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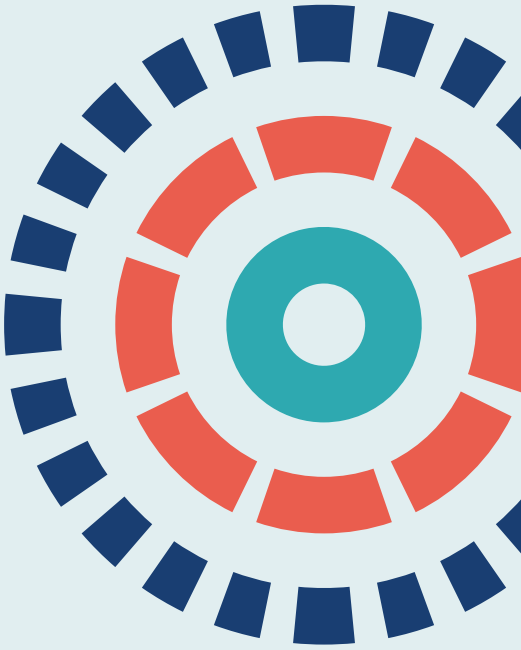

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Lactic acid gel versus metronidazole for recurrent bacterial vaginosis in women aged 16 years and over: the VITA RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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This report

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Abstract

Lactic acid gel versus metronidazole for recurrent bacterial vaginosis in women aged 16 years and over: the VITA RCT

Lindsay Armstrong-Buisseret,[1] Clare Brittain,[1] Joe Kai,[2] Miruna David,[3] Jocelyn Anstey Watkins,[4] Mara Ozolins,[1] Louise Jackson,[5] Zainab Abdali,[5] Trish Hepburn,[1] Frances Griffiths,[4,6] Alan Montgomery,[1] Jane Daniels,[1] Alice Manley,[7] Gillian Dean[8] and Jonathan DC Ross[7*]

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Background: Bacterial vaginosis is a common and distressing condition associated with serious comorbidities. Antibiotic treatment is usually clinically effective in the short term, but recurrence is common and side effects can occur.

Objectives: The objective is to assess whether or not intravaginal lactic acid gel is clinically effective and cost-effective for treating recurrent bacterial vaginosis compared with oral metronidazole (Flagyl, Sanofi).

Design: This was an open-label, multicentre, parallel-arm, randomised (1 : 1) controlled trial.

Setting: This took place in one general practice and 19 sexual health centres in the UK.

Participants: Women aged ≥ 16 years with bacterial vaginosis symptoms and one or more episode(s) within the past 2 years took part.

Interventions: The interventions were 5 ml of intravaginal lactic acid gel taken once daily for 7 days (intervention) or 400-mg oral metronidazole tablets taken twice daily for 7 days (control).

Main outcome measures: The primary outcome was the resolution of bacterial vaginosis symptoms 14 days after randomisation. The secondary outcomes were time to first recurrence of symptoms; number of recurrences and treatment courses over 6 months; microbiological resolution on microscopy of vaginal smears at week 2; time to resolution of symptoms; tolerability, adherence and acceptability of the treatment; prevalence of concurrent sexually transmitted infections; quality of life; and cost-effectiveness.

Results: Recruitment stopped prior to reaching the target of 1900 participants on recommendation from the Data Monitoring Committee and Trial Steering Committee after a planned review of the results indicated that the research question had been answered. Overall, 518 participants were randomised and primary outcome data were available for 409 participants (79%; 204 in the metronidazole arm, 205 in the lactic acid gel arm). Participant-reported symptom resolution at week 2 was higher with metronidazole (143/204; 70%) than with lactic acid gel (97/205; 47%) (adjusted risk difference −23.2%, 95% confidence interval −32.3% to −14.0%). Recurrence in 6 months in a subset of participants who had initial resolution and were available for follow-up was similar across arms (metronidazole arm: 51/72, 71%; lactic acid gel arm: 32/46, 70%). A higher incidence of some side effects was reported with metronidazole than with lactic acid gel (nausea 32% vs. 8%; taste changes 18% vs. 1%; diarrhoea 20% vs. 6%, respectively). At week 2, the average cost per participant with resolved symptoms was £86.94 (metronidazole), compared with £147.00 (lactic acid gel). Some participants preferred using lactic acid gel even if they perceived it to be less effective than metronidazole.

Limitations: Loss to follow-up for collection of the primary outcome data was 21% and was similar in both arms. There is a risk of bias owing to missing outcome data at 3 and 6 months post treatment.

Conclusions: A higher initial response was seen with metronidazole than with lactic acid gel, but subsequent treatment failure was common with both. Lactic acid gel was less cost-effective than metronidazole. In general, women disliked taking repeated courses of metronidazole and preferred lactic acid gel, even when they were aware that it was less likely to provide symptom resolution. In the absence of effective curative therapy, further evaluation of non-antibiotic treatments to control the symptoms of recurrent bacterial vaginosis is required to improve quality of life for these patients. Further microbiological analysis of vaginal samples would be useful to identify additional factors affecting response to treatment.

Trial registration: Current Controlled Trials ISRCTN14161293.

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List of abbreviations

AMR	antimicrobial resistance
BV	bacterial vaginosis
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
GBP	Great British pound
GP	general practitioner
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IMP	investigational medicinal product
ISRCTN	International Standard Randomised Controlled Trial Number
NAAT	nucleic acid amplification test
NCTU	Nottingham Clinical Trials Unit
PI	principal investigator
PID	pelvic inflammatory disease
PPI	patient and public involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-6D	Short Form questionnaire-6 Dimensions
SF-12	Short Form questionnaire-12 items
SmPC	summary of product characteristics
STI	sexually transmitted infection
TSC	Trial Steering Committee
VITA	metronidazole Versus lactic acId for Treating bacterial vAginosis

Plain English summary

Bacterial vaginosis is a common cause of unpleasant vaginal discharge that is caused by an imbalance of vaginal bacteria. The usual treatment is an antibiotic called metronidazole (Flagyl, Sanofi). Although this generally works in the short term, symptoms often return, leading to the repeated use of antibiotics; this can cause side effects as well as increase the risk of antibiotic resistance. Lactic acid gel might be an alternative treatment, but previous studies have not confirmed how clinically effective it is. We wanted to find out if lactic acid gel was better than metronidazole for treating recurrent bacterial vaginosis.

Women with typical symptoms and a history of bacterial vaginosis who were taking part in our trial were selected randomly to receive either 7 days of treatment with lactic acid gel inserted into the vagina once per day or 7 days of treatment with metronidazole tablets taken by mouth twice per day. Overall, 518 women took part in the trial. We originally intended to recruit 1900 women but the trial was stopped early because a planned review of the data showed which treatment was better.

Most of the women took all of their treatment and 70% reported that symptoms had cleared 2 weeks after taking metronidazole, compared with 47% after using lactic acid gel. Less than half of the women stayed in the trial for the full 6 months; however, the data suggested that the majority of those whose symptoms cleared within 2 weeks with either treatment had symptoms return over the next 6 months. More side effects were reported for metronidazole than for lactic acid gel: nausea 32% compared with 8%, taste changes 18% compared with 1%, and diarrhoea 20% compared with 6%, respectively.

Despite thinking that it was less effective, women preferred lactic acid gel because it avoided the need to take an antibiotic and had a soothing effect. The cost-effectiveness analysis found that lactic acid gel was less effective than metronidazole in clearing symptoms by 2 weeks and that the average costs for women whose symptoms resolved were higher (£86.94 with metronidazole vs. £147.00 with lactic acid gel).

Scientific summary

Background

Bacterial vaginosis affects 30–50% of women at some time in their lives and is a distressing condition that is associated with potentially serious comorbidities. Current antibiotic treatments, such as metronidazole (Flagyl, Sanofi), are usually effective, but they can result in side effects, and recurrence is common. The metronidazole Versus lactic acId for Treating bacterial vAginosis (VITA) trial aimed to investigate whether or not lactic acid gel is clinically effective and cost-effective for the treatment of recurrent bacterial vaginosis compared with metronidazole.

Objectives

The primary objective was to determine whether or not intravaginal lactic acid gel is better than oral metronidazole for symptomatic resolution of recurrent bacterial vaginosis.

The secondary objectives were to:

- compare the time to first recurrence of bacterial vaginosis symptoms
- compare the frequency of bacterial vaginosis episodes over 6 months
- compare the frequency of bacterial vaginosis treatments required over 6 months
- compare microbiological resolution of bacterial vaginosis on microscopy 2 weeks after presentation
- compare the time to resolution of bacterial vaginosis symptoms
- compare the tolerability profiles of lactic acid gel and metronidazole
- compare adherence to lactic acid gel and metronidazole
- compare acceptability of the use of lactic acid gel and metronidazole
- determine the prevalence of sexually transmitted infections at baseline and week 2
- compare quality of life (measured using the Short Form-12 items health survey)
- compare the cost-effectiveness of using lactic acid gel with that of using metronidazole.

Methods

Trial design

This was an open-label, multicentre, parallel-arm, randomised (1 : 1) controlled trial.

Recruitment and follow-up

One general practice and 19 sexual health outpatient clinics in the UK recruited participants. Treatment was for 7 days, with follow-up taking place 2 weeks, 3 months and 6 months after randomisation.

Eligibility criteria

Inclusion criteria were women aged $\geq$ 16 years with a clinical diagnosis of bacterial vaginosis based on patient-reported symptoms and a history of one or more bacterial vaginosis episode(s) within the past 2 years that had resolved with treatment. Participants had to be willing to use the study treatment, take their own vaginal samples, avoid vaginal douching during the treatment, provide their contact details for follow-up, be able to complete a web-based questionnaire, avoid sexual intercourse or use effective contraception for the 7-day duration of the study treatment, and provide written informed consent. Exclusion criteria were contraindications or allergy to lactic acid gel or metronidazole tablets; pregnancy

or breastfeeding; currently trying to conceive; use of oral antibiotics (other than the study treatment) or antifungal agents concurrently within the last 2 weeks or planned use within the next 2 weeks; use of topical vaginal antibiotics, antifungals or acidifying products (other than the study treatment) concurrently within the last 2 weeks or planned use within the next 2 weeks; previous participation in the study; and concurrent participation in another trial involving an investigational medicinal product.

Study treatment

The two study treatment arms were:

- lactic acid gel (intervention) – 5 ml of gel inserted into the vagina before bedtime each day for 7 days
- metronidazole tablets (control) – 400 mg taken orally twice per day, approximately 12 hours apart, for 7 days.

Outcome measures

The primary outcome measure was participant-reported resolution of bacterial vaginosis symptoms at week 2.

The secondary outcomes were:

- time to first recurrence of bacterial vaginosis symptoms, as reported by participants
- number of participant-reported bacterial vaginosis episodes over 6 months
- number of participant-reported bacterial vaginosis treatment courses over 6 months
- microbiological resolution of bacterial vaginosis on microscopy of vaginal smears taken at week 2 and analysed at a central laboratory
- time to participant-reported resolution of bacterial vaginosis symptoms
- tolerability of lactic acid gel and metronidazole assessed by participant reporting of side effects (including nausea, vomiting, taste disturbance, vaginal irritation, diarrhoea and abdominal pain) and by participant interviews
- participant-reported adherence to treatment
- acceptability of treatments via qualitative assessment in a subgroup of participants
- prevalence of concurrent sexually transmitted infections (gonorrhoea, chlamydia and trichomoniasis) from vaginal swabs taken at baseline and at week 2, and analysed at a central laboratory
- quality of life assessed by Short Form-12 items health survey at baseline, 2 weeks, 3 months and 6 months
- comparative cost-effectiveness of lactic acid gel and metronidazole.

Participant-reported outcome measures were collected via web-based questionnaires, with several reminders sent to encourage completion. During the later stages of the trial, a follow-up telephone call was attempted to collect key outcomes from the week 2 and 6-month questionnaires when these had not been completed.

Sample size

Assuming that 80% of participants receiving oral metronidazole would achieve resolution of symptoms, 1710 participants (855 in each treatment arm) were required for analysis to detect a 6% increase in response rate to 86% in those receiving lactic acid gel (risk ratio 1.08) at the 5% significance level (two sided) with 90% power. To allow for a loss to follow-up of 10% (i.e. non-collection of the primary outcome data), the target sample size was 1900 participants.

Randomisation and blinding

Participants were randomised 1 : 1 to lactic acid gel (intervention) or metronidazole (control). A minimisation algorithm was used with the following variables: site, type of site (general practice or sexual health clinic),

number of episodes of bacterial vaginosis in the previous 12 months (0, 1–3 or > 3) and whether or not they had had a female sexual partner in the previous 12 months (yes/no). Randomisation was via a secure web server created and maintained by the Nottingham Clinical Trials Unit.

Given that this was an open-label trial, there was no blinding to treatment allocation for participants, site research teams or the trial team. However, the central laboratory staff performing bacterial vaginosis microscopy and sexually transmitted infection testing were blinded to treatment allocation. In addition, the trial statistician remained blinded to treatment allocation until after database lock. Analyses requiring knowledge of treatment codes were conducted by an independent statistician. Data presented to the Trial Steering Committee were not split by treatment allocation.

Statistical methods

The primary approach to between-group comparative analyses was by modified intention to treat, that is analysis of all participants who were randomised without imputation of missing outcome data according to the treatment arm that they were allocated to irrespective of adherence. Sensitivity analyses were conducted to investigate the impact of missing data and adherence to treatment.

The primary outcome measure was evaluated using a generalised estimating equation for the binary outcome, which included the minimisation factors with site as a panel variable. The comparison of lactic acid gel with metronidazole was presented using the risk difference in the proportion of participants who reported symptom resolution at week 2, along with the 95% confidence interval. Planned subgroup analyses included determining whether or not treatment effectiveness differed according to the following subgroups: (1) presence of concomitant sexually transmitted infection, (2) confirmation of bacterial vaginosis by positive microscopy and (3) type of centre that the participant presented at. The analyses according to presence of concomitant sexually transmitted infection could not be conducted owing to the small number of participants with an infection; however, summary statistics were provided. The analyses by type of centre were also not conducted given that only one general practice and no gynaecology clinics took part. In addition, the following subgroup analyses for symptom resolution at week 2 were included: the number of episodes of bacterial vaginosis in the 12 months before baseline and the total time with bacterial vaginosis in the 12 months before baseline. Between-group treatment effects were provided for each subgroup, but interpretation of any effects was based on the treatment by subgroup interaction and 95% confidence intervals, estimated by fitting an appropriate interaction term in the regression models. Given that the trial was powered to detect overall differences between the groups rather than interactions of this kind, these subgroup analyses were regarded as exploratory.

Secondary outcomes were analysed using appropriate regression models dependent on data type (e.g. binary, continuous, count and survival), and included factors used in the minimisation and baseline value of the outcome when measured. The analyses of secondary outcomes were considered supportive to the primary outcomes, and estimates and *p*-values, when presented, were interpreted in this light.

Health economics

The health economic analysis explored the cost-effectiveness of the study treatments from an NHS perspective. Resource use data collected via participant questionnaires included information on treatment use, general practice visits, clinic visits and other health-care resource use to estimate the costs associated with administrating both treatments. Data from the Short Form questionnaire-12 items were converted to a preference-based Short Form questionnaire-6 Dimensions score to allow quality-adjusted life-years to be calculated. An overall cost per patient successfully treated at 2 weeks was calculated, along with a cost per quality-adjusted life-year at 6 months. The difference in cost and health outcomes was compared between the two treatments.

Qualitative data analysis

A subgroup of participants was consecutively sampled and interviewed to further explore the adherence, tolerability and acceptability of treatment. The target sample size was approximately 30 participants (15 from each treatment arm). Data were coded thematically, with the codes based on interview questions and emergent themes. Coded data were compared between participants in the same arm of the trial and between treatment arms, and synthesised using a framework approach.

Results

In May 2019, the Data Monitoring Committee reviewed unblinded trial data at a planned meeting. Its recommendation was that recruitment should be stopped because its opinion was that the research question had been answered with the number of participants recruited at that time. There were no concerns raised around any safety issues. To ensure that this was a robust decision, further analyses were conducted by an independent statistician and reviewed by the Data Monitoring Committee in June 2019. The recommendation of the Data Monitoring Committee, supported by the Trial Steering Committee, remained the same and recruitment into the trial was terminated on 28 June 2019.

Between October 2017 and June 2019, 518 participants were randomised and primary outcome data were available for 409 participants (79%; 204 in the metronidazole arm, 205 in the lactic acid gel arm). Participant-reported resolution of bacterial vaginosis symptoms at week 2 was higher in the metronidazole arm (143/204; 70%) than in the lactic acid gel arm (97/205; 47%) (adjusted risk difference −23.2%, 95% confidence interval −32.3% to −14.0%). Sensitivity analyses were supportive of this treatment difference.

Among the participants who had symptom resolution by week 2, data on whether or not they experienced a recurrence over 6 months were available for only 72 out of 143 (50%) participants in the metronidazole arm and 46 out of 97 (47%) participants in the lactic acid gel arm. These data indicated that 51 out of 72 (71%) participants in the metronidazole arm and 32 out of 46 (70%) participants in the lactic acid gel arm experienced a recurrence within 6 months, with median times to first recurrence of 92 days and 124 days, respectively. The number of bacterial vaginosis episodes within 6 months in participants for whom complete episode data were available (metronidazole arm: 48/143, 34%; lactic acid gel arm: 29/97, 30%) was similar between arms (both had a median of one episode and maximums of six episodes in the metronidazole arm and 10 episodes in the lactic acid gel arm) (adjusted incidence rate ratio 0.97, 95% confidence interval 0.56 to 1.69). For those resolving by week 2, the median number of bacterial vaginosis treatment courses received between week 2 and 6 months was one in the metronidazole arm and one in the lactic acid gel arm (adjusted incidence rate 1.03, 95% confidence interval 0.53 to 2.01). However, this was based on participants with complete data (only 59 in the metronidazole arm and 35 in the lactic acid gel arm).

Microbiological resolution of bacterial vaginosis at week 2 in those in whom the condition was confirmed at baseline (based on microscopy of a vaginal smear) was higher in the metronidazole arm (59/77, 77%) than in the lactic acid gel arm (31/73, 42%) (adjusted risk difference −34.3%, 95% confidence interval −49.1% to −19.5%). The median time to symptom resolution was 14 days in both arms (adjusted difference 0%, 95% confidence interval −1.9% to 1.9%). A higher incidence of some side effects was reported in the metronidazole arm than in the lactic acid gel arm (nausea 32% vs. 8%, taste changes 18% vs. 1%, diarrhoea 20% vs. 6%, respectively). Adherence to treatment was good across both arms, with 316 out of 318 (99%) participants who returned a week 2 questionnaire reporting that they took at least some of their study treatment and 294 (92%) taking at least 85% of the course (metronidazole arm: 146/157, 93%; lactic acid gel arm: 148/161, 92%). Prevalence of sexually transmitted infections at both baseline and week 2 was very low.

The cost-effectiveness analysis found that lactic acid gel was less clinically effective than metronidazole in terms of participants with resolved symptoms at week 2 and that the average costs were higher (£86.94 in the metronidazole arm vs. £147.00 in the lactic acid gel arm). However, the sensitivity analysis indicated uncertainty around whether or not lactic acid gel was more or less costly than metronidazole. The cost–utility analysis suggested that lactic acid gel resulted in 0.003 fewer quality-adjusted life-years (95% confidence interval −0.013 to 0.009 quality-adjusted life-years) and was more costly by £58.60 (95% confidence interval −£55.05 to £185.32) than metronidazole at 6 months; however, the sensitivity analysis demonstrated that there was considerable uncertainty around these results.

In qualitative interviews, participants in general preferred lactic acid gel as a treatment, even if they perceived it to be less effective than metronidazole.

Conclusions

Participants with recurrent bacterial vaginosis had a higher response to treatment with metronidazole than with lactic acid gel at 14 days, but subsequent recurrence of symptoms over 6 months was common in both arms. Metronidazole is more likely to be cost-effective with lower associated resource use and higher efficacy than lactic acid gel, but there is uncertainty surrounding the resource use estimates. Participants interviewed in a qualitative substudy disliked taking a repeated course of antibiotics for bacterial vaginosis and in general preferred lactic acid gel, even if its short-term efficacy was lower than metronidazole.

Implications for health-care practice

The evidence suggests that intravaginal lactic acid may be an appropriate treatment option for some women with bacterial vaginosis. A discussion on its use should include information about lower short-term efficacy than metronidazole but fewer side effects, similar recurrence rates and its potential to avoid the use of antibiotic therapy.

Recommendations for research

1. In the absence of effective curative therapy, further investigation of non-antibiotic continuous or intermittent treatment regimens to control the symptoms of recurrent bacterial vaginosis is required to improve quality of life in this patient group.
2. Further analysis of vaginal samples would be useful to identify whether or not microbiological factors affect the short-term and long-term response to metronidazole or lactic acid gel in a subgroup of women with bacterial vaginosis.

Trial registration

This trial is registered as ISRCTN14161293.

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Chapter 1 Introduction

Background

Bacterial vaginosis (BV) is a common condition that predisposes women to potentially serious comorbidities, such as human immunodeficiency virus (HIV) infections, other sexually transmitted infections (STIs), pelvic inflammatory disease (PID), and preterm birth, miscarriage and other adverse pregnancy outcomes.[1–5] Typical symptoms include vaginal discharge accompanied by an unpleasant fishy odour that frequently occurs in association with menstruation and can have a significant impact on the woman's quality of life.[5]

In women of reproductive age, the pH of the vagina is normally moderately acidic, in part because of the presence of lactobacilli species that produce lactic acid, which helps to prevent the overgrowth of other vaginal bacteria. An alteration in the usual vaginal flora occurs in BV, with a loss of lactobacilli and an associated increase in pH to more alkaline levels, which allows the proliferation of other primarily anaerobic bacteria, including *Gardnerella*.[5,6] The exact pathophysiological mechanism responsible for BV remains to be elucidated, although the sexual transmission of bacteria and the development of a biofilm containing specific bacterial species may be contributory factors to the dysbiosis observed in the vaginal flora.[5,7,8]

Guidelines recommend the use of antibiotics as the first-line treatment for BV, with oral metronidazole (Flagyl, Sanofi) having been a standard choice for over 25 years and producing cure rates of up to 85% at 4 weeks post treatment.[9–11] However, antibiotic side effects can affect adherence to treatment and, although antibiotics may be initially effective, BV symptoms frequently recur within a few months.[10,12–14] This results in repeated antibiotic use and the potential for antibiotic resistance to develop.

Public Health England data from 2018 indicate that over 86,000 women had a diagnosis of BV when presenting at a sexual health clinic in England[15] and symptoms are likely to recur in about one-third of women in the 3 months following initial treatment.[10,12–14] New treatment options are, therefore, required to reduce antibiotic use, provide better efficacy and lower recurrence rates.

Rationale for the VITA trial

Given that intravaginal lactic acid gel (pH 4.5) replicates the production of lactic acid by lactobacilli in the normal vagina, the use of lactic acid gel as treatment for BV could reduce antibiotic exposure in the population, as recommended in the *Tackling Antimicrobial Resistance 2019–2024: The UK's Five-year National Action Plan*[16] and *A European One Health Action Plan Against Antimicrobial Resistance (AMR)*.[17] The avoidance of systemic antibiotics would help maintain the balance of the gut bacteria (microbiome) in individual participants and reduce the potential for the development of antimicrobial resistance (AMR) in the community. In addition, it would provide an alternative treatment for women who have failed to respond to current treatment for BV with systemic antibiotics.

The aim of the metronidazole Versus lactic acId for Treating bacterial vAginosis (VITA) trial was to determine whether or not using intravaginal lactic acid gel to replace vaginal acidity would be better than oral metronidazole for the symptomatic resolution of recurrent BV. Previous small studies of daily intravaginal acid gel or pessary for the treatment of BV have reported inconsistent results, with little difference between dosing regimens (23–93% efficacy with the more common once-daily dosing vs. 18–100% with twice-daily dosing).[13,18–23] For the VITA trial, a once-daily dose of 4.5% intravaginal lactic

acid gel for 7 days was used because this was likely to be a more acceptable regimen than twice-daily dosing. UK management guidelines for BV[10] do not currently include lactic acid as a recommended treatment because there is insufficient evidence from randomised controlled trials (RCTs) on reproducible efficacy. It was, therefore, anticipated that the VITA trial would advance our understanding by assessing whether or not lactic acid gel is effective and well tolerated for the treatment of recurrent BV, and whether or not it can reduce antibiotic usage in this large group of women. The comparator was 400-mg oral metronidazole tablets twice daily for 7 days and was chosen because it is recommended as first-line therapy in the UK national BV treatment guidelines,[10] being active against a wide range of the anaerobic bacteria associated with BV and being commonly used in clinical practice supported by evidence from RCTs.[24]

In addition, a qualitative assessment was performed to explore factors affecting the acceptability of, and adherence to, intravaginal treatment for BV and how these could be improved. A pragmatic trial design was used to maximise its relevance to patients and clinicians and to facilitate rapid adoption of the trial results into clinical practice.

Bacterial vaginosis is a common disease with serious physical and psychological sequelae. There is, therefore, the potential for a substantial health gain if a more effective and well-tolerated regimen, which also reduces antibiotic exposure, can be identified. The prospects for the study findings to influence clinical practice were high based on the multicentre approach including primary care, robust study design, existing widespread availability of lactic acid gel and identified need to limit antibiotic use to reduce the development of AMR.

Chapter 2 Methods

The full VITA trial protocol is available on the National Institute for Health Research project web page (www.fundingawards.nihr.ac.uk/award/15/110/02) and a summary protocol has been published.[25] Consolidated Standards of Reporting Trials (CONSORT) guidelines have been followed for data analysis and reporting.[26]

Regulatory approval for the trial was given by the Medicines and Healthcare products Regulatory Agency on 12 July 2017 (reference 16719/0230/001–0001; European Union Drug Regulating Authorities Clinical Trials 2016-004483-19) and ethics approval was given by the London – Harrow Research Ethics Committee on 9 September 2017 (reference 17/LO/1245). Local research and development departments gave their own approval prior to recruitment commencing at each participating site. The trial was registered on the International Standard Randomised Controlled Trial Number (ISRCTN) register as ISRCTN14161293 on 8 September 2017 (https://doi.org/10.1186/ISRCTN14161293; accessed 27 April 2021).

There were no updates made to the protocol after the original approved version (version 1.0); however, the following changes were introduced to the trial procedures and the collection and analysis of some outcome measures:

- As per the protocol, the Short Form questionnaire-12 items (SF-12) health survey was administered at baseline, 2 weeks and 6 months. In addition, it was administered at 3 months (which was also included as a secondary outcome), although this was inadvertently not stated in the protocol.
- Participant-reported outcomes were collected via web-based questionnaires as detailed in the protocol. During the course of the trial, a follow-up telephone call was introduced to try to improve the collection of key outcomes for participants for whom the week 2 and 6-month web-based questionnaires had not been completed, despite several reminders being sent. The key outcome information was a subset of the information included in the web-based questionnaires. Collection of these data via a telephone call was not specifically stated in the protocol; however, consent to be contacted via telephone was included on the informed consent form.
- To assist with interpretation of the primary outcome, additional subgroup analyses for symptom resolution at week 2 were included as follows, although these were inadvertently not stated in the protocol:
  - number of episodes of BV in the 12 months before baseline (1, 1–3 or > 3)
  - total time with BV in the 12 months before baseline (< 2 weeks, ≥ 2 weeks and < 3 months, ≥ 3 months).
- An additional secondary objective was included that was to compare the time to resolution of BV symptoms, although this was inadvertently not stated in the protocol.

Trial objectives

The primary objective was to determine whether or not intravaginal lactic acid gel is better than oral metronidazole for symptomatic resolution of recurrent BV.

The secondary objectives were to:

- compare the time to first recurrence of BV symptoms
- compare the frequency of BV episodes over 6 months
- compare the frequency of BV treatments required over 6 months
- compare microbiological resolution of BV on microscopy 2 weeks after presentation
- compare the time to resolution of BV symptoms
- compare the tolerability profiles of lactic acid gel and metronidazole
- compare the adherence to lactic acid gel with adherence to metronidazole tablets
- compare the acceptability of use of lactic acid gel with that of the use of metronidazole tablets
- determine the prevalence of concurrent STIs at baseline and week 2
- compare quality of life (measured using the SF-12 health survey[27])
- compare the cost-effectiveness of intravaginal lactic acid gel with that of oral metronidazole tablets.

In addition, samples for further microbiological analysis, including gene sequencing, were collected for future investigation into the factors associated with successful treatment.

Outcome measures

The primary outcome was participant-reported resolution of BV symptoms at week 2. Secondary outcome measures were as follows:

- time to first recurrence of BV as reported by participants
- number of participant-reported BV episodes over 6 months
- number of participant-reported BV treatment courses over 6 months
- microbiological resolution of BV on microscopy of vaginal smears taken at week 2 and analysed at a central laboratory
- time to participant-reported resolution of BV symptoms
- tolerability of lactic acid gel and metronidazole assessed by participant reporting of side effects (including nausea, vomiting, taste disturbance, vaginal irritation, diarrhoea and abdominal pain) and via participant interviews
- participant-reported adherence to treatment
- acceptability of treatments via qualitative assessment in a subgroup of participants
- prevalence of concurrent STIs (gonorrhoea, chlamydia and trichomoniasis) from vaginal swabs taken at baseline and week 2, and analysed at a central laboratory
- quality of life as assessed by the SF-12 health survey[27] at baseline, 2 weeks, 3 months and 6 months
- comparative cost-effectiveness of intravaginal lactic acid gel and oral metronidazole tablets.

Participant-reported outcome measures were collected using web-based questionnaires, with several reminders sent to encourage completion. During the later stages of the trial, a follow-up telephone call was attempted to collect key outcomes from the week 2 and 6-month questionnaires when these had not been completed.

Trial design and setting

The VITA trial was an open-label, multicentre, parallel-arm RCT. Participants were randomised 1 : 1 to receive either intravaginal lactic acid gel treatment (intervention) or oral metronidazole tablets (control). The treatment was for 7 days, with follow-up taking place at 2 weeks, 3 months and 6 months

after randomisation. A health economic evaluation was performed to assess the cost-effectiveness of the study treatments from a UK NHS perspective (see *Chapter 4*). In addition, a subgroup of participants were interviewed to further explore the adherence, tolerability and acceptability of treatment (see *Chapter 5*).

Women presenting with symptoms of BV and a history of one or more episodes within the previous 2 years that had been resolved with treatment were approached by a member of the site research team to determine whether or not they were interested in participating in the trial. In normal clinical practice, a diagnosis of BV would be made based on an assessment of symptoms alone or in conjunction with the microscopy appearances of a vaginal smear; therefore, microscopy confirmation of BV was not required for entry into the trial.

Recruitment was planned to take place in approximately 25 primary care general practices and 15 sexual health centres and gynaecology clinics via several routes in the UK (*Figure 1*).

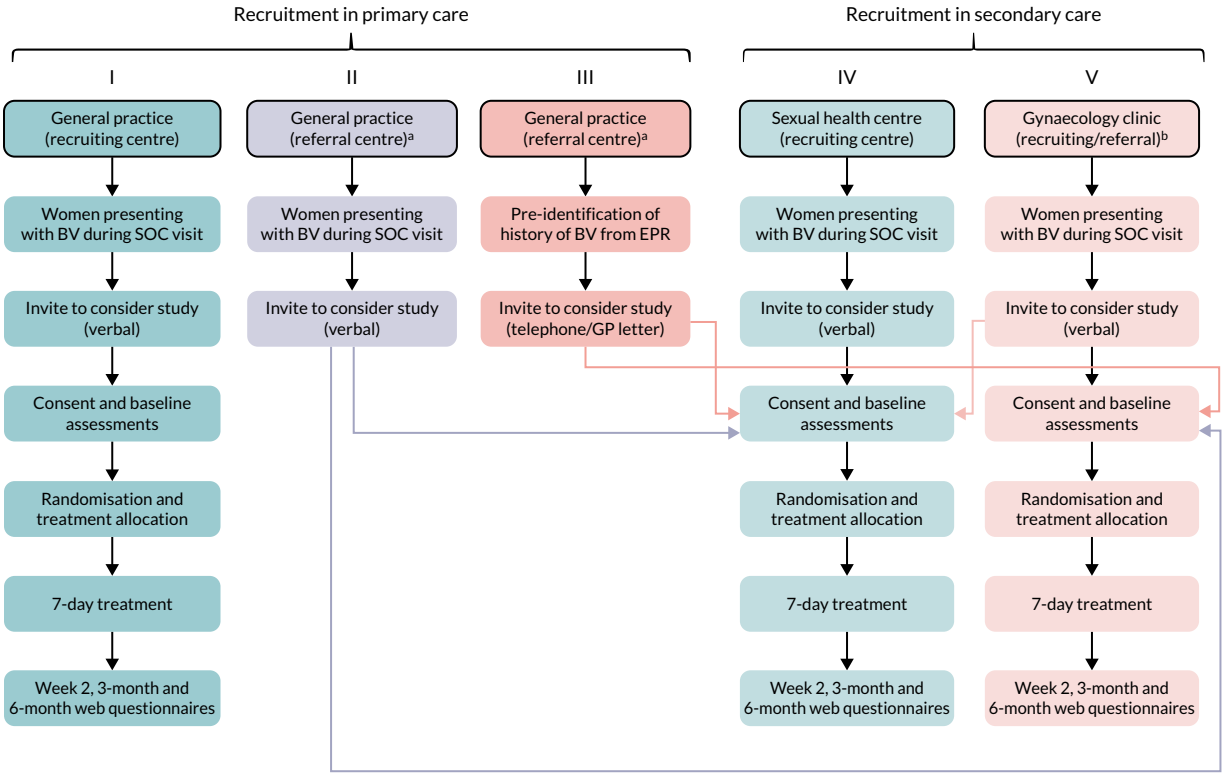


FIGURE 1 The VITA trial participant pathways in primary and secondary care settings. EPR, electronic patient record; SOC, standard of care. a, Acting as a participant identification centres: identification and referral of women with BV to recruiting centre; b, identification and recruitment at local clinic or referral to a recruiting sexual health centre depending on local facilities. Reproduced with permission from Armstrong-Buisseret *et al.*[25] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

Primary care (general practices)

i. Opportunistic identification of women presenting with BV in general practices that were VITA trial recruiting centres with trained research staff on site. Participants were identified, consented, randomised and prescribed study treatment at the practice. These research-ready sites required on-site availability of trained research nurses and facilities to directly consent and randomise patients.
ii. Opportunistic identification and referral of women with BV attending general practices without on-site research staff (participant identification centres) to local participating VITA trial recruiting centres for invitation to participate in the trial.
iii. Pre-identification of women with a history of BV by general practitioners (GPs) from electronic patient records/primary care databases. GPs would provide potential participants with information on the trial via telephone or letter and invite them to attend a local recruiting centre for consent if they developed BV and were interested in participating.

In addition, GP practices could use computerised 'pop-up' alerts to support the identification and recruitment of suitable women when they presented with possible BV symptoms.

Secondary care

iv. Opportunistic identification of women presenting with BV in sexual health centres that were VITA trial recruiting centres with trained research staff on site. Participants were identified, consented, randomised and dispensed study treatment at the centre. These research-ready sites required on-site availability of trained research nurses and facilities to directly consent and randomise patients.
v. Opportunistic identification of women presenting with BV in gynaecology clinics that either were VITA trial recruiting centres with trained research staff on site where participants would be identified, consented, randomised and prescribed study treatment within the clinic; or acted as VITA trial referral clinics (participant identification centres) where women presenting with BV could be referred to a nearby participating recruiting sexual health centre for invitation to participate in the trial.

Participants and eligibility

The flow of participants from presentation to follow-up is shown in *Figure 2*.

Inclusion criteria

Individuals had to meet all of the following inclusion criteria to be included in the trial:

1. aged $\geq$ 16 years
2. clinical diagnosis of BV based on patient-reported symptoms of discharge with an unpleasant (typically fishy) odour, with or without positive microscopy according to local site practice
3. history of at least one previous episode of BV in the past 2 years (clinically diagnosed or patient reported) that had been resolved with treatment
4. willing to use either intravaginal lactic acid gel or oral metronidazole tablets for the management of BV
5. willing to take their own vaginal samples
6. willing to avoid vaginal douching during treatment
7. willing to provide contact details and be contacted for the purpose of collecting follow-up information
8. willing to avoid sexual intercourse or use effective contraception for the 7-day duration of study treatment (condoms were not considered to be effective contraception owing to a potential interaction with the lactic acid gel)
9. access to the internet and e-mail and willing to complete web-based follow-up questionnaires in English
10. written informed consent.

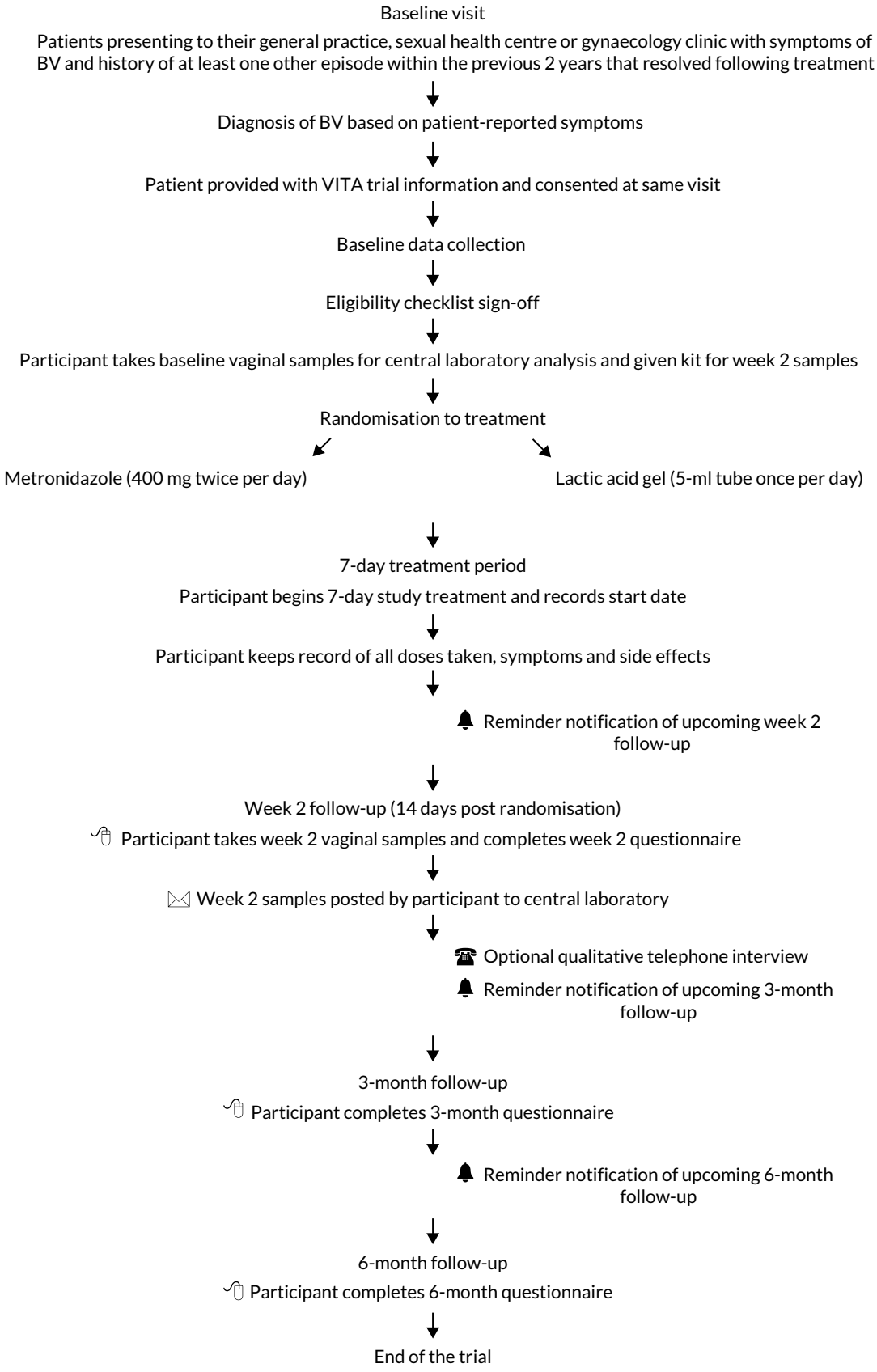


FIGURE 2 Participant flow through the trial. Reproduced with permission from Armstrong-Buisseret *et al.*[25] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

Exclusion criteria

Individuals were excluded from the trial if they met any of the following exclusion criteria:

1. contraindications or allergy to lactic acid gel or metronidazole tablets
2. pregnant or breastfeeding
3. patients currently trying to conceive and not willing to avoid sexual intercourse or use effective contraception for the 7-day duration of study treatment
4. using oral antibiotics (other than the study treatment) or antifungal agents concurrently, within the last 2 weeks or planned use within the next 2 weeks
5. using topical vaginal antibiotics, antifungals or acidifying products (other than the study treatment) concurrently, within the last 2 weeks or planned use within the next 2 weeks
6. previous participation in this study
7. current participation in another trial involving an investigational medicinal product (IMP).

Contraindications and concomitant medications

Metronidazole

As per the exclusion criteria, any known hypersensitivity to metronidazole, other nitroimidazole derivatives or any of the ingredients in metronidazole tablets would exclude patients from the trial. Sites were advised to refer to the summary of product characteristics (SmPC) for metronidazole for details, but to take particular note of the following:

- Alcohol was to be avoided (including products containing alcohol) during the course of treatment and for 48 hours afterwards.
- Warfarin (warfarin, Ranbaxy) – elevated international normalised ratio (INR) and bleeding events have been reported with concurrent use of warfarin and metronidazole.

Lactic acid gel

There is no SmPC for lactic acid gel, but sites were advised to take particular note of the following:

- Shellfish allergy – some lactic acid gel brands may contain glycogen obtained from oysters.
- Condom use – the effects of lactic acid gel on condom degradation have not been fully determined. Therefore, it was advised that condoms should not be assumed to be an effective method of contraception during the 7-day treatment period with lactic acid gel.

Concomitant medications

Concomitant medications relevant to BV, such as oral or topical antibiotics and/or antifungals, were recorded at baseline to determine participant eligibility.

Screening and consent

Screening

Women either pre-identified by or presenting to referring or recruiting general practices, sexual health centres or gynaecology clinics who had symptoms of BV (and a history of one or more episodes within the previous 2 years that resolved following treatment) were invited (by telephone or letter) or approached by a member of the site research team to determine whether or not they were interested in participating in the trial. If they were interested, they were given a participant information sheet.

Women who were identified in general practices and gynaecology clinics that were acting as referral centres were introduced to the trial and directed to a local recruiting practice, sexual health centre or gynaecology clinic for consent if they were interested in participating in the trial.

A screening log was maintained at each recruiting site detailing all patients approached about the study, the number of patients agreeing to participate, the reasons for not participating and, where relevant, the route of referral.

Consent

Women were given time to read the participant information sheet and had the opportunity to ask the site research team any questions about the trial prior to consent. Written informed consent was requested during the same clinic visit by the principal investigator (PI) or the delegated study doctor or nurse prior to performing any trial-related procedure. A copy of the completed informed consent form was given to the participant, a copy was filed in the medical notes and the original copy was placed in the investigator site file.

The consent process included optional consent to be approached by researchers from the University of Warwick for a qualitative telephone interview. When participants who had given this optional consent were contacted to arrange an interview, verbal consent that they remained willing to take part was recorded by the researcher before the interview began.

Participants recruited from sexual health centres and gynaecology clinics were also asked for their optional consent to inform their GP that they were taking part in the trial.

Randomisation and blinding

After obtaining informed consent, baseline data were collected by a member of the site research team. Participant eligibility was confirmed by the PI (or the delegated study doctor) prior to randomisation. Participants were randomised 1 : 1 to receive lactic acid gel or metronidazole using a remote internet-based randomisation system developed and maintained by Nottingham Clinical Trials Unit (NCTU). The concealed allocation system used a minimisation algorithm with the following variables and levels: site, type of site (general practice and sexual health clinic), number of episodes of BV in the previous 12 months (0, 1–3 and > 3) and whether or not they had had a female sexual partner in the previous 12 months (yes/no). The allocation system was held on a secure University of Nottingham server.

Given that this was an open-label trial, there was no blinding to treatment allocation of the participants, site research teams or trial team. However, the central laboratory staff performing BV microscopy and STI testing were blinded to participant's treatment allocation. In addition, the trial statistician remained blinded to treatment allocation until after database lock. Analyses requiring knowledge of treatment codes were conducted by an independent statistician. Data presented to both the trial team and the Trial Steering Committee (TSC) were aggregated, that is they were not split by treatment allocation.

Trial intervention

There were two treatment arms in the trial:

1. lactic acid gel – 5 ml of gel inserted into the vagina before bedtime each day for 7 days
2. metronidazole tablets – 400 mg taken orally twice daily, approximately 12 hours apart, for 7 days.

Metronidazole tablets were an IMP in the trial and are licensed for use in the treatment of BV as per the SmPC. Lactic acid gel is a registered medical device consisting of a colourless viscous gel administered through an intravaginal tube applicator. Known side effects of lactic acid gel include vaginal irritation, for example redness, stinging and itching. In rare cases an allergic skin reaction, for example severe redness, swelling or burning, may occur.

Treatment supplies, labelling and storage

Participants received their study treatment via the routine method of dispensing used in the setting of each recruiting site. This could be via dispensing directly from standard clinic stocks or the provision of a standard prescription to be taken to a pharmacy for dispensing. Any licensed brands of metronidazole or lactic acid gel could be used and the brand of lactic acid gel was recorded by the participant in the web-based questionnaire.

Trial-specific labelling was not required given that the IMP has a marketing authorisation in the UK and was being used within the terms of its marketing authorisation. The IMP was dispensed to a trial participant in accordance with a prescription given by an authorised health-care professional and was labelled in accordance with the requirements of Schedule 5 to The Medicines for Human Use (SI 1994/31 94) (Marketing Authorisations Etc.) Regulations 1994[28] that apply to relevant dispensed medicinal products.

The IMP was stored in accordance with usual site policy and as per manufacturer's instructions. Accountability records for treatment dispensing were in accordance with local site procedures and no additional trial-specific accountability was mandated.

Dosing schedule

It was requested that treatment was started on the day of receipt, and participants were advised to record their actual start date and time (morning or evening) of dosing in a paper patient diary that was given at the baseline visit. If they were menstruating at the time, those on the lactic acid gel arm were advised to delay starting treatment until menstruation had finished. Participants were also asked to use this diary with log all subsequent doses taken and/or missed doses over the treatment period to aid compliance with the treatment schedule and to record any symptoms, side effects or additional health-care use. The patient diaries were intended to be used as an aid for participants when completing their web-based questionnaires at 2 weeks, 3 months and 6 months.

No treatment or dose modifications were expected in this trial. Where a dose was accidentally missed, participants were advised to follow the manufacturer's instructions or to seek advice from their physician. In the case of any missed dose, participants were advised to continue to complete their treatment course. Lactic acid gel was to be inserted vaginally before going to bed. Metronidazole tablets were to be taken during or after meals with a glass of water and not to be crushed or chewed, and were to be swallowed whole.

Trial assessments and procedures

All assessments and procedures performed at each time point for participants are indicated in *Table 1*. Assessments carried out at baseline included:

- Demographics.
- Symptoms.
- Previous BV episodes.
- Medical history.
- Sexual history.
- Concomitant medication.
- Contraception and condom use.
- Verbal confirmation that the participant was not pregnant.
- SF-12 health survey.
- Vaginal samples for BV/STI screening. Participants took their own vaginal samples following instruction from site personnel, and sites sent the baseline samples to a central laboratory at University Hospitals Birmingham NHS Foundation Trust, which is accredited under the UK Accreditation Service to perform the tests.

TABLE 1 Summary of assessments at baseline and follow-up

	Baseline		Follow-up		
Trial procedure	**Baseline**	**Post randomisation**	**2 weeks**	**3 months**	**6 months**
Assessments					
Informed consent	✗				
Baseline data collection	✗				
Eligibility screen	✗				
Vaginal swabs for BV/STI screen	✗ (participant)		✗ (participant)		
Randomisation	✗				
Posting of vaginal swabs to central laboratory	✗ (site)		✗ (participant)		
Intervention					
Lactic acid gel (intervention arm)		✗ (7-day treatment)			
Metronidazole (control arm)		✗ (7-day treatment)			
Follow-up					
Participant web-based questionnaires	✗ (site)		✗	✗	✗
Telephone interviews for the qualitative substudy			✗ (2–4 weeks from randomisation)		

After randomisation into the trial, participants took their first dose of study treatment and continued taking study treatment for 7 days.

At 2 weeks, participants took their own vaginal samples using kits provided at the baseline visit and sent them to the central laboratory using pre-addressed and prepaid envelopes. They also completed a web-based questionnaire (see *Appendices 1* and *2*) with details of symptoms, treatment adherence and tolerability, any known side effects, health-care use, additional BV treatments, sexual history, contraception/condom use and another SF-12 health survey. A £15 voucher was provided to each participant on completion of the week 2 questionnaire as a thank you for their time. If requested to do so by a participant, the time frame for completing the questionnaire was extended.

Participants were also asked to complete two further web-based questionnaires at 3 months (see *Appendix 3*) and 6 months (see *Appendix 4*), with details of BV recurrence, sexual history, health-care use, additional BV treatments, contraception/condom use and the SF-12 health survey. Those not responding to requests to complete the week 2 and 6-month web-based questionnaires were contacted by telephone to collect follow-up data.

Participants could discontinue study treatment at any time but remain in the trial, taking week 2 vaginal samples and completing all follow-up questionnaires. They could also withdraw from the follow-up assessments at any time. Reason(s) for withdrawal were requested, but participants were not obliged to provide these.

Collection and analysis of vaginal samples

The central laboratory performed the following tests on vaginal samples taken at baseline and at week 2:

- Microscopic assessment of BV based on a Gram-stained vaginal smear using the Ison–Hay scoring system.[29]
- Nucleic acid amplification tests (NAATs) for chlamydia, gonorrhoea and trichomoniasis. Positive results were returned within 1–2 months to the recruiting site to review (PI and research nurse) and to arrange further testing or treatment in accordance with local protocols.

These trial-related tests did not form the basis for patient management at the baseline visit; clinicians took additional tests that were processed locally to inform immediate patient care as indicated by the patient's clinical presentation.

Substudies

Optional consent was sought from trial participants to store residual vaginal swabs taken at baseline and week 2 for future ethics-approved research, including microbiological analysis and gene sequencing into the factors associated with BV and its successful treatment.

Adverse events and pregnancy reporting

The safety profiles of the treatments in this trial are well characterised. To provide secondary outcome data to compare the tolerability of the two treatments, specified side effects experienced during study treatment were reported. The following were regarded as expected for the purpose of the trial and were reported on the week 2 questionnaire completed by the participant: nausea, vomiting, taste changes, vaginal irritation, abdominal pain and diarrhoea. Serious adverse events (SAEs) were not anticipated in this low-risk trial, but were recorded if reported by participants and were followed up until resolution or stabilisation.

Although lactic acid gel is considered safe for use in pregnancy and metronidazole is frequently prescribed for treatment of BV in pregnancy, caution is advised for their use in pregnant women and participants were asked to confirm that they were not pregnant as part of the screening process. Participants were also asked to confirm their pregnancy status during their follow-up period. Any pregnancies reported during the period between randomisation and week 2 were followed up for outcomes.

Data management

All baseline trial data were entered by site staff into a trial-specific database through the electronic case report form (MACRO 4.2.1 version 3800; Elsevier, London, UK), with participants identified by their unique trial number and initials only. All data collected after the baseline visit, that is at week 2, 3 months and 6 months, were entered by participants into the trial-specific database using a web-based questionnaire. The database was developed and maintained by NCTU. Access to the database was restricted and secure, and all data transactions were logged in a full audit trail.

Participant contact details were stored in a separate secure database using encryption with restricted password-protected access. Only appropriate members of the site team and the trial team had access to these data.

Statistical considerations

Analysis of outcome measures

A full statistical analysis plan was developed and agreed to prior to database lock and unblinding of the analysing statistician, and all analyses were carried out using Stata® version 15.1 (StataCorp LP, College Station, TX, USA). Continuous variables were summarised in terms of the mean, standard deviation (SD), median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables were summarised in terms of frequency counts and percentages. Descriptive statistics of demographic and clinical measures were used to assess the balance between the treatment arms at baseline, but no formal statistical comparisons were made.

The primary approach to between-arm comparative analyses was by modified intention to treat, that is it included all participants who were randomised and without imputation of missing outcome data. Sensitivity analyses were conducted to investigate the impact of missing data, additional baseline variables and adherence to allocated treatment.

Evaluation of the primary outcome was performed using a generalised estimating equation for the binary outcome that included factors used in the minimisation, with site as the panel variable. This was changed prior to database lock (and before finalising the statistical analysis plan and unblinding the trial statistician) from the originally planned mixed-effects model owing to model non-convergence because some sites had very small numbers of participants. It had been planned to also include whether or not vaginal douching had occurred in the 3 months prior to randomisation, but model convergence issues resulted in this being excluded from the model. The comparison of lactic acid gel with oral metronidazole was presented using the risk difference of the proportion of participants who reported resolution of symptoms at week 2, along with the 95% confidence interval (CI). The adjusted risk ratio and 95% CI were also presented. Owing to non-convergence of several of the models, sensitivity analyses also used a random-effects logit model including the same factors, presenting the odds ratio and 95% CI.

Secondary outcomes were analysed using appropriate regression models dependent on data type (e.g. binary, continuous, count and survival), and included factors used in the minimisation and baseline value of the outcome where measured. The analyses of secondary outcomes were considered supportive to the primary outcomes, and estimates and *p*-values, where presented, were interpreted in this light.

Presentations of quantitative tolerability data were descriptive. Frequency counts and percentages of the proportion of participants reporting nausea, vomiting, taste disturbance, vaginal irritation, abdominal pain and diarrhoea were presented by treatment arms.

Planned subgroup analyses

The primary analysis for symptom resolution was investigated to determine whether or not treatment effectiveness differed according to the following subgroups:

- presence of concomitant STI (yes/no)
- BV confirmed by positive microscopy (yes/no)
- number of episodes of BV in the 12 months before baseline (0, 1–3 and > 3)
- total time with BV in the 12 months before baseline (< 2 weeks, ≥ 2 weeks and < 3 months, ≥ 3 months).

A further subgroup analysis was planned to determine whether or not treatment effectiveness differed according to the type of centre at which the participant presented (sexual health vs. GP/other clinics); however, this was not performed given that no gynaecology clinics and only one GP practice took part in the trial. Between-group treatment effects were provided for each subgroup, but interpretation of any subgroup effects was based on the treatment–subgroup interaction and 95% CI, estimated by

fitting an appropriate interaction term in the regression models. Given that the trial was powered to detect overall differences between the groups rather than interactions of this kind, these subgroup analyses were regarded as exploratory. An interaction term could not be fitted when investigating the subgroup for the presence of concomitant STI at baseline owing to the small number of participants with a STI.

Feasibility

There was no planned interim analysis of treatment efficacy. However, an assessment of recruitment and adherence to treatment was performed using data from the first 6 months of participant recruitment. This was to determine how feasible it was that the trial would be able to adequately address its primary and secondary objectives.

The TSC and Data Monitoring Committee (DMC) used the following criteria as a guide to determine whether or not the trial should progress:

- Review of the number of participants completing their week 2 assessment against the following targets –
  - > 90% – continue the trial
  - 65–90% – review recruitment and retention procedures to identify underlying problems and put in place strategies to address these, with review in 6 months
  - 35–65% – review recruitment and retention procedures to identify underlying problems and put in place strategies to address these. Ongoing review over 6 months and terminate the trial if the recruitment trajectory does not indicate that full recruitment can occur within an acceptable recruitment period
  - < 35% – terminate the trial.
- Review of adherence to lactic acid gel and metronidazole against the following predefined targets –
  - median adherence 5–7 days per week – continue the trial
  - median adherence 3–4 days per week – review data from the qualitative interviews on adherence and tolerability to identify underlying problems and put in place strategies to address these, with review in 6 months
  - median adherence < 3 days per week – terminate the trial.

Power calculation/sample size calculation

Assuming that 80% of participants receiving oral metronidazole would achieve resolution of symptoms,[24,30–32] 1710 participants (855 in each treatment arm) were required for analysis to detect a 6% increase in response rate to 86% in those receiving lactic acid gel (risk ratio 1.08) at the 5% significance level (two-sided) with 90% power. To allow for loss to follow-up of 10% (i.e. non-collection of the primary outcome), a total of 1900 participants were required to be recruited.

Patient and public involvement

Patient and public involvement (PPI) representatives provided input during the development of the grant application into the trial design, including feedback on the importance of the research question, the effect size used in the power calculation and ideas on how to make participation in the trial appealing to potential recruits. They also requested the addition of the secondary outcome of time to recurrence of BV because it was felt that this was an important measure. In addition, PPI representatives reviewed all participant-facing documents prior to submission for ethics approval. These documents included the participant information sheet; informed consent form; participant invitation letter; participant kit instruction leaflet; all participant questionnaires, reminders and diaries; all advertising materials; and the qualitative interview schedule.

The PPI representatives sat on the TSC as independent members and contributed to the oversight of the trial, including reviewing and interpretating the results and providing input to the *Plain English summary*. Once the trial results have been published, a summary will be disseminated to participants, and PPI representatives will be invited to review the summary prior to distribution.

Chapter 3 Clinical results

Sites

Recruitment was originally planned to take place at approximately 25 primary care general practices and 15 sexual health outpatient and gynaecology clinics in the UK. However, during the course of the trial, a total of one general practice and 21 sexual health centres were opened to recruitment; the general practice and 19 of the sexual health centres recruited at least one participant. Although the Primary Care Clinical Research Network was involved in the planning of the trial, fewer primary care centres than expected had sufficient research nurse resources to support recruitment and, with approval from the TSC, additional sexual health centres were identified to take part. One gynaecology clinic was approached but none was identified that was willing to participate in the trial.

Recruitment

Recruitment took place between October 2017 and June 2019. It was originally planned that recruitment would continue until 1900 participants had been randomised, with an initial projected date for completion of recruitment of November 2019. However, in May 2019 the DMC reviewed the unblinded trial data at a planned meeting and its recommendation from this review was that trial recruitment should be stopped, because its opinion was that the primary research question had been answered with the number of participants, recruited at that time. There were no concerns raised around any safety issues. To ensure that this was a robust decision, further analyses were conducted that were reviewed by the DMC in June 2019, and its recommendation remained the same. The TSC supported this opinion and recruitment into the trial was terminated on 28 June 2019, with follow-up of ongoing participants continuing for 6 months (completed 26 February 2020 to allow sufficient time for receipt of the final questionnaires after sending all reminders), as per the protocol. No additional information about the reason for the recommendation was provided to any member of the trial team.

During the recruitment period, a total of 3141 patients were approached (*Figure 3*), of whom 2618 (83%) were excluded prior to consent; the main reason given was not having a history of at least one previous episode of BV within the last 2 years ($n = 695$) (see *Appendix 5*, *Table 28*). A total of 523 (17%) participants consented to take part in the trial, of whom five were excluded after consent because they were not eligible ($n = 3$) or they changed their mind about participating ($n = 2$) (see *Figure 3*). This gave a total of 518 participants who were randomised into the trial (metronidazole arm, $n = 259$; lactic acid gel arm, $n = 259$), who represented 16% of those presenting with BV and 99% of those who consented.

A total of three participants (metronidazole arm, $n = 1$; lactic acid gel arm, $n = 2$) withdrew their consent in the first 2 weeks, resulting in 258 participants in the metronidazole arm and 257 in the lactic acid gel arm remaining in the trial at week 2 (see *Figure 3*). A further three participants withdrew between week 2 and 3 months, two from the metronidazole arm (both because of withdrawal of consent) and one from the lactic acid gel arm (because of being dissatisfied with the efficacy of the treatment), giving a total of 512 participants remaining in the trial at 3 months (256 per arm). There were no known participant withdrawals between 3 months and 6 months.

Of the 22 sites that were opened, 20 screened and recruited at least one participant (see *Appendix 5*, *Table 29*).

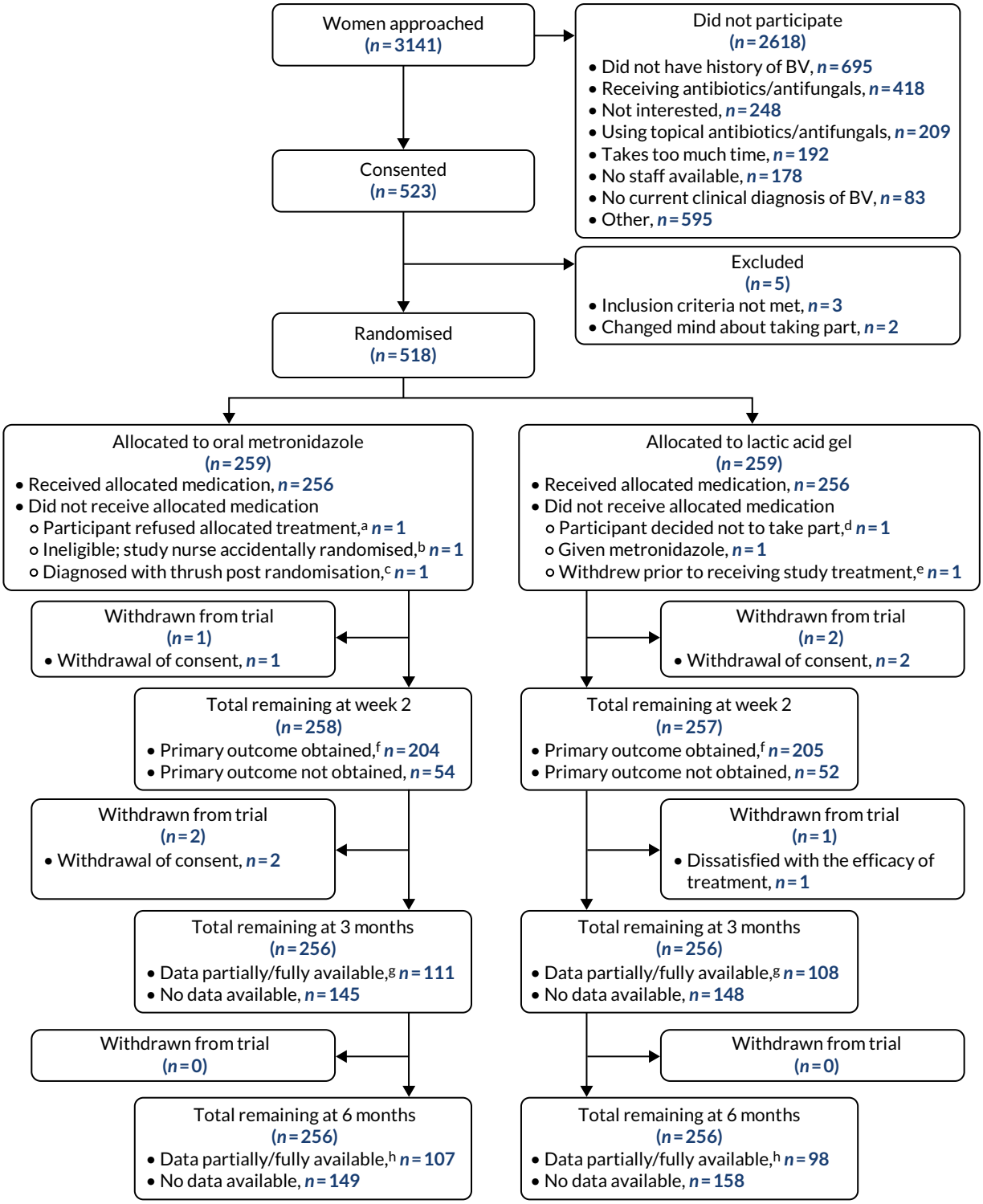


FIGURE 3 The CONSORT flow diagram. a, Prescribed lactic acid gel as refused allocated study treatment; b, ineligible as taking warfarin, prescribed lactic acid gel instead; c, no study treatment given as participant received medication to treat thrush; d, preferred metronidazole after being randomised to lactic acid gel; e, included as one of the two withdrawn before week 2 in the next box down; f, includes outcomes obtained from the week 2 questionnaire for which a date of resolution was given without an answer to the 'Have your BV symptoms cleared' question, and primary outcome data collected by telephone, includes outcomes obtained from the 3-month questionnaire asking about resolution by week 2; g, at least one data item entered on the questionnaire; and h, at least one data item entered on the questionnaire or obtained by telephone.

Baseline characteristics

The baseline characteristics of the participants were similar between the two treatment arms (*Table 2*). The age of the participants ranged from 16 to 58 years, with a mean of 29 (SD 8.3) years. Forty-eight per cent of the participants were of white ethnicity and 23% were black Caribbean. Vaginal douching was carried out by 12% of the participants in the 3 months before baseline. A total of 198 (38%) participants had experienced more than three episodes of BV in the previous 12 months, and BV was confirmed microscopically at baseline in 436 (84%) participants by local laboratories and in 266 (51%) participants using Ison–Hay grade 3[29] by the central laboratory.

TABLE 2 Baseline characteristics of the participants

Characteristic	Treatment arm		Total (*N* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Age at randomisation (years)			
Mean (SD)	29.0 (8.41)	29.4 (8.12)	29.2 (8.26)
Median (25th, 75th centile)	27 (23, 34)	27 (23, 34)	27 (23, 34)
Minimum, maximum	16, 58	18, 57	16, 58
Ethnicity*, n *(%)			
White	125 (48)	126 (49)	251 (48)
Black Caribbean	62 (24)	57 (22)	119 (23)
Mixed race	24 (9)	27 (10)	51 (10)
Black African	26 (10)	15 (6)	41 (8)
Other	8 (3)	8 (3)	16 (3)
Other Asian (non-Chinese)	5 (2)	6 (2)	11 (2)
Indian	4 (2)	5 (2)	9 (2)
Black (other)	1 (< 0.5)	6 (2)	7 (1)
Chinese	1 (< 0.5)	4 (2)	5 (1)
Pakistani	3 (1)	1 (< 0.5)	4 (1)
Bangladeshi	0	3 (1)	3 (1)
Not given	0	1 (< 0.5)	1 (< 0.5)
Vaginal douching in the past 3 months*, n *(%)			
Yes	36 (14)	25 (10)	61 (12)
No	223 (86)	233 (90)	456 (88)
Missing	0	1 (< 0.5)	1 (< 0.5)
Frequency of douching per month*, n *(%)			
0–2	9 (25)	6 (24)	15 (25)
3–4	9 (25)	5 (20)	14 (23)
5–6	1 (3)	3 (12)	4 (7)
≥ 7	17 (47)	11 (44)	28 (46)

continued

TABLE 2 Baseline characteristics of the participants (*continued*)

Characteristic	Treatment arm		Total (*N* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Current use of oral contraceptive pill*, n *(%)			
Yes	45 (17)	44 (17)	89 (17)
No	214 (83)	214 (83)	428 (83)
Missing	0	1 (< 0.5)	1 (< 0.5)
Type of contraceptive pill*, n *(%)			
Combined oral contraceptive pill	27 (60)	30 (68)	57 (64)
Progesterone-only pill	18 (40)	14 (32)	32 (36)
Past history of BV *Approximate age when BV first occurred (years)*			
n	258	258	516
Mean (SD)	23.8 (7.26)	23.4 (6.49)	23.6 (6.88)
Median (25th, 75th centile)	22 (18, 27)	22 (19, 27)	22 (19, 27)
Minimum, maximum	14, 58	11, 50	11, 58
Number of previous episodes of BV in the past 12 months, n *(%)*			
0	3 (1)	3 (1)	6 (1)
1–3	157 (61)	157 (61)	314 (61)
> 3	99 (38)	99 (38)	198 (38)
Approximate total length of time in past year with BV symptoms, n *(%)*			
< 2 weeks	56 (22)	40 (15)	96 (19)
≥ 2 weeks and < 3 months	135 (52)	130 (50)	265 (51)
≥ 3 months	68 (26)	88 (34)	156 (30)
Missing	0	1 (< 0.5)	1 (< 0.5)
BV confirmed at baseline visit (local laboratory)*, n *(%)			
Yes	217 (84)	219 (85)	436 (84)
No	31 (12)	29 (11)	60 (12)
Not tested	11 (4)	10 (4)	21 (4)
Missing	0	1 (< 0.5)	1 (< 0.5)
Baseline sample Ison–Hay grade for BV (central laboratory)*,[a] n *(%)			
0 (no bacteria)	1 (< 0.5)	1 (< 0.5)	2 (< 0.5)
1 (normal flora)	48 (19)	62 (24)	110 (21)
2 (intermediate BV)	62 (24)	61 (24)	123 (24)
3 (confirmed BV)	138 (53)	128 (49)	266 (51)
U (Gram-positive cocci)	3 (1)	1 (< 0.5)	4 (1)
Missing	7 (3)	6 (2)	13 (3)

a Positive for BV = grade 3, negative for BV = grades 0, 1, 2 and U.

The differences in BV microscopy results obtained from local and central laboratory analyses of samples are available in *Appendix 5*, *Table 30*.

Medical and sexual histories are summarised in *Appendix 5*, *Tables 31* and *32*. The vast majority of participants were HIV negative (99%) and around half (48%) reported having had thrush in the 12 months before baseline. A total of 365 (71%) participants had a sexual partner at baseline and 51 (10%) had a female sexual partner in the 12 months before baseline.

Participant-reported symptoms at baseline are summarised in *Table 3*, and included 470 out of 518 (91%) participants with genital discharge, 440 out of 518 (85%) with an offensive vaginal smell, 193 out of 518 (37%) with vaginal irritation and 406 out of 518 (78%) had both discharge and an offensive smell.

Data completeness

All of the 518 randomised participants were considered in the analysis of primary and secondary outcomes. Details of where data were missing, for example because of questionnaires or samples not being returned, are given below.

Questionnaires and telephone calls

The completion of data via web-based questionnaires and telephone calls was similar between the two treatment arms (see *Appendix 5*, *Tables 33* and *34*). The web-based questionnaire response rates were 318 out of 515 (62%) at week 2, 219 out of 512 (43%) at 3 months and 176 out of 512 (34%) at 6 months (see *Appendix 5*, *Table 33*). Further key data were obtained by telephone, with week 2 primary outcome information on BV resolution provided by an additional 88 out of the 202 participants for whom contact was attempted (success rate of 44%); secondary outcomes on recurrence were given by an additional 29 out of the 105 participants for whom contact was attempted at 6 months (success rate of 28%).

The median (minimum–maximum) time from randomisation to return of the week 2 questionnaires was 15 (14–55) days, with most of the questionnaires being returned within 28 days. For week 2 telephone data, the median time for obtaining these was 55.5 (29–155) days. This latter time was much longer than that for the questionnaires because the decision to collect data by telephone was made part-way through the trial to try to improve response rates. In addition, participants were given up to 28 days after randomisation to return questionnaires before a telephone call was attempted. The median time to return of the 3- and 6-month questionnaires was 93 (89–113) days and 186 (181–208) days, respectively. Six-month telephone data were collected after a median (minimum–maximum) time of 231 (203–265) days.

Week 2 vaginal samples

Week 2 vaginal samples were received by the central laboratory from 301 (58%) participants and numbers were similar between the treatment arms (see *Appendix 5*, *Table 35*). Overall, 280 out of 515 (54%) participants reported a primary outcome at week 2 and returned their week 2 samples, with similar numbers in both treatment arms (see *Appendix 5*, *Table 35*).

Nucleic acid amplification test analysis for sexually transmitted infections

Kits were provided for participants to take vaginal swab samples at baseline and week 2 for NAAT analysis of STIs. At each time point, one swab sample was placed into a tube containing a transport fluid and the tube was shipped directly to the central laboratory that was responsible for performing the analysis. On 16 January 2019, an issue was identified at three sites that some kits had been given to participants that contained time-expired NAAT sample tubes. The manufacturer of the tubes confirmed that there were no stability data past the point of expiry; therefore, it was decided that

TABLE 3 Participant-reported symptoms at baseline

Symptom	Treatment arm		Total (*N* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Abnormal genital discharge,[a] **n *(%)***			
Yes	239 (92)	231 (89)	470 (91)
No	20 (8)	27 (10)	47 (9)
Missing	0	1 (< 0.5)	1 (< 0.5)
For those with discharge, length of time present during this episode (days)			
n	239	231	470
Mean (SD)	31 (58.6)	31 (57.0)	31 (57.7)
Median (25th, 75th centile)	14 (7, 28)	14 (7, 28)	14 (7, 28)
Minimum, maximum	1, 365	1, 365	1, 365
Offensive vaginal smell,[b] **n *(%)***			
Yes	227 (88)	213 (82)	440 (85)
No	32 (12)	45 (17)	77 (15)
Missing	0	1 (< 0.5)	1 (< 0.5)
For those with smell, length of time present during this episode (days)			
n	227	212	439
Mean (SD)	26 (45.0)	32 (55.2)	29 (50.2)
Median (25th, 75th centile)	10 (5, 28)	14 (7, 30)	14 (6, 28)
Minimum, maximum	1, 351	1, 365	1, 365
Presence of both discharge and smell,* n *(%)			
Yes	211 (81)	195 (75)	406 (78)
No	48 (19)	63 (24)	111 (21)
Missing	0	1 (< 0.5)	1 (< 0.5)
Vaginal irritation,* n *(%)			
Yes	100 (39)	93 (36)	193 (37)
No	159 (61)	165 (64)	324 (63)
Missing	0	1 (< 0.5)	1 (< 0.5)
For those with irritation, length of time present during this episode (days)[c]			
n	100	93	193
Mean (SD)	27 (101.8)	22 (48.1)	25 (80.4)
Median (25th, 75th centile)	7 (3, 21)	7 (3, 14)	7 (3, 20)
Minimum, maximum	1, 999	1, 364	1, 999

a All participants reported having a vaginal discharge with an unpleasant odour. The presence of self-reported abnormal genital discharge was recorded separately.
b All participants reported having a vaginal discharge with an unpleasant odour. The presence of self-reported offensive vaginal smell was recorded separately.
c Time with vaginal irritation for one participant was several years, which was recorded as 999 days.

any samples received in expired tubes would be considered as void. An investigation took place into the expiry dates of existing stock at all sites and it became apparent that use of expired sample tubes was a wider issue.

Given that the expiry dates of sample tubes were not recorded by the manufacturer, site or NCTU, an audit was conducted at the central laboratory on 4 June 2019 of all NAAT samples received to determine whether or not sample tubes had expired prior to the date that each sample was taken. This audit revealed that the central laboratory had discarded some residual samples in error; therefore, for some participants it was not possible to determine whether or not the sample tubes had expired before use. For those baseline NAAT samples that were available at the central laboratory and for which expiry dates could be checked, a total of 339 samples were confirmed as being valid and within the expiry date, and a further 32 samples were confirmed as being void (i.e. the tube had expired prior to use) (see *Appendix 5*, *Table 36*). Expiry status could not be confirmed for 138 baseline samples because, although the central laboratory records indicated that these had been received, the residual samples had since been discarded. The remaining nine baseline samples either were not received by the central laboratory according to their records ($n = 7$) or were received but without accurate identifiable information ($n = 2$). For those week 2 NAAT samples that were available at the central laboratory and for which expiry dates could be checked, a total of 224 samples were confirmed as being valid and within the expiry date, and a further 19 samples were confirmed as being void (i.e. the tube had expired prior to use) (see *Appendix 5*, *Table 36*). Expiry status could not be confirmed for 58 week 2 samples because, although the central laboratory records indicated that these had been received, the residual samples had since been discarded. The remaining 214 week 2 samples either were not received by the central laboratory according to their records ($n = 213$) or were received but without accurate identifiable information ($n = 1$).

Sites followed their usual guidelines for treatment of suspected STIs during the participant's baseline visit and clinical care of participants was not dependent on these NAAT results, which were taken purely for trial purposes.

Protocol non-compliance

Of the 518 participants who were randomised, six did not receive their allocated treatment (metronidazole arm, $n = 3$; lactic acid gel arm, $n = 3$) as a result of refusing to take the allocated study treatment ($n = 1$), being found to be ineligible post randomisation ($n = 1$), being diagnosed post randomisation with thrush, requiring antifungal treatment ($n = 1$), declining to take part post randomisation ($n = 1$), being given the other study treatment ($n = 1$) or withdrawing prior to receiving study treatment ($n = 1$) (see *Figure 3*). For a further two participants allocated to the lactic acid gel arm, the wrong value of the minimisation variable 'any female sexual partners in previous 12 months' was entered onto the system; they both received lactic acid gel and continued in the trial. No further incidents of non-compliance were recorded.

Primary outcome

Primary outcome data were available for 409 (79%) participants (see *Figure 3*): 321 who entered their primary outcome data into the questionnaire and 88 for whom primary outcome data were collected via a follow-up telephone call. Of the 321 participants who provided the primary outcome on the questionnaire, 316 entered this on the week 2 questionnaire (314 answered yes or no to the primary outcome question and two did not respond to the yes/no question but provided a date of resolution) and a further five with missing primary outcome data at week 2 provided a response on the 3-month questionnaire indicating either that their BV had resolved by week 2 or that their BV was ongoing.

Resolution of BV symptoms was higher in the metronidazole arm than in the lactic acid gel arm: 143 out of 204 (70%) participants in the metronidazole arm reported resolution at week 2, compared with 97 out of 205 (47%) participants in the lactic acid gel arm. The adjusted risk difference was −23.2% (95% CI −32.3% to −14.0%) and the adjusted risk ratio was 0.67 (95% CI 0.57 to 0.79) (*Table 4*). The analysis was adjusted for site, number of BV episodes in the 12 months before baseline (0, 1–3 or > 3) and female partner in the 12 months before baseline (yes/no), but not for vaginal douching owing to non-convergence of the model.

The sensitivity analyses showed similar results (*Table 5* and *Figure 4*; see also *Table 4*). Odds ratios were presented for comparison of the sensitivity analyses owing to non-convergence of two of the models for treatment difference.

A planned post hoc investigation showed that resolution rates were lower in both treatment arms when the data were collected via questionnaires than via telephone calls (see *Appendix 5*, *Table 37*). Of the 158 participants in the metronidazole arm who provided resolution data via a questionnaire, 105 (66%) reported that symptoms had resolved, whereas of the 46 who provided these data via a telephone call, 38 (83%) reported that symptoms had resolved. Of the 163 participants in the lactic acid gel arm who provided resolution data via a questionnaire, 75 (46%) reported that symptoms had resolved, whereas of the 42 who provided the data via a telephone call, 22 (52%) reported that symptoms had resolved.

Of those participants who reported resolution of symptoms at week 2, 154 in the metronidazole arm and 158 in the lactic acid gel arm also gave information on whether or not any additional treatment had been taken for their BV (*Table 6*). A total of 22 out of 154 (14%) participants in the metronidazole arm and 20 out of 158 (13%) participants in the lactic acid gel arm had taken additional treatment, of whom 12 out of 22 (55%) and 7 out of 20 (35%), respectively, had resolution of their symptoms. Although resolution rates were lower for those taking additional treatment, the difference between treatment arms was similar with an unadjusted risk difference for resolution with additional treatment of −19.5% (95% CI −49.0% to 10.0%) compared with −19.6% (95% CI −31.1% to −8.1%) for resolution without additional treatment (see *Table 6*).

There were no statistically significant treatment-by-subgroup interactions. The number of valid STI samples available at baseline and week 2 was small owing to the expiry date issue and, consequently, the number of participants with a STI (from a valid sample) at baseline and who had resolution data at week 2 ($n = 8$) was too small to allow any analysis. In each of the other subgroups, resolution rates were consistently higher in the metronidazole arm than in the lactic acid gel arm (*Tables 7* and *8*). Treatment outcomes in the subgroup of participants who had confirmation of a BV diagnosis by positive microscopy are given in *Microbiological resolution of bacterial vaginosis on microscopy of vaginal smears at week 2*.

TABLE 4 Participant-reported resolution of BV symptoms at week 2: between-arm comparison

Resolution of BV at week 2	Treatment arm, *n* (%)		Adjusted risk difference (95% CI)[a]	Adjusted risk ratio (95% CI)[a]	Adjusted odds ratio (95% CI)[a,b]
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)			
Yes	143 (70)	97 (47)	−23.2% (−32.3% to −14.0%)	0.67 (0.57 to 0.79)	0.38 (0.25 to 0.57)
No	61 (30)	108 (53)			
Missing	55	54			

a Adjusted for site, number of BV episodes in 12 months before baseline (0, 1–3 or > 3) and female partner in 12 months before baseline (yes/no). Vaginal douching was not included as a covariate owing to being omitted from the output. Baseline imbalanced variables are only included in a sensitivity analysis because of non-convergence of the analysis model.
b Odds ratio is presented for comparison with sensitivity analyses.

TABLE 5 Sensitivity analyses of BV symptom resolution at week 2

Scenario	Resolution of BV symptoms, *n* (%)	Adjusted risk difference (95% CI)[a]	Adjusted odds ratio (95% CI)[a]
Multiple imputation of missing resolution data[b]			
Oral metronidazole (*N* = 259)	(70)	Not estimable[c]	0.37 (0.25 to 0.54)
Intravaginal lactic acid gel (*N* = 259)	(47)		
Excluding those who did not receive allocated treatment			
Oral metronidazole (*N* = 256)	143 (70)	−23.5% (−32.6% to −14.3%)	0.37 (0.25 to 0.56)
Intravaginal lactic acid gel (*N* = 256)	96 (47)		
Further adjustment for baseline variables[d]			
Oral metronidazole (*N* = 259)	143 (70)	Not estimable[c]	0.39 (0.26 to 0.60)
Intravaginal lactic acid gel (*N* = 259)	97 (47)		
Assuming missing symptom resolution as not resolved			
Oral metronidazole (*N* = 259)	143 (55)	−17.8% (−26.2% to −9.3%)	0.48 (0.34 to 0.69)
Intravaginal lactic acid gel (*N* = 259)	97 (37)		
Assuming missing symptom resolution as resolved			
Oral metronidazole (*N* = 259)	199 (77)	−18.5% (−26.3% to −10.7%)	0.43 (0.29 to 0.62)
Intravaginal lactic acid gel (*N* = 259)	153 (59)		
Included in arm as treatment received			
Oral metronidazole (*N* = 258)	144 (71)	−23.6% (−32.8% to −14.5%)	0.38 (0.25 to 0.57)
Intravaginal lactic acid gel (*N* = 258)	96 (48)		

a Adjusted for site, number of BV episodes in 12 months before baseline (0, 1–3, > 3) and female partner in 12 months before baseline (yes/no).
b No missing covariate data. Overall resolution is the only imputed variable, using chained equations and augment option owing to prediction problems. Estimation uses a general linear model for binary outcome.
c Not estimable owing to non-convergence of the model.
d Additional variables included in the model: vaginal douching, ethnicity and time with BV symptoms.

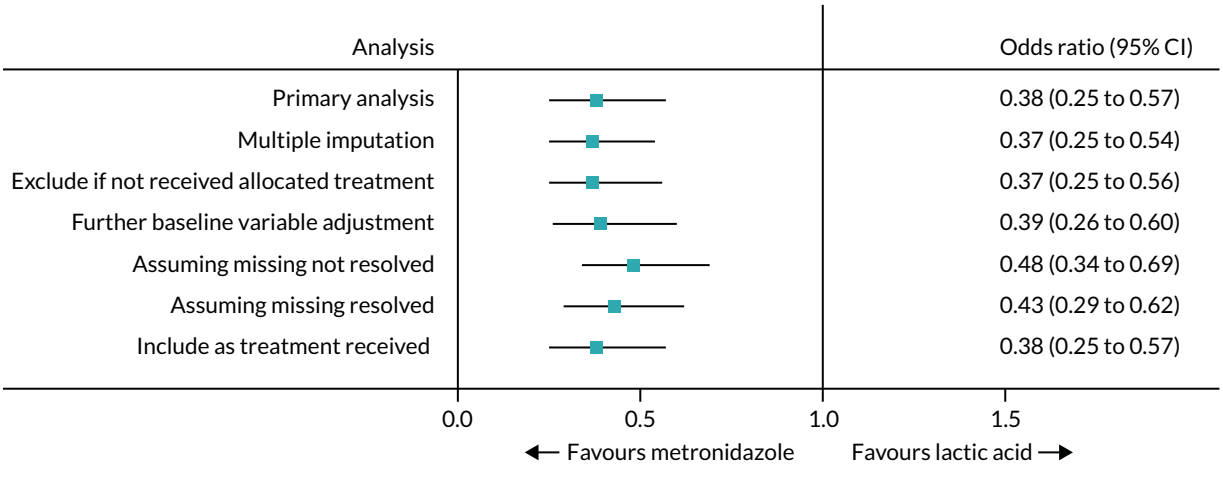


FIGURE 4 Forest plot for the primary outcome and sensitivity analyses.

TABLE 6 Participant-reported resolution of BV symptoms at week 2: split by additional treatment

Resolution of BV	Treatment arm, *n* (%)		Unadjusted risk difference (95% CI)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
With additional treatment			
N	22	20	
Yes	12 (55)	7 (35)	−19.5% (−49.0% to 10.0%)
No	10 (45)	13 (65)	
Without additional treatment			
N	132	138	
Yes	90 (68)	67 (49)	−19.6% (−31.1% to −8.1%)
No	42 (32)	71 (51)	

For some participants, their additional treatment data were missing, so even if primary outcome data were available they are not included in this table. Note that comparisons between those with and those without additional treatment are non-randomised.

TABLE 7 Participant-reported resolution of BV symptoms at week 2: cross tabulation by baseline subgroup

Baseline subgroup	Treatment arm: BV resolution at 2 weeks, *n* (%)					
	Oral metronidazole (*N* = 259)			Intravaginal lactic acid gel (*N* = 259)		
	Yes	No	Missing	Yes	No	Missing
Presence of concomitant STI at baseline[a]						
Yes	5 (100)	0	7	0	3 (100)	0
No	85 (67)	41 (33)	26	66 (50)	67 (50)	36
Missing	53	20	22	31	3	18
BV confirmed by positive baseline microscopy (central laboratory Ison–Hay grade 3)						
Yes	83 (75)	28 (25)	27	49 (49)	52 (51)	27
No	58 (65)	31 (35)	25	46 (46)	55 (54)	24
Missing	2	2	3	2	1	3
Number of episodes of BV in 12 months before baseline						
0	1 (100)	0	2	2 (67)	1 (33)	0
1–3	91 (75)	31 (25)	35	61 (51)	59 (49)	37
> 3	51 (63)	30 (37)	18	34 (41)	48 (59)	17
Missing	0	0	0	0	0	0
Total time with BV in 12 months before baseline						
< 2 weeks	31 (72)	12 (28)	13	20 (57)	15 (43)	5
≥ 2 weeks and < 3 months	78 (73)	29 (27)	28	54 (53)	48 (47)	28
≥ 3 months	34 (63)	20 (37)	14	23 (34)	45 (66)	20
Missing	0	0	0	0	0	1

a Chlamydia, gonorrhoea or trichomoniasis in central laboratory sample (excluding out-of-date samples and those with an unknown expiry status). Two non-expired samples had an indeterminate result for all three STIs and a third had a mixture of indeterminate and negative results; all three samples are, therefore, missing for overall STIs.

TABLE 8 Participant-reported resolution of BV symptoms at week 2: between-group comparison by subgroup

Subgroup	Treatment difference (95% CI)[a]	Estimate of treatment–subgroup interaction (95% CI); *p*-value[b]
Presence of concomitant STI at baseline		
No ($n = 259$)	−17.8% (−29.6% to −6.0%)	Not enough data to analyse
Yes ($n = 8$)[c]	−100% (not calculable)	
BV confirmed by positive baseline microscopy (central laboratory Ison–Hay grade 3)[d]		
No ($n = 190$)	−19.6% (−33.5% to −5.8%)	2.1% (−11.6% to 15.7%); 0.77
Yes ($n = 212$)	−26.3% (−38.9% to −13.6%)	
Number of episodes of BV in 12 months before baseline		
0 ($n = 4$)	−33.3% (−86.7% to 20.0%)	
1–3 ($n = 242$)	−23.8% (−35.6% to −11.9%)	−2.0% (−21.2% to 17.0%); 0.83
> 3 ($n = 163$)	−21.5% (−36.5% to −6.5%)	
Total time with BV in 12 months before baseline		
< 2 weeks ($n = 78$)	−15.0% (−36.1% to 6.2%)	
≥ 2 weeks and < 3 months ($n = 209$)	−20.0% (−32.8% to −7.1%)	−3.1% (−27.8% to 21.6%); 0.81
≥ 3 months ($n = 122$)	−29.1% (−46.2% to −12.0%)	−11.1% (−38.5% to 16.4%); 0.43

a Simple treatment differences are presented owing to non-convergence of more complicated models.
b Adjusted for number of female partners in last 12 months and number of episodes of BV in last 12 months.
c All in metronidazole arm resolved; none resolved in lactic acid gel arm.
d The baseline covariate is dependent on other variables in the analysis.

Secondary outcomes

Time to first recurrence of bacterial vaginosis

Among those participants who reported symptom resolution by week 2 (metronidazole arm, $n = 143$; lactic acid gel arm, $n = 97$), data on recurrence at 3 months were available for 73 (51%) and 50 (52%) participants, respectively, and at 6 months for 72 (50%) and 46 (47%) participants, respectively (*Table 9*). Of these participants, 37 out of 73 (51%) in the metronidazole arm and 23 out of 50 (46%) in the lactic acid gel arm reported recurrence by 3 months, whereas 51 out of 72 (71%) and 32 out of 46 (70%) reported recurrence by 6 months, respectively (see *Table 9*). The median [standard error (SE)] times to recurrence, allowing for censored times (when there was no reported recurrence up to 6 months, the 6-month data were used to calculate the censored time; if there was no reported recurrence up to 3 months and 6-month data were missing, the 3-month data were used; times were not available for recurrences reported by telephone at 6 months), were 92 (34.6) days in the metronidazole arm and 124 (SE not calculable) days in the lactic acid gel arm. It was possible to calculate only the lower limits of the 95% CIs (as there were not enough uncensored 'events') and these were 71 and 74 days, respectively (see *Table 9*). Including only those who had a time to recurrence gave median times of 54 ($n = 43$) days and 66 ($n = 25$) days in the metronidazole and the lactic acid gel arms, respectively. Times to first recurrence were not compared between treatment arms using statistical tests given that they comprised only those who had symptom resolution within 2 weeks and any comparison would, therefore, not be between randomised arms. A post hoc investigation showed that baseline characteristics were similar between treatment arms for the subset of participants resolving by week 2 (see *Appendix 5*, *Table 38*).

A Kaplan–Meier plot of recurrence against time is shown in *Figure 5*.

TABLE 9 Time to first recurrence (new episodes) of BV (days) for those whose symptoms resolved within 2 weeks (participant reported)

Resolution/recurrence of BV	Treatment arm	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Resolved by 2 weeks (*n*)	143	97
Recurred within 3 months, *n*/*N* (%)	37/73 (51)	23/50 (46)
Recurred within 6 months, *n*/*N* (%)	51/72 (71)	32/46 (70)
Number with time to recurrence (including censored times) (*n*)	73	50
Median time to recurrence (SE) (days)	92 (34.6)	124 (–)[a]
95% CI (days)	(71 to –)[a]	(74 to –)[a]

a Upper bound not calculable.

Notes
Time is censored for those without recurrence at the latest time for which data up to that point are available and is calculated from the date of resolution. If a participant had no recurrence up to 3 months, and 6-month data were missing, overall (6-month) recurrence status would also be missing and time to recurrence is censored at 3 months. Denominators are greater for median times than for 6-month recurrence data owing to times censored at 3 months.

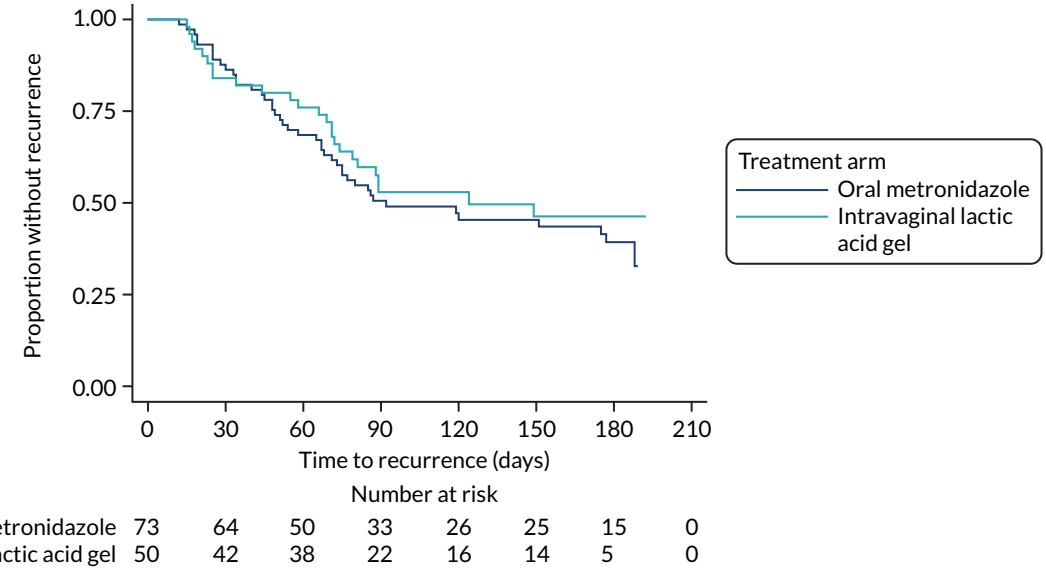


FIGURE 5 Kaplan–Meier plot of recurrence of BV symptoms against time.

There were few participants (*n* = 13) who resolved, had time to recurrence data and reported that additional treatment was taken during the first 2 weeks; therefore, the difference between those with and those without additional treatment could not be assessed (see *Appendix 5*, *Table 39*).

Time to recurrence was censored at 6 months if data were available at both 3 months and 6 months, but no recurrence had been reported. Of the times used in the analysis, 30 (41%) in the metronidazole arm and 25 (50%) in the lactic acid gel arm were censored times.

Including only those with data at both 3 months and 6 months gave the percentage recurring at 6 months as 60% (32/53) in the metronidazole arm and 56% (18/32) in the lactic acid gel arm. This removes inflation of the recurrence rate resulting from needing an episode at only one time for recurrence, but data at both times to record no recurrence.

Number of participant-reported bacterial vaginosis episodes over 6 months

The number of participants whose symptoms resolved by week 2 and who had complete episode data available at both 3 months and 6 months was small (metronidazole arm, $n = 48$; lactic acid gel arm, $n = 29$). There was little difference between treatment arms in the number of subsequent episodes of BV between week 2 and 6 months for those who had resolved by week 2. Both treatment arms had a median of one episode over the 6-month period, with a maximum of six episodes in the metronidazole arm and 10 episodes in the lactic acid gel arm (*Table 10*). The adjusted incidence rate ratio was 0.97 (95% CI 0.56 to 1.69). The analysis was adjusted for site, number of BV episodes in the 12 months before baseline and female partner in the 12 months before baseline (yes/no). Although vaginal douching could be included in the negative binomial model, it made little difference to the estimates (incidence rate ratio 1.00, 95% CI 0.58 to 1.72) and it was more consistent with the other analyses not to include this variable. The incidence rate is defined as the number of episodes per time at risk, that is if both treatment arms were followed up for the same length of time (in this case 6 months), the ratio of episodes in the metronidazole arm compared with the lactic acid gel arm was estimated as 0.97.

TABLE 10 Summary of the number of episodes of BV symptoms within 6 months

Resolution/persistence of BV	Treatment arm	
	Oral metronidazole (*N* = 259)	**Intravaginal lactic acid gel (*N* = 259)**
Resolved by week 2	**n = *143***	**n = *97***
Number of episodes within 3 months per participant whose symptoms resolved within 2 weeks		
Total resolved by week 2 with 3-month episode data	71	46
Median number of episodes (25th, 75th centile)	0 (0, 1)	0 (0, 1)
Minimum, maximum	0, 4	0, 8
Number of episodes within 6 months per participant whose symptoms resolved within 2 weeks		
Total resolved by week 2 with complete episode data[a]	48	29
Median number of episodes (25th, 75th centile)	1 (0, 3)	1 (0, 2)
Minimum, maximum	0, 6	0, 10
Did not resolve by week 2	**n = *61***	**n = *108***
Number of episodes within 3 months per participant whose symptoms did not resolve within 2 weeks		
Total not resolved by week 2, with 3-month episode data	26	40
Median number of episodes (25th, 75th centile)	1 (0, 2)	1.5 (0, 2)
Minimum, maximum	0, 6	0, 5
Number of episodes within 6 months per participant whose symptoms did not resolve within 2 weeks		
Total not resolved by week 2, with complete episode data[a]	16	25
Median number of episodes (25th, 75th centile)	1 (0, 2)	3 (1, 4)
Minimum, maximum	0, 13	0, 93[b]

a Complete episode data: has both 3-month and 6-month episode data.
b Next largest number is 13 (participant-reported data).

Note
Although new episodes were to be reported only once resolved, many participants reported new episodes even when they did not report previous resolution.

Number of participant-reported bacterial vaginosis treatment courses over 6 months

Data on the number of BV treatment courses over the 6 months of the trial (excluding the study treatment) for those who had resolved by week 2 were available for 59 out of 143 (41%) participants in the metronidazole arm and 35 out of 97 (36%) participants in the lactic acid gel arm (see *Appendix 5*, *Table 40*). For those resolving by week 2, the median number of BV treatment courses received between week 2 and 6 months was similar between the treatment arms (metronidazole arm, median = 1; lactic acid gel arm, median = 1), with an adjusted incidence rate of 1.03 (95% CI 0.53 to 2.01) (see *Appendix 5*, *Tables 40* and *41*), and are explored further in the health economic analysis (see *Chapter 5*).

Microbiological resolution of bacterial vaginosis on microscopy of vaginal smears at week 2

The number of participants with central laboratory microbiological confirmation of BV (Ison–Hay grade 3) on vaginal smears taken at baseline was 138 participants in the metronidazole arm and 128 participants in the lactic acid gel arm (*Table 11*). Of those participants, 77 (56%) in the metronidazole arm and 73 (57%) in the lactic acid gel arm had central laboratory BV results available at week 2. Microbiological resolution of BV at week 2 in those with confirmed BV at baseline was higher in the metronidazole arm (59/77 participants; 77%) than in the lactic acid gel arm (31/73 participants; 42%), with an adjusted risk difference of −34.3% (95% CI −49.1% to −19.5%) (see *Table 11*). Microbiological resolution was defined as having Ison–Hay grade 3 at baseline followed by Ison–Hay grades 0, 1, 2 or U at week 2.

Of those participants with microbiological confirmation of BV at baseline, resolution of symptoms occurred in 83 out of 111 (75%) participants in the metronidazole arm and 49 out of 101 (49%) participants in the lactic acid gel arm.

When rates of resolution were compared between microbiological results and participant-reported symptomatic results, they were similar (60% indicating microbiological resolution and 61% indicating symptomatic resolution) (see *Appendix 5*, *Table 42*). However, these results were not consistent in about one-third of cases with data; that is, 25 out of 145 (17%) samples did not indicate microbiological resolution while the participant did report symptomatic resolution, and a further 24 out of 145 (17%) samples showed microbiological resolution without symptomatic resolution.

Time to participant-reported resolution of bacterial vaginosis symptoms

The median time to participant-reported resolution of BV symptoms (overall, not just up to week 2) was 14 days in both treatment arms (see *Appendix 5*, *Table 43*), with missing times in the first 2 weeks

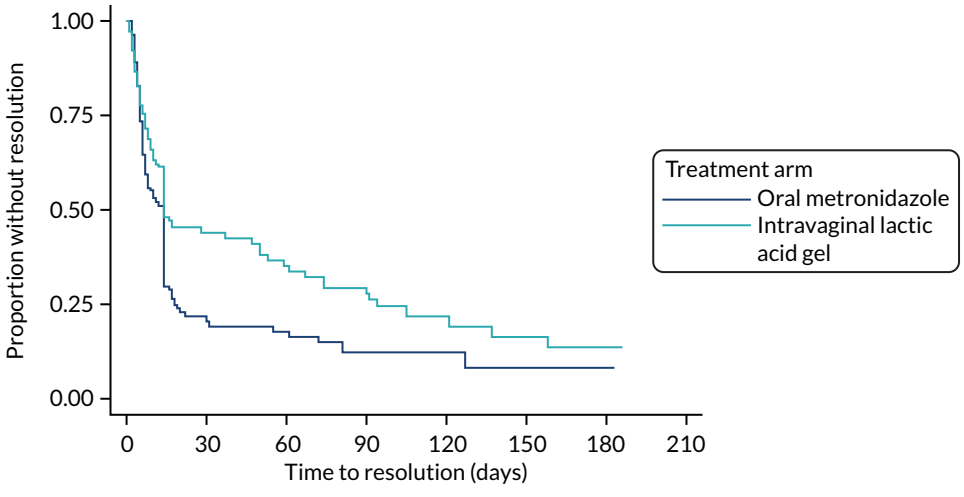
TABLE 11 Microbiological resolution of BV on microscopy of vaginal smears at week 2 in those with positive baseline smear for BV using central laboratory results

Resolution of BV	Treatment arm, *n* (%)		Adjusted risk difference (95% CI)[a]	Adjusted odds ratio (95% CI)[a]
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)		
Number with baseline-confirmed BV (Ison–Hay grade 3 by central laboratory)	138	128		
Microbiological resolution of BV by week 2				
Yes	59 (77)	31 (42)	−34.3% (−49.1% to −19.5%)	0.22 (0.10 to 0.46)
No	18 (23)	42 (58)		
Missing	61	55		

a Adjusted for site and female partners in in 12 months before baseline; adding number of episodes in 12 months before baseline or vaginal douching causes the analysis to not converge.

being substituted by 14 days [40/142 (28%) and 22/97 (23%) of times were substituted in the metronidazole and lactic acid gel arms, respectively], and times for those not recording resolution censored at the latest time without resolution (adjusted difference 0, 95% CI −1.9 to 1.9; 134 values were censored). Without censoring, the median times were 7 days in the metronidazole arm and 8.5 days in the lactic acid gel arm (*Figure 6*; see *Appendix 5*, *Table 43*), and without censoring or substitution median times were 5 days in both arms.

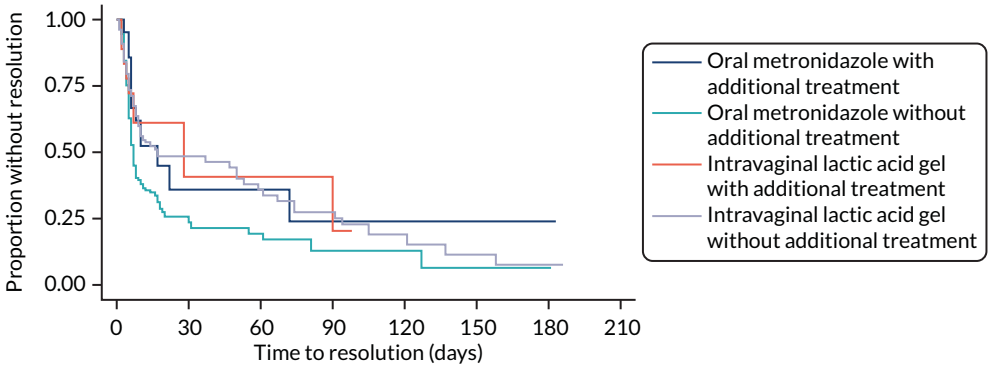
The majority of participants did not report using additional treatment, but, of those who did, median times were slightly longer than for those without (*Figure 7*; see *Appendix 5*, *Table 43*).



Number at risk

Oral metronidazole	192	16	13	9	3	2	2	0
Intravaginal lactic acid gel	179	30	24	20	8	6	5	0

FIGURE 6 Kaplan–Meier plot of time to resolution of BV symptoms at any time up to 6 months.



Number at risk

Oral metronidazole with	21	3	3	2	1	1	1	0
Oral metronidazole without	129	12	9	6	2	1	1	0
Intravaginal lactic acid gel with	18	2	2	2	0	0	0	0
Intravaginal lactic acid gel without	132	23	17	13	5	3	2	0

FIGURE 7 Kaplan–Meier plot of time to resolution of BV symptoms at any time up to 6 months, split by additional treatment. Lines plotted are for oral metronidazole and intravaginal lactic acid gel either with or without additional treatment.

Tolerability of study treatments assessed by participant reporting of side effects

The description of the tolerability data included 516 participants summarised according to the study treatment that they received: 258 in each treatment arm. One participant in each arm did not receive any study treatment [one in the metronidazole arm because they received clotrimazole (Canesten®, Bayer) for thrush diagnosed post randomisation and did not provide any safety data; one withdrew from the lactic acid gel arm prior to receiving any study treatment] (see *Figure 3*). Of the 516 participants included in the tolerability analyses, two in each arm received the other study treatment from that allocated (see *Figure 3*). In addition, of the 258 participants in the metronidazole arm who were included in the tolerability analyses, two withdrew (one of whom was allocated lactic acid gel), whereas no participants withdrew of the 258 participants in the lactic acid gel arm who were included in the tolerability analyses.

In those participants returning week 2 questionnaires, there was a higher reported incidence of side effects in the metronidazole arm than in the lactic acid gel arm, particularly of nausea (32% vs. 8%, respectively), taste changes (18% vs. 1%, respectively) and diarrhoea (20% vs. 6%, respectively) (*Table 12*).

Further details of these side effects are available (see *Appendix 5*, *Tables 44–51*). The proportion of participants with vaginal irritation at week 2 was lower in the group who did not have irritation at baseline than in the group who did (see *Appendix 5*, *Tables 48* and *49*).

Participant-reported adherence to treatment

Of the 318 participants who returned a week 2 questionnaire, 316 (99%) reported that they took at least some of their study treatment (*Table 13*). A total of 294 (92%) participants took at least 85% of their course: 146 out of 157 (93%) participants in the metronidazole arm compared with 148 out of 161 (92%) participants in the lactic acid gel arm (see *Table 13*). For 113 out of 157 (72%) participants in the metronidazole arm, the antibiotic was easy or very easy to take, whereas 142 out of 161 (88%) participants in the lactic acid gel arm reported that their treatment was easy or very easy to use. The brands of lactic acid gel that were used are reported in *Appendix 5*, *Table 53*.

Prevalence of concurrent sexually transmitted infections at baseline and week 2

Prevalence of concurrent STIs at both baseline and week 2 was very low (*Table 14*; see *Appendix 5*, *Tables 54–56*). Out of the samples from unexpired kits (both known and uncertain expiry), there was none positive for gonorrhoea at baseline or week 2, between 1% and 5% positive for chlamydia, and 0–2% positive for trichomoniasis.

Out of the 339 baseline samples that were confirmed as being valid, none had gonorrhoea, 10 (3%) had chlamydia and five (1%) had trichomoniasis (see *Appendix 5*, *Tables 54–56*). Out of the 224 week 2 samples confirmed as being valid, none had gonorrhoea, five (2%) had chlamydia and one (< 1%) had trichomoniasis (see *Appendix 5*, *Tables 54–56*).

Overall, there were 12 participants in the metronidazole arm and three in the lactic acid gel arm with a diagnosed STI at baseline. By week 2, some participants had acquired a STI, whereas in others the infection had resolved (*Table 15*).

An analysis of the prevalence of STIs at week 2, adjusting for baseline STIs and site, showed little difference between the treatment arms, with an odds ratio of 0.15 (95% CI 0.01 to 1.60) (*Table 16*).

Additional follow-up data

Time with bacterial vaginosis recurrence after first resolution of symptoms

The total time with BV recurrence symptoms (in weeks) if they resolved within 2 weeks was reported by a subset of participants. Over the 6-month trial period, this was similar between the two treatment arms (see *Appendix 5*, *Table 57*). At 3 months, 37 out of 143 (26%) participants in the metronidazole

TABLE 12 Overall summary of side effects reported on the week 2 questionnaire

Side effect	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
Nausea		
Yes	50 (32)	13 (8)
No	103 (66)	144 (89)
Missing	3 (2)	4 (2)
Vomiting		
Yes	9 (6)	2 (1)
No	141 (90)	152 (94)
Missing	6 (4)	7 (4)
Taste changes		
Yes	28 (18)	2 (1)
No	127 (81)	156 (97)
Missing	1 (1)	3 (2)
Vaginal irritation[a]		
Yes	44 (28)	34 (21)
No	110 (71)	125 (78)
Missing	2 (1)	2 (1)
Abdominal pain		
Yes	31 (20)	27 (17)
No	123 (79)	132 (82)
Missing	2 (1)	2 (1)
Diarrhoea		
Yes	31 (20)	9 (6)
No	123 (79)	150 (93)
Missing	2 (1)	2 (1)

a For a tabulation split by participants with or without baseline irritation, see *Appendix 5*.

Notes
Tabulated by treatment received. Two participants from each treatment arm received the other study treatment; one participant allocated to lactic acid received no study treatment and withdrew before any follow-up; and one participant allocated to metronidazole received a non-study treatment, but provided no safety data and hence is not included in this table.

arm reported recurrence compared with 23 out of 97 (24%) participants in the lactic acid gel arm. At 6 months, 51 out of 143 (36%) participants in the metronidazole arm reported recurrence compared with 32 out of 97 (33%) participants in the lactic acid gel arm.

Status of symptoms for those without resolution at week 2

The status of symptoms for those without resolution at week 2 was 'better but not cleared/disappeared' or 'improved initially but worsened again' in more than half of the participants and similar in both treatment arms (see *Appendix 5*, *Table 58*). In total, 39 out of 60 (65%) participants in the metronidazole arm reported 'better' or 'improved' compared with 64 out of 106 (60%) participants in the lactic acid gel arm.

TABLE 13 Summary of adherence to study treatment (participant reported)

Participant-reported adherence	Treatment arm		Total (*N* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Number of participants returning questionnaire	157	161	318
Participant took/used any randomised treatment*, n *(%)			
Yes	156 (99)	160 (99)	316 (99)
No	1 (1)	1 (1)	2 (1)
Missing	0	0	0
***Course of study treatment completed*, n *(%)*[a]**			
Yes	144 (92)	147 (91)	291 (92)
No	13 (8)	14 (9)	27 (8)
Missing	0	0	0
Percentage of treatment course completed			
n	157	161	318
Mean (SD)	94% (18.4%)	95% (12.9%)	95% (15.8%)
Median (25th, 75th centile)	100% (100%, 100%)	100% (100%, 100%)	100% (100%, 100%)
Minimum, maximum	0%, 100%	0%, 100%	0%, 100%
Received at least 85%, *n* (%)	146 (93)	148 (92)	294 (92)
***Reason if treatment course not completed*, n *(%)*[b]**			
Accidentally missed	10 (48)	7 (58)	17 (52)
Did not like using/taking it	1 (5)	1 (8)	2 (6)
Side effects of treatment	4 (19)	0	4 (12)
Other[c]	6 (29)	4 (33)	10 (30)
Ease of taking study treatment*, n *(%)			
Very easy	63 (40)	81 (50)	144 (45)
Easy	50 (32)	61 (38)	111 (35)
Neither easy nor difficult	35 (22)	16 (10)	51 (16)
Difficult	7 (4)	2 (1)	9 (3)
Very difficult	1 (1)	0	1 (< 0.5)
Missing	1 (1)	1 (1)	2 (1)
***Time from randomisation to treatment start (days)*[d]**			
n	156	156	312
Median (25th, 75th centile)	0 (0, 1)	0 (0, 1)	0 (0, 1)
Minimum, maximum	0, 26	0, 17	0, 26

a As reported by the participant. Response was not changed even when contradicted by other data.
b Reasons (mutually exclusive) are included even when the participant reported completing the course (metronidazole arm, *n* = 8; lactic acid gel arm, *n* = 2). Four in the lactic acid gel arm reported not completing the course but did not give one of the four reasons; of these three added text (see *Appendix 5*, *Table 52*).
c Other reasons are given (see *Appendix 5*, *Table 52*), including some for which the 'other' reason was not given as 'yes'.
d Treatment start dates recorded as before randomisation dates are assumed to be incorrect and are substituted by the randomisation date: seven participants in the metronidazole arm and four participants in the lactic acid gel arm gave a treatment start date before the randomisation date. One start date was the same as the week 2 questionnaire date, although they indicated taking all doses.

TABLE 14 Prevalence of STIs at baseline and week 2

STI present (gonorrhoea, chlamydia or trichomoniasis)	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Baseline samples received by the central laboratory	253	256
Week 2 samples received by the central laboratory	148	153
Baseline (excludes out-of-date sample kits)		
N	237	240
Yes	20 (8)	8 (3)
No	214 (90)	230 (96)
Missing	3 (1)	2 (1)
Week 2 (excludes out-of-date sample kits)		
N	140	142
Yes	8 (6)	3 (2)
No	126 (90)	136 (96)
Missing	6 (4)	3 (2)
Baseline (excludes out-of-date sample kits and those with unknown expiry status)		
N	166	173
Yes	12 (7)	3 (2)
No	152 (92)	169 (98)
Missing	2 (1)	1 (1)
Week 2 (excludes out-of-date sample kits and those with unknown expiry status)		
N	110	114
Yes	5 (5)	1 (1)
No	103 (94)	110 (97)
Missing	2 (2)	3 (3)

Some sample kits were found to have expired; for some the expiry status was unknown for the time of use. Missing include those with no outcome as well as no sample received.

TABLE 15 Prevalence of STIs at baseline and week 2

	Treatment arm: STI at week 2 (*n*)			
	Oral metronidazole (*N* = 259)		Intravaginal lactic acid gel (*N* = 259)	
STI at baseline	Yes	No	Yes	No
Yes	2	2	1	2
No	3	84	0	97

Includes results from samples where both baseline and week 2 kits were available and in date.

TABLE 16 Analysis of prevalence of STIs at week 2

Excludes out-of-date sample kits and those with expiry date unknown	Treatment arm, *n* (%)		Adjusted odds ratio (95% CI)[a]
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Number with a STI at baseline	12	3	
Number with a STI at week 2			
Yes	5 (5)	1 (1)	0.15 (0.01 to 1.60)
No	103 (95)	110 (99)	
Missing	151	148	

a Adjusted for site and baseline STI; the only covariates that can be included without collinearity problems.

Note
The unadjusted difference is −3.7% (95% CI −8.1% to 0.6%); the unadjusted odds ratio is 0.19 (0.02, 1.63).
In the metronidazole arm, three out of the five participants with an STI at week 2 did not have an STI at baseline.

Symptoms at week 2

Around one-third of participants reported the presence of typical BV symptoms at week 2, including genital discharge, offensive vaginal smell and vaginal irritation (see *Appendix 5*, *Table 59*). Slightly fewer participants (33%) in the metronidazole arm than in the lactic acid gel arm (41%) reported genital discharge at week 2. This was similar for those having an offensive vaginal smell (27% in the metronidazole arm vs. 40% in the lactic acid gel arm). Fewer participants reported vaginal irritation at week 2 in the lactic acid gel arm than in the metronidazole arm (23% vs. 30%, respectively).

Symptoms at recurrence compared with typical symptoms

Where reported, recurrence symptoms were mostly typical of usual BV symptoms in both treatment arms (see *Appendix 5*, *Table 60*). At 3 months, 28 out of 37 (76%) participants in the metronidazole arm reported recurrence symptoms that were 'always' typical of usual symptoms, compared with 15 out of 23 (65%) participants in the lactic acid gel arm. The corresponding results at 6 months were 22 out of 51 (43%) participants in the metronidazole arm and 13 out of 32 (41%) participants in the lactic acid gel arm. There was only one report of recurrence symptoms seldom being typical of usual symptoms, and this was in the lactic acid gel arm.

Additional medication for bacterial vaginosis

Nearly half of all participants in both treatment arms reported taking additional medication for BV after the first 2 weeks. Metronidazole tablets and lactic acid gel were the most frequently used additional medication, with similar proportions of each being taken in both treatment arms (see *Appendix 5*, *Tables 61* and *62*). A total of 52 out of 111 (47%) participants in the metronidazole arm and 51 out of 108 (47%) participants in the lactic acid gel arm took additional medication within 3 months, whereas 44 out of 92 (48%) and 39 out of 84 (46%) participants, respectively, took additional medication within 6 months.

Antibiotics for other conditions/illness

Around 10% of participants in both treatment arms took antibiotics for other conditions or illness in each reporting time period (see *Appendix 5*, *Tables 63* and *64*). In total, 15 out of 157 (10%) participants in the metronidazole arm and 21 out of 161 (13%) participants in the lactic acid gel arm took antibiotics for other conditions within the first 2 weeks, 8 out of 111 (7%) and 12 out of 108 (11%), respectively, took antibiotics within 3 months, and 9 out of 92 (10%) and 10 out of 84 (12%), respectively, took antibiotics within 6 months.

Vaginal thrush post randomisation

In the first 2 weeks post randomisation, of those returning a week 2 questionnaire, 42 out of 157 (27%) participants in the metronidazole arm and 27 out of 161 (17%) participants in the lactic acid gel

arm reported developing thrush, for which around half of the participants took treatment (see *Appendix 5*, *Table 65*). Between week 2 and 3 months, of those returning a 3-month questionnaire, 20 out of 111 (18%) participants in the metronidazole arm and 26 out of 108 (24%) participants in the lactic acid gel arm developed thrush. Of those returning a 6-month questionnaire, 23 out of 92 (25%) and 20 out of 84 (24%) participants developed thrush between 3 and 6 months, respectively, in the two arms. The overall incidence over the 6 months was 60 out of 259 (23%) participants in the metronidazole arm and 58 out of 259 (22%) participants in the lactic acid gel arm (where no incidence over 6 months meant that 'no' was reported on all three questionnaires).

Sexual contact post baseline

Having sex, use of condoms and new sexual partners were similar between the two arms (see *Appendix 5*, *Table 66*). Nearly half of all participants reported having sex between the start of study treatment and the week 2 assessment in both treatment arms [71/157 (45%) in the metronidazole arm vs. 67/161 (42%) in the lactic acid gel arm]. Around three-quarters of participants did not use condoms [52/71 (73%) in the metronidazole arm vs. 48/67 (72%) in the lactic acid gel arm].

Vaginal douching post randomisation

Few participants (< 9%) reported vaginal douching during the trial, with similar percentages in each treatment arm (see *Appendix 5*, *Table 67*). At week 2, 6 out of 157 (4%) participants in the metronidazole arm reported that vaginal douching had been performed, compared with 6 out of 161 (4%) participants in the lactic acid gel arm. At 3 months, 6 out of 111 (5%) compared with 8 out of 108 (7%) participants, respectively, reported vaginal douching. At 6 months, 6 out of 92 (7%) compared with 7 out of 84 (8%), respectively, reported vaginal douching.

Participant-reported sexually transmitted infections diagnosed from 2 weeks post baseline

The incidence of participant-reported STIs diagnosed from 2 weeks post baseline was low (see *Appendix 5*, *Table 68*). In the metronidazole arm, there were five episodes of gonorrhoea, three of chlamydia, four of trichomoniasis and three of PID. In the lactic acid gel arm, there was one episode of gonorrhoea, four of chlamydia, zero of trichomoniasis and five of PID.

Other reasons reported by participants for not returning a week 2 sample

Other reasons reported by participants for not returning a week 2 sample are given in *Appendix 5*, *Table 69*. These are summarised when a sample was not received by the laboratory; often the questionnaire was completed before taking the sample. There were eight in total, five of which were because of the participant having their period (three in the metronidazole arm and two in the lactic acid gel arm).

Symptoms over the 6 months

A post hoc investigation looked at the number of participants whose symptoms resolved and remained so for 6 months compared with those whose symptoms did not resolve or who had symptoms at some point in the 6 months (see *Appendix 5*, *Table 70*). Of those with data reported at all three time points over the 6 months, 21 out of 91 (23%) participants in the metronidazole arm and 14 out of 88 (16%) participants in the lactic acid gel arm resolved and remained so for the 6 months.

Additional safety data

There were no participant-reported hospitalisations in the 2 weeks from randomisation, either for BV or for treatment-related side effects, and no SAEs or suspected unexpected serious adverse reactions were reported. There were two known pregnancies, both in the lactic acid gel arm. The estimated conception dates were 20 days pre randomisation (participant chose to have an induced abortion) and 63 days after randomisation (outcome unknown as the site was unable to make contact with the participant).

Chapter 4 Health economic evaluation

Introduction

The global economic burden of BV is substantial, with almost US$4.8B spent on treatments each year around the world.[9] The standard antibiotic treatment for BV, metronidazole, is associated with side effects and high recurrence rates,[9,33] and alternative options are, therefore, required to reduce antibiotic use, provide better efficacy and reduce the recurrence of this condition. Intravaginal lactic acid gel has been proposed as an alternative treatment; however, more evidence is required on the costs of this treatment compared with oral metronidazole, in addition to assessing its clinical effectiveness. The objective of the economic evaluation in the VITA trial was to compare the cost-effectiveness of intravaginal lactic acid gel with oral metronidazole in the treatment of recurrent BV.[25] In addition, given that the trial was investigating whether or not intravaginal lactic acid gel could be used to help reduce antibiotic exposure, exploratory analyses were included to investigate the costs associated with antibiotic resistance as a penalty cost for antibiotic use. It is important to consider this type of cost because economic evaluations that include antibiotic treatments but do not include the cost of AMR may provide suboptimal information for decision-makers.[34]

Methods

The health economic analysis involved both a cost-effectiveness analysis (using the primary clinical outcome) and a cost–utility analysis. The economic evaluation was conducted from a health-care (NHS) perspective. The methods used for this within-trial analysis were guided by National Institute for Health and Care Excellence recommendations[35] and followed Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for reporting.[36] Discounting was not required for costs and outcomes because participants were followed up for a period of 6 months.

Health outcomes

The cost-effectiveness analysis reflected the primary outcome of the trial, which was participant-reported resolution of BV symptoms at week 2. The cost–utility analysis assessed health-related quality of life (HRQoL) using the SF-12 health survey (version 2), which was completed by participants at baseline, week 2, 3 months and 6 months. The SF-12 was selected as a measure of HRQoL because previous research had suggested that the derived utility scores [Short Form questionnaire-6 Dimensions (SF-6D)] were more efficient at detecting differences in self-reported health status in a related area (maternal health).[37] An algorithm developed by Brazier and Roberts[38] was used to predict the SF-6D preference-based score from the SF-12 health survey. The values were obtained from a survey of the UK population to derive a utility-based algorithm. The SF-6D is a preference-based measure that is composed of a six-dimensional health state classification and uses information from the SF-12 health survey.[38] The SF-6D values take into account societal preferences for health states and, therefore, can be used to obtain quality-adjusted life-years (QALYs). Following the trapezium rule, these data were used to calculate QALY gain at 6 months.[39]

Resource use and costs

For the economic evaluation, the perspective that was adopted was that of the NHS (health-care perspective), meaning that only direct health-care costs were considered. Self-reported web-based questionnaires were distributed to all participants at each follow-up point to collect resource use data in primary and secondary care settings, such as treatment use, GP visits, clinic visits, additional medication for BV and thrush, and other health-care resource use to estimate the costs associated with the

administration of both treatments. A separate analysis was conducted to consider any 'out-of-pocket' expenses incurred by participants, including the cost of non-prescribed medications as part of the sensitivity analysis.

The following assumptions were made in relation to resource use:

- Where participants reported that a health resource was utilised without specifying the number of health-care contacts, a minimum number of contacts was assumed. For example, if a GP visit was reported without further data, it was assumed that there had been one GP visit. Although it was planned to use multiple imputation to account for missing data, this was not possible owing to the extent of missing data.[40]
- If thrush was reported and treatment obtained, it was assumed that the participant had obtained one course of the treatment specified.

Valuation of resource use

A microcosting approach was used to estimate the total costs associated with each treatment arm. This approach assigned costs to each component of resource use to capture the participant-level variation in costs.

Data on unit costs were obtained from routine and published literature, such as *Unit Costs of Health and Social Care*[41] and NHS reference costs.[42] The prices of study treatment and additional medication were obtained from the *British National Formulary*.[43] Relevant items of resource use, their associated unit costs, their description and the source from which these costs were obtained are given in *Appendix 5*, *Table 71*. All costs were reported in UK currency [Great British pounds (GBP)] for 2018–19. Where necessary, costs were inflated using the Hospital and Community Health Services Pay and Prices Index.[41] Baseline characteristics were not controlled for in relation to costs because exploratory analyses suggested that baseline characteristics were not significant predictors of costs.

Analysis

Main analysis

Initially, a cost–consequence analysis was carried out in which all costs and outcomes were reported in a disaggregated manner. The costs and outcomes associated with the alternative treatment, intravaginal lactic acid gel, were compared with those for oral metronidazole. A cost-effectiveness analysis was also carried out with results reported in terms of the cost per case successfully treated at week 2. In addition, the cost–utility analysis evaluated the results in terms of cost per QALY gained at 6 months.

The cost-effectiveness analysis was presented as cost per case successfully resolved at week 2 for both treatment arms. For the cost–utility analysis, the incremental cost-effectiveness ratio (ICER) was estimated by dividing the difference in mean total cost between the study treatments by the difference in QALYs at 6 months.

The approach for the cost-effectiveness analysis was intention to treat, to reflect the approach taken in the clinical analysis. For the cost–utility analysis, a complete-case approach was adopted. Any participant randomised in error was analysed as randomised in keeping with the clinical analysis. Given that cost data are likely to be positively skewed, a bootstrapping approach was undertaken to calculate 95% CIs around mean costs.[44] This approach was used to generate repeated random samples with replacement from the original data.[44] In this approach, if the CIs of the difference in mean costs between arms cross zero, this indicates no significant difference.

All analyses were performed using Stata® version 16 (StataCorp LP, College Stations, TX, USA). Only a within-trial analysis was conducted. In view of the trial results, a longer-term decision-analytic model extrapolating findings beyond the trial period was not deemed necessary.

Sensitivity analysis

A bootstrapping approach was employed to determine the sampling uncertainty around the final outcomes by generating 5000 replications of incremental cost and benefit estimates.[45] The estimates of both cost-effectiveness and cost–utility analyses were presented on a cost-effectiveness plane as a scatterplot to aid interpretation.[46] A number of deterministic sensitivity and scenario analyses were carried out to explore the impact of variation in the estimated values and assumptions on the results. Taking a broader perspective, we considered out-of-pocket costs of non-prescribed medication at week 2 and 6 months for the primary and secondary outcomes. The cost of metronidazole was increased to take into account that the more expensive metronidazole Flagyl® (400 mg), which was administered in the trial rather than a cheaper alternative. In addition, the BV resolution rate at week 2 was varied using the data reported in *Table 5* (see *Chapter 3*); this assumed that if all participants did not report symptoms at that time point, their BV had resolved.

Given that limited data on thrush treatment were provided at 3 and 6 months, the number of episodes of vaginal thrush was used and combined with the cost of clotrimazole to estimate the cost of thrush treatment over 6 months. The assumption was that each participant with thrush symptoms was administered one course of clotrimazole pessary for each episode.

A further analysis was conducted assuming that all those who developed symptoms post treatment would be given an additional course of oral metronidazole, irrespective of the treatment arm that they were allocated to. Data from a post hoc analysis showed that 77% of participants in the metronidazole arm developed symptoms after finishing treatment, along with 84% of participants in the lactic acid gel arm (see *Appendix 5*, *Table 70*). These findings were used and presented in the sensitivity analysis, assuming that each participant who developed symptoms was treated with one additional course of oral metronidazole.

The cost associated with antibiotic resistance has been estimated as a penalty cost for using antibiotics.[34] The impact of including such a penalty cost was analysed as part of the sensitivity analysis. Owing to a lack of evidence on the costs associated with AMR for metronidazole, a range of costs of AMR associated with different antibiotics was used to represent the potential economic cost of consuming oral metronidazole in terms of increasing resistance.[47] Economic costs from both a health-care perspective and a societal perspective were used in the sensitivity analyses, drawing on published estimates.[47] These estimates were converted from US dollars (USD) to GBP using the market exchange rate (1 USD = 0.76 GBP).

Results

Questionnaire response rate

As reported in *Chapter 3*, 518 participants were randomised into the trial, of whom 294 (57%) completed the resource use questionnaire at week 2: 143 in the metronidazole arm and 151 in the lactic acid gel arm. A total of 123 (24%) participants completed the resource use questionnaire at all time points (week 2, 3 months and 6 months) and were included in the base-case analysis at 6 months. The number of participants who responded to the resource use questionnaire and SF-12 health survey at different time points is provided for each treatment arm (see *Appendix 5*, *Table 72*). The baseline characteristics for those who completed resource use questionnaires at week 2 and at all time points are available (see *Appendix 5*, *Table 73*). It had been planned to use multiple imputation to generate estimates of missing values based on the distribution of observed data;[48,49] however, given

that resource use questionnaire data were missing for > 40% of participants at different time points, multiple imputation could not be used and a complete-case analysis was adopted.[40]

Health outcomes

The mean SF-6D scores at each time point for each treatment arm are presented in *Table 17*. The results indicate that the differences in the mean values between the two treatment arms were not significant. The QALY gains were slightly lower for the lactic acid gel arm than for the metronidazole arm, with a mean difference of −0.003 QALYs (95% CI −0.013 to 0.009 QALYs). However, this difference was not statistically significant.

Cost and resource use

Week 2

The mean resource use and costs at week 2 are presented in *Table 18* for each treatment arm. On average, participants in the lactic gel acid arm reported more health-care resource use than those in the metronidazole arm.

The mean total cost was slightly higher for participants in the lactic acid gel arm (£55.38) than for those in the metronidazole arm (£48) at week 2 (*Table 19*). The mean difference in costs between the two arms was £7.38 (95% CI −£20.15 to £36.38), although the difference was not statistically significant. The main costs for both arms related to primary and secondary care costs (88–90% of total costs). In general, the difference in costs between the treatment arms was related to the need for additional GP and sexual clinic consultations. Hence, the initial analysis found that treatment with intravaginal lactic acid gel resulted in slightly higher health-care costs.

Six months

A breakdown of the resource use data and the mean health-care costs by treatment arm is presented in *Table 20*. Those in the lactic acid gel arm generally reported more health service utilisation than those in the metronidazole arm.

Over the 6-month follow-up period, the accumulated total mean costs were £273 in the lactic acid gel arm and £214 in the metronidazole arm (*Table 21*). For both arms, the highest proportion of costs related to the utilisation of primary and secondary care services. The cost difference between the two arms was £58.60; however, this difference in costs was not statistically significant (95% CI −£55.05 to £185.32).

TABLE 17 Mean SF-6D values by time point and treatment arm

Quality of life	Treatment arm, mean (SD)		Mean bootstrap difference (95% CI)
	Oral metronidazole ($n = 61$)	Intravaginal lactic acid gel ($n = 48$)	
SF-6D[a]			
Baseline	0.786 (0.127)	0.765 (0.126)	−0.021 (−0.066 to 0.026)
Week 2	0.711 (0.076)	0.712 (0.068)	0.001 (−0.025 to 0.031)
3 months	0.692 (0.069)	0.688 (0.068)	−0.004 (−0.029 to 0.022)
6 months	0.696 (0.075)	0.684 (0.085)	−0.012 (−0.044 to 0.017)
QALYs			
QALYs gained at 6 months	0.351 (0.030)	0.348 (0.028)	−0.003 (−0.013 to 0.009)

a SF-6D scores were derived from SF-12 health survey scores.

TABLE 18 Mean resource use and disaggregated costs across treatment arms at week 2

Resource use	Treatment arm					
	Oral metronidazole (*N* = 143)			Intravaginal lactic acid gel (*N* = 151)		
	Participants accessing the service (*n*)	Mean resource use per participant (SD)	Mean cost per participant (SD) (£)	Participants accessing the service (*n*)	Mean resource use per participant (SD)	Mean cost per participant (SD) (£)
GP contact						
Face to face	6	0.04 (0.20)	1.64 (7.85)	10	0.08 (0.32)	3.10 (12.35)
Telephone	1	0.01 (0.17)	0.22 (2.59)	3	0.03 (0.20)	0.41 (3.07)
Nurse						
Face to face	0	0	0	0	0	0
Telephone	0	0	0	0	0	0
NHS walk-in centre						
Face to face	6	0.06 (0.28)	2.18 (11.12)	4	0.03 (0.21)	1.29 (8.32)
Telephone	0	0	0	0	0	0
NHS 111						
Telephone	0	0	0	0	0	0
Pharmacy						
Face to face	6	0.05 (0.27)	1.43 (7.23)	6	0.06 (0.31)	1.75 (9.10)
Telephone	0	0	0	0	0	0
Sexual health clinic						
Face to face	18	0.17 (0.49)	20.48 (59.67)	25	0.29 (0.98)	34.74 (119.02)
Telephone	6	0.04 (0.20)	0.33 (1.57)	9	0.06 (0.24)	0.46 (1.85)
NHS outpatient						
Face to face	5	0.10 (0.62)	14.10 (89.32)	3	0.03 (0.24)	4.77 (34.95)
Telephone	3	0.04 (0.35)	1.58 (13.29)	0	0	0
Out-of-hours service						
Face to face	1	0.01 (0.08)	0.48 (5.69)	1	0.01 (0.08)	0.45 (5.53)
Telephone	0	0	0	0	0	0
A&E						
Face to face	1	0.01 (0.08)	0.93 (11.12)	2	0.01 (0.11)	1.76 (15.26)

A&E, accident and emergency.

TABLE 19 Mean total cost per participant (2018/19 prices): complete case at week 2

Type of health-care cost	Treatment arm, mean cost (SD) (£)		Mean bootstrap difference (95% CI) (£)
	Oral metronidazole (*n* = 143)	Intravaginal lactic acid gel (*n* = 151)	
Study treatment	3.97 (NA)	5.25 (NA)	1.28 (NA)
Primary and secondary care	43.35 (112.00)	48.44 (113.49)	5.09 (–22.09 to 33.67)
Additional medication: prescribed	0.707 (2.49)	1.42 (4.21)	0.71 (–0.05 to 1.51)
Total cost	48.00 (112.68)	55.38 (134.89)	7.38 (–20.15 to 36.38)

NA, not applicable.

TABLE 20 Mean resource use and disaggregated costs across treatment arms at 6 months

Resource use	Treatment arm					
	Oral metronidazole (*N* = 69)			Intravaginal lactic acid gel (*N* = 54)		
	Participants accessing the service (*n*)	Mean resource use per participant (SD)	Mean cost per participant (SD) (£)	Participants accessing the service (*n*)	Mean resource use per participant (SD)	Mean cost per participant (SD) (£)
GP contact						
Face to face	12	0.28 (0.70)	10.74 (27.48)	18	0.69 (1.38)	26.72 (54.01)
Telephone	4	0.13 (0.59)	2.02 (9.17)	5	0.19 (0.62)	2.87 (9.56)
Nurse						
Face to face	2	0.03 (0.17)	0.63 (3.67)	5	0.11 (0.37)	2.41 (8.08)
Telephone	1	0.01 (0.12)	0.11 (0.94)	2	0.04 (0.19)	0.29 (1.49)
NHS walk-in centre						
Face to face	7	0.13 (0.42)	5.09 (16.26)	2	0.06 (0.30)	2.17 (11.78)
Telephone	0	0	0	0	0	0
NHS 111						
Telephone	4	0.07 (0.31)	1.03 (4.46)	0	0	0
Pharmacy						
Face to face	8	0.17 (0.54)	5.10 (15.86)	16	0.54 (1.00)	15.74 (29.42)
Telephone	0	0	0	1	0.02 (0.14)	0.26 (1.91)
Sexual health clinic						
Face to face	31	1.12 (1.74)	136.14 (211.86)	30	1.39 (2.30)	169.44 (280.83)
Telephone	9	0.23 (0.69)	1.81 (5.37)	9	0.22 (0.88)	1.73 (6.89)
NHS outpatient						
Face to face	7	0.23 (0.89)	33.39 (128.67)	5	0.20 (0.88)	29.33 (126.28)
Telephone	3	0.09 (0.51)	3.27 (19.06)	1	0.04 (0.27)	1.39 (10.23)
Out-of-hours service						
Face to face	2	0.03 (0.17)	1.97 (11.49)	1	0.02 (0.14)	1.26 (9.25)
Telephone	0	0	0	0	0	0
A&E						
Face to face	1	0.01 (0.12)	1.93 (16.01)	1	0.04 (0.27)	4.93 (36.20)
Telephone	0	0	0	0	0	0
Other services: GP						
Three face-to-face visits and three telephone calls	0	0	0	3	6	2.98 (21.91)

A&E, accident and emergency.

TABLE 21 Mean total cost per participant (2018/19 prices): complete case at 6 months

Type of health-care cost	Treatment arm, mean cost (SD) (£)		Mean bootstrap difference (95% CI) (£)
	Oral metronidazole ($n = 69$)	Intravaginal lactic acid gel ($n = 54$)	
Study treatment	3.97 (NA)	5.25 (NA)	1.28 (NA)
Primary and secondary care	203.23 (295.55)	258.54 (359.33)	55.31 (–57.38 to 184.12)
Additional medication: prescribed	8.28 (16.45)	6.84 (9.85)	–1.16 (–3.74 to 1.32)
Total cost	214.48 (302.45)	273.08 (366.14)	58.60 (–55.05 to 185.32)

NA, not applicable.

Base-case analysis

Cost-effectiveness analysis

The results of the base-case cost-effectiveness analysis are presented in *Table 22*. It is evident that lactic acid gel was less clinically effective than metronidazole in terms of participants with resolved symptoms at week 2, and that the average costs were higher. The average cost per participant with resolved BV for those in the lactic acid gel arm was £147.00, compared with £86.94 for those in the metronidazole arm.

Cost–utility analysis

The base-case cost–utility analysis demonstrated that intravaginal lactic acid gel was dominated by oral metronidazole, which meant that the alternative treatment was likely to be more costly and less effective at 6 months (*Table 23*). The analysis suggested that oral metronidazole resulted in more QALYs and was less costly than intravaginal lactic acid gel at 6 months; however, the differences in costs and outcomes were not statistically significant.

Sensitivity analysis

The results of the deterministic sensitivity analyses in which we explored the impact of varying the assumptions and for different scenarios are presented for both the cost-effectiveness and the cost–utility analyses in *Tables 24* and *25*. Using alternative cost estimates for metronidazole and including the cost of non-prescribed (out-of-pocket) medications administered at different time points did not affect the overall results. Including additional costs of the management of thrush at 3 and 6 months and a further course of treatment for those who developed symptoms post study treatment did slightly increase the total mean cost for both arms, but intravaginal lactic acid was still more costly than oral metronidazole.

TABLE 22 Cost-effectiveness results

Economic evaluation	Treatment arm	
	Oral metronidazole ($n = 259$)	Intravaginal lactic acid gel ($n = 259$)
Mean total cost (£) for participants who returned the week 2 questionnaire	48.00	55.38
Number of participants with resolution of BV symptoms at week 2[a]	143	97
Cost (£) per participant with resolved BV[b]	86.94	147.00

a See *Chapter 3*, *Table 4*, for further details on participant-reported resolution at week 2.
b See *Table 19* for further details on costs.

TABLE 23 Cost–utility results: complete case

Economic evaluation	Treatment arm	
	Oral metronidazole ($n = 61$)	Intravaginal lactic acid gel ($n = 48$)
Mean cost per participant (£)	214.48	273.08
Incremental cost (£)	–	58.60
Mean QALYs	0.351	0.348
Incremental QALYs	–	–0.003
ICER (cost per QALY)[a]	–	Dominated

a Intravaginal lactic acid is dominated by oral metronidazole given that it is more costly and less clinically effective.

TABLE 24 Deterministic sensitivity analyses: cost-effectiveness analysis

Deterministic sensitivity analysis scenario	Treatment arm, average cost per participant with resolved BV (£)	
	Oral metronidazole	Intravaginal lactic acid gel
Including the cost of non-prescribed (out-of-pocket) additional medication	88.82	149.87
Varying the cost of metronidazole to £6.34	91.61	147.00
Assuming missing data on symptom resolution as symptoms resolved	62.47	93.75
Considering economic cost of AMR: health-care perspective	87.03–88.24	147.00
Considering economic cost of AMR: societal perspective	88.86–119.65	147.00

TABLE 25 Deterministic sensitivity analyses: cost–utility analysis

Deterministic sensitivity analysis scenario	Treatment arm				Mean difference		ICER
	Oral metronidazole		Intravaginal lactic acid gel				
	Mean cost (£)	Mean QALYs	Mean cost (£)	Mean QALYs	Cost (£)	QALYs	QALYs per cost
Including the cost of non-prescribed (out-of-pocket) additional medication	220.08	0.351	281.92	0.348	61.84	–0.003	Dominated
Including cost of thrush treatment at 3–6 months	215.81	0.351	274.19	0.348	58.38	–0.003	Dominated
Including cost of treating symptoms after initial study treatment	217.53	0.351	276.39	0.348	59.92	–0.003	Dominated

Considering the cost of AMR associated with the use of metronidazole led to an increased mean cost for the metronidazole arm, but the average cost per participant with resolved BV remained higher for intravaginal lactic acid gel across all estimates for the potential cost of AMR that was used.

The results of 5000 bootstrap replications plotted on the cost-effectiveness plane for the primary analysis (*Figure 8*) suggest that lactic acid gel is likely to be less clinically effective than metronidazole because all replicates are to the left of the origin (worse health outcome). However, there is some uncertainty around the difference in costs between the treatment arms, as replicates are distributed almost equally across the north-west quadrant (less clinically effective and greater cost) and the south-west quadrant (less clinically effective and lower cost). Accordingly, there is uncertainty around whether intravaginal lactic acid gel was more or less costly than oral metronidazole at week 2.

For the cost–utility analysis, the cost-effectiveness plane (*Figure 9*) shows that the majority of the bootstrap replicates were located in the north-west quadrant, suggesting that intravaginal lactic acid gel is more costly and less clinically effective than oral metronidazole at 6 months. However, some uncertainty was apparent, as some replicates were found in the north-east quadrant (more effective and more costly) and in the south-west quadrant (less clinically effective and less costly).

Discussion

Principal findings

The results of the primary analysis suggest that intravaginal lactic acid gel is less clinically effective and slightly more costly than oral metronidazole in resolving BV symptoms by week 2. At week 2, lactic acid gel was associated with an additional cost of £7.38 (95% CI −£20.15 to £36.38) per participant. The additional cost was mainly attributed to the utilisation of secondary care resources, mainly sexual health clinics. The total cost might have been lower if more participants from primary care (general)

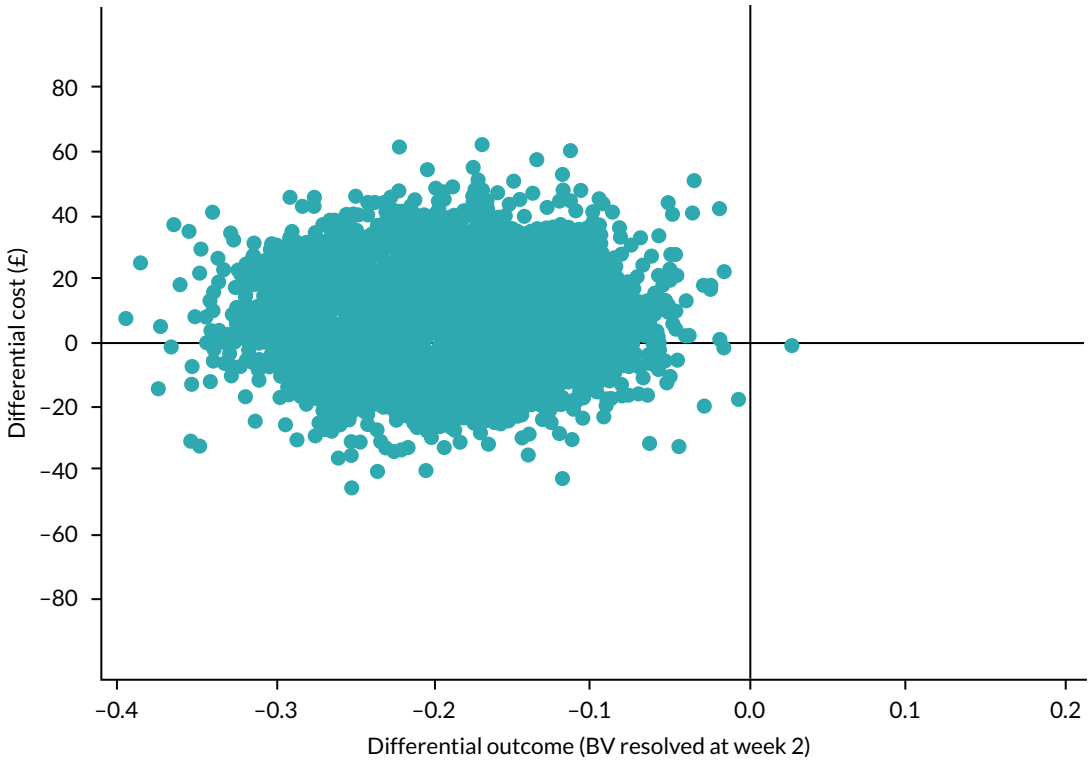


FIGURE 8 Cost-effectiveness plane of the primary outcome at week 2 (oral metronidazole vs. intravaginal lactic acid gel).

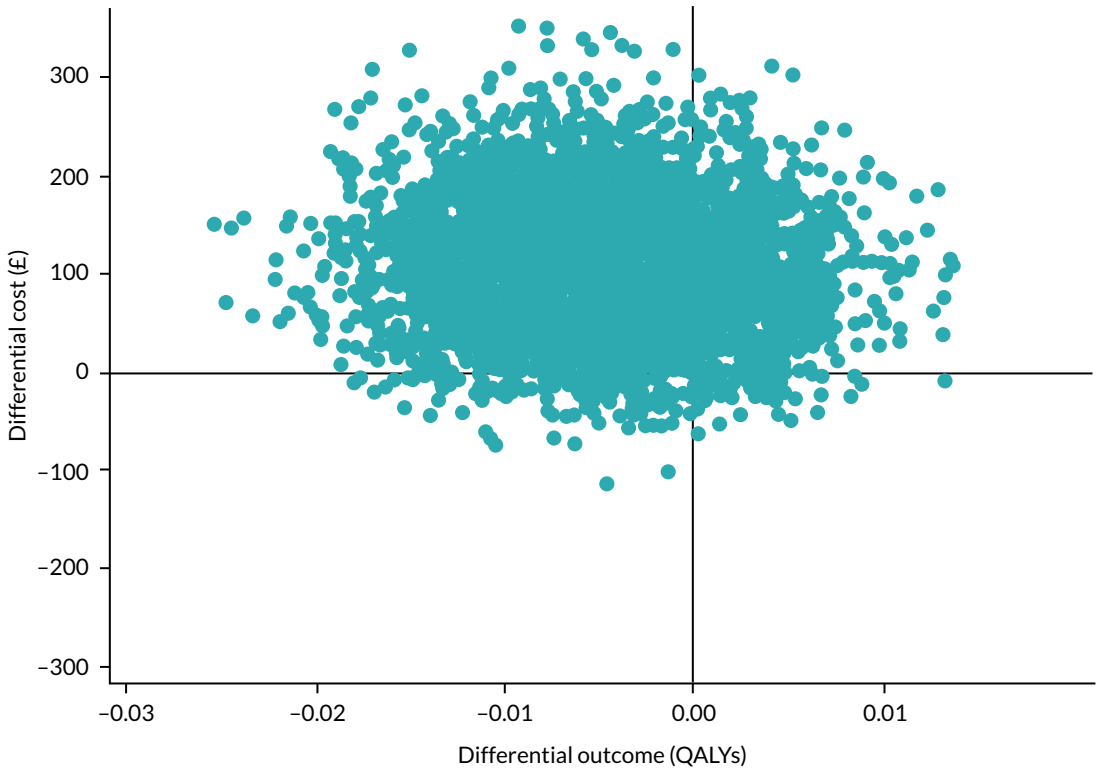


FIGURE 9 Cost-effectiveness plane of the secondary outcome at 6 months (oral metronidazole vs. intravaginal lactic acid gel).

practices had been recruited into the trial. The cost per participant with resolved BV was £147.00 in the lactic acid gel arm, compared with £86.94 in the metronidazole arm. The cost-effectiveness plane that incorporates the uncertainty around each point estimate in the results shows that, relative to oral metronidazole, intravaginal lactic acid gel is likely to be less effective. However, there is uncertainty around the difference in costs, suggesting that intravaginal lactic acid gel could be either more or less costly than oral metronidazole.

The cost–utility analysis showed that intravaginal lactic acid gel was dominated by oral metronidazole at 6 months, although there was some uncertainty around the differences in costs and outcomes.

Strengths and limitations

The strength of the economic evaluation is that it was based on a multicentre RCT exploring the potential cost-effectiveness of intravaginal lactic acid gel compared with the current standard treatment of oral metronidazole. To our knowledge, this is the first economic evaluation conducted alongside a trial that has explored intravaginal lactic acid gel as an alternative treatment for BV. Detailed data on resource use and health outcomes were collected at different time points using web-based questionnaires that were completed by participants.

The main limitation of the analysis was the small sample size and the level of missing data on resource use and quality of life at all time points. Accordingly, multiple imputation methods could not be employed. This could have introduced bias and affected the final results. Another limitation was that the follow-up was for 6 months only, which may not capture the longer-term effects of the treatments given that the trial focused on participants with recurring BV. Some pragmatic assumptions were required to address missing data relating to resource use and thrush management, but the impact associated with these assumptions was explored as part of the sensitivity analysis.

The economic cost of AMR was explored as part of the sensitivity analysis. However, there is considerable uncertainty around the role of AMR in relation to recurrent BV[50] and our exploration of the potential costs associated with AMR was, therefore, necessarily limited.

Recommendations and conclusions

The early termination of recruitment into the trial limited the ability to obtain definitive evidence on the cost-effectiveness of intravaginal lactic acid gel compared with oral metronidazole. The data collected suggest that, in both arms, participants needed to access further health care. Further research would be beneficial to reduce the uncertainty in the findings around resource use and health outcomes, particularly over the longer term. In addition, there is a need for greater understanding of the externalities associated with AMR in connection with recurrent BV. It is currently unclear what the best approaches would be for BV, as more powerful second- and third-line antibiotics are not usually given. Instead, patients are usually prescribed further treatment with metronidazole or clindamycin.[10]

Chapter 5 Qualitative study of participants' views on the acceptability of and treatment preferences for recurrent bacterial vaginosis

Introduction

Qualitative methods of data collection and analysis enable an in-depth exploration of participants' views and perceptions of their experiences. This is particularly valuable in discussion of little-known, complex and sensitive topics[51] such as BV: 'a common condition of unknown aetiology'.[52] Furthermore, there is inconclusive evidence about which treatment regimen is most effective for women with recurrent BV, and its propensity for recurrence makes treatment of BV a challenge.[53] Greater treatment acceptance is associated with higher adherence, better compliance and improved persistence.[54] To this end, acceptability has become a key consideration in the design, evaluation and implementation of health-care interventions.[55] However, very few studies have qualitatively explored the acceptability and tolerability of different BV treatment options.[56]

This qualitative substudy from the VITA trial was outlined at the start of the research design phase, as per the published protocol.[25] The value of hearing women's voices as well as collecting their clinical BV results from the microscopy slides and web-based questionnaires at different time points would allow the research team to better understand what was deemed more acceptable and tolerable given their experiences of the condition. To do this, during interviews we explored a diverse subgroup of participants' prospective, concurrent and retrospective perspectives in relation to the trial. We examined the acceptability and tolerability of study treatments for participants along with their preferences for biomedical treatment, what factors they perceived to contribute to the development and recurrence of BV, and how BV made them feel physically and emotionally.

Methods

Design

This qualitative substudy was completed during recruitment into the VITA trial and the results have been published.[57] The lead qualitative researcher (JAW) worked independently of the trial team and was blinded to the post-treatment results. All participants who were included in the interview subgroup had given optional consent to be contacted about the interview at the time of randomisation to the trial. Those who gave consent and had completed study treatment were consecutively sampled from both treatment arms. An invitation to take part in the interview was e-mailed to participants, which was followed by a telephone call invitation if they did not respond to the e-mail. Interviews were scheduled for a time that was convenient to the participants and were expected to take approximately 20 minutes. It was planned to interview approximately 30 participants (15 in each arm) and recruitment continued until data saturation was reached.

Data collection and analysis

Semistructured interviews took place from January 2018 to May 2018, which was part-way through recruitment into the trial, and were conducted over the telephone using a qualitative interview schedule (see *Appendix 6*). Only the qualitative researcher (JAW) and the participant were involved, and consent was verbally confirmed at the start of the interview. Participants were given a unique interview code to identify all data collected from them. All interviews were audio-recorded, transcribed and anonymised,

and lasted between 10 and 45 minutes. Qualitative data were managed using NVivo 11 (QSR International, Warrington, UK) and all files were stored on a secure server at the University of Warwick. Data from the interviews were not analysed or triangulated with those from the web-based questionnaires.

Data were coded thematically[58] and then comparatively by two researchers, with the codes being based on interview questions and emergent themes. Word-spotting of descriptive adjectives assisted in summarising all contextual data describing BV symptoms. Data were synthesised using a framework approach by comparison with the acceptability of health interventions framework[55] to reflect the extent to which women receiving a health-care intervention consider treatment to be appropriate based on their anticipated or experiential cognitive and emotional responses. We considered constructs, such as perceived effectiveness and burden, according to women's perspectives on BV treatments.

The analysis of the data required a sound narrative of the participants' history of BV, including previous and current treatments. This helped to ensure that the analysis reflected the participants' voices as faithfully as possible. To achieve a prolonged and intense engagement with the totality of the data, we concurrently analysed data. This helped to ensure that questions were being asked in a way that captured participants' descriptions of their experience of BV, possible triggers of BV, perceived effectiveness of both treatments and treatment outcomes.

The quotations included fairly represent the participants' opinions reflecting similarities, differences and nuances of opinion, experience and perception.

Results

Across the six trial sites that were open to recruitment during the interview time frame, a total of 52 participants were invited to take part in the interview, of whom 18 either were not contactable or declined to take part and one withdrew from the trial. This gave a total of 33 participants who were interviewed (lactic acid gel arm, $n = 20$; metronidazole arm, $n = 13$). The participants were from diverse ethnic backgrounds and ranged in age from 21 to 51 years; just over one-third of participants had experienced BV more than three times. Baseline characteristics of the interview subgroup are summarised in *Table 26* and show that the interviewees were somewhat representative of the main trial population.

We present our findings under four main themes:

- theme 1 – context of BV
- theme 2 – experiences and perspectives around the acceptability and use of treatment for BV
- theme 3 – treatment preference for BV
- theme 4 – participant's views on which treatment they would suggest that other women take.

Theme 1: context of bacterial vaginosis

Characteristics of the physical symptoms of bacterial vaginosis

The symptoms of BV were described by participants in terms of colour, texture, smell and physical sensations using a range of adjectives (*Box 1*).

The characteristics of BV, such as an offensive smell and abnormal vaginal discharge, that so greatly affect women's lives are consistent with findings from other qualitative studies.[52,59] There is a complex interaction of multiple components, including the vaginal microbial ecosystem and the human host, that is modulated by a woman's behaviour and environment and further complicates the overall 'BV cause equation'.[60]

TABLE 26 Baseline characteristics of the interview subgroup

Characteristic	Treatment arm	
	Oral metronidazole (*N* = 13)	Intravaginal lactic acid gel (*N* = 20)
Age at randomisation (years)		
Mean (SD)	34.0 (8.20)	30.6 (5.93)
Ethnicity,* n *(%)		
Black Caribbean	5 (38.5)	6 (30.0)
White	2 (15.4)	7 (35.0)
Black African	3 (23.1)	2 (10.0)
Mixed race	0	3 (15.0)
Other Asian	1 (7.7)	1 (5.0)
Indian	1 (7.7)	0
Pakistani	1 (7.7)	0
Chinese	0	1 (5.0)
Number of previous episodes of BV in the past 12 months,* n *(%)		
0	0	0
1–3	5 (38.5)	16 (80.0)
> 3	8 (61.5)	4 (20.0)

BOX 1 Characteristics of the physical symptoms of BV

Colour of the discharge: dark greenish, brown, yellowy, translucent, magnolia, creamy white, dark in colour, clear or whitish, pinky, cloudy.

Texture of the discharge: solidified, crustated, mucousy, opaque, very fluid, like lotion, watery, milky, thick.

Malodour of the discharge: rancid, very smelly, sour smell, foul kind of odour, fishy, seafood odour, potent smell, vinegary, disgusting, horrendous, stinking smell.

Physical sensation associated with the discharge: itchiness, slight burning, irritation (symptoms worsened pre- and post-menstruation).

Impact of bacterial vaginosis on participants' lives

The symptoms of BV affected participants psychologically and physically beyond the bacterial symptomatology, leading to emotional trauma. Feelings of depression, anxiety and self-consciousness were described. The social burden of living with recurrent BV has also been described by others.[56]

Participants noted that vaginal discharge malodour affected personal relationships and made them have feelings of 'embarrassment', 'paranoia' and 'body-consciousness', as well as being 'self-aware' that their partners, children, colleagues and even strangers could smell it:

> *I just don't feel comfortable because I feel like I always smell.*
>
> *V33, aged 33 years: lactic acid gel*

> *I sat on the bus and I think people can smell me and I just stay away from people, you know.*
>
> *V24, aged 37 years: lactic acid gel*

Episodes and recurrence of bacterial vaginosis

Bacterial vaginosis was described 'a nightmare', always returning and persisting. Its recurrence led to participants' frustration and confusion as to how and why they get BV. Some could start to see patterns in its recurrence:

> *Like me now, I've mastered BV; I know when it's coming.*
>
> *V45, aged 34 years: metronidazole tablets*

Perceived triggers of bacterial vaginosis

Participants identified a number of different reasons for developing BV, such as:

- Sexual practices, for example unprotected, unsafe sexual intercourse (e.g. not using condoms); multiple sexual partners (same or not same sex); and male semen post ejaculation.
- The use of contraceptive coils, such as an intrauterine device [copper or hormonal implant, Mirena (Bayer, Reading, UK) branded], menstrual cycle, application of tampons, not changing tampons regularly or forgetting to wash hands before the application of tampon.
- Hygiene practices, that is the type of soap product used by the sexual partner on their 'intimate areas'; personal bathing in perfumed bubble bath water; the use of 'cheap' shower gels; cleaning with an antiseptic solution; or activities such as douching were described by almost all participants as detrimental to the development of BV (as described previously where lifestyle behaviours such as douching, bathing and using vaginal cleaning agents were significantly associated with BV due to the disruption of vaginal flora[61]).
- Type of clothing material such as non-cotton underwear, type of laundry detergent such as fabric softener and wearing perfumed sanitary pads.
- Lifestyle choices such as consumption of poor diets including caffeinated energy drinks and high-fat processed foods, excessive cigarette smoking or alcohol consumption. These behaviours were all attributed to working shifts, having multiple jobs, a lack of time and stress at work, all of which women felt contributed to BV.

Self-help: changes in personal hygiene habits, self-help medication and home remedies

Some participants had been advised by nurses to mainly wash with water only, dermatological soaps or emollient creams. The frequency of washing habits to remove BV discharge varied from several times per day owing to religious beliefs or to commonly twice per day or to every few days to weekly. Many were concerned about the chemicals in soaps affecting their natural pH balance, as it 'still feel like it might be passing down there' (V23, aged 23 years: metronidazole tablets).

Self-medication included using over-the-counter liquid lactic acid gels or waxy bullet-like pessaries bought either from a pharmacy or online, or the use of homemade remedies including steaming, apple cider vinegar or yoghurt internally in the vagina. This is congruent with women in Australia who were frustrated and dissatisfied with current treatment regimens for BV, in particular antimicrobials, leading them to take ineffective non-evidence-based therapies.[59]

Theme 2: experiences and perspectives around the acceptability and use of treatment for bacterial vaginosis

Prior experience of treatment for bacterial vaginosis

Only one participant had never been prescribed oral metronidazole for BV before and one other had never used lactic acid gel previously.

Intervention treatment: acceptability and ease of use of lactic acid gel

The majority of participants who were randomised to receive lactic acid gel described the tube applicator as comfortable and easy to use with no side effects, yet it could be messy:

> *Yeah, it was easy to use, it was fine yeah. Simple to follow instructions and everything yeah.*
>
> *V9, aged 37 years: lactic acid gel*

> *Obviously there is some sort of drippiness that happens a bit. But as it happens mostly overnight, it hasn't affected me during the day at all.*
>
> *V8, aged 25 years: lactic acid gel*

Two participants said that the gel applicator leaked even when applying it lying down correctly as instructed, which caused concern as to whether or not they had received the full dose. A similar experience was reported in another study, in which reasons given for not accepting the lactic acid gel were messiness and leakage.[62]

Perceived effectiveness of the lactic acid gel

The lactic acid gel was described as fast acting and improvement was felt and seen quickly. As a result, participants would use it 'happily' again in the future:

> *Yes. I mean, you know, so it's gone, so assuming it stays away then yes, it did definitely work.*
>
> *V41, aged 33 years: lactic acid gel*

> *Well I felt like, oh my God, at last something's going to work you know, within 7 days I'm going to be fine . . . and I can also have a drink as well.*
>
> *V24, aged 37 years: lactic acid gel*

Negative aspects of the lactic acid gel

Gel application every night was presented as a 'faff' because participants had to change their bedtime routine. Others said that they were scared to cough as the gel may leak:

> *I think there's still some in there still doing good, but there's some that comes out. So, I don't know if it will affect it or not.*
>
> *V5, aged 38 years: lactic acid gel*

A few participants felt that they could not drink water or urinate after application. In addition, abstaining from sexual intercourse while using the gel was considered an inconvenience.

Control treatment: acceptability and ease of use of oral metronidazole

Overall, antibiotics were generally not acceptable to participants because of the frequency with which they were prescribed. However, metronidazole was considered an effective first-line prescribed treatment, particularly for 'intense' cases of BV.

The confidence in metronidazole clearing up the BV was high because it was classified as an 'antibiotic' drug. Therefore, participants were willing to take these tablets to get 'rid of that BV' (V46, aged 42 years: metronidazole tablets).

Perceived effectiveness of metronidazole

There were differences in how quickly metronidazole cleared up the BV, but effects were short-lived before the next episode began and improvements were temporary. Concerns about antibiotic resistance were common:

> *I don't really like taking antibiotic, because I know your body can become like resistant to them.*
>
> *V11, aged 22 years: lactic acid gel*

Yet, paradoxically in these cases, participants were still prepared to take the tablets because 'they worked':

> *The metronidazole . . . I remember when I took it, everything was cleared up and then it just came back out of nowhere.*
>
> *V11, aged 22 years: lactic acid gel*

Negative aspects of metronidazole

The process of taking the antibiotics twice per day was defined as a chore:

> *Even if I halve it, I can't swallow them, they're quite big. Two, the taste. Then it causes me to be ill, makes me feel nauseated more.*
>
> *V44, aged 51 years: metronidazole tablets*

Theme 3: treatment preference for bacterial vaginosis

Participants described their individual preferences based on the effectiveness of treatment (what they think worked) and based on personal choice (what they would rather take given individual lifestyle factors or beliefs). Treatment preference was usually dependent on the severity of symptoms, the time interval between perceived recurrences and the advantages and disadvantages of each treatment (*Table 27*).

TABLE 27 Summary of participants' preferences based on differences between treatments

Treatment preference depending on	Treatment arm	
	Oral metronidazole	Intravaginal lactic acid gel
Severity of symptoms	Severe BV	Mild BV
How often the treatment can be taken	Short-term treatment	Long-term treatment
Perceived speed of cure	Quick results (all cleared up)	Quick to mid-term results
Duration between perceived recurrence	Longer durations between episodes	Shorter duration between episodes
Perceived effectiveness	Know antibiotic tablets work better = strong form of treatment	Prefers using the lactic acid gel = less intense form of treatment
Treatment option	First-line treatment on the first sign of 'severe' symptoms	First-line treatment on the first sign of 'mild' symptoms
	Back-up drug (if lactic acid gel did not work the first time around)	Use in addition to antibiotics or straight after a course of antibiotics
Description of treatment type	Last-resort treatment	Substitute treatment/precaution/ preventative treatment

Treatment preferences of lactic acid gel over metronidazole tablets

Positive factors

- The tube applicator was comfortable.
- The availability of self-medicated lactic acid gel without requiring health-care consultation for a prescription.
- Insertion of the gel directly to the target area at which they have the symptoms.
- No risk of antibiotic resistance.
- Minimal side effects.
- Do not have to abstain from alcohol, thus altering social behaviours.
- Can bring instant relief (but did not cure the BV, rather it delayed the onset of the next episode).
- Idea that the gel can be used preventatively straight after having sexual intercourse to reduce risk of BV.
- Reduced discharge and the associated odour to some degree.

Negative factors

- Too much gel liquid in the tube.
- Not affordable if self-bought.

Treatment preference of metronidazole tablets over lactic acid gel

Positive factors

- It is easier to swallow the tablets than insert the gel and can take tablets anywhere (e.g. at work).
- Can still have sexual intercourse.
- More effective and faster to clear symptoms.
- Period of time between recurrence was longer when prescribed antibiotics.
- Reduced discharge and the associated odour to some degree.

Negative factors

- Stigma associated with being seen at a sexual health clinic to get treatment.
- Time off work to go to the appointment or simply 'fed up going to the clinic' (V46, aged 42 years: metronidazole tablets).

Poor outcomes and disbelief that there was actually a cure for bacterial vaginosis led to the following choices

- Delay in seeking treatment as they felt that any treatment was ineffective.
- Do nothing and live with the symptoms.
  'I didn't actually go and seek any help at that point. And then I waited a few months' V41, aged 33 years: lactic acid gel
- Seek treatment when at their 'wits' end' owing to the 'life sentence' of BV and taking antibiotics frequently.
- Self-medicate using home remedies; buying gel was deemed as unaffordable.

Theme 4: participants' views on which treatment they would suggest that other women take

Participants were asked which treatment they would recommend, if any. Lactic acid gel was considered a milder option and a useful 'top-up'-type treatment for minor cases of BV:

> *I would recommend to try it, because it's better than nothing, definitely. But I'm very interested in trying the gel to see if that has a better impact. I think it's socially better as well.*
>
> *V23, aged 23 years: metronidazole tablets*

Taking metronidazole was regarded as a safer option to clear up moderate to severe BV, with longer time periods between episodes:

> *Probably the antibiotics, because it seemed to get rid of it for longer.*
>
> *V9, aged 37 years: lactic acid gel*

One participant said that she would like to take both treatments to test the foolproof method and ensure that 'it does not come back' (V7, aged 26 years: lactic acid gel). Others felt that lactic acid gel worked well enough and that they would be happy to be on it for longer periods of time.

Discussion

There is much debate around the causes of BV and optimal treatments, with usually 'more questions than answers'.[63] However, this qualitative assessment has enabled insight into what women think about their treatment options for BV and what influences their choice.

This substudy has revealed that participants hold quite complex views on treatment[57] and have provided rich accounts of why they prefer either treatment. In general, participants preferred to opt for intravaginal lactic acid gel, even if they perceived the treatment to be less effective than metronidazole therapy. By using gel, they avoided taking antibiotics but felt that they were still 'doing something' and benefited from its soothing effect. Many participants were confused about the cause of BV, describing many different possible triggers and none.

The diverse ethnicity of the participants who took part in the interview reflects both the prevalence of BV[60] and the ethnic mix of the site localities, with nearly half of the sample self-identifying as black Caribbean or black African and just over one-quarter as white.

For some participants in this substudy, BV was a cause of despair. All participants associated BV with being sexually active, but many were confused about its cause. Participants talked about unprotected sexual intercourse, use of tampons and douches, using an intrauterine contraceptive device and poor hygiene or use of cheap soap as triggers for BV.

Limitations

Many of the participants had previous experience in taking both treatment options, and this meant that these experiences merged when recalling when and what they had taken, especially when taken back to back.

Implications for health care

Although metronidazole proved to be more effective at treating BV in the short term in the VITA trial, recurrence within 6 months in a subset of participants who had initial resolution and were available for follow-up was similar in both treatment arms. In many instances, women were likely to still want to use lactic acid gel for its soothing effect and to avoid recurrent use of antibiotics. Participants were willing to purchase lactic acid gel themselves, although some found that this was not affordable.

To achieve better informed and shared decision-making about treatments, health professionals need an understanding of what women think about the use of antibiotics or intravaginal gel when weighing up the pros and cons of the available options.

Recommendations for research

The overall findings of the substudy are not straightforward to communicate given the higher treatment effectiveness of metronidazole but preference, despite this, in some women for lactic acid gel. Given that women already struggle to understand BV and its cause, research is needed to understand how best to communicate treatment recommendations.

Chapter 6 Discussion

Summary of main findings

The VITA trial compared oral metronidazole with intravaginal lactic acid gel for the treatment of women with recurrent BV. Metronidazole was more clinically effective, with resolution of BV symptoms in 70% of participants, compared with 47% for those receiving lactic acid gel, 2 weeks after treatment.

The recurrence of BV within 6 months, in a smaller subset of participants who had initial resolution and were available for follow-up, was similar across arms [metronidazole: 51/72 (71%); lactic acid gel: 32/46 (70%)]. A higher incidence of some side effects was reported with metronidazole than with lactic acid gel (nausea: 32% vs. 8%; taste changes: 18% vs. 1%; diarrhoea: 20% vs. 6%, respectively).

The findings of the economic evaluation suggest that intravaginal lactic acid gel is less clinically effective and slightly more costly than oral metronidazole in resolving BV symptoms by week 2. The cost–utility analysis showed that intravaginal lactic acid gel was dominated by oral metronidazole at 6 months. Intravaginal lactic acid gel was associated with slightly fewer QALYs gained and more resource use than metronidazole. However, there is uncertainty around the difference in costs in both analyses, suggesting that intravaginal lactic acid gel could be either more or less costly than oral metronidazole and there is some uncertainty around the differences in QALY gains in the cost–utility analysis.

Qualitative interviews with a small subgroup of participants found that both treatments were acceptable. However, there was high awareness that recurrence of symptoms was likely, with an associated emotional and physical impact in some. In general, participants preferred to use intravaginal lactic acid gel, even if they perceived it to be less effective than antibiotics. By using lactic acid gel, they avoided taking antibiotics and some of their associated side effects, but felt that they were still 'doing something' and appreciated its immediate local soothing effect.

The trial was undertaken in symptomatic women with recurrent BV who self-referred for first-contact health care to either a sexual health clinic or a primary care clinic. The findings are, thus, likely to be generalisable to women with recurrent BV across these and wider primary care settings.

Existing evidence

Current treatment of bacterial vaginosis

Current international guidelines recommend the use of antibiotics as first-line treatment for BV. In practice, this is usually metronidazole (given either orally or as a topical intravaginal gel) and less often clindamycin.[10,33,64] Metronidazole has a broad spectrum of actions against anaerobic bacteria often associated with BV and a minimal effect on commensal vaginal lactobacilli.[65] In those with frequent BV recurrences, short courses of antibiotics to treat each symptomatic episode are recommended or regular antibiotic therapy over several weeks or months as prophylaxis.

Treatment of BV using these antibiotic regimens leads to cure within 2–4 weeks in 51–82% of patients,[66] but BV symptoms recur in the majority (69–80%) of patients over the next 12 months.[12,67] The cause of initial treatment failure and subsequent frequent relapse is not known, but has been postulated to be because of AMR, failure to re-establish the normal lactobacilli-dominated vaginal flora,[68] the development of a treatment-resistant bacterial biofilm on the vaginal mucosa[69] and/or reinfection from a sexual partner.[70] The use of metronidazole is associated with drug side effects including vaginal candidiasis, nausea, vomiting, change in taste perception and diarrhoea,[71,72] which can limit acceptability of and

adherence to treatment. Patients also dislike taking multiple courses of antibiotics to treat BV and are concerned that they may develop antibiotic resistance.[57] Preventing and reducing AMR is a priority in many countries, and improving antibiotic stewardship through optimisation of and reduction in antibiotic use is a central theme of the UK's 5-year plan to address this issue.[16]

Antibiotic therapy and resistance

Following treatment, resistance to clindamycin commonly develops in the vaginal bacteria that are associated with BV,[73] and resistance to metronidazole is also found in *Gardnerella vaginalis*[74,75] and *Atopobium vaginae*,[76] which are commonly associated with BV. Repeated antibiotic use fails to eradicate BV-associated bacteria in a substantial proportion of patients with recurrent symptoms, which also suggests that resistance might be important.[76,77] In addition to their effects on the vaginal microbiome, metronidazole and clindamycin frequently cause disruption of the gut microbial flora, with associated gastrointestinal side effects and a risk of progression to pseudomembranous enterocolitis.[78–80]

Alternative bacterial vaginosis treatment approaches

The limited initial efficacy, frequent subsequent recurrences, risk of AMR and unpleasant side effects of antibiotics, in addition to patient preference in this group of trial participants, suggest that alternative approaches for the treatment of BV are needed.

A number of different approaches have been explored to try to improve the outcome of BV treatment. These include high-dose metronidazole,[81] antibiotic combination therapy,[82] extended release clindamycin,[83] agents to disrupt the bacterial biofilm[84] and probiotics.[85,86] At best, these have provided a modest improvement in efficacy compared with standard treatment[87] and have not been added as recommended therapy into treatment guidelines.

Lactic acid is produced by commensal lactobacilli in the vagina and the resulting low vaginal pH helps prevent the anaerobic bacterial overgrowth that characterises BV.[88] The loss of lactobacilli that occurs in women with BV is associated with a rise in pH, and the therapeutic use of intravaginal lactic acid gel aims to restore the level of acidity to normal and, thus, inhibit the growth of BV-associated bacteria. Previous studies have been small and evaluated a variety of different intravaginal acid gels or pessaries for the treatment of BV. These have led to a variable response, with between 18% and 100% of patients achieving resolution of their BV.[13,18–23,89,90] The regimen used most often in previous trials was once per day application for 1 week, and increasing the frequency of dosing did not appear to improve the response rate (efficacy 23–93% for once per day compared with 18–100% for twice per day).

What the current trial adds

Efficacy of lactic acid gel for the treatment of bacterial vaginosis

In the VITA trial, which included a large sample of symptomatic participants with frequent recurrent BV, we found that lactic acid gel was less effective in clearing BV symptoms than oral metronidazole. However, a substantial proportion of participants in both arms did not respond to either treatment (30% of those receiving metronidazole and 53% of those receiving lactic acid gel). Moreover, in those who did respond, the limited data we had suggested that the subsequent risk of recurrent BV was very similar in both treatment arms.

In a post hoc analysis, we found no major differences in the demographic, behavioural or disease characteristics of those who responded to metronidazole compared with those who responded to lactic acid gel. Specifically, the proportion with 'severe' BV (based on the number of episodes or duration of symptoms in the past year) was the same in both arms. A greater proportion of participants in the lactic acid gel arm had positive microscopy for BV at week 2 (28% vs. 10% in the metronidazole arm). Overall treatment success over the 6 months of the trial was poor in both arms,

with only 23% of those in the metronidazole arm and 16% of those in the lactic acid gel arm having symptom resolution and no recurrences over the 6 months following treatment, although these estimates are based on < 50% of the original trial population.

Metronidazole was associated with notably more side effects than lactic acid gel in the 2 weeks after taking study treatment, including one-quarter of participants who reported vaginal candidiasis (27% in the metronidazole arm vs. 17% in the lactic acid gel arm). However, adherence to both therapies was nevertheless high.

Our previously published qualitative study undertaken in a subset of VITA trial participants[57] indicates that women dislike taking repeat courses of metronidazole to treat BV and many prefer lactic acid gel, despite perceiving it to be less effective. A preference for the lactic acid gel was based on a desire to apply treatment directly to the site of the BV, the gel having an immediate soothing effect, concerns that frequent use of antibiotics would lead to resistance and the ready availability of lactic acid gel without requiring a medical consultation or prescription. Avoiding the need to take antibiotic tablets twice per day and being able to drink alcohol were also reported as being benefits of using lactic acid gel, whereas greater efficacy and tablets being more convenient than using intravaginal lactic acid gel were advantages of metronidazole. Participants' preferences for treatment were, thus, not based solely on short-term effectiveness but also related to ease of use, side effects, the individual's value system and beliefs, and the possible long-term consequences of treatment.

Health economics

The health economic analysis found lactic acid gel to be more costly than oral metronidazole for the treatment of BV, which was mostly linked to reduced efficacy, leading to increased utilisation of secondary care. This difference persisted in a number of sensitivity analyses but there was uncertainty around the difference in costs, suggesting that intravaginal lactic acid gel could be either more or less costly than oral metronidazole. We attempted to include a 'penalty' cost for the risk of AMR associated with the use of metronidazole. This reduced the cost difference, but a robust methodology to measure the cost of resistance is not available and it is difficult to know how accurate our estimates of the cost of resistance were.

Safety, tolerability and adherence

Oral metronidazole is recognised to cause systemic side effects[71] and participants who received it reported more gastrointestinal symptoms than those in the lactic acid gel arm, although these were generally of mild severity. Vaginal irritation occurred in 21% of those receiving lactic acid gel, which was similar to those receiving metronidazole (28%). Antibiotics are known to increase the risk of vaginal candidiasis,[91] and thrush was reported to occur after treatment in 27% of participants in the metronidazole arm compared with 17% of those in the lactic acid gel arm in the 2 weeks after initiating treatment.

No SAEs or suspected unexpected serious adverse reactions were reported.

Rates of adherence to metronidazole for the treatment of BV have been reported to be only 50–68%.[92] However, in our clinical trial setting adherence was high, with > 90% of participants in both arms finishing their treatment course. Participants found that both treatments were easy to take, and the most common reason for missing a dose was forgetting to take it. However, these data were based on the 61% of participants who returned their week 2 questionnaire. It is not known whether or not those who did not return their questionnaires took their study treatment.

Clinical and microscopy diagnosis of bacterial vaginosis

Entry into the VITA trial and assessment of treatment response were based on the presence or absence of participant-reported BV symptoms to mirror 'real life' in most clinical primary care practice. Participants were symptomatic at the time of randomisation and had a history of at least one other

episode of BV within the past 2 years that had resolved following treatment. Vaginal discharge can have multiple causes, although BV is typically associated with a characteristic fishy odour. A pre-planned analysis that was restricted to participants who had positive microscopic confirmation of BV[29] at baseline showed a similar response rate to that seen in the primary analysis: resolution of BV symptoms in 75% of participants receiving metronidazole and 49% for those receiving lactic acid gel. Resolution at week 2, confirmed via microscopy, occurred in 77% of participants receiving metronidazole compared with 42% of those receiving lactic acid gel, suggesting that metronidazole may have a greater effect on the pattern of vaginal bacteria seen on microscopy than lactic acid gel. However, the clinical relevance of greater microbiological resolution of BV (compared with clinical symptom resolution) is uncertain because, following a clinical treatment response (resolution of symptoms) in either treatment arm, no differences were detected in the frequency or timing of BV recurrences over the next 6 months. Caution is, however, required in interpreting the limited data that were available over the 6-month follow-up period.

We chose resolution of BV symptoms as the primary end point to maximise the trial's relevance to clinical practice where, in many settings, microscopy is not available and management is based on history and examination. In addition, microbiological evidence of BV can be present without symptoms[93] and cyclical changes in the vaginal flora (including BV-type flora) can occur in the absence of treatment,[94] which makes interpretation of microbiological cures difficult. Microscopy diagnosis of BV at week 2 was included as a secondary outcome in the trial and was based on the criteria described by Ison and Hay,[29] as recommended in the UK National Guideline for the management of Bacterial Vaginosis.[10] Diagnosis using Ison and Hay criteria[29] correlates with the two other commonly used approaches to microbiologic BV diagnosis: Amsel's criteria[29] and Nugent's score.[95,96]

From a patient perspective, the symptoms of discharge and malodour are the main causes of the physical and emotional distress associated with BV, have an impact on self-esteem and restrict sexual activity.[56,57] Our findings are, therefore, of direct relevance to patients and those providing treatment for BV.

Other factors that might have affected treatment efficacy

The VITA trial enrolled participants with severe recurrent BV. Women with frequent recurrent BV respond less well to treatment[81] and this was evident in our trial as the response rate was lower in both treatment arms in those with multiple recent episodes of BV. However, the frequency of prior BV did not predict symptom resolution differently between the two treatment arms. In those successfully treated with either metronidazole or lactic acid gel, the same proportion (around one-third) reported having BV on more than three occasions in the past year.

Participants were advised to pause using lactic acid gel if they were menstruating heavily, reflecting usual practice, but overall adherence to therapy was high with few missed doses.

Strengths and limitations

The VITA trial was a large trial that successfully included an ethnically diverse patient population. Our findings help to inform evidence-based care for women with severe recurrent BV who suffer considerable physical and psychological sequelae[56,57] and incur considerable costs to health-care systems.[9] There were no major protocol violations recorded and participants had good adherence to the study treatments. Our trial design was robust and the primary findings remained consistent on multiple sensitivity analyses. The trial was pragmatic and reflected common clinical practice, ensuring that our results are likely to be applicable in a range of primary care settings.

We recognise several limitations or potential limitations. It was not practical or feasible to blind participants or clinicians to the treatment allocation, which raises the possibility of reporting bias.

Our previous work suggests that women with recurrent BV may consider lactic acid gel to be less effective than metronidazole.[57] However, we think that this is unlikely to be a major cause of bias because a pre-planned secondary analysis of outcomes based on microscopy findings (carried out by technicians who were blind to treatment allocation) showed a similar, if slightly larger, difference in treatment efficacy to that found in the primary analysis.

The primary outcome, participant-reported resolution of BV symptoms, was collected both through a web-based questionnaire and via direct questioning during a telephone call. The proportion reporting symptom resolution was higher when data were collected over the telephone in both treatment arms, particularly in the metronidazole arm (83% via the telephone compared with 66% via the questionnaire who reported resolution). The telephone call was used as a 'back-up' when the questionnaire had not been completed and, therefore, the time interval after treatment to collect data was longer than that for the web-based questionnaire, raising the possibility of response or recall bias in the telephone group. Despite this, we do not believe that this is likely to have had a major effect because telephone collection of the primary outcome was used for a minority of participants only (88/409; 22%) and a similar number of telephone calls had to be made in both treatment arms.

The loss to follow-up rate for collection of the primary end point was 21% compared with a predicted rate of 10%.[25] Sensitivity analyses were undertaken including assumptions that all participants with missing data had symptom resolution or that they all did not have symptom resolution. In both scenarios, the adjusted risk difference was −18%, compared with the primary analysis risk difference of −23%. It is, therefore, possible that the difference in efficacy between metronidazole and lactic acid gel is not as large as we found, but the short-term (2 weeks after starting treatment) efficacy of metronidazole is very likely to remain substantially greater than lactic acid gel. The recurrence rate in both arms may also have been elevated because 'no recurrence' required reporting an absence of symptoms at all follow-up time points, whereas 'recurrence' required reporting of symptoms at a only single time point, that is missing data were more likely to be recorded as a 'recurrence' (given that this needed to be reported as 'yes' at only one time point) rather than 'no recurrence' (given that this needed to be reported as 'no' at every time point).

A large number of participants did not provide data at week 2 (with the exception of the primary outcome for which telephone calls were made to obtain these data) or at 3 and 6 months post treatment. Various assumptions, therefore, had to be made owing to incomplete or inconsistent recording of the data provided, meaning that some outcomes were based on small and potentially non-random subsets of participants.

Data for the full 6 months of the trial were available for < 40% of randomised participants, and for outcomes related to recurrence and the number of additional treatment courses it was available for even fewer participants. To be classed as a recurrence, participants had to have data to show that their BV symptoms had resolved within the 2 weeks after treatment had started. Therefore, any between-arm comparisons were between non-randomised groups and any results need to be interpreted with caution. Although participants who had symptom resolution in both treatment arms appeared similar in many measured characteristics, there were some differences, and indeed they could have differed with respect to characteristics that were not measured. In addition, there may have been differences between the two arms in the participants who provided follow-up data with respect to their actual recurrence and/or characteristics associated with their recurrence(s). This may also have influenced the quality of questionnaire completion. We do not have information to assess this.

Although the sample size remained large in comparison with previous BV treatment trials (219 participants at 3 months and 176 participants at 6 months), given the low proportion of those originally randomised and the potential for bias in the between-treatment comparisons, caution is required in interpreting the longer-term trial findings.

Data on resource use were available for < 40% of randomised participants at different time points. Excluding those who did not complete the resource use questionnaire can introduce bias and some degree of inefficiency. Further research would be required to estimate the resource use and HRQoL associated with use of oral metronidazole and lactic acid gel with more precision, particularly over the longer term.

Chapter 7 Conclusions

Conclusions

In the VITA trial, participants with recurrent BV had a substantially higher response to treatment at 2 weeks with oral metronidazole than with intravaginal lactic acid gel, but treatment failure was relatively common in both arms. Subsequent recurrences of BV in the subset of participants who provided longer-term data appeared to be frequent and did not differ between those who had an initial treatment response following either therapy. Metronidazole is more likely to be cost-effective, with lower associated resource use and higher efficacy than lactic acid gel, but there is uncertainty surrounding the resource use estimates. Participants interviewed in a qualitative substudy about their experiences of treatment for BV disliked taking repeated course of antibiotics for BV and in general preferred lactic acid gel even if its short-term efficacy was lower.

Implications for health-care practice

In the absence of an effective treatment for recurrent BV, shared clinical decision-making with women about their therapeutic options assumes particular importance. The VITA trial provides robust measures of treatment response and side effects for metronidazole and lactic acid gel at 2 weeks, with additional, more limited, data over a 6-month time period. These findings can help women with BV and their clinicians make more informed decisions about therapy, taking account of women's individual contexts and preferences.

Women should be informed of the higher initial clinical response to metronidazole but that recurrence of BV following either of these treatments is common. For some women, oral metronidazole may be favoured because of its higher short-term efficacy. However, other women may prefer intravaginal lactic acid gel if ease of use, avoiding antibiotic side effects and resistance, or access to treatment without need for medical prescription are of greater importance.

Recommendations for research

In the absence of effective curative therapy, further investigation of non-antibiotic continuous or intermittent treatment regimens to control the symptoms of recurrent BV are required to improve quality of life in this patient group.

Further analysis of vaginal samples collected in the trial would be useful to identify whether or not microbiological factors, such as specific bacterial subspecies, inflammatory co-factors or antimicrobial susceptibility, affect the short- and long-term response to metronidazole or lactic acid gel in a subgroup of women with BV.

Further development of the methods for incorporating costs and the impact of AMR specific to the antibiotic consumed in relation to recurrent BV is required.

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Lindsay Armstrong-Buisseret (https://orcid.org/0000-0002-8045-5464) (Clinical Trial Manager) managed delivery and co-ordination of the trial from June 2019 onwards. She also drafted sections of the Health Technology Assessment (HTA) report and revised it critically for important intellectual content.

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Publications

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Data-sharing statement

The data sets analysed during the VITA trial will be available on request from the corresponding author. Access to the data will be subject to review of a data sharing and use request by a committee including the chief investigator and sponsor and will be granted only on receipt of a data-sharing and use agreement. Any data shared will be pseudo-anonymised, which may have an impact on the reproducibility of published analyses. Data from the qualitative substudy cannot be shared publicly beyond that contained within this report because it is human research data on a potentially sensitive subject relating to sexual health.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments,

monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 VITA participant questionnaire: lactic acid week 2

PARTICIPANT QUESTIONNAIRE – WEEK 2

TREATMENT ALLOCATION: LACTIC ACID GEL

Please complete this questionnaire 2 weeks after starting your study treatment.

Date of questionnaire completion (dd-mmm-yyyy): | | | | | | | | | | |

Thank you very much for taking the time to answer these questions for the VITA study.
Please be assured that all the data collected remains confidential. The VITA website is secure and only the study team have access to the information you are entering.

Please answer the questions as fully as possible. This should take approximately 10 minutes to complete.

If you have any problems please contact the trial team on vitahelp@nottingham.ac.uk

STUDY TREATMENT

This section refers to your allocated study treatment.

LACTIC ACID GEL	
Which brand of lactic acid gel did you use?	☐Balance Activ® ☐Relactagel® ☐Canesbalance® ☐Other – please specify:
What date did you start using your lactic acid gel? (dd-mmm-yyyy)	☐☐ ☐☐☐ ☐☐☐☐
Treatment confirmation	**Lactic acid gel used?**
Day 1 (Start of treatment)	☐ Yes ☐ No
Day 2	☐ Yes ☐ No
Day 3	☐ Yes ☐ No
Day 4	☐ Yes ☐ No
Day 5	☐ Yes ☐ No
Day 6	☐ Yes ☐ No
Day 7	☐ Yes ☐ No
Did you complete your course of lactic acid gel? * If you answered no, please select why:	☐ Yes ☐ No* ☐ I accidentally missed applying the gel ☐ I didn't like using the gel ☐ Side effects of the gel ☐ Other – please specify:
How easy did you find using the lactic acid gel?	☐ Very easy ☐ Easy ☐ Neither easy nor difficult ☐ Difficult ☐ Very difficult

BACTERIAL VAGINOSIS (BV) SYMPTOMS

Have your BV symptoms cleared and stayed cleared **following your study treatment**?	☐ **Yes** – If yes what was the date they cleared? (dd-mmm-yyyy) ☐☐ ☐☐☐ ☐☐☐☐ ☐ **No** – If no how are your symptoms today compared to when you started study treatment? ☐ Better but not cleared/disappeared ☐ Improved initially but worsened again ☐ No change ☐ Worse

Are any of the following present today?	A genital discharge which you think is not normal: ☐Yes ☐No An offensive vaginal smell (a smell that is unpleasant to you): ☐Yes ☐No Vaginal irritation (may include itching/pain/burning): ☐Yes ☐No

SIDE EFFECTS – STUDY TREATMENT

NAUSEA		
During treatment, did you feel nauseous or sick?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did you first feel nauseous or sick?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How did the nausea/sickness affect you?	☐ Able to eat normally ☐ Ability to eat or drink fluids significantly decreased ☐ Unable to eat or drink fluids	
Approximately how long did your nausea/sickness last, in hours **or** days?	Hours ☐☐	Days ☐☐
Is your nausea/sickness fully resolved now?	☐ Yes ☐ No	

VOMITING		
During treatment, did you experienced any vomiting?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did your vomiting start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was your vomiting?	☐ 1 episode in 24 hours ☐ 2 to 5 episodes in 24 hours ☐ 6 or more episodes in 24 hours or need IV fluids	
Approximately how long did your vomiting last in total, in hours **or** days (i.e. from the first time you vomited to the last time?)	Hours ⌊__⌋	Days ⌊__⌋
Is your vomiting fully resolved now?	☐ Yes ☐ No	

TASTE / ABNORMAL TASTE		
During treatment, did you have any changes in taste or experience abnormal taste?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did the change in taste/abnormal taste start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was the change in your taste/abnormal taste?	☐ Mild ☐ Moderate ☐ Severe	
Approximately how long did the change in your taste/abnormal taste last, in hours **or** days?	Hours ⌊__⌋	Days ⌊__⌋
Is your change in taste/ abnormal taste fully resolved now?	☐ Yes ☐ No	

VAGINAL IRRITATION (may include itching/pain/burning)		
During treatment, did you experience any vaginal irritation?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did your vaginal irritation start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was the vaginal irritation?	☐ Mild ☐ Moderate ☐ Severe	
Approximately how long did the vaginal irritation last, in hours **or** days?	Hours ⌊__⌋	Days ⌊__⌋
Is your vaginal irritation fully resolved now?	☐ Yes ☐ No	

ABDOMINAL PAIN		
During treatment, did you experience any abdominal pain?	Yes* ☐ No ☐	
***If YES, please answer the following questions:**		
How long after starting study treatment did your abdominal pain start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was the abdominal pain?	☐ Mild ☐ Moderate ☐ Severe	
Approximately how long did the abdominal pain last, in hours **or** days?	Hours ⌊__⌋	Days ⌊__⌋
Is your abdominal pain fully resolved now?	☐ Yes ☐ No	

DIARRHOEA		
During treatment, did you experience any diarrhoea?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did your diarrhoea start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was the diarrhoea?	☐ Mild ☐ Moderate ☐ Severe	
Approximately how long did the diarrhoea last, in hours **or** days?	Hours ⌊_⌊_⌋⌋	Days ⌊_⌊_⌋⌋
Is your diarrhoea fully resolved now?	☐ Yes ☐ No	

ADDITIONAL MEDICATIONS FOR YOUR BV

In addition to your study treatment, have you used any additional medications for your BV since joining the study? (Either prescribed to you by a doctor or bought over the counter e.g. bought separately in a pharmacy or online)	☐Yes* ☐No
***If YES, please select the additional medication below:**	
	☐ **Metronidazole tablets** Were these prescribed? ☐Yes ☐No Number of courses taken? ☐☐
	☐ **Metronidazole vaginal gel** Was this prescribed? ☐Yes ☐No Number of courses taken? ☐☐
	☐ **Lactic acid vaginal gel** (e.g. Balance Activ®, Relactagel®, Canesbalance®) Was this prescribed? ☐Yes ☐No Number of courses taken? ☐☐
	☐ **Clindamycin cream** (e.g. Dalacin) Was this prescribed? ☐Yes ☐No Number of courses taken? ☐☐
	☐ **Other – please specify:** Was this prescribed? ☐Yes ☐No Number of courses taken? ☐☐

ANTIBIOTICS	
Have you received any **antibiotics for any other condition/illness (not your BV)** since starting your study treatment?	☐ Yes* ☐ No
***If YES, please select the antibiotic below:**	
☐ **Amoxicillin** Was this prescribed? ☐Yes ☐No	
☐ **Flucloxacillin** Was this prescribed? ☐Yes ☐No	
☐ **Doxycycline** Was this prescribed? ☐Yes ☐No	
☐ **Other – Please specify:** Was this prescribed? ☐Yes ☐No	

THRUSH	
Have you developed **vaginal thrush** since starting your study treatment?	☐ Yes* ☐ No
***If YES, please select thrush treatment taken below:**	
☐ **No treatment taken**	
☐ **Clotrimazole** (e.g. Canesten) Was this prescribed? ☐Yes ☐No	
☐ **Fluconazole** (e.g. Diflucan) Was this prescribed? ☐Yes ☐No	
☐ **Itraconazole** (e.g. Sporanox) Was this prescribed? ☐Yes ☐No	
☐ **Other – Please specify:** Was this prescribed? ☐Yes ☐No	

Are you pregnant?	☐ Yes ☐ No

Have you performed vaginal douching since starting study treatment (by vaginal douching, we mean washing inside your vagina)?	☐ Yes ☐ No

SEXUAL CONTACT

Have you had sex since starting study treatment?	☐Yes* ☐No
***If YES, please answer the questions below:**	
If yes, how soon after starting study treatment did you first have sex?	☐ I had sex the same day as starting my study treatment If not the same day please specify how many days after study treatment you first had sex: ____
Did you use condoms?	☐ Yes* ☐ No *If yes did you use condoms: ☐ Always (including oral sex) ☐ Not for oral sex but otherwise always ☐ Sometimes
Have you had any new sexual partners since starting study treatment?	☐ Yes ☐ No

USE OF HEALTH SERVICES FOR YOUR BV

Please record how many face-to-face or telephone consultations you have had with each of the following NHS services since you started the study treatment.
Only include those consultations that are related to your bacterial vaginosis or study treament.

(please do not record your original visit where you were first prescribed your treatment)

NHS SERVICE	**Service used?**	***If YES, provide details:**	
		Face-to-face contact (please record the number of times)	Telephone contact (please record the number of calls)
GP appointment	☐Yes* ☐No		
Nurse (GP Surgery) appointment	☐Yes* ☐No		
Specialist sexual health clinic appointment (e.g. GUM clinic)	☐Yes* ☐No		
NHS outpatient appointment (other than a specialist sexual health clinic/GUM clinic)	☐Yes* ☐No		
NHS walk in centre	☐Yes* ☐No		
NHS 111	☐Yes* ☐No		
GP out of hours service	☐Yes* ☐No		
Pharmacy	☐Yes* ☐No		
A & E Department	☐Yes* ☐No		
Other – Please specify:	☐Yes* ☐No		

HOSPITAL ADMISSIONS – BV	
In the two weeks since starting your study treatment, have you been to any hospital for an overnight stay because of problems related to your **bacterial vaginosis**?	☐ Yes* ☐ No
***If yes, please answer the questions below:**	
NHS or private hospital?	☐ NHS hospital ☐ Private hospital
Number of nights you stayed in hospital?	☐☐
Reason(s) for your stay(s) in hospital:	

HOSPITAL ADMISSIONS – STUDY TREATMENT	
In the two weeks since starting your study treatment, have you been to any hospital for an overnight stay because of side effects linked to your **study treatment**?	☐ Yes* ☐ No
***If yes, please answer the questions below:**	
NHS or private hospital?	☐ NHS hospital ☐ Private hospital
Number of nights you stayed in hospital?	☐☐
Reason(s) for your stay(s) in hospital:	

SF-12™ QUESTIONNAIRE

Validated Acute (1 week) SF-12™ Quality of Life Questionnaire

YOUR WEEK 2 VAGINAL SAMPLES

Have you taken your week 2 vaginal samples at the time of completing this questionnaire?

IF YES:

☐ **Yes – I have taken my week 2 samples**	
What date did you **take** your week 2 samples?	☐☐ ☐☐☐ ☐☐☐☐
Have you **posted** your week 2 samples? *If yes, what date were they **posted**? (dd-mmm-yyyy)	☐ Yes* ☐ No ☐☐ ☐☐☐ ☐☐☐☐
If you have not yet posted your week 2 samples please do so as soon as possible	

IF NO:

☐ **No – I have NOT yet taken my week 2 samples**	
If no, please specify why (select one of the options):	☐ I have not yet taken my week 2 samples but I will do so ☐ I can't remember how to take my week 2 samples (*Please refer to your kit instruction leaflet and the instructional video on **www.vitastudy.org** Please contact your local site team if you need additional advice)* ☐ I have lost my sample kit *(Please contact vitahelp@nottingham.ac.uk) for a replacement kit)* ☐ I will not be taking my 2 week samples – please specify reason:
If you have not yet taken your week 2 samples please do so as soon as possible	

– End of Week 2 Questions –

THANK YOU

Thank you for completing this questionnaire. Your continued participation in the study is very much appreciated.

If your contact details have changed *in the last 2 weeks* please *let us know by emailing:*
vitahelp@nottingham.ac.uk

We will send you another questionnaire in 3 months.

Other Comments
If you have any other comments about the study, please let us know below:
_____ _____ _____

Medical Attention
If you require any medical attention, please contact your GP / sexual health centre

Thank you for completing this questionnaire.

Appendix 2 VITA participant questionnaire: metronidazole week 2

PARTICIPANT QUESTIONNAIRE – WEEK 2

TREATMENT ALLOCATION: ORAL METRONIDAZOLE TABLETS

Please complete this questionnaire 2 weeks after starting your study treatment.

Date of questionnaire completion (dd-mmm-yyyy): | | | | | | | | | | |

Thank you very much for taking the time to answer these questions for the VITA study.
Please be assured that all the data collected remains confidential. The VITA website is secure and only the study team have access to the information you are entering.

Please answer the questions as fully as possible. This should take approximately 10 minutes to complete.

If you have any problems please contact the trial team at: vitahelp@nottingham.ac.uk

STUDY TREATMENT

This section refers to your allocated study treatment.

METRONIDAZOLE TABLETS		
What date did you start your metronidazole tablets? (dd-mmm-yyyy)	☐☐ ☐☐☐ ☐☐☐☐	
Treatment confirmation	**Morning dose (400mg) taken?**	**Evening dose (400mg) taken?**
Day 1 (Start of treatment)	☐ Yes ☐ No	☐ Yes ☐ No
Day 2	☐ Yes ☐ No	☐ Yes ☐ No
Day 3	☐ Yes ☐ No	☐ Yes ☐ No
Day 4	☐ Yes ☐ No	☐ Yes ☐ No
Day 5	☐ Yes ☐ No	☐ Yes ☐ No
Day 6	☐ Yes ☐ No	☐ Yes ☐ No
Day 7	☐ Yes ☐ No	☐ Yes ☐ No
Day 8	☐ Yes ☐ No	☐ Yes ☐ No
Did you complete your course of metronidazole tablets? *If you answered no, please select why:	☐ Yes ☐ No* ☐ I accidentally missed taking doses of the tablets ☐ I didn't like taking the tablets ☐ Side effects of the tablets ☐ Other – please specify:	
How easy did you find taking the metronidazole tablets?	☐ Very easy ☐ Easy ☐ Neither easy nor difficult ☐ Difficult ☐ Very difficult	

BACTERIAL VAGINOSIS (BV) SYMPTOMS

Have your BV symptoms cleared and stayed cleared **following your study treatment**?	☐ **Yes** – If yes what was the date they cleared? (dd-mmm-yyyy) __ __ ___ ____ ☐ **No** – If no how are your symptoms today compared to when you started study treatment? ☐ Better but not cleared/disappeared ☐ Improved initially but worsened again ☐ No change ☐ Worse

Are any of the following present today?	A genital discharge which you think is not normal: ☐Yes ☐No An offensive vaginal smell (a smell that is unpleasant to you): ☐Yes ☐No Vaginal irritation (may include itching/pain/burning): ☐Yes ☐No

SIDE EFFECTS – STUDY TREATMENT

NAUSEA		
During treatment, did you feel nauseous or sick?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did you first feel nauseous or sick?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How did the nausea/sickness affect you?	☐ Able to eat normally ☐ Ability to eat or drink fluids significantly decreased ☐ Unable to eat or drink fluids	
Approximately how long did your nausea/sickness last, in hours **or** days?	Hours __ __	Days __ __
Is your nausea/sickness fully resolved now?	☐ Yes ☐ No	

VOMITING		
During treatment, did you experienced any vomiting?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did your vomiting start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was your vomiting?	☐ 1 episode in 24 hours ☐ 2 to 5 episodes in 24 hours ☐ 6 or more episodes in 24 hours or need IV fluids	
Approximately how long did your vomiting last in total, in hours **or** days (i.e. from the first time you vomited to the last time?)	Hours ⌊__⌋	Days ⌊__⌋
Is your vomiting fully resolved now?	☐ Yes ☐ No	

TASTE / ABNORMAL TASTE		
During treatment, did you have any changes in taste or experience abnormal taste?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did the change in taste/abnormal taste start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was the change in your taste/abnormal taste?	☐ Mild ☐ Moderate ☐ Severe	
Approximately how long did the change in your taste/abnormal taste last, in hours **or** days?	Hours ⌊__⌋	Days ⌊__⌋
Is your change in taste/abnormal taste fully resolved now?	☐ Yes ☐ No	

VAGINAL IRRITATION (may include itching/pain/burning)		
During treatment, did you experience any vaginal irritation?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did your vaginal irritation start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was the vaginal irritation?	☐ Mild ☐ Moderate ☐ Severe	
Approximately how long did the vaginal irritation last, in hours **or** days?	Hours ⌊__⌋	Days ⌊__⌋
Is your vaginal irritation fully resolved now?	☐ Yes ☐ No	

ABDOMINAL PAIN		
During treatment, did you experience any abdominal pain?	Yes* ☐ No ☐	
***If YES, please answer the following questions:**		
How long after starting study treatment did your abdominal pain start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was the abdominal pain?	☐ Mild ☐ Moderate ☐ Severe	
Approximately how long did the abdominal pain last, in hours **or** days?	Hours ⌊__⌋	Days ⌊__⌋
Is your abdominal pain fully resolved now?	☐ Yes ☐ No	

DIARRHOEA		
During treatment, did you experience any diarrhoea?	☐ Yes* ☐ No	
***If YES, please answer the following questions:**		
How long after starting study treatment did your diarrhoea start?	☐ Less than 2 hours ☐ 2 to less than 6 hours ☐ 6 to less than 24 hours ☐ 1 to 3 days ☐ More than 3 days	
How severe was the diarrhoea?	☐ Mild ☐ Moderate ☐ Severe	
Approximately how long did the diarrhoea last, in hours **or** days?	Hours ⌊__⌋	Days ⌊__⌋
Is your diarrhoea fully resolved now?	☐ Yes ☐ No	

In addition to your study treatment, have you used any additional medications for your BV since joining the study? (Either prescribed to you by a doctor or bought over the counter e.g. bought separately in a pharmacy or online)	☐Yes* ☐No
***If YES, please select the additional medication below:**	
	☐ **Metronidazole tablets** Were these prescribed? ☐Yes ☐No Number of courses taken? ☐☐
	☐ **Metronidazole vaginal gel** Was this prescribed? ☐Yes ☐No Number of courses taken? ☐☐
	☐ **Lactic acid vaginal gel** (e.g. Balance Activ®, Relactagel®, Canesbalance®) Was this prescribed? ☐Yes ☐No Number of courses taken? ☐☐
	☐ **Clindamycin cream** (e.g. Dalacin) Was this prescribed? ☐Yes ☐No Number of courses taken? ☐☐
	☐ **Other – please specify:** Was this prescribed? ☐Yes ☐No Number of courses taken? ☐☐

ANTIBIOTICS	
Have you received any **antibiotics for any other condition/illness (not your BV)** since starting your study treatment?	☐ Yes* ☐ No
***If YES, please select the antibiotic below:**	
☐ **Amoxicillin** Was this prescribed? ☐Yes ☐No	
☐ **Flucloxacillin** Was this prescribed? ☐Yes ☐No	
☐ **Doxycycline** Was this prescribed? ☐Yes ☐No	
☐ **Other – Please specify:** Was this prescribed? ☐Yes ☐No	

THRUSH	
Have you developed **vaginal thrush** since starting your study treatment?	☐ Yes* ☐ No
***If YES, please select thrush treatment taken below:**	
☐ **No treatment taken**	
☐ **Clotrimazole** (e.g. Canesten) Was this prescribed? ☐Yes ☐No	
☐ **Fluconazole** (e.g. Diflucan) Was this prescribed? ☐Yes ☐No	
☐ **Itraconazole** (e.g. Sporanox) Was this prescribed? ☐Yes ☐No	
☐ **Other – Please specify:** Was this prescribed? ☐Yes ☐No	

Are you pregnant?	☐ Yes ☐ No

Have you performed vaginal douching since starting study treatment (by vaginal douching, we mean washing inside your vagina)?	☐ Yes ☐ No

SEXUAL CONTACT

Have you had sex since starting study treatment?	☐Yes* ☐No
***If YES, please answer the questions below:**	
If yes, how soon after starting study treatment did you first have sex?	☐ I had sex the same day as starting my study treatment If not the same day please specify how many days after study treatment you first had sex: ____
Did you use condoms?	☐ Yes* ☐ No *If yes did you use condoms: ☐ Always (including oral sex) ☐ Not for oral sex but otherwise always ☐ Sometimes
Have you had any new sexual partners since starting study treatment?	☐ Yes ☐ No

USE OF HEALTH SERVICES FOR YOUR BV

Please record how many face-to-face or telephone consultations you have had with each of the following NHS services since you started the study treatment.
Only include those consultations that are related to your bacterial vaginosis or study treament.

(please do not record your original visit where you were first prescribed your treatment)

NHS SERVICE	**Service used?**	***If YES, provide details:**	
		Face-to-face contact (please record the number of times)	Telephone contact (please record the number of calls)
GP appointment	☐Yes* ☐No		
Nurse (GP Surgery) appointment	☐Yes* ☐No		
Specialist sexual health clinic appointment (e.g. GUM clinic)	☐Yes* ☐No		
NHS outpatient appointment (other than a specialist sexual health clinic/GUM clinic)	☐Yes* ☐No		
NHS walk in centre	☐Yes* ☐No		
NHS 111	☐Yes* ☐No		
GP out of hours service	☐Yes* ☐No		
Pharmacy	☐Yes* ☐No		
A & E Department	☐Yes* ☐No		
Other – Please specify:	☐Yes* ☐No		

HOSPITAL ADMISSIONS – BV	
In the two weeks since starting your study treatment, have you been to any hospital for an overnight stay because of problems related to your **bacterial vaginosis**?	☐ Yes* ☐ No
***If yes, please answer the questions below:**	
NHS or private hospital?	☐ NHS hospital ☐ Private hospital
Number of nights you stayed in hospital?	☐☐
Reason(s) for your stay(s) in hospital:	

HOSPITAL ADMISSIONS – STUDY TREATMENT	
In the two weeks since starting your study treatment, have you been to any hospital for an overnight stay because of side effects linked to your **study treatment**?	☐ Yes* ☐ No
***If yes, please answer the questions below:**	
NHS or private hospital?	☐ NHS hospital ☐ Private hospital
Number of nights you stayed in hospital?	☐☐
Reason(s) for your stay(s) in hospital:	

SF-12™ QUESTIONNAIRE

Validated Acute (1 week) SF-12™ Quality of Life Questionnaire

YOUR WEEK 2 VAGINAL SAMPLES

Have you taken your week 2 vaginal samples at the time of completing this questionnaire?

IF YES:

☐ **Yes – I have taken my week 2 samples**	
What date did you **take** your week 2 samples?	☐☐ ☐☐☐ ☐☐☐☐
Have you **posted** your week 2 samples? *If yes, what date were they **posted**? (dd-mmm-yyyy)	☐ Yes* ☐ No ☐☐ ☐☐☐ ☐☐☐☐
If you have not yet posted your week 2 samples please do so as soon as possible	

IF NO:

☐ **No – I have NOT yet taken my week 2 samples**	
If no, please specify why (select one of the options):	☐ I have not yet taken my week 2 samples but I will do so ☐ I can't remember how to take my week 2 samples (*Please refer to your kit instruction leaflet and the instructional video on **www.vitastudy.org** Please contact your local site team if you need additional advice)* ☐ I have lost my sample kit *(Please contact vitahelp@nottingham.ac.uk) for a replacement kit)* ☐ I will not be taking my 2 week samples – please specify reason:
If you have not yet taken your week 2 samples please do so as soon as possible	

– End of Week 2 Questions –

THANK YOU

Thank you for completing this questionnaire. Your continued participation in the study is very much appreciated.

If your contact details have changed in the last 2 weeks please let us know by emailing: vitahelp@nottingham.ac.uk

We will send you another questionnaire in 3 months.

Other Comments
If you have any other comments about the study, please let us know below:
_____ _____ _____

Medical Attention
If you require any medical attention, please contact your GP/sexual health centre

Thank you for completing this questionnaire.

Appendix 3 VITA participant questionnaire: 3 months

PARTICIPANT QUESTIONNAIRE – 3 MONTHS

Please complete this questionnaire 3 months after starting your study treatment.

Date of questionnaire completion (dd-mmm-yyyy): | | | | | | | | | | |

Thank you very much for taking the time to answer these questions for the VITA study.
Please be assured that all the data collected remains confidential. The VITA website is secure and only the study team have access to the information you are entering.

Please answer the questions as fully as possible. This should take approximately 10 minutes to complete.

If you have any problems please contact the trial team on vitahelp@nottingham.ac.uk

BACTERIAL VAGINOSIS (BV) SYMPTOMS – RESOLUTION

Had your original BV symptoms cleared by the end of week 2 (when you completed the week 2 questionnaire)? *By "original" we mean your BV symptoms at the beginning of the study (before treatment)*	Choose **one** of the following **4** options: **1.** ☐ My original BV symptoms cleared within the first two weeks (this could be with or without additional treatment, and even if they then came back). **2.** ☐ My original BV symptoms never cleared in the first two weeks but they did clear between 2 weeks and 3 months without additional treatment. **3.** ☐ My original BV symptoms never cleared in the first two weeks but they did clear between 2 weeks and 3 months with additional treatment. If you **ticked option 2 or 3** please confirm the date they cleared: __ __ / __ __ __ / __ __ __ __ **4.** ☐ My original BV symptoms never cleared and are ongoing. ⓘ **If you chose option 4 please do NOT answer the section on "BV Symptoms – Recurrence" below but go straight to the section on "Additional Medications for your BV" and then complete the rest of the questionnaire.**

BACTERIAL VAGINOSIS (BV) SYMPTOMS – RECURRENCE

Have you experienced any **new** episodes of BV symptoms since your original symptoms cleared?	Yes* ☐ No☐
***If YES, please answer the following questions:**	
What was the date of your **first** new episode of BV?	☐☐ ☐☐☐ ☐☐☐☐
How many new episodes of BV type symptoms have you experienced?	☐☐
In total, approximately how many weeks have you had BV symptoms since your first episode of BV cleared?	☐ Less than 1 Week ☐ 1 to less than 2 Weeks ☐ 2 to 4 Weeks ☐ More than 4 Weeks
Were the recurrence(s) of your BV symptoms typical of your usual symptoms?	☐ Always ☐ Sometimes ☐ Seldom

ADDITIONAL MEDICATIONS FOR YOUR BV

In addition to your study treatment, have you used any additional medications for your BV **since completing your week 2 questionnaire?** (Either prescribed to you by a doctor or bought over the counter e.g. bought separately in a pharmacy or online)	☐Yes* ☐No
***If YES, please select the additional medication below:**	
	☐ **Metronidazole tablets** Were these prescribed? ☐Yes ☐No Number of courses taken? ___|___
	☐ **Metronidazole vaginal gel** Was this prescribed? ☐Yes ☐No Number of courses taken? ___|___
	☐ **Lactic acid vaginal gel** (e.g. Balance Activ®, Relactagel®, Canesbalance®) Was this prescribed? ☐Yes ☐No Number of courses taken? ___|___
	☐ **Clindamycin cream** (e.g. Dalacin) Was this prescribed? ☐Yes ☐No Number of courses taken? ___|___
	☐ **Other – please specify:** Was this prescribed? ☐Yes ☐No Number of courses taken? ___|___

ANTIBIOTICS	
Have you received any **antibiotics for any other condition/illness (not your BV)** since completing your week 2 questionnaire?	☐ Yes* ☐ No
***If YES, please select the antibiotic below:**	
☐ **Amoxicillin** Was this prescribed? ☐Yes ☐No	
☐ **Flucloxacillin** Was this prescribed? ☐Yes ☐No	
☐ **Doxycycline** Was this prescribed? ☐Yes ☐No	
☐ **Other – Please specify:** Was this prescribed? ☐Yes ☐No	

THRUSH	
Have you developed **vaginal thrush since completing your week 2 questionnaire?**	☐Yes* ☐No *If yes, please specify the date of onset (when the thrush started): |__|__| |__|__|__| |__|__|__|__|__| How many episodes of vaginal thrush have you had? |__|__|

Are you pregnant, or have you been pregnant **since completing your week 2 questionnaire**?	☐ Yes – currently pregnant. Please specify approx due date: |__|__| |__|__|__| |__|__|__|__|__| ☐ Yes – pregnant since completing the week 2 questionnaire but not currently ☐ No

Have you performed vaginal douching **since completing your week 2 questionnaire** (by vaginal douching, we mean washing inside your vagina)?	☐ Yes ☐ No

SEXUAL CONTACT

Have you had sex **since completing your week 2 questionnaire**?	☐ Yes* ☐ No
***If YES, please answer the questions below:**	
If yes, did you use condoms:	☐ Yes* ☐ No *If yes did you use condoms: ☐ Always (including oral sex) ☐ Not for oral sex but otherwise always ☐ Sometimes
Have you had any new sexual partners **since completing your week 2 questionnaire**?	☐ Yes ☐ No

Have you been diagnosed with HIV?	☐Yes ☐No

Have any of the following been diagnosed **since completing your 2 week questionnaire**? Please answer yes or no for each condition.		
Gonorrhoea	☐Yes* ☐No	*If yes Number of episodes: ___
Chlamydia	☐Yes* ☐No	*If yes Number of episodes: ___
Trichomonas	☐Yes* ☐No	*If yes Number of episodes: ___
Pelvic inflammatory disease	☐Yes* ☐No	*If yes Number of episodes: ___

USE OF HEALTH SERVICES FOR YOUR BV

Please record how many face-to-face or telephone consultations you have had with each of the following NHS services **since you completed your week 2 questionnaire**.
Only include those consultations that are related to your bacterial vaginosis or study treament

(please do not record your original visit where you were first prescribed your treatment)

NHS SERVICE	**Service used?**	***If YES, provide details:**	
		Face-to-face contact (please record the number of times)	Telephone contact (please record the number of calls)
GP appointment	☐Yes* ☐No	☐☐	☐☐
Nurse (GP Surgery) appointment	☐Yes* ☐No	☐☐	☐☐
Specialist sexual health clinic appointment (e.g. GUM clinic)	☐Yes* ☐No	☐☐	☐☐
NHS outpatient appointment (other than a specialist sexual health clinic/GUM clinic)	☐Yes* ☐No	☐☐	☐☐
NHS walk in centre	☐Yes* ☐No	☐☐	☐☐
NHS 111	☐Yes* ☐No		☐☐
GP out of hours service	☐Yes* ☐No	☐☐	☐☐
Pharmacy	☐Yes* ☐No	☐☐	☐☐
A & E Department	☐Yes* ☐No	☐☐	☐☐
Other – Please specify:	☐Yes* ☐No	☐☐	☐☐

HOSPITAL ADMISSIONS – BV	
Since completing your week 2 questionnaire, have you been to hospital for an overnight stay because of problems related to your **bacterial vaginosis**?	☐ Yes* ☐ No
***If yes, please answer the questions below:**	
NHS or private hospital?	☐ NHS hospital ☐ Private hospital
Number of nights you stayed in hospital?	☐☐
Reason(s) for your stay(s) in hospital:	

SF-12™ QUESTIONNAIRE

Validated SF-12™ (4 week) Quality of Life questionnaire

– End of 3 month Questions –

THANK YOU

Thank you for completing this questionnaire. Your continued participation in the study is very much appreciated.

If your contact details have changed in the last 3 months please let us know by emailing: vitahelp@nottingham.ac.uk

We will send you another questionnaire in 3 months.

Other Comments
If you have any other comments about the study, please let us know below:
_____ _____ _____

Medical Attention
If you require any medical attention, please contact your GP/sexual health centre

Thank you for completing this questionnaire.

Appendix 4 VITA participant questionnaire: 6 months

PARTICIPANT QUESTIONNAIRE – 6 MONTHS

Please complete this questionnaire 6 months after starting your study treatment.

Date of questionnaire completion (dd-mmm-yyyy): | | | | | | | | | | | |

Thank you very much for taking the time to answer these questions for the VITA study.
Please be assured that all the data collected remains confidential. The VITA website is secure and only the study team have access to the information you are entering.

Please answer the questions as fully as possible. This should take approximately 10 minutes to complete.

If you have any problems please contact the trial team on vitahelp@nottingham.ac.uk

BACTERIAL VAGINOSIS (BV) SYMPTOMS - RESOLUTION

Had your original BV symptoms cleared by 3 months i.e. when you completed the 3 month questionnaire? *By "original" we mean your BV symptoms at the beginning of the study (before treatment)*	Choose **one** of the following **4** options: **1.** ☐ My original BV symptoms had cleared by 3 months. **2.** ☐ My original BV symptoms did not clear in the first 3 months but they did clear by 6 months without additional treatment. **3.** ☐ My original BV symptoms did not clear in the first 3 months but they did clear by 6 months with additional treatment. If you **ticked option 2 or 3** please confirm the date they cleared: __ __ / __ __ __ / __ __ __ __ ⓘ **If you answered option 1, 2, or 3, please complete the section on "BV Symptoms - Recurrence" below and then continue to complete the rest of the questionnaire.** **4.** ☐ My original BV symptoms never cleared and are ongoing ⓘ **If you answered option 4 please do NOT answer the section on "BV Symptoms – Recurrence" below but go straight to the section on "Additional Medications for your BV" and then complete the rest of the questionnaire.**

BACTERIAL VAGINOSIS (BV) SYMPTOMS - RECURRENCE

Have you experienced any **new** episodes of bacterial vaginosis symptoms **in the last 3 months**?	Yes* ☐ No☐
***If YES, please answer the following questions:**	
What was the date of your first new episode of bacterial vaginosis symptoms (in the last 3 months)?	☐☐ ☐☐☐ ☐☐☐☐
How many new episodes of bacterial vaginosis type symptoms have you experienced (in the last 3 months)?	☐☐
In total, approximately how many weeks have you had bacterial vaginosis symptoms (in the last 3 months)?	☐ Less than 1 Week ☐ 1 to less than 2 Weeks ☐ 2 to 4 Weeks ☐ More than 4 Weeks
Were the recurrence(s) of your bacterial vaginosis symptoms typical of your usual symptoms?	☐ Always ☐ Sometimes ☐ Seldom

ADDITIONAL MEDICATIONS FOR YOUR BV

In addition to your study treatment, have you used any additional medications for your BV **in the last 3 months?** (Either prescribed to you by a doctor or bought over the counter e.g. bought separately in a pharmacy or online)	☐Yes* ☐No
***If YES, please select the additional medication below:**	
	☐ **Metronidazole tablets** Were these prescribed? ☐Yes ☐No Number of courses taken? __| __|
	☐ **Metronidazole vaginal gel** Was this prescribed? ☐Yes ☐No Number of courses taken? __| __|
	☐ **Lactic acid vaginal gel** (e.g. Balance Activ®, Relactagel®, Canesbalance®) Was this prescribed? ☐Yes ☐No Number of courses taken? __| __|
	☐ **Clindamycin cream** (e.g. Dalacin) Was this prescribed? ☐Yes ☐No Number of courses taken? __| __|
	☐ **Other – please specify:** Was this prescribed? ☐Yes ☐No Number of courses taken? __| __|

ANTIBIOTICS	
Have you received any **antibiotics for any other condition/illness (not your BV)** in the last 3 months?	☐ Yes* ☐ No
***If YES, please select the antibiotic below:**	
☐ **Amoxicillin** Was this prescribed? ☐Yes ☐No	
☐ **Flucloxacillin** Was this prescribed? ☐Yes ☐No	
☐ **Doxycycline** Was this prescribed? ☐Yes ☐No	
☐ **Other – Please specify:** Was this prescribed? ☐Yes ☐No	

THRUSH	
Have you developed **vaginal thrush in the last 3 months?**	☐Yes* ☐No *If yes please specify the date of onset (when the thrush started): __ __ ____ ____ How many episodes of vaginal thrush have you had? __

Have you performed vaginal douching **in the last 3 months** (by vaginal douching, we mean washing inside your vagina)?	☐ Yes ☐ No

SEXUAL CONTACT

Have you had sex **in the last 3 months**?	☐ Yes* ☐ No
***If YES, please answer the following questions:**	
If yes, did you use condoms:	☐ Yes* ☐ No *If yes did you use condoms: ☐ Always (including oral sex) ☐ Not for oral sex but otherwise always ☐ Sometimes
Have you had any new sexual partners **in the last 3 months**?	☐ Yes ☐ No

Have you been diagnosed with HIV in the last 3 months?	☐Yes ☐No

Have any of the following been diagnosed **in the last 3 months**? Please answer yes or no for each condition.		
Gonorrhoea	☐Yes* ☐No	*If yes Number of episodes: ___
Chlamydia	☐Yes* ☐No	*If yes Number of episodes: ___
Trichomonas	☐Yes* ☐No	*If yes Number of episodes: ___
Pelvic inflammatory disease	☐Yes* ☐No	*If yes Number of episodes: ___

USE OF HEALTH SERVICES FOR YOUR BV

Please record how many face-to-face or telephone consultations you have had with each of the following NHS services **in the last 3 months?**
Only include those consultations that are related to your bacterial vaginosis or study treament.

(please do not record your original visit where you were first prescribed your treatment).

NHS SERVICE	**Service used?**	***If YES, provide details:**	
		Face-to-face contact (please record the number of times)	Telephone contact (please record the number of calls)
GP appointment	☐Yes* ☐No	☐☐	☐☐
Nurse (GP Surgery) appointment	☐Yes* ☐No	☐☐	☐☐
Specialist sexual health clinic appointment (e.g. GUM clinic)	☐Yes* ☐No	☐☐	☐☐
NHS outpatient appointment (other than a specialist sexual health clinic/GUM clinic)	☐Yes* ☐No	☐☐	☐☐
NHS walk in centre	☐Yes* ☐No	☐☐	☐☐
NHS 111	☐Yes* ☐No		☐☐
GP out of hours service	☐Yes* ☐No	☐☐	☐☐
Pharmacy	☐Yes* ☐No	☐☐	☐☐
A & E Department	☐Yes* ☐No	☐☐	☐☐
Other – Please specify:	☐Yes* ☐No	☐☐	☐☐

HOSPITAL ADMISSIONS – BV	
In the last 3 months, have you been to hospital for an overnight stay because of problems related to your **bacterial vaginosis**?	☐ Yes* ☐ No
***If yes, please answer the questions below:**	
NHS or private hospital?	☐ NHS hospital ☐ Private hospital
Number of nights you stayed in hospital?	☐☐
Reason(s) for your stay(s) in hospital:	

SF-12™ QUESTIONNAIRE

Validated SF-12™ (4 week) Quality of Life questionnaire

– End of 6 month Questions –

THANK YOU

Thank you for completing this questionnaire. Your continued participation in the study is very much appreciated.

If your contact details have changed in the last 3 months please let us know by emailing: vitahelp@nottingham.ac.uk

This is your final questionnaire so you will not receive any further questionnaires to complete.

Other Comments
If you have any other comments about the study, please let us know below:
_____ _____ _____

Medical Attention
If you require any medical attention, please contact your GP/sexual health centre

Thank you for completing this questionnaire.

Appendix 5 Additional results tables

TABLE 28 Reasons for excluding women prior to consent

Reason ID[a]	Reason	Total, *n* (%)
A	Not interested	248 (9)
B	Takes too much time	192 (7)
C	Current treatment will be successful	68 (3)
D	Too many extra/intrusive samples	9 (< 0.5)
E	Outside age range (< 16 years)	5 (< 0.5)
F	Does not have access to the internet/e-mail	1 (< 0.5)
G	Does not have current clinical diagnosis of BV	83 (3)
H	Does not have history of at least one episode of BV within the last 2 years	695 (27)
I	Did not provide written informed consent	1 (< 0.5)
J	Has known contraindication or allergy to metronidazole or lactic acid	26 (1)
K	Is pregnant or breastfeeding	47 (2)
L	Receiving oral antibiotics or antifungal agents, concurrently (± 2 weeks)	418 (16)
M	Using topical vaginal antibiotics, antifungals or acidifying products concurrently (± 2 weeks)	209 (8)
N	Not willing to avoid sexual intercourse or use effective contraception for 7-day BV treatment	38 (1)
O	Not willing to avoid vaginal douching for 7-day BV treatment	3 (< 0.5)
P	Current participation in another clinical trial involving an IMP	2 (< 0.5)
Q	Previous participation in this study	60 (2)
R	Other reason	335 (13)
S	No staff available	178 (7)
Total		2618

a Reasons E–I, N and O are part of the inclusion criteria. Reasons J–N, P and Q are part of the exclusion criteria.

TABLE 29 Trial recruitment by treatment arm and participating site

Site	Treatment arm, *n* (%)		Total, *n* (%)
	Oral metronidazole	Intravaginal lactic acid gel	
Sexual health centres			
Birmingham: Whittall Street Clinic	85 (33)	91 (36)	176 (35)
London: Hammersmith Broadway	47 (18)	46 (18)	93 (18)
Leeds: Leeds Sexual Health	24 (9)	23 (9)	47 (9)
Brighton: Elton John Centre	18 (7)	15 (6)	33 (6)
London: Grahame Hayton Unit	16 (6)	17 (7)	33 (6)

continued

TABLE 29 Trial recruitment by treatment arm and participating site (*continued*)

Site	Treatment arm, *n* (%)		Total, *n* (%)
	Oral metronidazole	Intravaginal lactic acid gel	
London: St Mary's Hospital	16 (6)	14 (6)	30 (6)
London: Mortimer Market Centre	8 (3)	8 (3)	16 (3)
Liverpool: Axess Sexual Health Centre	8 (3)	7 (3)	15 (3)
Sheffield: Royal Hallamshire Hospital	9 (4)	5 (2)	14 (3)
Bournemouth: Royal Bournemouth Hospital	5 (2)	6 (2)	11 (2)
Coventry: Integrated Sexual Health Services	5 (2)	6 (2)	11 (2)
London: Burrell Street Sexual Health Centre	5 (2)	3 (1)	8 (2)
Derby: Derby Sexual Health	3 (1)	4 (2)	7 (1)
Cardiff: University Hospital of Wales	2 (1)	3 (1)	5 (1)
London: John Hunter Clinic	1 (< 0.5)	2 (1)	3 (1)
Shrewsbury: The Redwoods Centre	1 (< 0.5)	2 (1)	3 (1)
Birmingham: Heartlands Hospital	1 (< 0.5)	1 (< 0.5)	2 (< 0.5)
Bolton: Bolton Centre for Sexual and Reproductive Health	1 (< 0.5)	0	1 (< 0.5)
London: Trafalgar Clinic	0	1 (< 0.5)	1 (< 0.5)
Total	255	254	509
General practices			
Nottingham: Cripps Health Centre	4	5	9
Total: all sites	259	259	518

Two sites opened but did not recruit any participants: London – Sexual Health – West Middlesex Hospital; Reading – The Florey Sexual Health & Contraceptive Services.

TABLE 30 Comparison of local laboratory with central laboratory BV microscopy results

Ison–Hay grade for BV (from central laboratory)[a]	Local BV results, *n* (%)				Total, *n* (%)
	Positive	Negative	Not tested	Missing	
0 (no bacteria)	2 (0.5)	0	0	0	2 (< 0.5)
1 (normal flora)	73 (17)	32 (53)	5 (24)	0	110 (21)
2 (intermediate BV)	112 (26)	8 (13)	3 (14)	0	123 (24)
3 (confirmed BV)	236 (54)	17 (28)	13 (62)	0	266 (51)
U (Gram-positive cocci)	3 (1)	1 (2)	0	0	4 (1)
Missing	10 (2)	2 (3)	0	1 (100)	13 (3)
Total	436	60	21	1	518

a Positive for BV = grade 3, negative for BV = grades 0, 1, 2 and U.

TABLE 31 Medical history

Participant characteristic	Treatment arm		Total (*N* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
HIV positive*, n *(%)			
Yes	2 (1)	1 (< 0.5)	3 (1)
No	257 (99)	257 (99)	514 (99)
Missing	0	1 (< 0.5%)	1 (< 0.5)
Past history of immunosuppression other than HIV*, n *(%)			
Yes	2 (1)	6 (2)	8 (2)
No	257 (99)	252 (98)	509 (98)
Missing	0	1 (< 0.5)	1 (< 0.5)
Reported reason for immunosuppression, n *(%)*			
Took immunosuppressant drugs	1 (50)	1 (17)	2 (25)
Has inherited immune deficiency	1 (50)	0	1 (13)
Other[a]	0	5 (93)	5 (83)
Had vaginal thrush in the past 12 months*, n *(%)			
Yes	123 (47)	127 (49)	250 (48)
No	136 (53)	131 (51)	267 (52)
Missing	0	1 (< 0.5)	1 (< 0.5)
Number of episodes of vaginal thrush in past 12 months			
1, *n* (%)	49 (40)	58 (46)	107 (43)
2, *n* (%)	39 (32)	27 (21)	66 (26)
> 2, *n* (%)	35 (28)	42 (33)	77 (31)
Median (25th, 75th centile)	2 (1, 3)	2 (1, 4)	2 (1, 3)
Minimum, maximum	1, 12	1, 90	1, 90

a Other reasons: one rheumatoid arthritis, one eating disorder, one undifferentiated autoimmune disease and two diabetes.

TABLE 32 Sexual history

Participant characteristic	Treatment arm		Total (*N* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Has current sexual partner*, n *(%)			
Yes	192 (74)	173 (67)	365 (71)
No	67 (26)	85 (33)	152 (29)
Missing	0	1 (< 0.5)	1 (< 0.5)

continued

TABLE 32 Sexual history (*continued*)

Participant characteristic	Treatment arm		Total (*N* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Approximate time with current/most recent sexual partner for those with partner (months)			
n	191	173	364
Median (25th, 75th centile)	12 (4, 48)	11 (3.7, 36)	12 (3.8, 36)
Minimum, maximum	0.2, 300	0.1, 240	0.1, 300
Approximate time since most recent sexual intercourse (days)			
n	259	257	516
Median (25th, 75th centile)	10 (4, 30.4)	10 (4, 28)	10 (4, 30.4)
Minimum, maximum	1, 4018	0, 609	0, 4018
Approximate total number of sexual partners over the past 12 months (including current)			
N	259	258	517
0, *n* (%)	5 (2)	2 (1)	7 (1)
1, *n* (%)	102 (39)	106 (41)	208 (40)
2, *n* (%)	67 (26)	78 (30)	145 (28)
3–5, *n* (%)	62 (24)	46 (18)	108 (21)
6–10, *n* (%)	18 (7)	21 (8)	39 (8)
> 10, *n* (%)	5 (2)	5 (2)	10 (2)
Missing, *n* (%)	0	1 (< 0.5)	1 (< 0.5)
Median (25th, 75th centile)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Minimum, maximum	0, 20	0, 30	0, 30
Gender of sexual partners in lifetime*, n *(%)			
Male	233 (90)	229 (88)	462 (89)
Female	6 (2)	5 (2)	11 (2)
Both male and female	20 (8)	24 (9)	44 (8)
Missing	0	1 (< 0.5)	1 (< 0.5)
Female sexual partner in past 12 months*, n *(%)			
Yes	26 (10)	25 (10)	51 (10)
No	233 (90)	234 (90)	467 (90)
***Types of sexual contact in past 12 months*, n *(%)*[a]** *Vaginal sex*			
Yes	251 (97)	253 (98)	504 (97)
No	2 (1)	3 (1)	5 (1)
Missing	6 (2)	3 (1)	9 (2)
Giving oral sex			
Yes	206 (80)	217 (84)	423 (82)
No	47 (18)	39 (15)	86 (17)
Missing	6 (2)	3 (1)	9 (2)

TABLE 32 Sexual history (*continued*)

Participant characteristic	Treatment arm: Oral metronidazole (*N* = 259)	Treatment arm: Intravaginal lactic acid gel (*N* = 259)	Total (*N* = 518)
Receiving oral sex			
Yes	190 (73)	204 (79)	394 (76)
No	63 (24)	52 (20)	115 (22)
Missing	6 (2)	3 (1)	9 (2)
Receiving anal sex			
Yes	51 (20)	45 (17)	96 (19)
No	202 (78)	211 (81)	413 (80)
Missing	6 (2)	3 (1)	9 (2)
Use of condoms			
Yes always, including oral sex	9 (3)	3 (1)	12 (2)
Yes always, except oral sex	28 (11)	35 (14)	63 (12)
Yes sometimes	109 (42)	102 (39)	211 (41)
No	113 (44)	118 (46)	231 (45)
Missing	0	1 (< 0.5)	1 (< 0.5)

a Not mutually exclusive.

TABLE 33 Data completion

Completeness of patient questionnaire data and interval to receipt of data	Treatment arm: Oral metronidazole (*N* = 259)	Treatment arm: Intravaginal lactic acid gel (*N* = 259)	Total (*N* = 518)
Week 2 questionnaire*, n *(%)			
Total withdrawn before questionnaire expected	1	2	3
Questionnaire expected	258	257	515
Questionnaire returned[a]	157 (61)	161 (63)	318 (62)
Questionnaire not returned[b]	101 (39)	96 (37)	197 (38)
Primary outcome data collected by telephone	46	42	88
Time from randomisation to questionnaire return (days)			
n	157	161	318
Median (25th, 75th centile)	15 (14, 19)	15 (14, 19)	15 (14, 19)
Minimum, maximum	14, 35	14, 55	14, 55

continued

TABLE 33 Data completion (*continued*)

Completeness of patient questionnaire data and interval to receipt of data	Treatment arm		Total (*N* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Time from randomisation to telephone data collection (days)			
n	46	42	88
Median (25th, 75th centile)	50.5 (33, 86)	56 (37, 77)	55.5 (34, 85)
Minimum, maximum	29, 155	29, 153	29, 155
3-month questionnaire*, n *(%)			
Total withdrawn before questionnaire expected	3	3	6
Questionnaire expected	256	256	512
Questionnaire returned[a]	111 (43)	108 (42)	219 (43)
Questionnaire not returned[b]	145 (57)	148 (58)	293 (57)
Time from randomisation to questionnaire return (days)			
n	111	108	219
Median (25th, 75th centile)	92 (92, 97)	93 (92, 97)	93 (92, 97)
Minimum, maximum	89, 109	89, 113	89, 113
6-month questionnaire*, n *(%)			
Total withdrawn before questionnaire expected	3	3	6
Questionnaire expected	256	256	512
Questionnaire returned[a]	92 (36)	84 (33)	176 (34)
Questionnaire not returned[b]	164 (64)	172 (67)	336 (66)
Recurrence data collected by telephone[c]	15	14	29
Time from randomisation to questionnaire return (days)			
n	92	84	176
Median (25th, 75th centile)	186 (183, 189)	186 (182.5, 189)	186 (183, 189)
Minimum, maximum	181, 196	181, 208	181, 208
Time from randomisation to obtaining telephone data (days)			
n	15	14	29
Median (25th, 75th centile)	233 (219, 244)	231 (222, 239)	231 (222, 239)
Minimum, maximum	203, 265	213, 239	203, 265

a Questionnaire returned: at least one piece of data was entered on questionnaire.
b Questionnaire not returned: no questions were entered on the questionnaire.
c Either of or both of recurrence (experienced new episodes since original symptoms cleared) and number of new episodes.

Note
Questionnaire windows: 2 weeks (or longer if requested by the participant) after the expected date for the week 2 questionnaire and 1 calendar month after the expected date for the 3-month and 6-month questionnaires.

TABLE 34 Telephone follow-up

Frequency and completeness of telephone follow-up	Treatment arm, *n* (%)		Total (*N* = 518), *n* (%)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Week 2			
Primary outcomes to be obtained by telephone	101 (39)	96 (37)	197 (38)
Participants attempted follow-up by telephone[a]	103 (100)	99 (100)	202 (100)
Primary outcome obtained by telephone	46 (45)	42 (43)	88 (44)
Primary outcome not obtained by telephone	57 (55)	57 (57)	114 (56)
Contact made, but resolution status not known by participant	1 (2)	0	1 (1)
Contact made, but unwilling to provide outcome	4 (7)	9 (16)	13 (11)
Contact not made (three attempts)	52 (91)	48 (84)	100 (88)
6 months			
Secondary outcomes to be obtained by telephone[b]	58	61	119
Participants attempted follow-up by telephone[b]	53 (91)	52 (85)	105 (88)
Presence of recurrence outcome obtained by telephone	15 (28)	14 (27)	29 (28)
Number of episodes outcome obtained by telephone	7 (13)	7 (13)	14 (13)
Both outcomes obtained by telephone	13 (25)	13 (25)	26 (25)
Contact made, but recurrence outcome not known by participant	2	0	2
Contact made, but number of episodes not known by participant	2	1	3
Neither outcome obtained by telephone			
Contact made, but unwilling to provide either outcome	2 (4)	4 (8)	6 (6)
Contact not made (three attempts)	34 (64)	34 (65)	68 (65)

a Contact attempted for two participants in error (one gave no data and for the other no contact was made). Attempts for three participants were made for whom 3-month data were later available.
b Six-month telephone calls started in the latter part of the trial: a decision was made to make the calls in June 2019 and the process started in August 2019.

TABLE 35 Availability of week 2 samples

Sample characteristics	Treatment arm, *n* (%)		Total (*N* = 518), *n* (%)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Number of samples expected	258	257	515
Number of week 2 samples received by the laboratory	148 (57)	153 (60)	301 (58)
Number with primary outcome and sample results	135 (52)	145 (56)	280 (54)
Primary outcome from the questionnaire	121	132	253
Primary outcome by telephone	14	13	27

TABLE 36 Receipt of NAAT sample kits by the central laboratory for STI analysis

Sample characteristics	Treatment arm, *n* (%)		Total (*N* = 518), *n* (%)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
Baseline samples and expiry dates			
Sample kits in date	166 (64)	173 (67)	339 (65)
Excluded out-of-date sample kits	16 (6)	16 (6)	32 (6)
Sample kits with expiry status unknown	71 (27)	67 (26)	138 (27)
No identifiable sample received[a]	6 (2)	3 (1)	9 (2)
Week 2 samples and expiry dates			
Sample kits in date	110 (42)	114 (44)	224 (43)
Excluded out-of-date sample kits	8 (3)	11 (4)	19 (4)
Sample kits with expiry status unknown	30 (12)	28 (11)	58 (11)
Participant withdrawn before week 2	1 (< 0.5)	2 (1)	3 (1)
No identifiable sample received[b]	110 (42)	104 (40)	214 (41)

a Two samples were received but could not be reliably assigned to a participant.
b One sample was received but could not be reliably assigned to a participant.

TABLE 37 Resolution of BV at week 2 (participant reported)

Resolution of BV at week 2	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Data from all sources		
Yes	143 (70)	97 (47)
No	61 (30)	108 (53)
Missing	55	54
Questionnaire data only[a]		
Yes	105 (66)	75 (46)
No	53 (34)	88 (54)
Missing	101	96
Telephone data only		
Yes	38 (83)	22 (52)
No	8 (17)	20 (48)
Missing[b]	58	58

a Includes the use of date of resolution on the week 2 questionnaire ($n = 2$ lactic acid gel arm) and the question about resolution by 2 weeks ($n = 1$ lactic acid gel arm) or ongoing (not resolved: metronidazole arm, $n = 1$; lactic acid gel arm, $n = 2$) when the primary outcome question was not answered on the 3-month questionnaire.
b The total number of participants telephoned included some for whom data were later available on the 3-month questionnaire.

TABLE 38 Baseline characteristics of the subset of participants resolving by week 2

Characteristics of those who resolved by week 2	Treatment arm	
	Oral metronidazole (*N* = 143)	Intravaginal lactic acid gel (*N* = 97)
Age at randomisation (years)		
n	143	97
Mean (SD)	29.4 (8.43)	30.5 (8.50)
Median (25th, 75th centile)	27 (23, 35)	29 (24, 35)
Minimum, maximum	17, 55	19, 55
Ethnicity,* n *(%)		
White	68 (48)	43 (44)
Black Caribbean	36 (25)	28 (29)
Mixed race	15 (10)	9 (9)
Black African	11 (8)	7 (7)
Other	6 (4)	0
Other Asian (non-Chinese)	3 (2)	2 (2)
Indian	3 (2)	2 (2)
Chinese	0	3 (3)

continued

TABLE 38 Baseline characteristics of the subset of participants resolving by week 2 (*continued*)

Characteristics of those who resolved by week 2	Treatment arm	
	Oral metronidazole (*N* = 143)	Intravaginal lactic acid gel (*N* = 97)
Pakistani	1 (1)	1 (1)
Bangladeshi	0	1 (1)
Black (other)	0	1 (1)
Not given	0	0
Vaginal douching in the past 3 months*, n *(%)		
Yes	21 (15)	6 (6)
No	122 (85)	91 (94)
Missing	0	0
Frequency of douching per month, n *(%)*		
0–2	6 (29)	2 (33)
3–4	5 (24)	1 (17)
5–6	0	0
≥ 7	10 (48)	3 (50)
Current use of oral contraceptive pill*, n *(%)		
Yes	25 (17)	18 (19)
No	118 (83)	214 (83)
Missing	0	0
Type of contraceptive pill, n *(%)*		
Combined oral contraceptive pill	15 (60)	13 (72)
Progesterone-only pill	10 (40)	5 (28)
History of BV *Approximate age when BV first occurred (years)*		
n	142	97
Mean (SD)	23.9 (7.18)	24.3 (7.40)
Median (25th, 75th centile)	22 (19, 28)	23 (19, 28)
Minimum, maximum	15, 53	11, 50
Number of previous episodes of BV in the past 12 months, n *(%)*		
0	1 (1)	2 (2)
1–3	91 (64)	61 (63)
> 3	51 (36)	34 (35)
Approximate total length of time in past year with BV symptoms, n *(%)*		
< 2 weeks	31 (22)	20 (21)
≥ 2 weeks and < 3 months	78 (55)	54 (56)
≥ 3 months	34 (24)	23 (24)
Missing	0	0

TABLE 38 Baseline characteristics of the subset of participants resolving by week 2 (*continued*)

Characteristics of those who resolved by week 2	Treatment arm	
	Oral metronidazole (*N* = 143)	Intravaginal lactic acid gel (*N* = 97)
BV confirmed at baseline visit (local microscopy)*, n *(%)		
Yes	125 (87)	82 (85)
No	10 (7)	11 (11)
Not tested	8 (6)	4 (4)
Missing	0	0
Baseline sample Ison–Hay grade for BV (central laboratory)*, n *(%)		
0 (no bacteria)	1 (1)	0
1 (normal flora)	19 (13)	25 (26)
2 (intermediate BV)	38 (27)	21 (22)
3 (confirmed BV)	83 (58)	49 (51)
U (Gram-positive cocci)	0	0
Missing	2 (1)	6 (2)
Thrush in the last 12 months (before baseline)*, n *(%)		
Yes	68 (48)	48 (49)
No	75 (52)	49 (51)
Has current sexual partner (baseline)*, n *(%)		
Yes	109 (76)	65 (67)
No	34 (24)	32 (33)
Female sexual partner (in 12 months before baseline)*, n *(%)		
Yes	12 (8)	11 (11)
No	131 (92)	86 (89)
Genital discharge at baseline*, n *(%)		
Yes	129 (90)	84 (87)
No	14 (10)	13 (13)
Offensive vaginal smell at baseline*, n *(%)		
Yes	120 (84)	82 (85)
No	23 (16)	15 (15)
Vaginal irritation at baseline*, n *(%)		
Yes	45 (31)	41 (42)
No	98 (69)	56 (58)

TABLE 39 Time to first recurrence[a] of BV (days) for those whose symptoms resolved within 2 weeks: split by additional medication in the first 2 weeks

Resolved by week 2	Participants with time data (*n*)	Median time to recurrence (SE) (days)[b]	95% CI[b]
No additional medication			
Oral metronidazole (*n* = 90)	56	177 (–)	75 to –
Intravaginal lactic acid gel (*n* = 67)	41	149 (–)	71 to –
With additional medication			
Oral metronidazole (*n* = 12)	9	87 (20.9)	12 to 175
Intravaginal lactic acid gel (*n* = 7)	4	124 (27.5)	21 to –
All with medication data			
Oral metronidazole (*n* = 102)	65	119 (46.2)	75 to –
Intravaginal lactic acid gel (*n* = 74)	45	149 (–)	72 to –

a Participant-reported date of recurrence was based on symptoms for those who resolved their BV symptoms in the first 2 weeks.
b Some estimates are missing because they are not calculable with the available data.

Notes
Time is censored for those without recurrence (i.e. not recurred by 6 months) or for whom recurrence data are missing: 29 (45%) of values in the metronidazole arm and 22 (49%) in the lactic acid gel arm were censored. Overall median times, not including censored values, are 61.5 days (*n* = 36) in the metronidazole arm and 60.5 days (*n* = 22) in the lactic acid gel arm; these take no account of those who have not yet recurred.

TABLE 40 Summary of the number of participant-reported BV treatment courses within 6 months

Number of treatment courses	Treatment arm	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
For those resolving by week 2	**n = *143***	**n = *97***
Number of BV treatment courses between week 2 and 3 months per participant		
Number of 3-month questionnaires returned	111	108
Number of participants resolving by week 2, with 3-month additional treatment data	76	52
Median (25th, 75th centile)	0 (0, 1.5)	0 (0, 1)
Minimum, maximum[a]	0, 9	0, 9
Number of BV treatment courses between week 2 and 6 months per participant		
Number of 6-month questionnaires returned	92	84
Number of participants resolving by week 2, with 3- and 6-month additional treatment data	59	35
Median (25th, 75th centile)	1 (0, 3)	1 (0, 2)
Minimum, maximum[a]	0, 14	0, 14

TABLE 40 Summary of the number of participant-reported BV treatment courses within 6 months (*continued*)

Number of treatment courses	Treatment arm	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
For those not resolving by week 2	**n = *61***	**n = *108***
Number of BV treatment courses between week 2 and 3 months per participant		
Number of 3-month questionnaires returned	111	108
Number of participants with 3-month additional treatment data	33	53
Median (25th, 75th centile)	1 (0, 3)	1 (0, 2)
Minimum, maximum[a]	0, 7	0, 13
Number of BV treatment courses between week 2 and 6 months per participant		
Number of 6-month questionnaires returned	92	84
Number of participants with 3- and 6-month additional treatment data	19	30
Median (25th, 75th centile)	1 (0, 5)	2 (0, 4)
Minimum, maximum[a]	0, 9	0, 19

a Number of treatment courses.

Note
See *Appendix 5*, *Table 61*, for information on which medications were taken.

TABLE 41 Analysis of the number of participant-reported BV treatment courses between week 2 and 6 months, if BV resolved by week 2

Number of treatment courses	Treatment arm		
	Oral metronidazole (*n* = 259)	Intravaginal lactic acid gel (*n* = 259)	Adjusted incidence rate ratio (95% CI)[a]
Median number of courses between week 2 and 3 months	0	0	0.66 (0.32 to 1.35)
Median number of courses between week 2 and 6 months	1	1	1.03 (0.53 to 2.01)

a Courses between week 2 and 6 months adjusted for site, number of BV episodes in the 12 months before baseline and female partners in the 12 months before baseline.

TABLE 42 Microbiological resolution vs. symptomatic resolution of BV at week 2

Symptomatic resolution	Microbiological resolution, *n* (%)		
	Yes	No	Total, *n* (%)
Yes	63 (43)	25 (17)	88 (61)
No	24 (17)	33 (23)	57 (39)
Total	87 (60)	58 (40)	145

TABLE 43 Median time to resolution of BV symptoms (days)

Treatment arm	Resolved by, *n* (%)			Median time (days) to resolution (SE); minimum, maximum	95% CI[a] (days)
	Week 2	3 months	6 months		
With or without additional treatment (including missing data)					
Oral metronidazole (*N* = 192)	143 (70)	156	158	14 (0.65); 2, 183	8 to 14
Intravaginal lactic acid gel (*N* = 179)	97 (47)	117	124	14 (3.41); 1[b], 186	14 to 47
With or without additional treatment (excluding missing data)					
Oral metronidazole (*N* = 150)	102 (66)	113	115	7 (0.54); 2, 183	6 to 10
Intravaginal lactic acid gel (*N* = 150)	74 (47)	92	99	28 (14.61); 1[b], 186	10 to 53
With additional treatment					
Oral metronidazole (*N* = 21)	12 (55)	14	14	17 (6.2); 3, 183	6 to –
Intravaginal lactic acid gel (*N* = 18)	7 (35)	10	11	28 (7.2); 2, 98	5 to –
Without additional treatment[c]					
Oral metronidazole (*N* = 129)	90 (68)	99	101	7 (0.49); 2, 181	6 to 8
Intravaginal lactic acid gel (*N* = 132)	67 (49)	82	90	17 (14.27); 1[b], 186	10 to 53

a Some upper confidence limits are not calculable with the available data.
b There are two observations for which the time = 0: methods calculating medians with censoring exclude these.
c Additional treatment must be 'no' for all questionnaires up to resolution time, i.e. not included if interim data are missing.

Notes
Percentages are not given for numbers resolved by 3 and 6 months because 'no resolution' cannot be carried over from week 2 where 3-month data are missing, whereas 'resolved' can be carried over.
If times in first 2 weeks were missing (but known resolution), 14 days are substituted.
Censored times are included in the calculation of the median. If they were not included, the median time to resolution would be 7 days in the oral metronidazole arm and 8.5 days in the intravaginal lactic acid gel arm.
'*n*'s at week 2, 3 months and 6 months are the number of times to resolution included in the calculation of median time, including censored observations. If it was known that the participant had not resolved, the time to resolution was censored at the last known time they were known not to have resolved. There were 134 censored values.

TABLE 44 Summary of nausea reported on the week 2 questionnaire

Nausea	Treatment arm	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
Nausea reported*, n *(%)		
Yes	50 (32)	13 (8)
No	103 (66)	144 (89)
Missing	3 (2)	4 (2)
Severity (how participant was affected)*, n *(%)		
Able to eat normally	31 (62)	10 (77)
Ability to eat or drink fluids significantly decreased	16 (32)	3 (23)
Unable to eat or drink fluids	2 (4)	0
Missing	1 (2)	0
How long after starting study treatment did side effect start?* n *(%)		
< 2 hours	10 (20)	2 (15)
2 to < 6 hours	6 (12)	0
6 to < 24 hours	8 (16)	0
1–3 days	16 (32)	6 (46)
> 3 days	8 (16)	4 (31)
Missing	2 (4)	1 (8)
Approximate duration (hours)		
n	48	11
Median (25th, 75th centile)	48 (24, 108)	7 (2, 72)
Minimum, maximum	0, 192	1, 96
Fully resolved at week 2*, n *(%)		
Yes	45 (90)	10 (77)
No[a]	5 (10)	2 (15)
Missing	0	1 (8)

a Severity for those not resolved: metronidazole arm – three able to eat normally and two ability decreased; lactic acid gel arm – one able to eat normally and one ability decreased.

Note
Tabulated by treatment received; the participant who received no study treatment provided no safety data and is excluded from this table.

TABLE 45 Summary of vomiting reported on the week 2 questionnaire

Vomiting	Treatment arm	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
Vomiting reported*, n *(%)		
Yes	9 (6)	2 (1)
No	141 (90)	152 (94)
Missing	6 (4)	7 (4)
Severity*, n *(%)		
1 episode in 24 hours	6 (67)	1 (50)
2–5 episodes in 24 hours	1 (11)	0
≥ 6 episodes in 24 hours or i.v. fluids needed	0	0
Missing	2 (22)	1 (50)
How long after starting study treatment did side effect start?* n *(%)		
< 2 hours	3 (33)	0
2 to < 6 hours	2 (22)	0
6 to < 24 hours	2 (22)	0
1–3 days	1 (11)	1 (50)
> 3 days	0	0
Missing	1 (11)	1 (50)
Approximate duration (hours)		
n	8	1
Median (25th, 75th centile)	24.5 (4.5, 38)	1 (1, 1)
Minimum, maximum	0, 72	1, 1
Fully resolved at week 2*, n *(%)		
Yes	6 (67)	2 (100)
No[a]	2 (22)	0
Missing	1 (11)	0

i.v., intravenous.

a Severity for those not resolved: metronidazole arm – one participant had two to five episodes, for one participant the severity was missing.

Note

Tabulated by treatment received; the participant who received no study treatment provided no safety data and is excluded from this table.

TABLE 46 Summary of taste change reported on the week 2 questionnaire

Taste change	Treatment arm	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
Taste change reported*, n *(%)		
Yes	28 (18)	2 (1)
No	127 (81)	156 (97)
Missing	1 (1)	3 (2)
Severity*, n *(%)		
Mild	14 (50)	2 (100)
Moderate	13 (46)	0
Severe	1 (4)	0
Missing	0	0
How long after starting study treatment did side effect start?* n *(%)		
< 2 hours	9 (32)	0
2 to < 6 hours	2 (7)	0
6 to < 24 hours	5 (18)	0
1–3 days	11 (39)	0
> 3 days	0	1 (50)
Missing	1 (4)	1 (50)
Approximate duration (hours)		
n	28	2
Median (25th, 75th centile)	87 (36, 120)	24 (0, 48)
Minimum, maximum	0, 202	0, 48
Fully resolved at week 2*, n *(%)		
Yes	26 (93)	2 (100)
No[a]	1 (4)	0
Missing	1 (4)	0

a Severity for those not resolved (metronidazole): one mild.

Note
Tabulated by treatment received; the participant who received no study treatment provided no safety data and is excluded from this table.

TABLE 47 Summary of vaginal irritation reported on the week 2 questionnaire

Vaginal irritation	Treatment arm	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
Vaginal irritation reported at week 2*, n *(%)		
Yes	44 (28)	34 (21)
No	110 (71)	125 (78)
Missing	2 (1)	2 (1)
Severity*, n *(%)		
Mild	19 (43)	13 (38)
Moderate	19 (43)	18 (53)
Severe	4 (9)	3 (9)
Missing	2 (5)	0
How long after starting study treatment did side effect start?* n *(%)		
< 2 hours	7 (16)	8 (24)
2 to < 6 hours	0	2 (6)
6 to < 24 hours	2 (5)	1 (3)
1–3 days	19 (43)	12 (35)
> 3 days	13 (33)	11 (32)
Missing	3 (7)	0
Approximate duration (hours)		
n	40	34
Median (25th, 75th centile)	76.5 (48.5, 168)	72 (48, 120)
Minimum, maximum	24, 720	1, 336
Fully resolved at week 2*, n *(%)		
Yes	22 (50)	21 (62)
No[a]	21 (48)	13 (38)
Missing	1 (2)	0

a Severity for those not resolved: metronidazole arm – six mild, 11 moderate and four severe; lactic acid gel arm – one mild, 10 moderate and two severe.

Note
Tabulated by treatment received; the participant who received no study treatment provided no safety data and is excluded from this table.

TABLE 48 Summary of vaginal irritation, for those with baseline irritation, reported on the week 2 questionnaire

Vaginal irritation for those with baseline irritation	Treatment arm	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
Total returning questionnaire who had baseline irritation	52	53
Vaginal irritation reported at week 2*, n *(%)		
Yes	25 (48)	15 (28)
No	25 (48)	38 (72)
Missing	2 (4)	0
Severity*, n *(%)		
Mild	11 (44)	7 (47)
Moderate	9 (36)	7 (47)
Severe	4 (16)	1 (7)
Missing	1 (4)	0
How long after starting study treatment did side effect start?* n *(%)		
< 2 hours	6 (24)	4 (27)
2 to < 6 hours	0	2 (13)
6 to < 24 hours	1 (4)	1 (7)
1–3 days	9 (36)	5 (33)
> 3 days	8 (32)	3 (20)
Missing	1 (4)	0
Approximate duration (hours)		
n	23	15
Median (25th, 75th centile)	96 (72, 168)	72 (48, 168)
Minimum, maximum	24, 720	1, 168
Fully resolved at week 2*, n *(%)		
Yes	8 (32)	9 (60)
No[a]	16 (64)	6 (40)
Missing	1 (4)	0

a Severity for those not resolved: metronidazole arm – five mild, seven moderate and four severe; lactic acid gel arm – one mild, four moderate and one severe.

Note
Tabulated by treatment received; the participant who received no study treatment provided no safety data and is excluded from this table.

TABLE 49 Summary of vaginal irritation, for those without baseline irritation, reported on the week 2 questionnaire

Vaginal irritation for those without baseline irritation	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
And without baseline irritation	104	108
Vaginal irritation reported at week 2*, n *(%)		
Yes	19 (18)	19 (18)
No	85 (82)	87 (81)
Missing	0	2 (2)
Severity*, n *(%)		
Mild	8 (42)	6 (32)
Moderate	10 (53)	11 (58)
Severe	0	2 (11)
Missing	1 (5)	0
How long after starting study treatment did side effect start?* n *(%)		
< 2 hours	1 (5)	4 (21)
2 to < 6 hours	0	0
6 to < 24 hours	1 (5)	0
1–3 days	10 (53)	7 (37)
> 3 days	5 (26)	8 (42)
Missing	2 (11)	0
Approximate duration (hours)		
n	17	19
Median (25th, 75th centile)	72 (48, 72)	72 (48, 120)
Minimum, maximum	48, 240	1, 336
Fully resolved at week 2*, n *(%)		
Yes	14 (74)	12 (63)
No[a]	5 (26)	7 (37)
Missing	0	0

a Severity for those not resolved: metronidazole arm – one mild, four moderate and zero severe; lactic acid gel arm – zero mild, six moderate and one severe.

Note
Tabulated by treatment received; the participant who received no study treatment provided no safety data and is excluded from this table.

TABLE 50 Summary of abdominal pain reported on the week 2 questionnaire

Abdominal pain	Treatment arm	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
Abdominal pain reported*, n *(%)		
Yes	31 (20)	27 (17)
No	123 (79)	132 (82)
Missing	2 (1)	2 (1)
Severity*, n *(%)		
Mild	16 (52)	12 (44)
Moderate	13 (42)	11 (41)
Severe	2 (6)	3 (11)
Missing	0	1 (4)
How long after starting study treatment did side effect start?* n *(%)		
< 2 hours	3 (10)	6 (22)
2 to < 6 hours	7 (23)	1 (4)
6 to < 24 hours	4 (13)	2 (7)
1–3 days	13 (42)	11 (41)
> 3 days	4 (13)	6 (22)
Missing	0	1 (4)
Approximate duration (hours)		
n	31	24
Median (25th, 75th centile)	72 (24, 123)	72 (15.5, 108)
Minimum, maximum	1, 240	1, 240
Fully resolved at week 2*, n *(%)		
Yes	24 (77)	22 (81)
No[a]	7 (23)	3 (11)
Missing	0	2 (7)

a Severity for those not resolved: metronidazole arm – two mild, three moderate and two severe; lactic acid arm – two moderate and one severe.

Note
Tabulated by treatment received; the participant who received no study treatment provided no safety data and is excluded from this table.

TABLE 51 Summary of diarrhoea reported on the week 2 questionnaire

Diarrhoea	Treatment arm	
	Oral metronidazole (*N* = 258)	Intravaginal lactic acid gel (*N* = 258)
Total number of questionnaires expected	256	258
Total returning questionnaire	156	161
Diarrhoea reported*, n *(%)		
Yes	31 (20)	9 (6)
No	123 (79)	150 (93)
Missing	2 (1)	2 (1)
Severity*, n *(%)		
Mild	15 (48)	4 (44)
Moderate	11 (35)	4 (44)
Severe	4 (13)	0
Missing	1 (3)	1 (11)
How long after starting study treatment did the side effect start?* n *(%)		
< 2 hours	4 (13)	1 (11)
2 to < 6 hours	1 (3)	0
6 to < 24 hours	9 (29)	0
1–3 days	13 (42)	5 (56)
> 3 days	3 (10)	3 (33)
Missing	1 (3)	0
Approximate duration (hours)		
n	30	8
Median (25th, 75th centile)	72 (48, 120)	36 (24, 48)
Minimum, maximum	1, 240	2, 72
Fully resolved at week 2*, n *(%)		
Yes	28 (90)	8 (89)
No[a]	3 (10)	1 (11)
Missing	0	0

a Severity for those not resolved: metronidazole arm – two moderate and one missing; lactic acid gel arm – one mild.

Note
Tabulated by treatment received; the participant who received no study treatment provided no safety data and is excluded from this table.

TABLE 52 Other reasons study treatment course not completed

Reason	Treatment arm	
	Oral metronidazole ($n = 258$)	Intravaginal lactic acid gel ($n = 258$)
Period started during treatment	0	5
Misplaced treatment	1	0
Started treatment late owing to social engagements	1	0
Vaginal itching and bleeding	0	1
Lower abdominal pain	0	1
Misunderstood how to take treatment	1	0
Was not prescribed study treatment	1	0
Unknown	1	0
Total	5	7

The number of reasons in this table is not consistent with the number of 'other' reasons in the adherence to study treatment (*Table 13*). These are participant-reported data and were not queried.

TABLE 53 Brand of intravaginal lactic acid gel

Brand used	Intravaginal lactic acid gel ($n = 259$), *n* (%)
Number of participants returning week 2 questionnaire	161
Balance Activ® (BBI Healthcare, Crumlin, UK)	67 (42)
Relactagel® (Kora Healthcare, Swords, Ireland)	90 (56)
Canesbalance® (Bayer, Reading, UK)	0
Brand unknown[a]	1 (1)
Missing	3 (2)

a Participant entered 'lactic acid gel 5 ml'.

Note
Of the two participants randomised to the metronidazole arm who received lactic acid gel and the two randomised to the lactic acid gel arm who received metronidazole, none of them entered any data on the week 2 questionnaire.

TABLE 54 Prevalence of gonorrhoea at baseline and week 2

Gonorrhoea	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Baseline samples received by the central laboratory	253	256
Week 2 samples received by the central laboratory	148	153
Baseline (excludes out-of-date sample kits)		
n	237	240
Positive	2 (1)	1 (< 0.5)
Negative	233 (98)	237 (99)
Indeterminate	1 (< 0.5)	1 (< 0.5)
Equivocal	0	0
Missing	1 (< 0.5)	1 (< 0.5)
Week 2 (excludes out-of-date sample kits)		
n	140	142
Positive	1 (1)	0
Negative	134 (96)	139 (98)
Indeterminate	2 (1)	1 (1)
Equivocal	0	0
Missing	3 (2)	2 (1)
Baseline (excludes out-of-date sample kits and those with an unknown expiry date)		
n	166	173
Positive	0	0
Negative	165 (99)	172 (99)
Indeterminate	0	1 (1)
Equivocal	0	0
Missing	1 (1)	0
Week 2 (excludes out-of-date sample kits and those with an unknown expiry date)		
n	110	114
Positive	0	0
Negative	109 (99)	111 (97)
Indeterminate	1 (1)	1 (1)
Equivocal	0	0
Missing	0	2 (2)

Some sample kits were found to have expired; for some, the expiry status was unknown for the time of use.

TABLE 55 Prevalence of chlamydia at baseline and week 2

Chlamydia	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Baseline samples received by the central laboratory	253	256
Week 2 samples received by the central laboratory	148	153
Baseline (excludes out-of-date sample kits)		
n	237	240
Positive	15 (6)	5 (2)
Negative	220 (93)	233 (97)
Indeterminate	1 (< 0.5)	1 (< 0.5)
Equivocal	0	0
Missing	1 (< 0.5)	1 (< 0.5)
Week 2 (excludes out-of-date sample kits)		
n	140	142
Positive	6 (4)	2 (1)
Negative	128 (91)	137 (96)
Indeterminate	2 (1)	1 (1)
Equivocal	1 (1)	0
Missing	3 (2)	2 (1)
Baseline (excludes out-of-date sample kits and those with an unknown expiry status)		
n	166	173
Positive	8 (5)	2 (1)
Negative	157 (95)	170 (98)
Indeterminate	0	1 (1)
Equivocal	0	0
Missing	1 (1)	0
Week 2 (excludes out-of-date sample kits and those with an unknown expiry status)		
n	110	114
Positive	4 (4)	1 (1)
Negative	104 (95)	110 (96)
Indeterminate	1 (1)	1 (1)
Equivocal	1 (1)	0
Missing	0	2 (2)

Some sample kits were found to have expired; for some, the expiry status was unknown for the time of use.

TABLE 56 Prevalence of trichomoniasis at baseline and week 2

Trichomoniasis	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Baseline samples received by the central laboratory	253	256
Week 2 samples received by the central laboratory	148	153
Baseline (excludes out-of-date sample kits)		
n	237	240
Positive	4 (2)	2 (1)
Negative	230 (97)	236 (98)
Indeterminate	2 (1)	1 (< 0.5)
Equivocal	0	0
Missing	1 (< 0.5)	1 (< 0.5)
Week 2 (excludes out-of-date sample kits)		
n	140	142
Positive	1 (1)	1 (1)
Negative	134 (96)	139 (98)
Indeterminate	2 (1)	1 (1)
Equivocal	0	0
Missing	3 (2)	1 (1)
Baseline (excludes out-of-date sample kits and those with an unknown expiry status)		
n	166	173
Positive	4 (2)	1 (1)
Negative	160 (96)	171 (99)
Indeterminate	1 (1)	1 (1)
Equivocal	0	0
Missing	1 (1)	0
Week 2 (excludes out-of-date sample kits and those with an unknown expiry status)		
n	110	114
Positive	1 (1)	0
Negative	108 (98)	112 (98)
Indeterminate	1 (1)	1 (1)
Equivocal	0	0
Missing	0	1 (1)

Some sample kits were found to have expired; for some, the expiry status was unknown for the time of use.

TABLE 57 Summary of time with BV recurrence after first resolution of symptoms (within 2 weeks)

Time with symptoms of recurrence for those who resolved within 2 weeks	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
For those who recurred within 3 months, time with symptoms between week 2 and 3 months		
Number who resolved by week 2	143	97
Number who recurred by 3 months	37	23
Time with symptoms		
< 1 week	8 (22)	5 (22)
1–2 weeks	11 (30)	4 (17)
> 2 to 4 weeks	9 (24)	6 (26)
> 4 weeks	6 (16)	6 (26)
Missing	3 (8)	2 (9)
For those who recurred within 6 months, time with symptoms between 3 and 6 months		
Number who resolved by week 2	143	97
Number who recurred by 6 months	51	32
Time with symptoms		
< 1 week	6 (12)	1 (3)
1–2 weeks	2 (4)	4 (13)
> 2 to 4 weeks	10 (20)	5 (16)
> 4 weeks	5 (10)	6 (19)
Missing	28 (55)	16 (50)

Time with symptoms is given only for those with recurrence. For those recurring by 6 months, the time with symptoms is for the 3-month period between 3 and 6 months.

TABLE 58 Status of symptoms for those without resolution of BV at week 2 (participant reported)

Symptom status	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Number not resolving by week 2	60	106
Status of symptoms for those not resolving		
Better, but not cleared/disappeared	29 (48)	39 (36)
Improved initially, but worsened again	10 (16)	25 (23)
No change	9 (15)	13 (12)
Worse	3 (5)	8 (7)
Missing	10 (16)	23 (21)

TABLE 59 Symptom assessment at week 2

Symptom status	Treatment arm, *n* (%)	
	Oral metronidazole, (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Number of participants returning the week 2 questionnaire	157	161
Genital discharge		
Yes	52 (33)	66 (41)
No	99 (63)	93 (58)
Missing	6 (4)	2 (1)
Offensive vaginal smell		
Yes	42 (27)	65 (40)
No	111 (71)	94 (58)
Missing	4 (3)	2 (1)
Vaginal irritation		
Yes	47 (30)	37 (23)
No	104 (66)	122 (76)
Missing	6 (4)	2 (1)

TABLE 60 Recurrence symptoms compared with typical symptoms

Were recurrence symptoms typical of usual symptoms?	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
> 2 weeks to 3 months		
Number with recurrence between 2 weeks and 3 months	37	23
Always	28 (76)	15 (65)
Sometimes	6 (16)	6 (26)
Seldom	0	0
Missing	3 (8)	2 (9)
> 3 to 6 months		
Number with recurrence between 3 and 6 months	51	32
Always	22 (43)	13 (41)
Sometimes	2 (4)	2 (6)
Seldom	0	1 (3)
Missing	27 (53)	16 (50)

The table includes all participants who considered they had a recurrence whether or not they had documented resolution by week 2.

TABLE 61 Additional medication for BV

Additional medication for BV	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
During the first 2 weeks		
Number of participants returning the week 2 questionnaire	157	161
Number of participants taking at least one additional medication for BV	22 (14)	20 (12)
Number of participants taking the following medications for BV		
Metronidazole tablets	10 (6)	15 (9)
Metronidazole vaginal gel	4 (3)	2 (1)
Lactic acid vaginal gel	8 (5)	11 (7)
Clindamycin cream	5 (3)	4 (2)
Other treatments[a]	8 (5)	3 (2)
From week 2 to 3 months		
Number of participants returning the 3-month questionnaire	111	108
Number of participants taking at least one additional medication for BV	52 (47)	51 (47)
Number of participants taking the following medications for BV		
Metronidazole tablets	27 (24)	21 (19)
Metronidazole vaginal gel	5 (5)	10 (9)
Lactic acid vaginal gel	23 (21)	25 (23)
Clindamycin cream	8 (7)	2 (2)
Other treatments[a]	10 (9)	4 (4)
From 3 to 6 months		
Number of participants returning the 6-month questionnaire	92	84
Number of participants taking at least one additional medication for BV	44 (48)	39 (46)
Number of participants taking the following medications for BV		
Metronidazole tablets	18 (20)	15 (18)
Metronidazole vaginal gel	4 (4)	6 (7)
Lactic acid vaginal gel	27 (29)	21 (25)
Clindamycin cream	4 (4)	2 (2)
Other treatments[a]	8 (9)	6 (7)

a For other treatments see *Table 62*. Some are the treatments listed, but not identified as such by the participant.

TABLE 62 Additional medication for BV: other treatments

During the first 2 weeks	From week 2 to 3 months	From 3 to 6 months
Oral metronidazole treatment arm		
• Canesten® (Bayer plc) and a gel • Thrush pessary • *Aloe vera* gel • Lactic acid pessaries on alternate days (maintenance) • Canesbalance single tablet • Biocultures complex capsule (Nu U Nutrition, Manchester, UK) • Cream for vaginal irritation (post-trial medication) • Paracetamol	• Over the counter • Fluomizin tablets • BV 5 billion colony-forming unit capsule (including lactobacilli) • Optibac for women • One lactic acid pessary once per week to remain symptom free • Ice • *Lactobacillus* vaginal tablets • Amoxiclav and fluomizin • Balance Activ • Multi-Gyn ActiGel	• Bought cream • Not specified • Optibac (Wren Laboratories Ltd, Andover, UK) for women • Removal of coil • BV Boots (Nottingham, UK) gel • Balance Activ pessaries • Multi-Gyn ActiGel (BioClin BV, Delft, the Netherlands), BoricVag Plus (Reel Organics, Houston, TX, USA) vaginal suppositories
Intravaginal lactic acid gel treatment arm		
• Not started the course yet • Balance Activ (GP prescribed) • Three tubes not taken earlier	• GYNTIMA Probiotica Forte (Fyto Biotech Ltd, Berwick Close, UK) • Canesten tablet • Balance Activ pessaries • Balance Activ treatments	• Tea tree oil and sweet almond oil on a tampon overnight • Not specified • Antibiotics • Home remedy: 600 mg of boric acid suppository for 6 days • Antibiotics for chlamydia • Took them from the Republic of Korea

These are other treatments identified by the participant and may include categories in *Table 61*.

TABLE 63 Antibiotics for other conditions/illness (over 6 months)

Antibiotics for other conditions/illness	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
During the first 2 weeks		
Number of participants returning the week 2 questionnaire	157	161
Number of participants taking at least one antibiotic (other than for BV)	15 (10)	21 (13)
Number of participants taking the following antibiotics (other than for BV)		
Amoxicillin (Amoxicillin, Accord Healthcare)	5 (3)	11 (7)
Flucloxacillin (Flucloxacillin, Kent Pharma)	4 (3)	3 (2)
Doxycycline (Doxycycline, Kent Pharma)	5 (3)	3 (2)
Other[a]	4 (3)	5 (3)
From week 2 to 3 months		
Number of participants returning the 3-month questionnaire	111	108
Number of participants taking at least one antibiotic (other than for BV)	8 (7)	12 (11)
Number of participants taking the following antibiotics (other than for BV)		
Amoxicillin	2 (2)	4 (4)
Flucloxacillin	1 (1)	0
Doxycycline	3 (3)	5 (5)
Other[a]	6 (5)	8 (7)

TABLE 63 Antibiotics for other conditions/illness (over 6 months) (*continued*)

Antibiotics for other conditions/illness	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
From 3 to 6 months		
Number of participants returning the 6-month questionnaire	92	84
Number of participants taking at least one antibiotic (other than for BV)	9 (10)	10 (12)
Number of participants taking the following antibiotics (other than for BV)		
Amoxicillin	3 (3)	1 (1)
Flucloxacillin	2 (2)	1 (1)
Doxycycline	4 (4)	2 (2)
Other[a]	2 (2)	10 (12)

a Other antibiotics are given as identified by the participant and, for this reason, may include treatments that are not antibiotics (see *Table 64*).

TABLE 64 Antibiotics for other conditions/illness: other treatments

During first 2 weeks	From week 2 to 3 months	From 3 to 6 months
Oral metronidazole treatment arm		
• Antibiotics (unknown) for thrush • Nitrofurantoin: vomiting side affect • Metrinizolane for PID • Phenoxymethylpenicillin	• Multisymptom flu pills • Metronidazole and antibiotics for PID • Penicillin (beginning with 'ph'?), 10-day four times per day • Antibiotic injection for gonorrhoea • Metronidazole • Had mumps	• Medicine for gastritis • Isotretinoin
Intravaginal lactic acid gel treatment arm		
• Penicillin • Nitrofurantoin • Penicillin for tonsillitis • Co-amoxiclav for a kidney infection • Azithromycin	• Thrush: Canesten • Fluconazole • For UTI • Water infection • Clarithromycin • Kidney infection: coamoxacilin? • Zinnat (GlaxoSmithKline plc, Brentford, UK) • Fluconazole	• Trimethoprim • Metronidazole 400 mg • Fluconazole • Azithromycin • Ceftriaxone, nitrofurantoin • Lymecycline • Clarithromycin • Aciclovir • Penicillin for tonsillitis • Macrobid and trimethoprim

These are given by the participant and, for this reason, may include treatments that are not antibiotics, or categories in previous table.

TABLE 65 Vaginal thrush post randomisation

Vaginal thrush post randomisation	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Number of participants returning the questionnaire at week 2	157	161
Developed vaginal thrush in the 2 weeks since study treatment started		
Yes	42 (27)	27 (17)
No	110 (70)	132 (82)
Missing	5 (3)	2 (1)
Treatment taken in 2 weeks post start of study treatment		
None	25 (60)	12 (44)
Clotrimazole	13 (31)	13 (48)
Fluconazole	5 (12)	1 (4)
Itraconazole	1 (2)	1 (4)
Other	2 (5)	2 (7)
Developed vaginal thrush 2 weeks to 3 months post randomisation		
Number of participants returning questionnaire at 3 months	111	108
Yes	20 (18)	26 (24)
No	87 (78)	78 (72)
Missing	4 (4)	4 (4)
Number of episodes		
0	0	1 (4)
1	10 (50)	10 (38)
2	7 (35)	9 (35)
> 2	3 (15)	4 (15)
Missing	0	2 (8)
Developed vaginal thrush 3 to 6 months post randomisation		
Number of participants returning questionnaire at 6 months	92	84
Yes	23 (25)	20 (24)
No	69 (75)	55 (65)
Missing	0	9 (11)
Number of episodes		
0	0	0
1	15 (65)	14 (70)
2	7 (30)	2 (10)
> 2	1 (4)	4 (20)
Missing	0	0
Overall incidence of thrush[a]		
Yes	60 (23)	58 (22)
No	42 (16)	30 (12)
Missing	157 (61)	171 (66)

a Had thrush at any time in the 6 months post baseline. 'No' means that 'no' was answered on all three questionnaires. Denominator is all randomised participants.

TABLE 66 Sexual contact

Sexual contact	Treatment arm	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Number of participants returning the week 2 questionnaire	157	161
Sex in 2 weeks after start of treatment?* n *(%)		
Yes	71 (45)	67 (42)
No	81 (52)	92 (57)
Missing	5 (3)	2 (1)
Time after starting treatment until having sex		
n	71	67
Median (25th, 75th centile)	6 (3, 9)	7 (3, 9)
Minimum, maximum	0, 17	0, 15
Use of condoms, n *(%)*		
Yes always, including oral sex	8 (11)	6 (9)
Yes always, except oral sex	9 (13)	8 (12)
Yes sometimes	2 (3)	3 (4)
No	52 (73)	48 (72)
Missing	0	2 (3)
New sexual partners, n *(%)*		
Yes	12 (8)	14 (9)
No	72 (46)	64 (40)
Missing	73 (47)	83 (52)
Sex from week 2 to 3 months* n *(%)		
Number of participants returning 3-month questionnaire	111	108
Yes	94 (85)	89 (82)
No	14 (13)	16 (15)
Missing	3 (3)	3 (3)
Use of condoms, n *(%)*		
Yes always, including oral sex	7 (7)	6 (7)
Yes always, except oral sex	14 (15)	6 (7)
Yes sometimes	11 (12)	7 (8)
No	62 (66)	68 (76)
Missing	0	2 (2)
New sexual partners, n *(%)*		
Yes	23 (21)	21 (19)
No	75 (68)	76 (70)
Missing	13 (12)	11 (10)
Sex from 3 months to 6 months,* n *(%)		
Number of participants returning the 6-month questionnaire	92	84
Yes	74 (80)	67 (80)
No	18 (20)	9 (11)
Missing	0	8 (10)

continued

TABLE 66 Sexual contact (*continued*)

Sexual contact	Treatment arm	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Use of condoms, n *(%)*		
Yes always, including oral sex	10 (14)	2 (3)
Yes always, except oral sex	9 (12)	8 (12)
Yes sometimes	13 (18)	5 (7)
No	42 (57)	52 (78)
Missing	0	0
New sexual partners, n *(%)*		
Yes	22 (24)	24 (29)
No	53 (58)	43 (51)
Missing	17 (18)	17 (20)

TABLE 67 Vaginal douching post randomisation

Vaginal douching post randomisation	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Randomisation to week 2		
Number of participants returning the week 2 questionnaire	157	161
Vaginal douching		
Yes	6 (4)	6 (4)
No	141 (90)	143 (89)
Missing	10 (6)	12 (7)
> 2 weeks to 3 months		
Number of participants returning the 3-month questionnaire	111	108
Vaginal douching		
Yes	6 (5)	8 (7)
No	68 (61)	76 (70)
Missing	37 (33)	24 (22)
> 3 to 6 months		
Number of participants returning the 6-month questionnaire	92	84
Vaginal douching		
Yes	6 (7)	7 (8)
No	86 (93)	67 (80)
Missing	0	10 (12)

TABLE 68 Sexually transmitted infections diagnosed from 2 weeks post baseline (participant reported)

STIs diagnosed	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Gonorrhoea *> 2 weeks to 3 months*		
Number of participants returning the questionnaire	111	108
Number of episodes		
0	95 (86)	93 (86)
1	2 (2)	0
2	0	0
> 2	0	0
Missing	14 (13)	15 (14)
> 3 to 6 months		
Number of participants returning the questionnaire	92	84
Number of episodes		
0	83 (90)	64 (76)
1	1 (1)	1 (1)
2	1 (1)	0
> 2	0	0
Missing	7 (8)	19 (23)
Chlamydia *> 2 weeks to 3 months*		
Number of participants returning the questionnaire	111	108
Number of episodes		
0	96 (86)	90 (83)
1	0	4 (4)
2	1 (1)	0
> 2	0	0
Missing	14 (13)	14 (13)
> 3 to 6 months		
Number of participants returning the questionnaire	92	84
Number of episodes		
0	82 (89)	65 (77)
1	1 (1)	0
2	0	0
> 2	0	0
Missing	9 (10)	19 (23)

continued

TABLE 68 Sexually transmitted infections diagnosed from 2 weeks post baseline (participant reported) (*continued*)

STIs diagnosed	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)
Trichomoniasis *> 2 weeks to 3 months*		
Number responding to questionnaire	111	108
Number of episodes		
0	94 (85)	93 (86)
1	2 (2)	0
2	1 (1)	0
> 2	0	0
Missing	14 (13)	15 (14)
> 3 to 6 months		
Number responding to questionnaire	92	84
Number of episodes		
0	83 (90)	65 (77)
1	0	0
2	0	0
> 2	0	0
Missing	9 (10)	19 (23)
Pelvic inflammatory disease *> 2 weeks to 3 months*		
Number responding to questionnaire	111	108
Number of episodes		
0	94 (85)	93 (86)
1	1 (1)	1 (1)
2	0	0
> 2	0	0
Missing	16 (14)	14 (13)
> 3 to 6 months		
Number responding to questionnaire	92	84
Number of episodes		
0	82 (89)	62 (74)
1	2 (2)	4 (5)
2	0	0
> 2	0	0
Missing	8 (9)	18 (21)

The missing category includes any who say they have the infection, but do not say how many episodes (one in the metronidazole arm for gonorrhoea, trichomoniasis and PID at 3 months).

TABLE 69 Other reasons reported by participants for not returning a week 2 sample (if the laboratory did not receive a sample)

Reason	Treatment arm (*n*)	
	Oral metronidazole (*n* = 259)	Intravaginal lactic acid gel (*n* = 259)
Had period	3	2
Travelling abroad	0	1
Misunderstood instructions	0	1
Alternative diagnosis for symptoms made	0	1
Total	3	5

TABLE 70 Symptoms over the 6 months

Symptoms post treatment	Treatment arm, *n* (%)	
	Oral metronidazole (*N* = 91)	Intravaginal lactic acid gel (*N* = 88)
Yes	70 (77)	74 (84)
No	21 (23)	14 (16)

Includes only those with data at all three time points.

TABLE 71 NHS resource use costs (2018/19 prices)

Resource use	Unit cost (£)	Description	Source
Study treatments			
Oral metronidazole	3.97	400 mg twice daily for 7 days. Metronidazole 400 mg (AAH Pharmaceuticals, Coventry, UK)	BNF 2019[43]
Intravaginal lactic acid gel	5.25	5 ml once daily for 7 days. Balance Activ BV	BNF 2019[43]
Health services			
GP: face to face	39.00	Per-patient contact lasting 9.22 minutes, including direct care staff costs	PSSRU 2019[41]
GP: telephone	15.52	Telephone triage: GP led	PSSRU 2019[41]
Nurse: face to face	21.72	Duration of contact: 15.5 minutes; per-hour cost: £84	PSSRU 2015 for duration multiplied by 2019 cost[41]
Nurse: telephone	7.80	Telephone triage nurse led	NHS reference costs 2018/19[42]
Pharmacy consultation: face to face	29.30	Community pharmacy	Pharmaceutical Services Negotiating Committee website[97]
Pharmacy consultation: telephone/online	14.00	Community pharmacy	Pharmaceutical Services Negotiating Committee website[97]
NHS 111	14.26	Assumed to be equivalent to pharmacy consultation by telephone	

continued

TABLE 71 NHS resource use costs (2018/19 prices) (*continued*)

Resource use	Unit cost (£)	Description	Source
NHS walk in: face to face	39.00	Same as GP face to face	PSSRU 2019[41]
NHS walk in: telephone	15.52	Same as GP telephone	PSSRU 2019[41]
NHS outpatient: face to face	135.00	General	PSSRU 2019[41]
NHS outpatient: telephone	37.60	Average cost of e-consultation	PSSRU 2019[41]
A&E: face to face	174.00	Gynaecology: consultant led	NHS reference costs 2018/19[98]
Specialised sexual health clinic: face to face	122.00	Non-consultant led, non-admitted, face-to-face attendance, first	NHS reference costs 2018/19[98]
Specialised sexual health clinic: telephone	7.80	Nurse triage: GP led	PSSRU 2019[41]
NHS out of hours: face to face	68.00	A&E emergency medicine, category 1 investigation with category 1 or 2 treatment	NHS reference costs 2018/19[98]
NHS out of hours: telephone	37.60	Average cost of e-consultation	PSSRU 2019[41]
Additional medication			
Metronidazole vaginal gel (Zidoval, Mylan)	4.31	5 g once daily for 5 days; 0.75% Zidoval (Mylan, Hatfield, UK)	BNF 2019[43]
Clindamycin phosphate cream (Dalacin, Pfizer)	10.86	5 g once daily for 7 days; 2% Dalacin Cream (Pfizer Ltd, Sandwich, UK)	BNF 2019[43]
Clotrimazole pessary	5.54	500-mg single dose	BNF 2019[43]
Fluconazole	0.87	150-mg single dose	BNF 2019[43]
Itraconazole	3.14	200 mg twice daily for 1 day	BNF 2019[43]

A&E, accident and emergency.

TABLE 72 Number of participants responding to resource use questionnaire and SF-12 at different time points

Questionnaire	Treatment arm, *n* (%)		All participants (*n* = 518)
	Oral metronidazole (*N* = 259)	Intravaginal lactic acid gel (*N* = 259)	
NHS resource use			
Week 2	143 (55)	151 (58)	294 (57)
3 months	106 (41)	99 (38)	205 (40)
6 months	91 (35)	75 (29)	166 (32)
All time points	69 (27)	54 (21)	123 (24)
SF-12			
Baseline	257 (99)	254 (98)	511 (≈ 99)
Week 2	141 (54)	156 (60)	297 (57)
3 months	99 (38)	97 (37)	196 (38)
6 months	89 (34)	71 (27)	160 (31)
All time points	61 (23)	48 (18)	109 (21)

TABLE 73 Baseline characteristics of participants responding to resource use questionnaires

Characteristic	Participants who completed resource use questionnaire at					
	Treatment arm			Treatment arm		
	Week 2			All time points		
	Oral metronidazole (*N* = 143)	Intravaginal lactic acid gel (*N* = 151)	Total (*N* = 294)	Oral metronidazole (*N* = 69)	Intravaginal lactic acid gel (*N* = 54)	Total (*N* = 123)
Age at randomisation (years)						
n	143	151	294	69	54	123
Mean (SD)	29.8 (8.1)	29.9 (8.4)	29.8 (8.3)	31.2 (8.3)	31.7 (8.6)	31.4 (8.4)
Minimum, maximum	18, 55	18, 55	18, 55	18, 55	19, 51	18, 55
Ethnicity,* n *(%)						
White	70 (49)	73 (48)	143 (49)	41 (59)	27 (50)	68 (55)
Black Caribbean	32 (22)	33 (22)	65 (22)	13 (19)	14 (26)	27 (22)
Mixed race	13 (9)	20 (13)	33 (11)	2 (3)	7 (13)	9 (7)
Black African	11 (8)	10 (7)	21 (7)	4 (6)	4 (7)	8 (7)
Other	5 (3)	2 (1)	7 (2)	2 (3)	0	2 (2)
Other Asian (non-Chinese)	4 (3)	1 (1)	5 (2)	1 (1)	1 (2)	2 (2)
Indian	3 (2)	3 (2)	6 (2)	2 (3)	1 (2)	3 (2)
Black (other)	1 (1)	4 (3)	5 (2)	1 (1)	0	1 (< 1)
Chinese	1 (1)	3 (2)	4 (1)	1 (1)	0	1 (< 1)
Pakistani	3 (2)	1 (1)	4 (1)	2 (3)	0	2 (2)
Bangladeshi	0	1 (1)	1 (< 0.5)	0	0	0
Not given	0	0	0	0	0	0
Number of previous episodes of BV in the past 12 months,* n *(%)						
0	1 (1)	2 (1)	3 (1)	0	0	0
1–3	80 (56)	90 (60)	170 (58)	38 (55)	37 (69)	75 (61)
> 3	62 (43)	59 (39)	121 (41)	31 (45)	17 (31)	48 (39)
Female sexual partners in past 12 months,* n *(%)						
Yes	15 (10)	13 (9)	28 (10)	8 (12)	4 (7)	12 (10)
No	128 (90)	138 (91)	266 (90)	61 (88)	50 (93)	111 (90)

Appendix 6 VITA qualitative interview schedule outline

20-minute interview

Interview schedule for patients

Introductions

Introduction of researcher

Reminder of study (interviewee will have received participant information sheet and signed consent form)

Confirmation that participant is happy to proceed

Explanation of what happens to the data:

- Telephone interviews will be audio recorded. The audio recordings will be stored securely. For analysis the recording will be transcribed with anonymised.

Reminder that the interviewee can stop the interview at any time.

Opening questions

Tell me about your experiences while taking part in the VITA study?

Focusing on the treatment

Thank you. Tell me about the treatment you received.

Probes used as needed:

- *What were your initial expectations of the treatment?*
- Tell me how you used it.
- What was good about the treatment?
- What was not so good about the treatment?
- Any difficulties with using it?
- *Did you have to change what you do day to day when using it?*

How satisfied are you with the treatment you received overall?

Focusing on the modifications to make it more acceptable.

Is there anything that you would add to or change about the treatment you received?

Is there anything else that you would like to say about the treatment?

Would you recommend treatment to other patients with similar problems to your own?

Probes:

- *Explore reasons for their response.*

Focusing on use of the intervention in the other arm of the trial and its acceptability compared to what the patient received

You received treatment X and some of our patients received treatment Y which involves (description of how the treatment is used). Still thinking about the treatment you received, what are your views on treatment Y?

Probes:

- *What advantages/disadvantages do you think treatment Y may have in comparison to what you received?*

Close of interview

Thanks.

Any questions from interviewee.

Reminder of study contact details.

EME
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HTA
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