Metronidazole versus lactic acid for treating bacterial vaginosis (VITA)

Randomised controlled trial to assess the clinical and cost effectiveness of topical lactic acid gel for treating second and subsequent episodes of bacterial vaginosis

Health Economics Analysis Plan

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The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents				
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Introduction

The economic evaluation will be carried out alongside the VITA trial. The analysis will compare the costs and outcomes associated with the current treatment, oral metronidazole, with those of the alternative treatment, lactic acid gel, in the treatment of recurrent bacterial vaginosis (BV). The primary objective of the VITA trial is to determine whether intravaginal lactic acid is better than oral metronidazole for symptomatic resolution of recurrent BV. [1] This objective will be addressed via participant reported resolution of symptoms at Week 2. Secondary objectives include comparing the effectiveness, tolerability, and adherence to intravaginal lactic acid gel versus oral metronidazole.[1]

The economic analysis will therefore focus on comparing the cost-effectiveness of topical lactic acid gel versus oral metronidazole in the treatment of BV. This will involve examination of the costs and outcomes to determine whether there are any differences between the two treatments.

Methods

Overview

Data on resource use, costs and outcomes will be collected prospectively within the VITA trial. The economic evaluation will adopt the perspective of the National Health Service (NHS) and direct costs to the health service will be considered in the primary analysis. This perspective is the most relevant as the randomised controlled trial (RCT) is concerned with the effectiveness of lactic acid gel in the treatment of BV, and hence the costs to the NHS associated with the two treatments need to be taken into account. A broader perspective will be explored as part of the sensitivity analysis.

Resource use and costs

Resource use data will be collected via a questionnaire for participants at all participating sites. Data will be collected on treatment use, GP visits and other healthcare resource use to estimate the costs associated with both treatment arms. In addition, details of any adverse events will be recorded.

The main resources to be monitored include: (1) additional staff time for explanation about the lactic acid intervention and responding to concerns associated with treatment; (2) the costs associated with treatment, for example the cost of the lactic acid gel; (3) time and resources associated with clinical examination, consultation, additional medication and monitoring during the follow up period and to treat any adverse events. In line with the main clinical analysis, participants will be analysed according to randomised group regardless of adherence with the allocated intervention.

Where ambiguous answers have been given, the highest estimate will be used, for example if a participant states that they have had 2-3 GP appointments, it will be assumed that 3 appointments have been taken. Where an individual response is identified as an outlier and

likely to represent an input error, then this will be treated as missing data. Unit cost estimates will be applied to resource use data to generate individual level cost estimates. The sources of unit costs will include PSSRU Unit costs of Health and Social Care[2], NHS reference costs[3] and the British National Formulary[4]. The cost associated with antibiotic resistance to add as a penalty cost for using antibiotics has been estimated[5] and within this study we will explore whether a similar approach could be taken, as part of the sensitivity analysis.

Health outcomes

The primary outcome of the economic evaluation will reflect the primary outcome of the trial which is resolution of BV (based on participant reported resolution of symptoms at Week 2). Additionally, health related quality of life data will be collected using the SF-12™ Health Survey at baseline, Week 2, 3 months and 6 months. These data will be used to calculate quality-adjusted life years (QALYs). This instrument is recommended by the National Institute for Health and Care Excellence (NICE) for economic evaluations[6] and has been shown to be valid in a related area[7,8].

Missing data

For the resource use and SF12 data, multiple imputation methods will be used, where appropriate, to generate estimates of missing values based on the distribution of the observed data. This method is recommended in economic evaluations because it reflects the uncertainty that is inherent when replacing missing data.[9] It involves calculating the mean value with observed data for each variable, and the mean is then imputed in place of every missing observation for that variable.[10] For example, if a participant responded that an NHS service was used without providing details on the number of visits, imputation with the mean number of visits/calls will be used.

Analysis

The objectives of the trial and the duration of follow up mean that a within trial analysis is the most appropriate form of evaluation. Initially a cost-consequences analysis will be undertaken to compare all costs and outcomes for the two trial arms. This involves reporting all costs and outcomes in a disaggregated manner. The main analysis will be in the form of a cost-effectiveness analysis with results reported in terms of the cost per participant successfully treated. We will also report cost per QALY gained at 6 months as a secondary analysis. The final outcome will be presented as an incremental cost effectiveness ratio (ICER), this will present the additional costs that one treatment imposes over another, compared with the additional benefits. The primary approach of the analysis will be by intention to treat, to reflect the approach taken in the clinical analysis. Any participant randomised in error will be analysed as randomised, in keeping with the clinical analysis.

As cost data are likely to be skewed, a bootstrapping approach will be undertaken to calculate confidence intervals around mean costs. A decision tree will be constructed to represent the alternative treatment pathways and synthesise the available data using TreeAge Pro 2019.

Discounting

If necessary, the recommended approach to discounting will be followed, which involves discounting costs and benefits at 3.5%.[11] However, as the trial is concerned with the immediate post-treatment period, and therefore unlikely to extend beyond 6 months, this process is not likely to be necessary.

Sensitivity analysis

We will carry out a range of sensitivity analyses to explore the robustness of the results to plausible variations in key assumptions, and to consider the broader issue of the generalisability of the results. A deterministic sensitivity analysis will be undertaken; this involves varying one or more parameters while keeping the others at their baseline value. Deterministic analysis can help to identify which values are important in leading to a particular decision, and can help to identify threshold values. Where appropriate, a probabilistic sensitivity analysis (PSA) will also be undertaken to allow uncertainty to be represented more comprehensively. A PSA involves varying all parameters simultaneously, and multiple sets of parameter values are sampled from defined probability distributions. This will include analysing the impact of a range of costs associated with antimicrobial resistance.

A broader perspective will also be assessed in the sensitivity analysis. The analysis will consider the cost of additional medication and resource use paid by the participant as out of pocket expenses.

Conclusion

A cost-effectiveness analysis will be conducted to analyse the differences in cost and effectiveness between lactic acid gel and oral metronidazole. This economic analysis will provide evidence on the cost-effectiveness of lactic acid gel for recurrent BV compared to the standard treatment of oral metronidazole.

Draft Analysis Tables

Below are examples of the tables that will be used to present the economic analysis.

Table 1: Study treatments

Study Arm	Number of participants	Number of participants treated	Unit cost	Mean cost/ participant
Topical lactic acid gel				
Oral metronidazole				

Table 2: Resource use – visits to primary/ secondary care

Study Arm	Type of resource use	Number of participants	Number of visits	Unit cost (£)	Mean cost/ participant
Topical lactic acid gel	GP consultation Face to face Telephone				
	GP nurse Consultation Face to face Telephone				
	Sexual Health clinic consultation Face to face Telephone				
	NHS outpatient Face to face Telephone				
	NHS walk in centre Face to face Telephone				
	NHS 111				
	GP out of hours service Face to face Telephone				
	Pharmacy consultation Face to face Telephone				
	A & E Face to face Telephone				
	Other services				
Oral metronidazole	GP consultation Face to face Telephone				
	GP nurse Consultation Face to face Telephone				
	Sexual Health clinic consultation Face to face Telephone				

	NHS outpatient Face to face Telephone
	NHS walk in centre Face to face Telephone
	NHS 111
	GP out of hours service Face to face Telephone
	Pharmacy consultation Face to face Telephone
	A & E Face to face Telephone
	Other services

Table 3: Resource use – additional medication

Study Arm	Type of medication	Number of participants	Number of units	Unit cost	Mean cost/ participant
Topical lactic acid gel					
Name of the medication					
Oral metronidazole					
Name of the medication					

Table 4: Resource use – hospitalisation for BV (if required)

Study Arm	Number of participants	Number of days	Unit cost	Mean cost/ participant
Topical lactic acid gel				
Oral Metronidazole				

Table 5: Other resource use

Study Arm	Number of participants	Number of units	Unit cost	Mean cost/ participant
Topical lactic acid gel				
Oral Metronidazole				

Table 6: Adverse events

Study Arm	Number of participants	Type of event	Unit cost	Mean cost/ participant
Topical lactic acid gel				
Oral Metronidazole				

Table 7: Total costs (£)

Study Arm	Type of cost	Number of participants	Cost
Topical lactic acid gel			
	Study treatment		
	Primary / secondary care visits		
	Hospitalisation		
	Other medication		
	Other resource use		
	Adverse events		
	Total cost		
Oral Metronidazole			
	Study treatment		
	Primary / secondary care visits		
	Hospitalisation		
	Other medication		
	Other resource use		
	Adverse events		
	Total cost		

Table 8: Outcome data – Primary outcome (Resolution of BV symptoms at week 2)

Study Arm	Number of participants treated	Number of participants successfully treated (resolution of symptoms)	Percentage of participants successfully treated
Topical Lactic acid gel			
Oral Metronidazole			

Table 9: Outcome data – QALY gain at 6 months

Study Arm	Number of participants	QALY gain at 6 months	Mean QALY value
Topical Lactic acid gel			
Oral Metronidazole			

Table 10: Cost-effectiveness results

Study Arm	Number of participants treated	Total cost	Number of participants with resolved BV symptoms (at 2 weeks)	Cost per participant with resolved BV symptoms
Topical Lactic acid gel				
Oral Metronidazole				

Table 11: Cost-utility results

Study Arm	Number of participants treated	Total cost	QALY gain at 6 months	Cost per QALY gained
Topical lactic acid gel				
Oral Metronidazole				

Table 12: Deterministic sensitivity analyses – examples

	Original value	**Revised value**	**Lactic Acid gel: Revised result**	**Oral Metronidazole: Revised result**
Base case				
a) Varying the cost of antibiotics				
b) Increasing the cost of additional treatment where symptoms are not resolved				
c) Varying the rates of resolution of symptoms				
d) Varying the recurrence rate				
e) Increasing the cost of treatment with lactic acid (longer consultation time)				
f) Changing the QALY value				
g) Varying treatment pathways				
h) Varying the health care setting (GP practice, sexual health centre and gynaecology clinic)				
i) Including patient incurred costs				

References

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