More information on methods will be included within the SAP.

Secondary outcomes with the exception of side effect data will be analysed using appropriate (depending on outcome type e.g. binary, continuous, count, survival etc.) regression models that include minimisation variables and baseline values of the outcome if measured. The analyses of secondary outcomes will be considered supportive to the primary and estimates and p-values, where presented, should be interpreted in this light.

Side effects (vaginal irritation (itching, pain and/or burning), vaginal discharge, unpleasant vaginal smell, nausea, vomiting, diarrhoea, abdominal pain, unpleasant taste and candida infection) will be summarised (both presence and severity) by treatment groups using descriptive statistics, according to the trial treatment the participant actually received irrespective of randomisation.

See section 8.6 for analysis of SWAT.

### 13.3.1 Planned Randomisation Methodology

See sections 6.2 (main trial) and 8.6.3 (SWAT).

### 13.3.2 Planned Interim Analysis

There will be no planned interim effectiveness analyses. However, an internal pilot phase has been built into the trial to allow a feasibility assessment which will examine recruitment, retention and adherence. Stop-go criteria (table 2) 9 months after the first participant has been randomised will be used to determine the progression of the trial. Recruitment will be measured against the overall recruitment target. Retention will be determined by provision of primary outcome data. Adherence level will be measured using simple categories asking how much of the trial medication the

participant used/took (high >75% used/taken, more than half (50-75% used/taken), less than half (1-49% used/taken), from both treatment arms.

**Table 2: Stop-go criteria for internal pilot phase**

| Progression guidance | Recruitment vs target | Retention (providing primary outcome) | Adherence (proportion of participants who report high ≥75% medication taken) |
|---|---|---|---|
| Continue – no action required | >85% | >80% | >75% |
| Continue – action required | 35%-85% | 60%-80% | 50%-75% |
| Stop | <35% | <60% | <50% |

The 9 month review will be undertaken by the Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) and if recruitment, retention or adherence meet the 'continue – action required' category then additional strategies will be put in place to attempt to improve these. The review is planned to be conducted without knowledge of treatment allocation. However, the DMC will be able to access data by treatment allocation if requested.
The individual recruitment pathways, included as part of the Covid-19 pandemic adaptations, will be assessed on an ongoing basis as part of routine central monitoring. A more detailed assessment of these will be performed, along with the stop-go criteria outlined in Table 2. Recruitment pathway monitoring is detailed in the current version of the trial Monitoring Plan.

In addition to the feasibility assessment, the DMC will examine the proportion of participants reporting resolution of symptoms at week 4 to determine whether an adjustment to the sample size calculation is required. This will be performed when the TMG and DMC agree that there are sufficient data to provide a robust estimate.

The Study Within A Trial (SWAT) will also undergo its own interim analysis (see section 8.6) which will be detailed in the SAP for the SWAT.

### 13.3.3 Planned Final Analyses

The final analysis will be performed when the last data have been collected and cleaned, database locked, the SAP agreed and signed off by relevant parties, and treatment codes released.

### 13.3.4 Planned Subgroup Analyses

The trial is powered to detect overall differences between groups rather than interactions, therefore any subgroup analyses will be regarded as exploratory.

It is planned to investigate whether there could be a difference in resolution of BV between the following subgroups:

- Participants who were having their first episode of BV or an isolated recurrence versus participants who had recurrent BV.
- Participants who had any of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis* at baseline versus those who did not.

- Participants with baseline Nugent score for BV of 7 or 8 vs 9 or 10

An appropriate interaction term will be included in the regression model in order to conduct these investigations.

### 13.4 Health Economic Analysis

The economic analysis will compare the costs associated with dequalinium chloride with usual care antibiotics. If dequalinium chloride is shown to be non-inferior in the treatment of BV, then there may be important cost implications for the health sector which will have both current and future impacts.

The primary objective of the trial is to determine the non-inferiority of dequalinium chloride, so the economic analysis will focus on whether using dequalinium chloride rather than usual care antibiotics is cost neutral. An NHS/PSS perspective will be adopted in line with NICE recommendations (NICE 2013).[41] NHS Resource use and costs will be collected prospectively in both arms of the trial. Cost and resource use data will be captured via a variety of mechanisms. Firstly, the initial resource use and costs associated with delivering the treatment will be captured via trial reporting mechanisms. This will include the cost of dequalinium chloride, and the costs associated with the usual care antibiotics prescribed for the control arm. Other NHS resource use will be captured via the questionnaire for patients at week 4 and week 12; this will include the use of any further medication, GP visits, GUM clinic attendance (in-clinic or remote) and any other NHS resource use. Information on unit costs or prices will be sourced to attach to each resource use item, to enable an overall cost to be calculated (e.g. Curtis & Burns 2016).[42]

The economic analysis is deliberately simple to be in accordance with the primary aim of the trial to establish non-inferiority and will focus on whether using dequalinium chloride rather than usual care antibiotics is cost-neutral. The economic evaluation will use only data collected within the trial and so estimates of costs and outcomes will therefore relate only to the initial period and assessment at week 4 and week 12. The primary analysis will be based on cost per patient with resolved symptoms at week 4, with a secondary analysis of cost per patient without recurrence of symptoms at week 12.

Initially, the base-case analysis will be framed in terms of a cost-consequences analysis, reporting data in a disaggregated manner on the incremental cost and the important consequences as assessed in the trial. An economic analysis will be conducted to establish whether dequalinium chloride is cost-neutral in the treatment of BV. We shall also use both simple and probabilistic sensitivity analyses to explore the robustness of the results.

## 14 Trial Organisational Structure

### 14.1 Sponsor

The trial is sponsored by Leeds Teaching Hospitals NHS Trust.

### 14.2 Trials Unit

The trial is co-ordinated by the NCTU.

## 14.3 Trial Management Group

The TMG will be responsible for the day-to-day management of the trial. Membership includes (but is not limited to) the CI, Deputy Chief Investigator, Trial Manager, Trial Statistician and other members of the NCTU multidisciplinary team as appropriate. The TMG will ensure high quality trial conduct, to time and within budget, monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will also be responsible for ensuring project milestones are achieved. The TMG will meet regularly during the entire course of the trial.

## 14.4 Trial Steering Committee

A TSC will be established which includes an independent chair, independent and non-independent members and patient representatives. The role of the TSC is to provide oversight of the trial, the first meeting will take place 9 months after the first participant is recruited with all meetings thereafter taking place approximately every six months during the recruitment phase of the trial.

TSC members will be asked to sign the DEVA TSC Charter which will outline their roles and responsibilities. The TSC will consider and act, as appropriate, upon the recommendations of the DMC, and in accordance with the TSC Charter, and ultimately carries the responsibility for deciding whether the trial needs to be stopped on the grounds of safety or efficacy.

## 14.5 Data Monitoring Committee

Reports will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. During the recruitment phase of the trial the first DMC meeting will take place 9 months after first participant first visit and will meet approximately every six months thereafter.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Steering Committee (TSC) who will convey the findings of the DMC to the Trial Management Group, MHRA, funders, and/or Sponsors as applicable.

At the first DMC meeting the committee will be presented with the data required to assess the stop-go criteria for the internal pilot phase of the trial (see section 13.3.2). The DMC and TSC will review the data against the stop-go criteria and advise whether the trial should continue, outlining any concerns/modifications required for continuation (if applicable).

## 14.6 Finance

This trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (funder reference: 17/65/03).

### 14.7 Participant stipends and payments

Participants will not be paid to participate in the trial. However, they will be provided with a £15 voucher split into two part-payments. Each participant will be sent a £10 voucher on completion of their week 4 questionnaire and a further £5 voucher on completion of their week 12 questionnaire as a thank you for their additional time spent.

## 15 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2018, the applicable UK Statutory Instruments, which include the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act 2018 and The Human Tissue Act 2008 and Human Tissue (Scotland) Act 2006 (if applicable) and Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use (Clinical Trials) regulations. The protocol will be submitted to and approved by the REC prior to circulation.

## 16 Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Patients who are consented electronically will have their email addresses and/or mobile telephone numbers collected for the purpose of sharing the secure consent link with them. Participant names and contact details will be collected for the purpose of contacting participants to obtain follow-up information and to send important trial communications (e.g. reminder messages for trial questionnaires and sample taking) in accordance with the schedule outlined in this protocol.

Participants will always be identified using their initials and unique trial identification number on the eCRF and correspondence between the NCTU and the participating site.

Intravaginal samples taken from participants recruited in pathways 2 and 3 will be posted to Leeds Sexual Health, Leeds Teaching Hospitals NHS Trust, for analysis and will be labelled with the participant's screening or trial ID number, date of birth, and sample kit ID. Sample results will be reported by Laboratory staff performing sample analysis to the Leeds Sexual Health research team who will enter the results of samples onto the trial randomisation system(but will not have access to any other data collected for the participant (unless they are recruited from Leeds Sexual Health)).

Participants will give their explicit consent for a copy of their ICF to be shared with the NCTU. This will be accessible via the trial randomisation system and will be used by the NCTU to monitor the consent process.

The Investigator must maintain documents not for submission to the NCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

The NCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. competent authority, Sponsor). Representatives of the NCTU and Sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

## 17 Insurance and Indemnity

Leeds Teaching Hospitals NHS Trust will act as the sponsor for the trial. Delegated responsibilities will be assigned to the NHS trusts taking part, NCTU, University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham.

Insurance and indemnity for trial participants and NHS trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham has appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, and Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

Leeds Teaching Hospitals NHS Trust is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

## 18 Publication Policy

The dissemination of the proposed research findings will be via a published HTA monograph, research papers for publication in peer reviewed journals, presentation at medical conferences and communication of our findings to groups involved in guideline development.

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Chief Investigator and Deputy Chief Investigator and Trial Management Group and authorship will be determined by mutual agreement. The TSC and DMC will be given opportunity to comment on the manuscripts prior to submission.

Any secondary publications and presentations prepared by Investigators must be reviewed by the Chief Investigator (or Deputy Chief Investigator) and NCTU. Manuscripts must be submitted to either party in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of Leeds Teaching Hospitals NHS Trust.

During the course of the trial, press releases may be issued from NCTU. Presentations or other material prepared by local investigators to publicise the trial must be reviewed by the Chief Investigator (or Deputy Chief Investigator) and NCTU. No party will be entitled to submit any publicity material without prior approval from NCTU.

Trial participants will be asked whether or not they would like to receive a summary of the research findings, and invited to leave contact details by which they will be contacted with the research summary at the end of the project, following the publication of results.

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