Author's response to reviews

Title: BASIC Study. Is intravaginal boric acid non-inferior to metronidazole in symptomatic bacterial vaginosis? Study protocol for a randomized controlled trial.

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Author's response to reviews: see over
June 23, 2015

Dear Trials Editors and Reviewers:

Regarding MS: 1473618670155771-BASIC Study. Is intravaginal boric acid non-inferior to metronidazole in symptomatic bacterial vaginosis? Study protocol for a randomized controlled trial.

Thank you for your time reviewing our manuscript submission and for the comments and questions put forth by yourselves and the reviewers. We appreciate the suggestions to improve the manuscript and feel that the manuscript is now strengthened with the changes.

We have included our point-by-point responses for the reviewers concerns and questions following this letter.

Also, I have included a copy of the manuscript that includes the original with the changes tracked (includes the comments from our statistician Dr Jonathan Burkowitz) at the end of this document as well as the final copy with accepted changes uploaded to the website.

Thank you again for your time and consideration,

Dr Melinda Zeron Mullins
**Editorial requests:**
1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?________________: study protocol for a randomized controlled trial.? Please note that the title in the submission system should match that of your manuscript.

Revised as requested

2. Please include the date of registration with the trial registration number at the end of the Abstract.

Revised as requested

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

See the following comments.

Please also ensure that your revised manuscript conforms to the journal style

Revised as suggested.

**1st Reviewer's report:**
Major Compulsory Revisions
The authors define this RCT as a noninferiority study, but their hypothesis is that Boric acid is at least as effective and safe as Metronidazole. Noninferiority design is used to determine whether a treatment is not worse than a reference treatment by more than an acceptable amount. I therefore suggest that a statistician peer review the statistical part of the protocol to decide whether or not noninferiority design can be used.

Reviewed by statistician and revised as suggested.

**2nd Reviewer's report**
1. On page 5 it is stated that the objective of the trial is to determine non-inferiority of intravaginal BA to standard treatment metronidazole, for the cure of BV in symptomatic women compared to placebo. This is a strange way to describe a non-inferiority trial. Why is the placebo in the trial? Will there be a test of each drug to placebo and then to each other. The manuscript is never clear on this. The role of the placebo is needed. The comparison of the drugs needs a better explanation.

Reviewed by statistician and revised as suggested.

2. The Design section says nothing about the study design. It reads more like a
build up to the sample size determination.

*Revised as suggested.*

3. From where does the 10% non-inferiority margin come? This needs justification (both in terms of statistics and clinical significance).

*Revised as suggested.*

4. Should the Participants and Eligibility section make clear which visits (or which time period/days) are on drug, what visit is for the primary outcome and what visit is for the follow up? How many visits if any will be while the participants are on drug?

*Revised as suggested.*

5. The Randomization section is confusing. It appears routine, but reads as if it is very elaborate. It needs to be made clearer.

*Revised as suggested.*

6. The Outcomes and Assessment section does not make clear what is the primary outcome visit. It states "at the time of the outcome assessment." Why cannot something simple such as stating again what exactly is the visit for the primary outcome which is the Nugent score.

*Revised as suggested.*

6.1. The section says the primary outcome is measured at 7 days and 30 days. Are there two primary outcomes or is one time for the primary and one time for the secondary measure? See question 7.2. below.

*Revised as suggested.*

7. The Statistical Consideration section is very poorly written.

*Revised as suggested.*

7.1. What is the primary analysis (ITT or Per protocol)? If both are performed what if they do not agree?

*Revised as suggested.*

7.2. The Statistical section says analysis will be done at 7 days and 30 days after treatment end for effectiveness. What is primary? The Abstract states that the primary outcome is treatment effectiveness at day 7 but the main manuscript
confuses this. Do the authors want both the 7 and 30 day outcomes to be primary? Or is one primary and the other secondary? The use of the Nugent score at day 7 an 30 does not make them both primary outcomes. Clarification is needed.

**Revised as suggested.**

7.3. How does the placebo fit into the analyses?

**Revised as suggested.**

7.4. How will multiple testing be controlled? There are 3 treatments, two times when efficacy analyses will be performed and two data set (ITT and PP). How will the error rate be controlled?

**Revised as suggested.**

8. I believe missing data are covered, but it might be helpful that the authors give that another look.

**Revised as suggested.**

**1st Reviewer’s supplementary report:**

1. Will the study design adequately test the hypothesis?
The authors define this RCT as a noninferiority study, but their hypothesis is that BA is at least as effective and safe as metronidazole. A noninferiority trial “seeks to determine whether a new treatment is not worse than a reference treatment by more than an acceptable amount” (Piaggio et al. 2012). If the authors want to determine whether BA is at least as effective and safe as metronidazole, I doubt that noninferiority is the right design. The authors do not describe or discuss statistical methods for noninferiority trials in the “Statistical consideration” chapter of the protocol.

**Revised as suggested.**

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?
The protocol contains important but superficial information about the study design. The intervention and treatment regimen are adequately described, but I doubt that the protocol as a whole is detailed enough to allow replication or comparison with related analysis (see SPIRIT and TIDieR for details).

**Revised as suggested.**
The protocol deviates in some aspects from the information registered in ClinicalTrials.gov.
15 March 2015

ClinicalTrials.gov registration update has been submitted since to reflect this. Thank you.

3. Is the planned statistical analysis appropriate?
The described statistical analyses are not appropriate for noninferiority tests.
There is no information about whether superiority analysis will be performed (against placebo, in sub-group analysis?).
My opinion is that the statistical section needs peer-review by a statistician.

Reviewed by a statistician and revised as suggested.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*
Title 1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Comments: Preferable to use Noninferiority in title to identify the study as such.
Revised as suggested.

2b All items from the World Health Organization Trial Registration Data Set
Comments: See table 2. in SPIRIT 2013 (Chan, Tetzlaff et al. 2013)
ClinicalTrials.gov Protocol version 3 Date and version identifier?
Revised as suggested.

Funding 4 Sources and types of financial, material, and other support
Financial: British Columbia College of Family Physicians Research Award 2013
Material used: no specific information about support.
Other support: no information.
Revised as suggested.

Roles and responsibilities
5b Name and contact information for the trial sponsor
Comments: I could not find information about sponsor.
Revised as suggested.

5c Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
Comments: No information about role of founder.

Revised as suggested.

Methods: Participants, interventions, and outcomes
Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Comments: Participating family practice clinics – description?

Revised as suggested.

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Comments: Inclusion criteria in this protocol and the text in ClinicalTrials.gov differ slightly. The protocol does not have information about eligibility criteria for study centres i.e. participating family practice clinics.

Revised as suggested.

Interventions
+ TIDieR guideline

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Comment: To make replication possible an assessment battery and questionnaires would have been of great value.

Non-validated questionnaires were created for the study to determine participant demographics and past and present medical history.

The participant-level analysis metric:

Revised as suggested.

The method of aggregation:

Revised as suggested.

Rationale for choice of trial outcome: ?

Revised as suggested.
Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure).

Comments: I miss a figure with flow of participants and a schematic diagram giving key information about study visits, enrolment process etc.

We had considered this too but thought it would be more effective in the publication of the results.

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

Comments: Suggest this item peer-reviewed by a statistician or statistical familiar person.

Reviewed as suggested.

Methods: Assignment of interventions (for controlled trials)

Allocation:
Sequence generation 16a Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

Comment: Method of sequence generation: Computer-generated random numbers (www.randomization.com). Information about date of entry and version of sequence generator are missing.

Allocation ratio: no information.

Type of randomisation: no information.

Revised as suggested.

16b Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

Comment: The planned allocation concealment seems OK, but it is not described in detail.

Revised as suggested.

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

Randomisation section:
“Blinded recruiting clinicians select the package to be given out to patients on enrolment day and subsequently the treatment pack number becomes the participants’ identification number”.

Intervention and Control group section:
“The selection of the treatment pack (containing either boric acid compounded in emollient cream, metronidazole cream, or emollient cream) for the participant by the recruiting physician is blinded for both physician and participant as to the identity of the treatment in the pack.”

What is meant by selection?

Revised as suggested.

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

No information about outcome assessors or statisticians.

Revised as suggested.

Methods: Data collection, management, and analysis
Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Comment: Sparse information.

Revised as suggested.

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols?

Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).

Reference to where details of data management procedures can be found, if not in the protocol?

Statistical methods 20a Statistical methods for analysing primary and secondary outcomes.

Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Comment: No information about test of noninferiority. No information whether superiority analysis will be performed (against placebo, in sub-group analysis?).

Suggest this item peer-reviewed by a statistician.

Revised as suggested.

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

Comment: Suggest this item peer-reviewed by a statistician.

Reviewed as suggested.

20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Comment: Suggest this item peer-reviewed by a statistician.

The authors will perform intention to treat and per protocol analysis, but they do not define what
they mean by this terms. No information about how to handle missing data.

Revised as suggested.

**Methods: Monitoring**
Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed? 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial. Comments: Stopping guideline (Safety assessment section), serious adverse effects are defined as; neurological, cardiac, respiratory, gastrointestinal or anaphylactic reactions, but they are not clarified in detail. No information about interim analysis.

Revised as suggested.

**The TIDieR (Template for Intervention Description and Replication) Checklist®:**
WHERE
7. Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features. Comments: Family practice clinics in British Columbia, Canada. No information about the clinics.

Revised as suggested.
Title:

BASIC Study. Is intravaginal boric acid non-inferior to metronidazole in symptomatic bacterial vaginosis? Study protocol for a randomized controlled trial.

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Abstract

Background

Bacterial vaginosis is associated with increased transmission of sexually transmitted infections, pre-term labour, post-surgical infections, and endometritis. Current treatment for symptomatic bacterial vaginosis includes antibiotics, like metronidazole, which are 70-80% effective at one month after treatment and have high recurrence rates and secondary candida infections. Intravaginal boric acid has been used for over one hundred years to treat vaginal infections such as bacterial vaginosis. Boric acid is inexpensive, accessible, and has shown to be an effective treatment for other infections such as vaginal candidiasis. To date, there has been no clinical trial evaluation of boric acid effectiveness to treat bacterial vaginosis. This study will determine whether intravaginal boric acid is non-inferior to metronidazole in the treatment of bacterial vaginosis in symptomatic women.

Methods/Design

The BASIC (Boric Acid, Alternate Solution for Intravaginal Colonization) trial is a randomized, double-blinded, multi-center study. The study will enroll a minimum of 240 women 16-50 years of age who are symptomatic with bacterial vaginosis. Eligible participants will have Amsel and Nugent Scores confirming bacterial vaginosis. Those participants who are pregnant or menopausal or have other active co-infections will be excluded. Consentig participants who meet exclusion and inclusion criteria will be randomly assigned to one of three treatment groups: boric acid, metronidazole, or an inert placebo. Self-administration of treatment intravaginally for 10 days will be followed by clinical assessment at 7 and 30 days (day 17 and 40, respectively) after the end of the treatment phase. Primary outcome is a non-inferiority, per protocol comparison of effectiveness of boric acid to metronidazole at day 17 as measured by Nugent
Score in 16-50 year olds. Secondary outcomes include: non-inferiority, intent-to-treat comparison of effectiveness of boric acid to metronidazole at day 17, analysis for both per protocol and intent-to-treat at day 40 as well, and safety consideration including adverse effects requiring patient discontinuation of treatment.

**Trial Registration**

ClinicalTrials.gov NCT00799214, registered online Nov 10, 2008.

**Keywords**

Bacterial vaginosis, boric acid, metronidazole, placebo, intravaginal, randomized controlled trial, double blinded, multi-center, non-inferiority
**Background**

Bacterial vaginosis (BV) is thought to be more common than either vulvovaginal candidiasis or trichomoniases, and to represent 40-50% of all cases of vaginitis [1]. BV is associated with postpartum endometritis, increased risk of post-surgical infections, pelvic inflammatory disease, increased risk of spontaneous abortions, preterm rupture of membranes and delivery, and increased risk of sexually transmitted infection acquisition, including: human immunodeficiency virus, herpes simplex virus, Niesseria gonorrhoeae, Chlamydia trachomatis, and trichomonas vaginalis [1-6]. BV is caused by a shift from the normal peroxidase-producing Lactobacillus-dominant vaginal flora to a several log increase in total bacterial colony count, which may include a mix of anaerobes, genital mycoplasmas, and Gardnerella vaginalis [1,7]. BV is classically characterized by abnormal odor and vaginal discharge in symptomatic women, while 50% of women with BV are asymptomatic [7,8]. BV can also be painful, and is associated with dysuria and/or dyspareunia in symptomatic women [8]. BV is diagnosed by using the Amsel criteria as having 3 of the 4 following: elevated pH (>4.5), homogenous milky or creamy discharge, amine odor, and clue cells [4,7,9]. The gold standard for BV diagnosis is by Gram stain (Nugent score ≥7) demonstrating a decrease or absence of lactobacilli and the presence of other microbes that cause BV [4,7,9,10].

Untreated women show a 30% spontaneous resolution rate for BV [11,12]. Current recommended antimicrobial treatments for BV in non-pregnant, symptomatic women include oral and intravaginal metronidazole or clindamycin [1,8,13]. Oral and intravaginal metronidazole are considered equivalent and effective treatment for BV [9,11,14-16].
Standard treatment with metronidazole, according to these trials, has imperfect cure rates (approximately 70-80%) measured 1 month after treatment [9,11, 12,15-18] and high BV recurrence risks: 33% at 3 months [19] and approximately 49-66% at 1 year [18]. Metronidazole also carries a significant rate of side effects (10-20% of women), especially with the oral metronidazole preparation [20], that include secondary vaginal infection with candida [12,14,16]. At present, oral or vaginal metronidazole is the only recommended treatment option for recurrent BV as is vaginal metronidazole for long term suppression [9,21].

Boric acid (BA) has been used for over a hundred years for the treatment of vaginal infections and is commonly used by physicians and patients as an inexpensive, easy to use, accessible treatment of candidiasis and BV [22]. In addition to its proven effectiveness in the treatment of candidal infections, [22-31] including those that did not resolve with usual antifungal treatment [24-28], BA use seemed be associated with a reduced number of co-infections with BV in these women [25]. A retrospective study suggests clinical improvement in 7 of 9 patients following treatment with 600 mg intravaginal BA for 14 nights in women with a mixed infection of T. glabrata vaginitis and BV [25]. In an uncontrolled, non-randomized, retrospective chart review when BA was added to nitroimidazole there was promising long term (>88% cure rate at 12 weeks after the study and 50% at 36 weeks of follow up) suppression of recurrent BV [32]. Based on the aforementioned study, the physician evidence reference resource “UpToDate®” recommends that intravaginal BA 600 mg used for 21 days be added to 7 days of metronidazole or tinidazole treatment to induce a remission prior to starting long term suppression therapy [21]. No studies to date have determined BA effectiveness in the treatment of acute, chronic or recurrent BV.
The objective of this study was to determine whether intravaginal BA is comparable to standard treatment, metronidazole, for the cure of BV in symptomatic women.

Our research question is: Among women 16-50 years old symptomatic with BV is intravaginal treatment with BA non-inferior to metronidazole to achieve a Nugent score <7 (cure) by day 17.

**Hypothesis**

H₀: BA proportion of women cured ≤ metronidazole proportion of women cured - 10%.

**Methods/Design**

**Study design**

Institutional review board approval was granted for this study through the University of British Columbia Clinical Research Ethics Board (H07-02330). Health Canada Clinical Trial Application Notice of Authorization was obtained May 10, 2013: company code 31784, file number 187476. This trial is registered with ClinicalTrials.gov (NCT00799214). This study conforms to CONSORT 2010 guidelines for randomized control trials.

Based on preliminary data, the success rate of the boric acid treatment group is predicted to be approximately 77-88% [25,32] in treating bacterial vaginosis. Metronidazole treatment group would be expected to be 70-80% [11,12,15-18] effective in treating BV as compared to a 30% success rate of a placebo group [11,12]. The Nugent score is found to be >95% sensitive [33] for detecting bacterial vaginosis. We chose a non-inferiority limit of 10% as this will allow for a clinically relevant difference between the metronidazole treatment group and the boric acid group to be appreciated. Also, it is approximately 25% of the expected difference between the metronidazole standard treatment group and the placebo group. Accounting for a non-inferiority
limit (delta) of 10%, testing for a significance level of 0.05 and power of 80% we require approximately 63 subjects per group. To allow for a dropout rate of 25% we set target rate of 80 subjects per treatment arm. If there is a true difference in favour of the experimental treatment of 8%, then 126 patients (total for two groups of 63) are required to be 80% sure that the upper limit of a one-sided 95% confidence interval using the binary outcome, non-inferiority trial power calculator [34]

We felt it was important to include a placebo treatment arm in this study for a few different reasons: 1) this is the first RCT to use intravaginal boric acid and thus comparing it to placebo for safety and effectiveness would be of clinical interest (i.e. perhaps it is not comparable to metronidazole in effectiveness but is still significantly better than placebo), 2) having a placebo group in an non-inferiority trial acts as a sensitivity assay and internal validator for this type of trial [35], 3) comparing metronidazole effectiveness and safety to the placebo group in the 16-19 year old cohorts has not previously been done and would also be of clinical interest.

**Study Setting**

Recruitment began February 2014 for a minimum of 240 volunteer women through participating family practice clinics in British Columbia, Canada. Volunteer participating clinics represent a spectrum of different types of practice across British Columbia: rural, remote, urban, First Nations and non-First Nations communities, single and multi-clinician practices, general family practice offices, women’s health clinics, and youth clinics. Clinics were recruited to the study through province-wide medical journal advertisements, university family practice departmental email advertisements, personal emails, faxes, phone calls and in person. Eligible clinics agreed to
recruit five or more participants meeting inclusion and exclusion criteria and to use the study treatments and pre-made packages provided.

**Participants and Eligibility**

Women who present to their clinician at participating family practice clinics with symptoms of BV are offered an opportunity to participate in the study. Participants are given the informed consent form explaining the three possible treatment arms, and that participation will include 3 visits [including the initial visit-day 0, day 17-19 (7-9 days after the treatment end to measure the primary endpoint), and day 40-42 (30-32 days after the treatment end as a secondary endpoint] involving 3 examinations, including a pregnancy test. There are no visits to the clinic while the participants are administering the 10 day treatment unless there are any concerns. Women are included in the study if they are symptomatic for bacterial vaginosis, meet 3 of 4 Amsel criteria on the initial day of the study and subsequently have a swab graded with a Nugent score $\geq 7$. Detailed eligibility criteria are listed in Table 1. In general, participants cannot be pregnant, menopausal, have another vaginal infection, nor have an intrauterine device (IUD). Written consent is obtained prior to treatment intervention. Women who choose to participate receive their medication for free. There is a draw for recruited women to win a small gift certificate.

**Randomization**

Randomization in blocks of 80 was conducted by the study pharmacist (blinded to enrollment and outcome measurement) using the ‘first generator’ on the website: www.randomization.com in September 2013. These numbers then become the new identification on the treatment packs. All treatment packs are then distributed to participating clinics by the study pharmacist who sends out five sequentially numbered treatment packs to each participating site as sites are
recruited to the study. The study pharmacist is the only person with access to the master code to the randomized treatments. The participants, recruiting clinicians and investigators will be blinded to the controlled and randomized 10 day treatment pack that is given to the study participant. Blinded recruiting clinicians give out the physically indistinguishable treatment package in allocated randomization order to the sequential participant on enrolment day (day 0). Subsequently the treatment pack number becomes the participants’ identification number.

**Intervention and Control Groups**

Day 0 the enrolled participants will be blindly and randomly assigned to one of three 10 day treatments (minimum of 80 women per treatment arm): 1) placebo (emollient cream); 2) boric acid (600 mg boric acid compounded in emollient cream); 3) metronidazole 10% intravaginal cream (Sanofi-Aventis Canada Inc Product DIN 01926861) (for a total of 37.5 mg metronidazole) packaged by the study pharmacist. There is no detectable difference between the treatments either in appearance or scent.

**Study Procedure and Data Collection**

On day 0 a pregnancy test and history will be performed by the clinician. During the pelvic exam the clinician will ensure intact mucous membranes and anatomy, observe whether there is homogenous milky or creamy discharge (one of the 4 Amsel criteria), take swabs for chlamydia and gonorrhea, bacterial vaginosis (for the Nugent score), candidiasis, and trichomonas, and perform a Whiff Test using a provided standardized 10% potassium hydroxide solution (one of the 4 Amsel criteria). Vaginal discharge will also be tested for pH (one of the 4 Amsel criteria). Where facilities permit; clue cells will be examined for as the 4th of the 4 Amsel criteria. On this day, the recruiting clinician will confirm participation, eligibility and exclusion criteria using
provided protocol forms and will collect the signed consent form and the demographic/medical history questionnaire provided.

The blinded treatment pack (containing either boric acid compounded in emollient cream, metronidazole cream, or emollient cream) is allocated by the recruiting clinician in the randomization order to sequential participant on day 0. The participant package also contains: 1) vaginal applicator; 2) pads; 3) non-lubricated non-latex condoms; 4) a diary to record their daily use of the treatment 5) information sheet outlining follow up instructions and emergency contact numbers to reach the study members. Participants will self-administer the blinded treatment cream intravaginally each evening immediately prior to sleep for 10 days. The participant will be instructed to use a provided pad during the day and night. Each participant will record daily compliance, side effects and symptoms in the journal provided.

On both follow up visits: days 17-19 (one week after the treatment end) and 40-42 (one month after the treatment end), the participant will return to the clinic that enrolled her for reassessment, pregnancy test, and follow up examination including pelvic exam and repeat swabs. It will be noted whether her BV symptoms are still present, and if she had any side effects or problems during treatment. The participant returns her daily treatment diary on day 17 visit as well.

**Safety Assessments**

Emergency telephone contact with the investigators will be available for any questions or problems related to the treatment. On day 5 of the treatment, the participant will receive a call, text or email from one of the investigators to determine and record compliance, side effects, BV symptoms, and satisfaction of treatment. The study pharmacist will informed by the recruiting clinician of the participant’s full name, date of birth and personal health number and the study
number assigned so that the study pharmacist can enter the medication name into the provincial pharmacy database. This safety measure ensures subsequent treating physicians throughout the province will have access to the treatment received, in case there were to be a safety concern and a need to unblind the participant’s medication should the participant presents with an emergency. Non-emergency access to the provincial pharmacy database is not allowed by the recruiting physicians in order to protect the participant’s identification of the blinded treatment.

If at any time the participant reports intolerable side effects (i.e. vaginal discomfort, intolerable vaginal discharge, urticaria, secondary yeast infection) during treatment, or with exacerbation of symptoms at any point, they may voluntarily discontinue the treatment and leave the study without prejudice, and their doctor/another physician may provide treatment as per usual standard of care.

As neither metronidazole or boric acid treatments provided to patients are in amounts considered toxic when taken intravaginally or if accidentally ingested, should there be any occurrence of serious adverse effects (neurological, cardiac, respiratory, gastrointestinal or anaphylactic reactions) during any of the treatments, the study will be put on hold until an investigation can be done. In the case of serious adverse effects found to be caused by the treatment, the study will be stopped, and the study unblinded/decoded by the study pharmacist. The investigators, the participants and clinicians involved in the study would be informed for the reason for stopping the study.

**Outcomes and Assessment**

On days 17-19 and days 40-42, if the vaginal swab is positive for BV found by both meeting 3 of 4 Amsel criteria and has a Nugent score ≥7 and the participant is symptomatic for BV then the
physician prescribes a standard medication of their choice. This is considered a treatment failure addressing our primary and secondary outcomes: effectiveness at 7 days and 30 days after treatment end.

If the participant discontinued the treatment during the 10 days because of side effects or complained of intolerable side effects (major adverse effect) from the treatment this is considered a treatment failure referring to our secondary outcome: safety.

**Statistical Considerations**

Primary outcome: non-inferiority, per protocol comparison of effectiveness of boric acid to metronidazole at day 17 as measured by Nugent score in 16-50 year olds with a z-based confidence interval for the difference of two proportions. This was chosen as the primary outcome because the immediate effect of boric acid after a 10 day treatment compared to metronidazole was our most important question to answer for bacterial vaginosis treatment. Participant-level analysis metric measured as change from baseline Nugent score $\geq 7$ to a Nugent score $<7$ is considered a cure of bacterial vaginosis. Treatment failure will be reported as a positive Nugent score $\geq 7$ at day 17. Secondary outcomes include: 1) non-inferiority, intent-to-treat comparison of effectiveness of boric acid to metronidazole at day 17 as measured by Nugent score in 16-50 year olds with a z-based confidence interval for the difference of two proportions, We will use this to confirm the robustness of our per protocol comparison but the per protocol analysis will be the primary determinant of the non-inferiority test. 2) non-inferiority, comparison of effectiveness of boric acid to metronidazole at day 40 as measured by Nugent score in 16-50 years old analyzed both per protocol and intent-to treat with a z-based confidence interval for the difference of two proportions, and safety consideration including
intolerable adverse effects requiring patient discontinuation of the 10 day treatment. To control for multiple testing we will use a Bonferroni-type correction. In order to account for both ITT and PP analyses, and two time point analyses, the threshold for statistical significance will be set at 0.01 (i.e. approx. 0.05 divided by 4).

The following are tertiary outcomes and no formal sample size calculations were done. Minor adverse effects (side effects not causing the patient to discontinue treatment) will be reported and compared between the treatment arms but will not be considered as treatment failure. We will examine the adolescent population, the 16-19 year old sub-group, for non-inferiority for effectiveness of boric acid to metronidazole at the end of the study. Finally we will test for superiority of the effectiveness and safety of boric acid compared to placebo in both the 16-50 year olds and in the 16-19 year old sub group. Our study is the first to be able to examine the 16-19 year olds for the effectiveness and safety of metronidazole compared to placebo as well.

95% confidence intervals will be established. Missing data (participants who fail to complete follow up for any reason) are accounted for as a proposed 25% lost to follow up rate. Data will be blindly collected by the outcome assessors from the participating clinics and entered into an electronic database. The study pharmacist will provide the randomization code for the data to a third party statistician and the data will be analyzed. Self-reported participant satisfaction criteria included at the end of the daily treatment diary will use a 5 point rating scale to record: effectiveness in curing BV symptoms, side effects, ease of use, likelihood they would use it again for BV treatment, likelihood they would recommend it to someone else for BV treatment.

**Discussion**
The BASIC study will be the first prospective randomized control trial to determine the effectiveness of intravaginal BA compared to metronidazole for the treatment of BV in symptomatic women. If intravaginal BA is shown to be non-inferior to metronidazole in the treatment of BV then this may provide women less costly options to treating this common vaginal infection.

**Trial Status**

The trial is currently open to recruitment.

**List of Abbreviations**

BA-boric acid, BV-bacterial vaginosis, BASIC- Boric Acid, Alternate Solution for Intravaginal Colonization, IUD –intrauterine device

**Competing Interests**

None to declare

**Author’s Contributions**

MZM is the principal investigator. MZM conceived and designed the study, and will coordinate implementation and data acquisition, prepared the initial draft of grant proposals and wrote this manuscript. KT contributed to conception and design and will assist with enrollment, data acquisition, and manuscript revision. Both authors approved the final manuscript.

**Author’s Information**

MZM works in Bella Coola, BC, Canada with a special interest in women and adolescent health. MZM is a Clinic Instructor with the Department of Family Practice, University of British
Columbia. KT is medical director of Vancouver Island Women’s Clinic, Victoria, BC, Canada. KT is a Clinical Professor, with the Department of Family Practice, University of British Columbia.

Acknowledgements

Dr Teresa Wood was involved in study conception and initial design and protocol development. Dr Geoff Mullins helped to coordinate the study and reviewed the manuscript. MZM is supported during this study by the Clinical Scholar Program of the University of British Columbia. Jeff Giles, the study pharmacist, assisted with the Health Canada application, and will assist with study coordination. Dr Wendy V Norman reviewed the manuscript. Dr Jonathan Burkowitz, the study statistician, reviewed the initial design and the manuscript. This study is supported by a generous research grant from the British Columbia College of Family Physicians (BCCFP) Research Award 2013. No drugs, materials or monetary funding or support is derived from industry sponsor or funder.

Endnote

a British Columbia PharmaNet Database

References


34. sealed envelope™. Power (sample size) calculators.


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<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
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<tr>
<td>Must be 16-50 years old and pre-menopausal.</td>
<td>Less than 16 or post-menopausal.</td>
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<td>Capable of giving written informed consent.</td>
<td>Menstruating at diagnosis.</td>
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<td>Has fluent comprehension of spoken and written English.</td>
<td>Symptoms so severe as to make allocation to placebo unacceptable to the woman.</td>
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<td>Agrees to examination on enrollment day, day 17-19 and day 40-42.</td>
<td>Currently pregnant or at high risk for pregnancy.</td>
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<td>Has a negative pregnancy test during the study.</td>
<td>Current active sexually transmitted infection (chlamydia, gonorrhea, trichomonas).</td>
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<tr>
<td>Agrees to follow study protocol and is reliable for follow up.</td>
<td>Current yeast infection as determined by history, physical and swabs.</td>
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<tr>
<td>Has documented bacterial vaginosis infection by positive vaginal swab (minimum Nugent score of ≥7) and meet 3 of 4 Amsel criteria.</td>
<td>History of pelvic inflammatory disease.</td>
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<td>Agrees to refrain from vaginal intercourse for the 10 days of treatment (or to use non-lubricated non-latex condoms if unavoidable).</td>
<td>Allergy to metronidazole.</td>
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<td>Agrees not to douche or use any intravaginal products during treatment (including tampons, medications, devices).</td>
<td>Presently breast feeding.</td>
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<td>Agrees to abstain from alcohol during the 10 days of treatment (from 24 hours before through 72 hours after taking study</td>
<td>Any open wound, excoriation, vaginal irritation and including Bartholin's cyst/abscess/herpes simplex viral lesion as determined by physical exam.</td>
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<td>Presence of another vulvar, vaginal or medical condition, including cervical neoplasia/treatment, or medical device, including an intrauterine device (IUD), that</td>
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medication).

Agrees to no new medications or antibiotics during treatment.

Has no currently active sexually transmitted infection as determined by history, physical exam and negative swabs for chlamydia, gonorrhea, candidiasis, trichomonas.

might confound treatment response.

Using lithium, anti-coagulants or disulfiram drugs.

Any antifungal or antibiotic use 14 days prior to enrolment.

Papanicolaou smear done within one week of enrolment.

Meeting 3 of 4 Amsel’s criteria but having a Nugent score <7.