DEVA

Statistical Analysis Plan

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Based on Protocol version 5.0 (dated 17 Jul 2024)

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Approval

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Abbreviations

Abbreviation	Description
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Comment: 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.
BV	Bacterial Vaginosis
DMC	Data Monitoring Committee
SAP	Statistical Analysis Plan
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that: 1 Results in death **2** Is life-threatening* **3** Requires hospitalisation or prolongation of existing hospitalisation **4** Results in persistent or significant disability or incapacity **5** Is a congenital anomaly/birth defect **6** Or is otherwise considered medically significant by the Investigator** Comments: 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 participant's/event outcome or action criteria. * 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. ** 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.
SHC	Sexual Health Clinic
STI	Sexually Transmitted Infection
TMG	Trial Management Group
TSC	Trial Steering Committee

Changes from protocol

The table below details changes to the planned analyses in the SAP compared to the analyses listed in the trial protocol (version 5.0 17 July 2024), which after discussion with the TMG are not considered to require a protocol amendment.

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
Version: 5.0 Section: 8.4	The protocol version 5.0 does not specify the exact option to be sent through SMS for answering how much approximate amount of treatment was taken.	Version: 1.0 Section: 2.4	Before 23rd October 2024, if the full course of treatment was not completed, the following categories were listed as options to capture the approximate amount of treatment taken: Most (approx. 75% or more) Half to three quarters (approx. 50-74%) Less than half (approx. 1-49%) No treatment taken/used After 23rd October 2025, the additional option was added to get the responses from the participants more clearly: Most (approx. 75% or more) Half to three quarters (approx. 50-74%) Less than half (approx. 1-49%) None (don't plan to take it) I haven't started and/or finished yet but plan to	Before Day 14, for various reasons, there may be instances where a participant has not yet taken the treatment. In such cases, their response to the message might be "No treatment taken/used." However, the participant may still be willing to start the treatment after Day 14. To capture this distinction more clearly, an additional response option has been included to classify participants as either "None" or "I haven't started and/or finished yet but plan to."
Version: 5.0 Section: 13.3	The protocol version 5.0 does not specify the exact model to carry out the analysis for the secondary outcome	Version: 1.0 Section: 10	The evaluation of the secondary outcomes (Participant reported resolution of BV symptoms 4 weeks post treatment start date with or without additional treatment, microscopic resolution of BV on microscopy at week 4 as assessed by Leeds Sexual Health Clinical Laboratory, analysis of participant taken vaginal smears (in remote pathways only), participant reported recurrence of BV symptoms within 12 weeks of treatment start date) will be performed using a mixed-effects model for binary	For the secondary outcome analysis, the exact statistical model was not prespecified in the protocol.

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
			outcomes, incorporating the factors used in the minimisation (excluding recruiting site) as fixed effects and recruiting site as a random effect. If the model fails to converge, an alternative analysis will be performed using a generalized linear model without the recruiting site as random effects. The between group effect will be reported using an adjusted absolute risk difference and adjusted risk ratio along with corresponding 95% confidence intervals. For time to event outcomes, the difference between the two groups is evaluated using a shared-frailty Cox proportional hazards model, adjusting for minimisation factors (excluding recruiting site) as fixed effects and recruiting site as random effects. If the model does not converge, a Cox proportional hazards model without recruiting site as random effects will be fitted. The between group effect will be reported using an adjusted hazard ratio along with a corresponding 95% confidence interval. Kaplan-Meier curves will be presented for each of the outcomes by treatment group.	
Version: 5.0 Section: 12.3	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	Version: 1.0 Section: 7.1	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 doesn't converge, or the random effect variance is minimum; the outcome will be analysed using the generalised linear model without considering the recruiting sites as a random effect.	The analysis approach has been revised from Generalized Estimating Equations (GEE) to Generalized Linear Model (GLM) due to the assumed absence of strong correlation or clustering within the data. The observations are independent, and the random effect variance is assumed to be minimal, making GLM a more appropriate and efficient choice for analysing the binary outcome.

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
	contraception, pathway; site may or may not be included). If this model does not converge a generalised estimation model with site as a panel variable may be used instead.			
Version: 5.0 Section: 13.3	The original protocol version 5.0 does not outline or specify performing any exploratory data analysis.	Version: 1.0 Section: 10	The proportion of participants in each combination of participant-reported resolution of BV symptom (without need of additional treatment) and microscopic resolution of participant taken vaginal sample at week 4 (Pathway 2 &3 only) will be presented to explore the distribution of outcomes.	The participant-reported self-reported symptom resolution at 4th week and the microscopic resolution of participant taken vaginal sample at 4th week will help us to understand symptom perception and the relationship between the subjective and the objective clinical outcomes.
			The proportion of participants in each combination of participant-reported resolution of BV symptom (with or without need of additional treatment) and microscopic resolution of participant taken vaginal sample at week 4 (Pathway 2 &3 only) will be presented to explore the distribution of outcomes.	
			Microscopic resolution of participant taken vaginal samples (pathway 2 & 3 only) assessed using the Nugent score method at baseline and at 4th week will be presented among the treatment groups to explore changes in the distribution of outcomes over time.	Exploring baseline and 4th week Nugent score results will allow us to assess changes over time, providing insights into the effectiveness of the intervention. This will also contribute to a better understanding of disease progression or reduction, helping to evaluate the impact of the intervention on the clinical outcomes.
			Participant-reported resolution of BV symptoms at 4 weeks by additional treatment taken along with the randomised treatment will be presented among the randomised group. The additional treatment taken is classified as treatment which is (i)	As the additional treatment taken by the participants varies a lot and falls into different areas, the additional treatments were reviewed and categorised into two broad areas - those likely to affect the vaginal

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
			likely to affect the vaginal microbiome or (ii) not likely to affect the vaginal microbiome.	microbiome and those not likely to affect the vaginal microbiome. This allows for the assessment of BV symptom resolution at the fourth week between the two treatment groups, taking into account the additional treatment categorised as "likely to affect the vaginal microbiome" and "not likely to affect the vaginal microbiome" taken alongside the randomized treatment.
			Is the resolution of symptoms at 4th week different in women who have no sex throughout at 4 week follow-up compared with women who continue to have sex with a regular male partner?	Research has been recently published which has shown that treating male partners of women with bacterial vaginosis (BV) using combined oral and topical antimicrobial therapy leads to a significantly lower recurrence rate of BV within 12 weeks compared to standard care [1]. Since the DEVA study also collects relevant data pertaining to sexual activity and related factors, we will undertake exploratory analyses to further investigate and better understand the potential implications and inferences.
			Is the Nugent score of the participant taken vaginal sample at 4th week (pathway 2 & 3only) different in women who have no sex throughout the 4 week follow-up compared with women who continue to have sex with a regular male partner?	
			Is recurrence rate at Week 12 (no symptoms at Week 4 but symptoms at Week 12) different in women who have no sex throughout the trial compared with women who continue to have sex with a regular male partner?	
			Is the resolution of symptoms at 4th week different in women who have no sex throughout the 4 week follow-up compared with women who have sex with a new male partner?	
			Is the Nugent score of the participant taken vaginal sample at 4th week (pathway 2 & 3only) different in women who have no	

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
			sex throughout the 4 week follow-up compared with women who continue to have sex with a new male partner?	
			Is the recurrence rate at Week 12 (no symptoms at Week 4 but symptoms at Week 12) different in women who have no sex throughout the trial compared with women who have sex with a new male partner?	
			Symptom clearance at 4 weeks by each usual care antibiotic (chosen by the clinician in discussion with the participant pre-randomisation).	

Amendments to versions

Version	Date	Change/comment	Statistician

1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the NIHR funded DEVA trial.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform or replicate these analyses.

Additional exploratory or auxiliary analyses of data not specified in the protocol may be included in this analysis plan.

This analysis plan will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will be performed if considered appropriate. These should be documented in a file note.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial and where appropriate in publications arising from the analysis.

Health economic and qualitative analysis plans are beyond the scope of this document.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

[Synopsis from protocol V5.0]

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** To determine if the proportion of females reporting resolution of BV symptoms 4 weeks after treatment is not worse in females treated with dequalinium chloride compared to usual care antibiotics without the need for additional treatment**.** **Secondary objectives** To determine: • The proportion of females reporting resolution of BV symptoms 4 weeks after treatment (with or without the need for additional treatment) • The effect of dequalinium chloride on number of days to resolution of BV symptoms without the need for additional treatment • The effect of dequalinium chloride on microscopic resolution of BV at week 4 without the need for additional treatment • The adherence to dequalinium chloride and usual care antibiotics • The side effects of dequalinium chloride and usual care antibiotics • The satisfaction with BV treatment • The effect of dequalinium chloride on recurrence of BV symptoms within 12 weeks • The effect of dequalinium chloride on number of days to recurrence of BV symptoms • The cost of treating BV with dequalinium chloride compared with usual care antibiotics
Participant Population	Females, diagnosis of BV confirmed by microscopy examination of a sample with the symptom of vaginal odour plus or minus vaginal discharge, including either first or recurrent episodes.
Eligibility criteria	**Inclusion Criteria** • People with a vagina (assigned female at birth) 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 **Exclusion Criteria** • Contra-indications or allergy to dequalinium chloride or clinician selected usual care antibiotic BV treatment

	• Use of 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 past 14 days prior to randomisation or planned use over the next 14 days from randomisation • Pregnant females who are seeking a termination • Unwilling to provide GP information (only to be used for pregnant females or females who become pregnant in the first 4 weeks of the trial) • Current use of gender affirming hormones (androgens and anti-oestrogens) • Previous participation in this trial • Resident outside the UK (for shipment of trial medication and sample kits only)
Description of interventions	**Intervention** The intervention group will receive dequalinium chloride 10 mg vaginal tablet for 6 nights. **Control (usual care antibiotics)** The control group will receive clinician-chosen usual care antibiotics selected from UK guidelines recommended or alternative oral or topical antibiotic BV treatments. 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** Participant-reported resolution of BV symptoms 4 weeks post-treatment start date without the need for additional treatment. **Secondary** • Participant-reported resolution of BV symptoms 4-weeks post-treatment start date (with or without the need for additional treatment) • Time to participant-reported resolution of BV symptoms without the need for additional treatment • Microscopic resolution of BV on microscopy at week 4 (without the need for additional treatment) as assessed by Leeds Sexual Health Clinical Laboratory analysis of participant taken vaginal smears (in a subgroup of participants) • Participant reported proportion of prescribed trial BV treatment taken • 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 • Participant-reported satisfaction with treatment • Participant-reported recurrence of BV symptoms within 12 weeks of treatment start date, for those who resolved within 4 weeks without additional treatment • Time to participant reported recurrence of BV symptoms • Cost of BV treatment, including additional medication and healthcare usage relating to BV

Sample Size	The trial will recruit 1316 participants. The original sample size was based on the assumption that 78% of participants would 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) would 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 females 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 originally aimed to recruit 904 females. After the pooled resolution rate was found to be considerably lower than expected (50% vs 78%) consistently from 2022 onwards, the oversight committees advised that the sample size should be recalculated based on the observed pooled resolution rate. Assuming 50% of participants have bacterial vaginosis symptom resolution at week 4 in both groups, a total sample size of 1052 for analysis (526 in each group) will achieve 90% power to conclude non-inferiority with a lower confidence interval limit for the absolute risk difference of 10%, with a 1 sided significance level of 0.025. To allow a loss of primary outcome data of up to 20%, it is planned that 1316 participants are recruited. 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 Leeds General Infirmary Research and Innovation Laboratory. The inclusion of 150 participants in the sub-study is not based on a specific sample size calculation.
Expected recruitment duration	40 months

2.1. Sample size and justification

The original sample size was based on the assumption that 78% of participants would have BV symptom resolution at week 4 in both the control and intervention groups. A total sample size of 722 for analysis (361 in each group) would 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 females 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 originally aimed to recruit 904 females.

The pooled resolution rate was found to be considerably lower than expected (50% vs 78%) consistently from 2022 onwards; the oversight committees advised that the sample size should be recalculated based on the observed pooled resolution rate. Assuming 50% of participants have bacterial vaginosis symptom resolution at week 4 in both groups, a total sample size of 1052 for analysis (526 in each group) will achieve 90% power to conclude non-inferiority with a lower confidence interval limit for the absolute risk difference of 10%, with a 1 sided significance level of 0.025. To allow a loss of primary outcome data of up to 20%, it is planned that 1316 participants are recruited.

2.2. Blinding and breaking of blind

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.

Trial Management staff within NCTU will be blinded to treatment allocation as far as possible. 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. Data management staff and software programmers will be unblinded, as they are responsible for the management of the randomisation system and trial database.

2.3. Trial committees

A Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) will be assembled to oversee the trial. The general purpose, responsibilities and structure of the committees are described in the protocol. Further details of the roles and responsibilities of the TSC and DMC can be found in their charters agreed prior to the start of recruitment to the trial.

2.4. Outcome measures

Table 1: Summary of the outcome measures

Outcome measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time points
Primary outcome					
Participant-reported resolution of BV symptoms 4 weeks post-treatment start date without the need for additional treatment.	**Scale:** Participant answers 'Yes' or 'No' to questions "Are you symptom free today?" and "Did you use any additional treatment (this includes medicines, probiotics and home remedies)?" **Source**: participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls.	Combination of resolution from questionnaire(s), telephone calls and text message. The proportion of participants will be calculated as the number resolved (symptom free=yes) without additional treatment (additional treatment=no) out of the total providing resolution and additional treatment data. If the outcome has been received from multiple sources (week 4 questionnaire, text message or telephone call), the outcome obtained closest to 4 weeks will be used. See 4.4 on derived variables for further detail.	Binary	Number and percentage in each group	4 weeks
Secondary outcomes					
Participant-reported resolution of BV symptoms 4 weeks post-treatment start date with or without the need for additional treatment.	**Scale:** Participant answers 'Yes' or 'No' to question "Are you symptom free today?" **Source**: participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls.	Combination of resolution from questionnaire(s), telephone calls and text message. The proportion of participants will be calculated as the number resolved (symptom free=yes) out of the total providing resolution data. Participants with resolution data who do not provide details of	Binary	Number and percentage in each group	4 weeks

Outcome measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time points
		whether they have used additional treatment will be included. If the outcome has been collected from multiple sources (week 4 questionnaire, text message or telephone call), the outcome obtained closest to 4 weeks will be used. See 4.4 on derived variables for further detail.			
Time to participant-reported resolution of BV symptoms without the need for additional treatment	**Scale:** Time in days from treatment start date to date of resolution of BV symptoms for participants who had resolution without the need for additional treatment. **Source:** Resolution dates and need for additional treatment from participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls. **Treatment start date:** 14 day survey (SMS) and week 4 questionnaire	Resolution date minus treatment start date (in days), for those who reported BV symptom cleared without the need for any additional treatment. Participants reported that the symptom was not cleared will be censored at week 4 follow-up. See 4.4 on derived variables for further detail.	Continuous	Mean / Median in each group based on the distribution	4 weeks
Microscopic resolution of BV on microscopy at week 4 (without the need for additional treatment) as	**Scale:** The number with microbiological resolution is the number of negative results at week 4 out of those with positive results at baseline.	A negative result is 0-6 on the Nugent scale; a positive result is 7-10. A result of 'NI' (slide result is not interpretable) will be treated as missing result. Resolution is defined as being negative for BV (Nugent score 0-6) 4 weeks post treatment start	Binary	Number and percentage in each group	4 weeks

Outcome measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time points
assessed by Leeds Sexual Health Clinical Laboratory analysis of participant taken vaginal smears (in remote pathways only)	**Source:** BV microscopy data (baseline and week 4) received from Leeds Sexual Health Clinical Laboratory (pathways 2 and 3 only). Additional treatment data on week 4 questionnaire.	date without the need for additional treatment. All participants should be positive for BV at baseline (inclusion criteria). Denominator: Those participants whose sent the week 4 sample.			
Participant reported approximate amount of prescribed trial BV treatment taken	**Scale:** Adherence to medication will be calculated by sending the SMS at day 14 to all participant and asking about the treatment completion status. The following categories of adherence will be listed to classify the amount of treatment taken if the full course of treatment was not completed. As per the eSendex SMS text survey – before 23 Oct 2024 - Most (approx. 75% or more) - Half to three quarters (approx. 50-74%) - Less than half (approx. 1-49%) - No treatment taken/used As per the eSendex SMS text survey – after 23 Oct 2024 - Most (approx. 75% or more) - Half to three quarters (approx. 50-74%)	Proportions in each category will be calculated for two periods separately. Denominator: Those participants whose response marked as “no” to the question “Full course of treatment completed” based on the eSendex SMS text survey option sent at that time period.	Ordered categorical	Number and percentage in each category in each group	4 weeks

Outcome measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time points
	- Less than half (approx. 1-49%) - None (don't plan to take it) - I haven't started and/or finished yet but plan to **Source:** 14 day survey (SMS) and week 4 questionnaire				
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	**Scale:** For each of the side effects the participant recorded: presence (yes) and severity (mild/moderate/severe). **Source:** Data from week 4 questionnaire.	The proportion of participants reporting with symptoms will be calculated based on participants who answered at least one question in the questionnaire (actual treatment the participant taken (Safety dataset); proportions in severity categories will be out of those with side effect present. See 4.4 for further detail.	Ordered categorical	Number and percentage in each category in each group	4 weeks
Participant-reported satisfaction with treatment	**Scale:** categories are: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied. **Source:** week 4 questionnaire	Proportions in each category will be calculated based on participants who answered at least one question in the questionnaire	Ordered categorical	Number and percentage in each category in each group	4 weeks
Participant reported recurrence of BV symptoms within 12 weeks of treatment start date	**Scale:** Participant answers 'Yes'/ 'No' / 'n/a' to the question "Are you symptom free today", "Did you use any additional treatment (this includes medicines, probiotics and home remedies)?" and "Have you experienced any new episodes of BV since your symptoms cleared?"	The Week 12 questionnaire collects whether participants have experienced a new episode of BV. For analysis, only participants who 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	Binary	Number and percentage in each category in each group	12 weeks

Outcome measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time points
	Source: Recurrence 12 Week questionnaire, text, telephone call. Symptom clearance and additional treatment data on week 4 questionnaire	without additional treatment, whether or not they took additional treatment after 4 weeks. See 4.4 on derived variables for further detail.			
Time to participant reported recurrence of BV symptoms	**Scale:** Time in days from date of resolution of BV symptoms to date of first new episode, for those resolving within 4 weeks without additional treatment. Both resolution and recurrence are participant self-reported. **Source:** resolution (clearance) dates and additional treatment from week 4 questionnaire. Recurrence (new episode) dates from 12 week questionnaire.	The Week 12 questionnaire collects whether participants have experienced an any new episode of BV along with the date of recurrence of first episode. Only participants who have recorded resolution of BV by 4 weeks without the use of additional treatment can be judged to have had a recurrence, hence time to participant reported recurrence is the time in days between resolution (Week 4) and recurrence (Week 12), whether or not they took additional treatment after 4 weeks. Those who resolved without additional treatment but had not yet recurred by Week 12 are censored at 12 Week follow-up.	Continuous	Means / Median in each group based on distribution	12 weeks
Cost of BV treatment, including additional medication and healthcare usage relating to BV	**Scale:** See health economics analysis plan. **Source:** week 4 and week 12 questionnaires.	Healthcare resource use associated with BV and BV treatments. Details of alignment with associated costs are provided in section 13.4 of the protocol.	Described in HEAP	Described in HEAP	Baseline, 4 weeks and 12 weeks

3. INTERIM ANALYSIS

There were no planned interim effectiveness analyses, however, an internal pilot phase had been built into the trial to allow a feasibility assessment which examined recruitment, retention and adherence. Stop-go criteria (Table 2) 9 months after the first participant had been randomised were used to determine the progression of the trial. Recruitment was measured against the overall recruitment target. Retention was determined by provision of primary outcome data. Adherence level was 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 DMC met on 18 May 2022 and the TSC on 16 June 2022 (as planned to meet on 9th month review after the participant randomised into the study) to review trial progress, cumulative data, and assess continuation against progression criteria. Both committees acknowledged the pandemic's impact but praised the trial team's proactive efforts in site activation, study promotion especially for pathway 3 and recruitment strategies. They were particularly impressed by the innovative use of social media and search engines to advertise a clinical trial for a stigmatised condition, noting its potential significance for future remote recruitment efforts. They also reviewed advertising challenges and highlighted the value of collected data on cost, strategy, and optimisation for broader research use.

It was noted that the pooled response rate was lower than expected. Although only ~10% of the target sample had been recruited, the DMC recommended reassessing sample size and recruitment duration based on revised control group response rates.

The TSC acknowledged that the participant population was a different group than that initially expected, but that the question as to whether dequalinium chloride was a suitable alternative to usual care antibiotics for the treatment of BV was extremely relevant in the trial population, as these were representative of the women they are now seeing in clinic or who are seeking treatment.

Both committees strongly recommended continuing the trial under the Recovery Plan.

In addition to the feasibility assessment, the DMC examined the proportion of participants reporting resolution of symptoms at week 4 to determine whether an adjustment to the sample size calculation was required.
In November 2022, the pooled resolution rate was 50% but remained lower than the 78% assumed in the sample size calculation. Following in-depth discussions with both oversight committees and funder, it was agreed that the trial should proceed with an increased recruitment target of 1316, based

on 50% pooled response rate with 20% loss of primary outcome data (original target of 904 was based on 78% response with 15% loss of primary outcome data).

The committees emphasised the important value the trial was making to regarding the data collected on remote recruitment pathways, the accuracy of a diagnosis of BV, made by an individual participant and a clinician, based on symptoms and important information collected on current 'usual care' antibiotic efficacy. The 78% resolution rate figure used in the original sample size calculation was based on trials from 20-30 years ago and it's possible that due to repeated use, antibiotic resistance or tolerance that current efficacy is below 78%. Knowing what the current efficacy is will be important information for the management of BV and for managing patient's expectations.

The Study Within A Trial (SWAT) had also undergone independent prespecified interim analysis which was detailed in the SAP for the SWAT.

4. GENERAL ANALYSIS CONSIDERATIONS

4.1. Analysis sets

The primary approach to between-group comparative analyses will be by intention-to-treat (i.e., including all patients according to randomised allocation regardless of adherence to trial allocation). The analysis sets are described in Table 3. The primary estimand is described in Table 4.

Table 3: Analysis sets

Outcome	Analysis set	Definition
Primary outcome (resolution of BV symptoms)	Intention-to-treat (ITT) analysis set	Participants will be analysed according to their randomised group (i.e. as randomised) regardless of adherence with the allocated intervention. The only exclusion will be the participants who were randomised twice (i.e those with previous participation in the trial).
	Per-protocol set	Subset of participants in the full analysis set who sufficiently complied with the protocol without any major violations (Violation includes: Randomisation error due to wrong entry in minimisation variable, ineligible post randomisation, failure to take treatment, taken wrong treatment other than the treatment randomised), primary outcome available, treatment adherence greater than 75% or reported as taking most/all of tablets.
Secondary outcomes	Intention-to-treat (ITT) analysis set	As defined above for primary outcome
Safety outcomes	Safety analysis set	All participants who have received at least one dose of dequalinium / usual care antibiotics (self-reported) will be summarised according to the treatment they received; those not given the randomised treatment are documented with reason if provided. Participants who were randomised, but received no treatment will be summarised separately, if data are available.

Table 4: Primary estimand

Domain	
Population	People with a vagina (assigned female at birth), aged 16 years and over and diagnosis of BV confirmed by microscopy with a symptom of vaginal odour plus or minus vaginal discharge requiring treatment, including first or recurrent episode.
Outcome	Participant-reported resolution of BV symptoms 4 weeks post-treatment start date without the need for additional treatment.
Treatment	Intervention: Dequalinium Chloride 10 mg vaginal tablet for 6 nights Control: Clinician-chosen usual care antibiotics Clinicians will choose the control treatment prior to randomisation. If the participant is randomised to the control arm they will receive this predetermined BV treatment. The control treatment is selected from UK guideline recommended or alternative oral or topical antibiotic BV treatments.
Intercurrent events	Treatment discontinuation – participants included irrespective of discontinuation – treatment policy Non-adherence to the treatment – participants included irrespective of how much treatment taken – treatment policy Discontinuation / Withdrawal from trial: Participant information will be included prior to discontinuation / withdrawal from trial – treatment policy
Summary measures	Adjusted absolute risk difference with associated 95% CI

4.2. Timing of final analysis

All quantitative outcome data will be analysed at the end of the trial after final database lock.

4.3. Statistical software

Analyses will be performed using Stata version 18 or above.

4.4. Derived variables

For further information see Table 1.

Variable(s)	Derivation
Age (at randomisation) (years)	The integer part of (randomisation date in days – date of birth in days)/365.25
Treatment adherence	• Treatment completion details obtained at day 14 survey (SMS) in order to minimise recall bias and loss of data or by telephone or by week 4 questionnaire through online or post. Response obtained through survey (SMS): • If answered as "Yes" to the question "Did you finish all your treatment", indicate that participants started and completed the full course of treatment. • If answered as "No", options listed below to confirm how much of the treatment they took, if in the specified option they marked as "No", consider the participant completed "full course of treatment". From start of the trial to till 23rd Oct 2024, the following categories were available as reportable option for the

	participant if they answered as "No" to "Did you finish all your treatment". - Most (approx. 75% or more) - Half to three quarters (50% to 74%) - Less than half (1% to 49%) - No treatment taken Whereas from 23rd Oct 2024, the following categories were available as reportable option for the participant if they answered as "No" to "Did you finish all your treatment", - Most (approx. 75% or more) - Half to three quarters (50% to 74%) - Less than half (1% to 49%) - None (don't plan to take it) - I haven't started and/or finished yet but plan to. Response through week 4 questionnaire by online/post or by telephone call: • If answered as "Yes" to the question "Did you finish all your treatment", indicate that participants started and completed the full course of treatment. • If answered as "No", option listed below to confirm how much of the treatment they took, - Most (approx. 75% or more) - Half to three quarters (50% to 74%) - Less than half (1% to 49%) • If the response is available from more than one source, from Survey (SMS) or week 4 questionnaire through online or post, or telephone and the response don't match then the response closest to 4 week timepoint will be used. • Other reasons why treatment course is not completed will be categorised by the unblinded members of the TMG with wording for the categories agreed by the chief investigator (in blinded fashion), and tabulated.
Resolution of BV symptoms (clearance) without additional treatment at 4 weeks	Percentage resolved without additional treatment = (Resolved without additional treatment) / (Total number with response to the question about resolution) • Calculated based on responses received through at least one mode of contact questionnaire, text message, or telephone. • If responses from questionnaire, text message or telephone don't match then the response closest to 4 weeks will be used. • If yes/no to symptom resolution question is missing, but date of resolution (clearance) is provided and the response to additional treatment marked as "No", then this will be assumed as resolved without the use of additional treatment. • If response to symptom resolution is marked as "No", but the resolution date is provided, then this will be assumed as "Not cleared", and if appropriate sensitivity will be performed.

	• If response to the symptom resolution question is marked as "Yes", but the response to the additional treatment is missing, then this will be assumed as "Cleared" without additional treatment and if appropriate sensitivity will be performed. • If response to the symptom resolution is marked as "Yes", but the response to additional treatment is missing, then this will be assumed as "additional treatment is not taken". • The additional treatment question appears in two separate sections of the week 4 questionnaire. Both responses merged and will be considered in the analysis (if either one of them marked as "Yes" will be considered as "Yes").
Resolution of BV symptoms (clearance) regardless of additional treatment at 4 weeks	Percentage resolved = (Resolved with or without additional treatment) / (Total number with response to the question about resolution) • Calculated based on responses received through at least one mode of contact questionnaire, text message, or telephone. • If responses from questionnaire, text message or telephone don't match then the response closest to 4 weeks will be used. • If yes/no is missing, but date of resolution (clearance) is provided then this will be assumed as resolved. • If response is marked "No", but the resolution date is provided, then this will be assumed as "Not cleared".

Time to participant reported resolution of BV symptoms without the need for additional treatment	Time to resolution = Date of resolution of BV symptoms minus Date of starting treatment, for participants categorised has having resolution without the need for additional treatment.
	• If the date given for starting treatment is before randomisation, then the treatment start date will be replaced with a derived date calculated as follows:
	  • Pathway 1: *Randomisation date + 1 day*
	  • Pathways 2 and 3: *Randomisation date + 3 days*
	• If the treatment initiation status is obtained via survey (SMS) and the participant has not completed the Week 4 questionnaire, the treatment start date is unavailable. For participants with an unavailable response, or missing response, the treatment start date will be derived as follows:
	  • Pathway 1: *Randomisation date + 1 day*
	  • Pathways 2 and 3: *Randomisation date + 3 days*
	• If the BV symptom resolution is obtained through text message and the actual resolution date is not captured explicitly, the date of text message receipt will be considered as the resolution date.
	• If the BV symptom resolution is obtained through questionnaire and the actual resolution date is not available, the date of questionnaire completion will be considered as the resolution date.

Recurrence of BV symptoms	Percentage of participants experiencing a recurrence = Recurrence after symptom resolution by week 4 without additional treatment / total number resolved by week 4 without additional treatment, • Recurrence of BV symptom information will be included in the analysis only if the response to the symptom clearance question

	at week 4 is marked as “Yes”. If yes/no to recurrence question is missing, but date of recurrence is provided, then this will be assumed as recurrence of event.
Time to first recurrence of BV	Time to first recurrence = Date of recurrence of BV symptoms minus Date of resolution (for those resolving before week 4 and without additional treatment) • Set to missing if date of first episode is before date of resolution. • If the recurrence is marked as “Yes” and obtained through questionnaire/SMS and the actual recurrence date is missing, the date of questionnaire completion (week 12) / SMS received will be considered as the recurrence date.
Side effects	If presence of side effect =”no” or missing, but severity given, then assume as “yes”.
Adverse event	Adverse events not included among the predefined side effects will be documented and reported separately.
Microscopic resolution of BV sample, STI sample and any samples collected for sub-study results.	If a sample result is marked as 'Indeterminate', it will be reported as such in the descriptive analysis. However, for modelling purposes, it will be treated as missing.
Questionnaire completion	For the questionnaire completion table, completion defined as entering at least one item of data in the entire questionnaire.

4.5. Procedures for missing data

Missing baseline data

Missing baseline variable is treated as missing. The analysis covariates in this trial are those variables used for the minimisation algorithm (first/isolated episode or recurrent BV, female sexual partner in the previous year (yes/no), method of contraception (barrier/hormonal/device/none of the others), recruitment site (site may not be included if it causes convergence problems in analysis), pathway (1 vs 2&3). There are no missing values in these variables.

Missing outcome data

For the missing primary outcome data (resolution of symptoms at week 4 without additional treatment), the sensitivity analyses will be performed using the following imputations:

- missing primary outcome data assumed to be resolved,
- missing primary outcome data assumed to be not resolved, and
- multiple imputation

The multiple imputation will be performed by using chained equations[2], with the following covariates: recurrent episode or not, female partners in 12 months before baseline, method of contraception, site, pathway, plus any other variables that are imbalanced between allocated groups at baseline (visual inspection).

For secondary outcomes, inconsistent values/missing values will be replaced only as specified in the table above (4.4)

For laboratory data (BV Samples collected at baseline and Week 4, STI sample at baseline and the samples for further sub-study of microbiota) results 'I' (indeterminate) will be treated as missing.

5. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

5.1. Participant flow

The flow of participants through the study will be shown in a CONSORT flow chart:

- Number approached in pathway 1
- Number of exclusions between approached and consents in pathway 1
- Number of consents in pathway 1
- Number of randomisations in pathway 1
- Number of expressions of interest submitted to participate in the trial in pathways 2 & 3
- Number of exclusions between expression of interest and consents in pathway 2 & 3
- Number of consents in pathways 2 & 3
- Number of exclusion / ineligibles prior to randomisation but post consent in pathway 2 & 3
- Number of randomisations in pathway 2 & 3
- Number of randomisation (pathway 1,2 and 3)
- Number of participants randomised (pathway 1, 2 & 3)

  The CONSORT diagram detailing the above flow will also be presented by overall (combining the pathway).

The following will be presented by allocated group within pathway:

- Number of participants randomised
- Number receiving allocated medication, number not receiving allocated medication
- Number of participants fully withdrawn prior to week 4 and the reason for the withdrawn, number with week 4 questionnaire expected, number returned week 4 questionnaire at least some data marked on the questionnaire
- Number with primary outcome data expected, number with primary outcome data available, number with primary outcome data missing
- Number of participants fully withdrawn prior to week 12 and the reason for the withdrawn, number with week 12 questionnaire expected,
- Number of participants remaining after week 12 follow-up and the number of participants returned the questionnaire at least some data marked on the questionnaire.

The CONSORT diagram detailing the above flow will also be presented by overall (combining the pathway).

5.2. Baseline characteristics

Continuous variables will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations, as appropriate for normally distributed or skewed data. Categorical variables will be summarised in terms of frequency counts and percentages. No formal statistical comparisons will be made.

The following baseline characteristics will be presented: (a) by treatment group, along with overall totals; and (b) by pathway (Pathway 1 vs. Pathways 2 & 3), and treatment group.

- Age at randomisation (years)
- Pathway (1 vs 2 & 3), only reported when summarised overall
- Number of previous episodes of bacterial vaginosis within the past 12 months (0, 1-3, >3)
- Has had sex within the last 3 months (yes, no)
- Biological sex of sexual partners within the last 12 months (male, female, both male and female, none)
- Contraception currently used (barrier, hormonal, IUD/IUS, none of the others)
- Pregnancy status (pregnant, not pregnant)
- Ethnicity (White, Black, Asian, Chinese, Mixed Race, Other, not given)
- BV microscopically confirmed at baseline (yes)
- Genital discharge (yes, no)
- Unpleasant vaginal odour (yes, no)
- Presence of both discharge and odour (yes, no)
- Vaginal / vulval irritation (yes, no)

The baseline characteristics listed above will also be summarised according to the availability of primary outcome data.

6. ASSESSMENT OF STUDY QUALITY

6.1. Randomisation

Randomisation will be carried out using minimisation, including a random component that minimises imbalance.
The number of participants randomised to the two treatment groups at each recruitment centre and by pathway (1 vs 2&3) will be tabulated. The other minimisation variables will be tabulated as part of the baseline characteristics.

The minimisation variables are: first/isolated vs recurrent episode within last 12 months, female sexual partner in 12 months before baseline, method of contraception [none of the others, barrier, intrauterine, hormonal; if more than one method is used, they will be prioritised as intrauterine, hormonal then barrier], recruitment site, pathway (1 vs 2 & 3), whether provided sub-study self-taken samples or not.

Any participant who had been randomised on more than one occasion was recorded as an ineligible. All data relating to randomisations beyond the first, will not be included in the analyses.

After randomisation, if a minimisation variable is marked wrongly by mistake or if a participants is found to be ineligible will be indicated with reasons in the protocol non-compliance and will be summarised. Any such participants will be analysed as randomised.

6.2. Treatment Adherence

Adherence to treatment will be assessed by whether the participant took any of the trial treatment, participant reported treatment course completion, percentage of course received, reasons for not completing treatment course and time from randomisation to starting treatment. See section 2.4 and section 4.4.

6.3. Treatment satisfaction

Participants satisfaction with the treatment will be summarised based on the response in the week 4 questionnaire.

6.4. Follow-up and withdrawals

The number and percentage of participants completing the primary outcome (resolution of symptoms at Week 4 without addition medication) will be presented for week 4 questionnaire completion, telephone call completion, text data, and overall completion (i.e. all primary outcome data, whichever source); by treatment group, by pathway (1 vs 2 and 3) and overall.

The numbers and percentages returning the questionnaire will be presented by treatment group, pathway and overall. Additionally, the time from randomisation to questionnaire return or telephone data collection (week 4 only), as well as the time from treatment start to questionnaire return or telephone data collection (week 4 only), will be summarised by treatment group, pathway and overall using the mean, median, lower & upper quartiles, minimum and maximum.

Withdrawals and the reason (death, withdrawal of consent for trial, withdrawal from trial due to AE and others) will be summarised by treatment group. Details for 'other' will be given where available. Non-return of questionnaires is counted as missing data not withdrawal. Discontinuations from the following activities will also be tabulated by treatment group: Follow-up questionnaires and reminders, Samples and reminders, Reminder communications, Study results communications, All trial activities, other.

Follow up of participants starts at day 14 via survey (SMS), in order to minimize recall bias and loss of data, to collect information of treatment completion information and the questionnaires are available for completion at 14-28 days from randomisation for the week 4 questionnaire, 12-16 weeks for the week 12 questionnaire. 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 treatment completion question will be removed prior to sending the questionnaire by post, to the participant to ensure the questions will then not be asked again as part of the week 4 questionnaire.

The week 4 questionnaire remains open up to 56 days from date of randomisation (an additional 28 days window period) and similarly the week 12 remains open up to 115 days from date of randomisation (an additional 31 days window period). Questionnaires cannot be completed outside these times without request to the trial team. Not completing a questionnaire will be regarded as missing data rather than loss to follow-up.

Missing outcome data were followed up by a telephone call and text message. Not answering a telephone call/not responding to a text message, to obtain missing data, is not considered as loss to follow-up.

6.5. Non-compliance (protocol deviations)

Recorded incidences of protocol non-compliance (not routinely documented in this trial, and expected to be few because of the trial design) will be listed and tabulated by treatment group, using the following categories: Inclusion / Exclusion Criteria, Informed Consent, Treatment Randomisation Error, Wrong value of minimisation variable entered onto randomisation system, Did not receive randomised treatment, Did not receive pre-determined usual care, Other.

Participants not receiving their randomised treatment will be included in the primary analysis as randomised, but a sensitivity analysis will include them as treatment received (apart from those not receiving any treatment who will not be included in this sensitivity analysis).

7. ANALYSIS OF EFFECTIVENESS

Results of the analyses will be reported by point estimates and corresponding 2-sided 95% confidence intervals. Secondary outcomes will be considered supportive to the primary analysis.

7.1. Primary analysis

The primary analysis is planned to be based on all participants, without imputation of response data which could not be derived as per Section 4.4. However, if more than 20% of participants do not have evaluable primary outcome data, the primary analysis will use multiple imputation by chained equation and the planned analysis will become a sensitivity analysis.

Numbers and percentages of participants whose BV symptom resolved (participant reported) at week 4 and who did not take additional medication will be presented by treatment group. Data will be derived according to the rules defined in Section 4.4. Where this is not possible, data will be considered missing. The analysis will include data obtained from questionnaires, telephone calls and text messages.

The evaluation of the primary outcome will be performed using a generalized linear mixed effects regression model for binary outcome, adjusting for minimisation variables (site, first episode / isolated recurrence episode (No previous episode in the 12 months before baseline) or recurrence (Previous episode(s) in the 12 months before baseline), female partners in the 12 months before baseline, method of contraception, pathway (1 vs 2 & 3)). The model will include a random effect for recruiting site, while all other minimisation variables will be adjusted for using fixed effects.

If the model doesn't converge, or the random effect variance is minimum; the outcome will be analysed using the generalised linear model without considering the recruiting sites as a random effect.

The between group effect will be reported using an adjusted absolute risk difference and adjusted risk ratio along with corresponding 95% confidence intervals. Point estimates and confidence intervals will be obtained using Stata's Margins command with standard errors computed using the delta method[3]. The point estimates and the corresponding 95% confidence intervals determined for the primary outcome will be presented in a forest plot.

A non-inferiority trial can yield different possible outcome scenarios, which are illustrated in the forest plot (point estimate with 95% confidence interval) provided in Appendix 1. This plot will be used to aid the interpretation of results from the primary analysis.

7.2. Sensitivity analysis of primary outcome

Planned sensitivity analyses for investigating the robustness of the primary outcome data will be performed using the following approaches.

- Multiple imputation using chained equation
- Excluding the participants who did not receive the randomised treatment

- Including the participants who did not receive randomised treatment according to the treatment received (if a trial treatment)
- Including the variable found to be imbalance between the treatment group at baseline
- Including the variable that is found to have a significant interaction term
- Excluding participants with at least one protocol non-compliance
- Missing primary outcome data assumed to be resolved
- Missing primary outcome data assumed to be not resolved

The model will include a random effect for recruiting site, while all other minimisation variables will be adjusted for using fixed effects. If the model doesn't converge, or the random effect variance is minimum; the outcome will be analysed using the generalised linear model without considering the recruiting sites as a random effect. The between group effect will be reported using adjusted absolute risk differences, adjusted risk ratio and 95% confidence intervals. Point estimates and confidence intervals will be obtained using Stata's Margins command with standard errors computed using the delta method[3].

A forest plot will be used to present the analysis results obtained.

7.3. Secondary analysis of primary outcome

The secondary analysis of primary outcome (supplementary analysis) may be conducted to provide additional insights and to additional robustness to the primary analysis.

If ≥80% of the participants reported that more than 75% of their treatment was not taken, then we will estimate the CACE (Complier average casual effect) to access the treatment effect of participants who complied with the assigned treatment.

7.4. Subgroup analysis of primary outcome

The primary outcome of symptom resolution will be further investigated if appropriate, irrespective of the primary analysis results, to determine whether treatment effectiveness differs according to the following sub-groups as specified in the protocol:

a) Pathway (1 vs 2 & 3)
b) Previous episodes of BV (single/recurrent) at baseline
c) Presence of concomitant STI (yes/no) at baseline
d) BV Nugent score (7/8 vs 9/10) at baseline
e) Female sexual partner in past 12 months (Female alone & both male and female) at baseline

Data will be summarised by treatment group and subgroup.

Between-group treatment effects will be provided for each subgroup, but interpretation of any subgroup effects will be based on the treatment-subgroup interaction, 95% confidence interval and p value, estimated by fitting an appropriate interaction term in the regression models. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, these subgroup analyses will be regarded as exploratory.
If any of the above mentioned subgroups are found to have a statistically significant interaction with the treatment (p value less than 0.01), a sensitivity analysis will be conducted by including the interaction term in the model to assess their impact on the estimated treatment effects described in section 7.1.

7.5. Secondary outcomes

The following secondary outcomes will be summarised by treatment group as appropriate: continuous variables will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum and number of observations, as appropriate for normally distributed or skewed data. Categorical variables will be summarised in terms of frequency and percentages.

- Participant-reported resolution of BV symptoms 4-weeks post-treatment start date (with or without the need for additional treatment)
- Time to participant reported resolution of BV symptoms without the need for additional treatment.
- Microscopic resolution of BV on microscopy at week 4 (without the need for additional treatment) as assessed by Leeds Sexual Health Clinical Laboratory analysis of participant taken vaginal smears (in a subgroup of participants – pathways 2 and 3)
- Participant-reported approximate amount of prescribed trial BV treatment taken
- Participant-reported satisfaction with treatment
- Participant-reported recurrence of BV symptoms within 12 weeks of treatment start date, for those who resolved within 4 weeks without additional treatment
- Time to participant reported recurrence of BV symptoms

Binary outcomes

The following secondary outcomes will be analysed using mixed effects regression models for binary outcome, adjusting for minimisation variables. The model will include a random effect for recruiting site, while all other minimisation variables will be adjusted for using fixed effects. If the model doesn't converge, or the random effect variance is minimum; the outcome will be analysed using the generalised linear model for binary outcome without considering the recruiting sites as a random effect. The between group effect will be reported using an adjusted absolute risk difference and adjusted risk ratio along with corresponding 95% confidence intervals. Point estimates and confidence intervals will be obtained using Stata's Margins command with standard errors computed using the delta method[3].

- Participant-reported resolution of BV symptoms 4-weeks post-treatment start date (with or 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 – pathways 2 and 3)
- Participant-reported recurrence of BV symptoms within 12 weeks of treatment start date, for those who resolved within 4 weeks without additional treatment

Time to event outcomes

The following time to event outcomes

- Time to participant reported resolution of BV symptoms without the need for additional treatment
- Time to participant reported recurrence of BV symptoms

will be compared between groups using a shared-frailty Cox proportional hazards model, adjusting for minimisation variables. The model will be specified so that participants from the same recruitment site have a shared frailty, while all other minimisation variables will be included as fixed effects. If the model doesn't converge, the outcome will be analysed using a Cox proportional hazard model.

These outcomes will be censored at the end of follow-up, which for most participants will be 4th week (resolution of BV symptoms) / 12th week (recurrence of BV symptoms) following randomisation but could be earlier (e.g. due to withdrawal).

The between group effect will be reported using an adjusted hazard ratio along with a corresponding 95% confidence interval. Kaplan-Meier curves will be presented for each of the outcomes by trial arm.

Treatment groups will not be formally compared for participant reported recurrence of BV symptom outcome because the starting point is resolution, meaning the comparison would not be between randomised groups. Instead, we will provide an unadjusted 95% confidence interval for interpretation.

7.6. Other outcomes

The following data will be summarised by allocated treatment group:

- Treatment satisfaction for BV (Very satisfied, Satisfied, Neither satisfied nor dissatisfied, Dissatisfied , Very dissatisfied)
- Additional medication for BV: in first 4 weeks, 4-12 weeks, with numbers taking metronidazole tablets, metronidazole gel, lactic acid gel, clindamycin cream, other treatments.
- Treatments for vaginal candidiasis post randomisation (0-4 and 4-12 weeks): clotrimazole, fluconazole, itraconazole, other.
- Sexual contact, for each questionnaire: yes/no, new sexual partners, use of condoms.
- Vaginal douching post randomisation (yes/no) for each of 0-4 weeks, 4-12 weeks.

8. ANALYSIS OF SAFETY

8.1. Adverse events (side effects)

In order to provide secondary outcome data to compare tolerability of the two treatments, only specified side effects experienced during treatment with either usual care antibiotics or dequalinium will be reported. The following are regarded as expected for the purpose of this trial and will be reported on the week 4 follow-up questionnaire completed by the participant:

- Vaginal discharge
- Unpleasant vaginal smell
- Vaginal irritation (itching, pain and/or burning)
- Nausea
- Vomiting
- Unpleasant taste
- Abdominal pain
- Diarrhoea
- Presumptive candida infection

Presence and severity of each of these side effects will be summarised by treatment received overall and by pathway (Pathway 1 vs Pathway 2 and 3). No formal statistical analysis of these data is planned.

Serious Adverse Events (SAEs) are not anticipated in this low risk trial, but there is a reporting procedure specified in the protocol. Participant's attendance at an A&E department or unplanned hospital admission relating to their BV or BV treatment since the date of randomisation are prompted in the week 4 questionnaire, and they will (together with the 'other' category) be checked by the CI to determine whether the admission indicated a serious adverse event. Planned hospital admissions are not to be reported as SAEs. If there are any SAEs, these will be

summarised by the treatment the participant received. Hospital admissions (for BV or BV treatment) will be summarised.

Adverse events not included among the predefined side effects will be documented and reported separately.

8.2. Pregnancies

If the participant is pregnant or becomes pregnant during the trial, this will be reported on the pregnancy notification form alongside any additional information required by NCTU. The pregnancy outcome will be summarised by treatment groups.

9. OTHER ANALYSIS

Health economics cost data will be analysed by the health economist, with details in a separate health economics analysis plan.

10. EXPLORATORY ANALYSES

No formal statistical modelling will be performed; instead, the frequencies and corresponding percentages for the following outcome measures will be presented as described in the table.

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
The proportion of participants in each combination of participant-reported resolution of BV symptom (without need of additional treatment) and microscopic resolution of participant taken vaginal sample at week 4 (Pathway 2 &3) will be performed to explore the distribution of outcomes.	**Scale:** Participant answers 'Yes' or 'No' to questions "Are you symptom free today?", "Did you use any additional treatment (this includes medicines, probiotics and home remedies)?" and Nugent score results are reported on a scale from 0 to 10 **Source**: Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls. BV microscopy data (week 4) received from Leeds General infirmary microbiology laboratory.	Combination of resolution from questionnaire(s), telephone calls and text message. A negative result is 0-6 on the Nugent scale; a positive result is 7 to 10; 7 and 8 is categorised into one group and similarly 9 and 10 categorised into another group. If the outcome has been received from multiple sources (week 4 questionnaire, text message or phone call), the outcome obtained closest to 4 weeks will be used.	Categorical variable	Number and percentages will be presented for each combination of the two variables.	4 weeks
The proportion of participants in each combination of participant-reported	**Scale:** Participant answers 'Yes' or 'No' to question "Are you symptom free today?" and	Combination of resolution from questionnaire(s), telephone calls and text message.	Categorical variable	Number and percentages will be presented for each	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
resolution of BV symptom (with or without need of additional treatment) and microscopic resolution of participant taken vaginal sample at week 4 (Pathway 2 &3) will be performed to explore the distribution of outcomes.	Nugent score results are reported on a scale from 0 to 10 **Source**: Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls. BV microscopy data (week 4) received from Leeds Sexual Health Clinical Laboratory (pathway 2 & 3 only)	A negative result is 0-6 on the Nugent scale; a positive result is 7 to 10; 7 and 8 is categorised into one group and similarly 9 and 10 categorised into another group. If the outcome has been received from multiple sources (week 4 questionnaire, text message or phone call), the outcome obtained closest to 4 weeks will be used.		combination of the two variables.	
Microscopic resolution of participant taken vaginal samples (Pathway 2 & 3) assessed using the Nugent score method at baseline and at 4th week will be presented among the treatment groups to explore changes in the distribution of outcomes over time.	**Scale:** Nugent score results are reported on a scale from 0 to 10 **Source:** BV microscopy data (baseline and week 4) received from Leeds General infirmary microbiology laboratory.	A negative result is score 0-6 on the Nugent scale; a positive result is 7 - 10; score 7 and 8 is categorised into one group and similarly score 9 and 10 categorised into another group.	Categorical variable	Number and percentages will be presented for each combination of the two variables between the treatment groups.	4 weeks
Participant-reported resolution of BV symptoms at 4 weeks by	**Scale:** Participant answers 'Yes' or 'No' to question	Combination of resolution from questionnaire(s), telephone calls and text message.	Categorical variable	Number and percentages will be presented between	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
additional treatment taken along with the randomised treatment, the additional treatment taken is classified as treatment which is likely to affect the vaginal microbiome or not likely to affect the vaginal microbiome.	"Are you symptom free today?" Additional treatments reported by participants were subsequently categorised as follows "treatment which is likely to affect the vaginal microbiome" or "treatment which is not likely to affect the vaginal microbiome" Appendix 2. **Source**: Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls.	If the outcome has been received from multiple sources (week 4 questionnaire, text message or phone call), the outcome obtained closest to 4 weeks will be used.		the treatment groups. Adjusted risk difference along with 95%CI will also be provided.	
Is the resolution of symptom at 4th week is different in women who have no sex throughout the 4 week follow-up compared with women who continue to have sex with a regular male partner?	**Scale:** Participant answers 'Yes' or 'No' to question "Are you symptom free today?" Participant reported to the following question during the baseline visit a) Had sex in the past 3 months?	Combination of resolution from questionnaire(s), telephone calls and text message. If the outcome has been received from multiple sources (week 4 questionnaire, text message or phone call), the outcome obtained closest to 4 weeks will be used. **No sex:** Any responses to sexual health-related questions in the baseline	Binary	Number and percentages will be presented, along with unadjusted CI.	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
	b) Biological sex of sexual partners over the last 12 months c) Contraception currently used by participant Participant response to the following question during the 4th week follow-up a) Have you had vaginal sex since joining the study? b) Was this with someone new? c) Did you use condoms? **Source**: Baseline questionnaire, Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls.	questionnaire and marked "No" to the question "Have you had vaginal sex since joining the study" in the week 4 questionnaire. **Regular male partner:** Marked "Yes" to the question "Had sex in the past 3 months" and "Male" or "Both male or female" to the question "biological sex of sexual partner over the last 12 months and "Hormonal" or "Intrauterine system or device" or "None of the above" to the question "Contraception currently used by patient" in the baseline questionnaire. At the week 4 questionnaire participant marked as "Yes" to the question "Have you had vaginal sex since joining the study" and "No" to "was this with someone new?" and marked "No" or "sometimes" to the "Did you use condoms?".			
Is the Nugent score of the participant taken vaginal sample at 4th week (pathway 2 & 3 only) is different in women who	**Scale:** Nugent score results are reported on a scale from 0 to 10	A negative result is score 0-6 on the Nugent scale; a positive result is 7 - 10; score 7 and 8 is categorised into one group and similarly score 9 and 10 categorised into another group.	Categorical	Number and percentages will be presented, along with unadjusted CI.	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
have no sex throughout the 4 week follow-up compared with women who continue to have sex with a regular male partner?	Participant reported to the following question during the baseline visit d) Had sex in the past 3 months? e) Biological sex of sexual partners over the last 12 months f) Contraception currently used by participant Participant response to the following question during the 4th week follow-up d) Have you had vaginal sex since joining the study? e) Was this with someone new? f) Did you use condoms? **Source**: Baseline questionnaire, Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls. BV microscopy data (week 4)	**No sex:** Any responses to sexual health-related questions in the baseline questionnaire and marked "No" to the question "Have you had vaginal sex since joining the study" at the week 4 questionnaire. **Regular male partner:** Marked "Yes" to the question "Had sex in the past 3 months" and "Male" or "Both male or female" to the question "biological sex of sexual partner over the last 12 months and "Hormonal" or "Intrauterine system or device" or "None of the above" to the question "Contraception currently used by patient" in the baseline questionnaire. At the week 4 questionnaire participant marked as "Yes" to the question "Have you had vaginal sex since joining the study" and "No" to "was this with someone new?" and marked "No" or "sometimes" to the "Did you use condoms?"			

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
	received from Leeds General infirmary microbiology laboratory (pathways 2 and 3 only).				
Is the recurrence at Week 12 (no symptoms at Week 4 but symptoms at Week 12) different in women who have no sex throughout the trial compared with women who continue to have sex with a regular male partner?	**Scale:** Participant answers 'Yes'/ 'No' / 'n/a' to the question "Are you symptom free today" at 4th week and "Have you experienced any new episodes of BV since your symptoms cleared?" as 'yes' / 'No' / 'n/a' at 12th week. Participant reported to the following question during the baseline visit g) Had sex in the past 3 months? h) Biological sex of sexual partners over the last 12 months i) Contraception currently used by participant Participant response to the following question during the 4th week and 12th week follow-up	The Week 12 questionnaire collects whether participants have experienced a new episode of BV. For analysis, only participants who have recorded resolution of BV by 4 weeks can be judged to have had a recurrence. **No Sex:** Any responses to sexual health-related questions in the baseline questionnaire and marked "No" to the question "Have you had vaginal sex since joining the study" at the week 4 and week 12 questionnaire. **Regular male partner:** Marked "Yes" to the question "Had sex in the past 3 months" and "Male" or "Both male or female" to the question "biological sex of sexual partner over the last 12 months and "Hormonal" or "Intrauterine system or device" or "None of the above" to the question "Contraception currently used by patient" in the baseline questionnaire. At the week 4 and week 12	Binary	Number and percentages will be presented, and if appropriate unadjusted CI will be provided.	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
	g) Have you had vaginal sex since joining the study? h) Was this with someone new? i) Did you use condoms? **Source**: Baseline questionnaire, Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls. Participant completed questionnaire at week 12.	questionnaire participant marked as "Yes" to the question "Have you had vaginal sex since joining the study" and "No" to "was this with someone new?" and marked "No" or "sometimes" to the "Did you use condoms?"			
Is the resolution of symptom at 4th week different in women who have no sex throughout the 4 week follow-up compared with women who have sex with a new male partner?	**Scale:** Participant answers 'Yes' or 'No' to question "Are you symptom free today?" Participant reported to the following question during the baseline visit a) Had sex in the past 3 months? b) Biological sex of sexual partners over the last 12 months	Combination of resolution from questionnaire(s), telephone calls and text message. If the outcome has been received from multiple sources (week 4 questionnaire, text message or phone call), the outcome obtained closest to 4 weeks will be used. **No Sex:** Any responses to sexual health-related questions in the baseline questionnaire and marked "No" to the	Binary	Number and percentages will be presented, along with unadjusted CI.	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
	c) Contraception currently used by participant Participant response to the following question during the 4th week follow-up a) Have you had vaginal sex since joining the study? b) Was this with someone new? c) Did you use condoms? **Source**: Baseline questionnaire, Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls.	question "Have you had vaginal sex since joining the study" at the week 4 questionnaire. **New male partner:** Any responses to sexual health-related questions in the baseline questionnaire. At the week 4 questionnaire participant marked as "Yes" to the question "Have you had vaginal sex since joining the study" and "Yes" to "was this with someone new?" and marked "No" or "sometimes" to the "Did you use condoms?".			
Is the Nugent score of the participant taken vaginal sample at 4th week (pathway 2 & 3) is different in women who have no sex throughout the 4 week follow-up compared with women	**Scale:** Nugent score results are reported on a scale from 0 to 10 Participant reported to the following question during the baseline visit j) Had sex in the past 3 months?	A negative result is score 0-6 on the Nugent scale; a positive result is 7 - 10; score 7 and 8 is categorised into one group and similarly score 9 and 10 categorised into another group. **No sex:** Any responses to sexual health-related questions in the baseline questionnaire and marked "No" to the	Categorical	Number and percentages will be presented, along with unadjusted CI.	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
who have sex with a new male partner?	k) Biological sex of sexual partners over the last 12 months l) Contraception currently used by participant Participant response to the following question during the 4th week follow-up j) Have you had vaginal sex since joining the study? k) Was this with someone new? l) Did you use condoms? **Source**: Baseline questionnaire, Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone calls. BV microscopy data (week 4) received from Leeds General infirmary microbiology laboratory (pathways 2 and 3 only).	question "Have you had vaginal sex since joining the study" at the week 4 questionnaire. **New male partner:** Any responses to sexual health-related questions in the baseline questionnaire. At the week 4 questionnaire participant marked as "Yes" to the question "Have you had vaginal sex since joining the study" and "Yes" to "was this with someone new?" and marked "No" or "sometimes" to the "Did you use condoms?".			

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
Is the recurrence at Week 12 (no symptoms at Week 4 but symptoms at Week 12) different in women who have no sex throughout the trial compared with women who have sex with a new male partner?	**Scale:** Participant answers 'Yes'/ 'No' / 'n/a' to the question "Are you symptom free today" at 4th week and "Have you experienced any new episodes of BV since your symptoms cleared?" as 'yes' / 'No' / 'n/a' at 12th week. Participant reported to the following question during the baseline visit m) Had sex in the past 3 months? n) Biological sex of sexual partners over the last 12 months o) Contraception currently used by participant Participant response to the following question during the 4th week and 12th week follow-up m) Have you had vaginal sex since joining the study? n) Was this with someone new?	The Week 12 questionnaire collects whether participants have experienced a new episode of BV. For analysis, only participants who have recorded resolution of BV by 4 weeks can be judged to have had a recurrence. **No Sex:** Any responses to sexual health-related questions in the baseline questionnaire and marked "No" to the question "Have you had vaginal sex since joining the study" at the week 4 and week 12 questionnaire. **New male partner:** Any responses to sexual health-related questions in the baseline questionnaire. At the week 4 ad week 12 questionnaire participant marked as "Yes" to the question "Have you had vaginal sex since joining the study" and "Yes" to "was this with someone new?" and marked "No" or "sometimes" to the "Did you use condoms?".	Binary	Number and percentages will be presented, and if appropriate unadjusted CI will be provided.	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
	o) Did you use condoms? **Source**: Baseline questionnaire, Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone call, Participant completed questionnaire at week 12, week 12 text message responses and week 12 telephone calls.				
Symptom clearance at 4 weeks by each usual care antibiotic (chosen by the clinician in discussion with the participant pre-randomisation).	Scale: Participant answers 'Yes' or 'No' to question "Are you symptom free today?" Treatment received by the participant (chosen by the clinician in discussion with the participant pre-randomisation) **Source**: Participant completed questionnaire at week 4, week 4 text	Combination of resolution from questionnaire(s), telephone calls and text message. If the outcome has been received from multiple sources (week 4 questionnaire, text message or phone call), the outcome obtained closest to 4 weeks will be used.	categorical	Number and percentage will be presented in each category among symptom resolution.	4 weeks

Outcome Measures	Scale, description and source	Derivation of scores	Type	Method of aggregation	Analysis time point
	message responses and week 4 telephone calls. Source: Treatment allocation form Participant completed questionnaire at week 4, week 4 text message responses and week 4 telephone call.				

11. FINAL REPORT TABLES AND FIGURES

1737DEVA Dummy Tables final V2.0 19June2025

12. PUBLICATIONS

Haydock R, Hepburn T, Ross J, Daniels J, Brittain C, Jackson L, Ozolins M, Wilson J. The DEVA trial: protocol for a randomised controlled trial of dequalinium chloride versus usual care antibiotics for the treatment of bacterial vaginosis. Trials. 2022 Dec 21;23(1):1040. doi: 10.1186/s13063-022-06954-x. PMID: 36544202; PMCID: PMC9768774.

13. REFERENCE

1. Vodstrcil LA, Plummer EL, Fairley CK, Hocking JS, Law MG, Petoumenos K, Bateson D, Murray GL, Donovan B, Chow EPF, Chen MY, Kaldor J, Bradshaw CS; StepUp Team. *Male-Partner Treatment to Prevent Recurrence of Bacterial Vaginosis*. N Engl J Med. 2025 Mar 6;392(10):947-957. doi: 10.1056/NEJMoa2405404. PMID: 40043236.

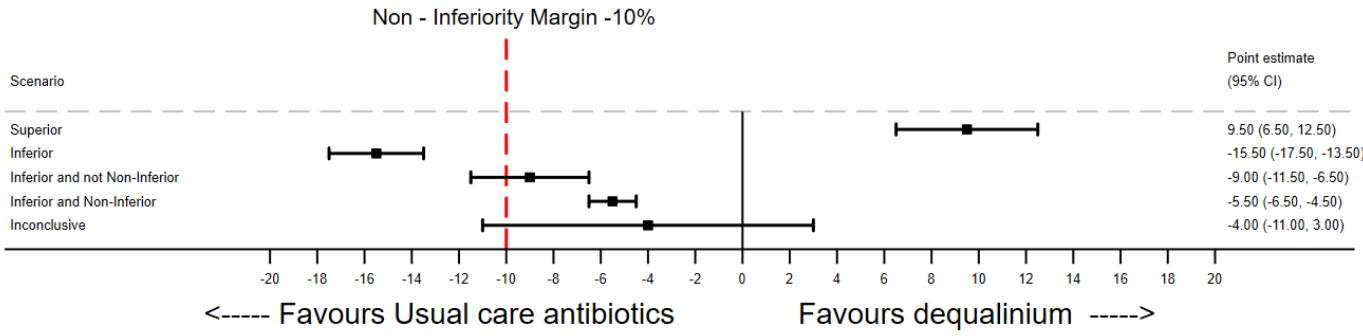
2. White IR, Royston P, Wood AM. *Multiple imputation using chained equations: Issues and guidance for practice*. Stat Med. 2011 Feb 20;30(4):377-99. doi: 10.1002/sim.4067. Epub 2010 Nov 30. PMID: 21225900.

3. Norton, E.C., M.M. Miller, and L.C. Kleinman, *Computing adjusted risk ratios and risk differences in Stata.* Stata Journal, 2013. **13**(3): p. 492-509.

14. APPENDICES

Appendix 1: Forest plot

Figure 1: Possible outcome of non-inferiority trial



Appendix 2: Additional Medication categorisation

To further refine the explanatory analysis on additional medication taken along with the randomised treatment, additional medications will be categorized and analysed separately based on their usage patterns listed below.

Medication listed below will be considered to classify the participants falls into the category:

"Treatment which is likely to affect the vaginal microbiome"

azithromycin, Balance Activ gel, Balance Activ pessaries, boric acid, broad-spectrum antibiotic, Canesbalance gel, clindamycin capsules, clindamycin cream, dequalinium chloride (trade name Fluomizin), doxycycline, Gina - the internal hormone cream for menopausal women, lactic acid gel or pessary, Relactagel, tinidazole, trimethoprim, Vagifem - 10 micrograms vaginal tablets, Zidoval (vaginal gel)

"Treatment which is not likely to affect the vaginal microbiome"

aqueous cream, Canesten, condoms, fasting, fluconazole tablets, garlic capsules, home remedies for itchiness, Lactobacillus supplement, no sugar, nystatin, over the counter shower gel, probiotics, soothing cream, tea tree oil, Vulvovagi Spray (produced by Erbagil) containing ozonides, Vagisil, yogurt, yeast infection treatment, Yoni steams/Yoni pill