Author’s response to reviews

Title: 7 versus 14 days of Antibiotic Treatment for Critically Ill Patients with Bloodstream Infection: A Pilot Randomized Clinical Trial

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Dear Dr. Holubkov,

Thank you for your consideration of our manuscript, entitled “7 versus 14 days of Antibiotic Treatment for Critically Ill Patients with Bloodstream Infection: A Pilot Randomized Clinical Trial” for publication in Trials. We greatly appreciated the reviewers’ feedback, and have strived to incorporate the suggestions into the manuscript. We believe the paper has been greatly strengthened in the process. The detailed point-by-point responses to the reviewer comments are provided below.

We look forward to hearing from you,

Sincerely,

Nick Daneman

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Nick Daneman, MD, FRCPC, MSc
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Reviewer #1: Dear Authors.

This is an interesting article about a Randomized Clinical Trial (RCT) comparing 7 days versus (vs) 14 days antibiotic treatment for critically ill patients with bloodstream infections. After its review the following comments have been raised up.

ABSTRACT. It would interesting if the authors could comment quite more extensively the "Background" subsection.

We have extended the background subsection to better describe the study context and objective.

In addition, in the "Methods" subsection, it would be correct if the authors could define better the RCT : it was an open RCT, it was a single, Double or Triple blinded RCT ? Or it was a double dummy RCT?

We have clarified that it was an open RCT.

In addition, please precise better the inclusion- exclusion criteria. And please mention briefly the Primary - Secondary objectives and outcomes.
There is insufficient word count to describe all of the inclusion/exclusion criteria in the abstract. We have now listed the secondary outcomes in the abstract.

Please describe briefly, in this section, the interventions done during the study (antibiotics used, doses used, and posology).

We have clarified that it was an open RCT with antibiotic selection, dosing and route at the discretion of the treating physicians. The intervention arms related only to the duration of treatment, which was fixed at either 7 or 14 days.

Regarding the "Results" subsection, the fact about the "recruiting rate" should be better explained because it is aligned with the primary feasibility outcome. Please explain better the "adherence results" because when reading them are quite confusing.

We feel that the results are clear for these two outcomes. The recruitment rate was 1 patient/ICU/month. The adherence to treatment duration was 89/115 (77%). We have separated the adherence description into two sentences. Please let us know if any other specific changes to the wording would be helpful.

Please comment to some extent the "Conclusion" subsection: it is considered that, if the principal outcomes are feasibility and adherence to treatment, then the achievement/not achievement of these outcomes should be better commented in the Conclusion Section. And if a "90 days survival" concept is mentioned in the Conclusion "subsection", this same concept should be defined in the "methods" subsection as a primary-secondary objective or outcome.

We have now mentioned the secondary outcomes in the methods subsection of the abstract. There is no further word count available to extend the conclusions subsection, and we believe the current statement is concise and accurate.
BACKGROUND.

The authors comment that "both antibiotic use and antibiotic resistant organisms are high in the in the Intensive Care Unit (ICU) where critically ill patients are vulnerable to bacterial infections and antibiotic complications". It would be interesting if the authors could comment to some extent, this clinical information (commenting about its epidemiology, the principal antibiotics used in the ICU, their principal indications in the ICU, the principal resistant microorganisms, the main antibiotics to whom bacteria have developed resistance, the principal mechanisms of resistance, etc).

We feel that a broad review of bacteremia, antimicrobial treatment and resistance in ICU might detract from the concise 3 paragraph argument that we have provided in the background section. However, we can add additional paragraphs if the editor prefers.

Additionally, the authors comment that RCTs have established that "shorter duration treatments are sufficient for a wide of bacterial infections, including some infections in critically ill patients". It would be correct if the authors could comment, to some extent, these RCTs, these shorter regimens, the addressed infections (in non critically ill patients and critically ill patients), and the evaluated antibiotics (as pooled data). The authors also comment, that through a literature systematic review, they identified studies of other bacterial infections where pooled data showed similar clinical outcomes when giving short term antibiotic treatment versus long term antibiotic treatments. It would correct if the author could comment also, and to some extent, this information too (type of infections, antibiotics used, interventions done (short and long treatments), main results (already explained but commenting them quite longer) safety aspects etc) commenting them as pooled data. All these information could describe better the actual "state of the art" of this important medical field (bloodstream infections) giving a complete view of what it is done and what has to be done. And it would give a better support to the rationale of this RCT explaining why it is important to carry out this study.

We have now provided some quantitative data from the systematic review in order to better describe the state of the art of this medical field (Background, paragraph 2).

PRIMARY AND SECONDARY OBJECTIVES. Please explain the Primary and Secondary Objectives that were defined for the Randomized Clinical Trial.
We have now clarified the co-primary feasibility objectives of this feasibility pilot RCT (Background, paragraph 3).

METHODS.

General Study Design. Please define better the Clinical Trial. Opened?, Single Blinded ?, Double Blinded?, Triple Blinded? Double dummy ? Superiority ?, Non inferiority ? (Already commented). Please explain better why one of the aims of this RCT is to inform the results of a non - inferiority CT ?. Is this study that one non inferiority CT ? In addition please explain the relationship between this RCT and the BALANCE Clinical Trial (CT). If this CT is non randomized and is the BALANCE CT please include it in its definition. Additionally please explain why did the authors decided an experimental design (CT) for the evaluation of the feasibility of a project and the adherence to a treatment?. This is so, because an observational - analytical study (cohort study) could possibly demonstrate, better than a CT, these objectives (feasibility and adherence).

We have clarified that this is an open RCT aimed at establishing the feasibility of the main BALANCE RCT (Methods paragraph 1). We have clarified that his pilot RCT involves 1:1 randomization to 7 versus 14 days of treatment (Methods paragraph 3). The pilot RCT has the identical study design as the main BALANCE RCT. The pilot has served as a vanguard for the main trial. This is common practice in the Canadian Critical Care Trials Group. An observational study would not demonstrate feasibility of the main trial, because it would not be able to test recruitment rates or adherence to treatment duration protocol (the two main feasibility outcomes of interest). For example, enrolment rates would be much higher in an observational study in which clinicians and patients would not need to consent to have treatment duration fixed by study randomization assignment. Adherence to treatment duration protocol would not be meaningful it was not being assigned in the same randomized fashion as the main trial.
Study Setting. If the authors consider so, a brief description of the study setting could be done. It considered that it is enough with mentioning that the CT was carried out in 11 centers (sites) in 10 cities across 5 Canadian provinces. And in the annexes to include a list with all the participant Intensive Care Units (ICU´s) and Hospitals (with their respective city and province).

We have listed all of the participating sites (Methods, Paragraph 2).

Patient Selection Criteria.

It is considered that this section should be reorganized: divided in two sections with defined the Inclusion Criteria and the defined Exclusion Criteria.

We have now separated this into two sections.

Inclusion Criteria. Please define better the Inclusion Criteria: Accepted Minimum and Maximum Patient Ages, Gender, Pregnancy State (did the authors considered to do a pregnancy test to all those eligible female patients before including them in the CT?).

There were no restrictions by age, sex/gender or pregnancy and so we have not mentioned these factors.

Do patients with other chronic infections (High Blood Pressure, Diabetes, Hypercholesterolemia, Ischemic Cardiomyopathy, Atrial Fibrillation, COPD, Asthma, etc) and having a concomitant bloodstream infection were considered eligible patients?

There were no restrictions by any of these comorbidities and so we have not mentioned these factors.
Non Risk Factor Patients with acute infections (community acquired pneumonia, Gastrointestinal Infections, Central Nervous System (CNS) Infections, Dermatologic Infections, etc) and with concomitant Bloodstream Infections were eligible to participate in the CT? Please define better all these aspects. Please define what do the authors consider as a Bloodstream Infection (principal clinical criteria) to be eligible for inclusion in the CT. How many positive blood cultures were considered to be needed for the inclusion of patients? Please specify the protocol followed for the correct extraction of blood for the blood culture in order to avoid false positive results? (risk of ibas).

We have clarified that any single positive blood culture with a potential pathogen qualified for inclusion in the study. Two blood culture sets were required for common contaminant species (but this is mentioned in the exclusion criteria). Almost all sources of bloodstream infections and almost all pathogens are eligible for inclusion; we have listed the exceptions in the exclusion criteria.

Exclusion Criteria please define if patients taking immunosuppresant medications (ciclosprine, azathoiprine, mophetil mycophenolate, etc), HIV patients, HCV patients, Lung, Breast, Prostate, Cancer Patients, receiving chemotherapy - hormonetherapy or not, (all of them susceptible for the acquisition of severe infections) were excluded from participaron in the CT.

We have clarified that the only immune compromising conditions that we have excluded are neutropenia and transplantation (bone marrow and solid organ).

Please explain why patients having cultures with Coagulase negtive Staphylococi, Corynebacterium, Staphylococcus aureus and fungal organisms were excluded form the CT. It could be because habitually the treatment for all these infections last for more than 14 days?

Patients with a single set positive for a common contaminant were excluded because they may not have true bloodstream infection. Patients with Staphylococcus aureus and fungal organisms were excluded due to requirement for more prolonged treatment. We have clarified these exclusions.
Please explain better these aspects and if patients with medication (antibiotic) allergy were considered to be excluded.

There is no role for exclusion based on medication allergy, because all of these patients receive antimicrobials, and the choice of antimicrobials are left to the discretion of the treating team.

Intervention: 7 versus 14 days of Adequate Antimicrobial Treatment. According to the article, the clinical team was allowed to select the most suitable antimicrobial treatment based on their criteria. Please explain if this criteria was supported by appropriate and recognized International Clinical Guidelines - Protocols for the Treatment of Bacteremia in the ICU setting. If so, please refer those Clinical Guidelines - Protocols used for the selection of the antibiotic treatments by the Clinical Teams in this CT. In addition please comment if the selection of the most appropriate antimicrobial treatment were guided by the realization of Antibiograms and please describe better what do the authors consider as "in vitro" activity.

We aim to have the BALANCE trial be as pragmatic as possible, to maximize generalizability of findings. Therefore, we have not sought to protocolize treatment selection. We have clarified this important point (Methods, page 8 first paragraph).

Please explain better the methodology followed for the selection of the treatment duration: does this shouldn’t be established undergoing the randomization and the allocation (concealed or not) rather than calendar days?

The treatment duration is defined by randomization assignment as either 7 or 14 days. There are many ways in which days can be counted. We elected to count any day on which the patient received an antibiotic active against the bloodstream pathogen. Some of these days will occur prior to randomization. As an example, consider a patient that has a blood culture collected on January 1st at 1600h, and is started on ceftriaxone on January 1st at 1700h, and the culture is identified as positive on January 3rd, they are randomized into the study on January 4th. If it turns out that the causative pathogen is sensitive to ceftriaxone, then we would count January 1st as the first calendar day of adequate treatment. This patient would have their randomization assignment revealed on January 7th and would then either stop at the end of that day (if randomized to 7d treatment) or on January 14th (if randomized to 14d treatment).
INFORMED CONSENT SIGNATURE AND RANDOMIZATION. Please describe the procedures for the explanation of the CT to patients /relatives (in case of patients with severe illness) and the informed consnt signature. In addition please explain better the procedures for the randomization and the allocation concealment of the eligible patients to the experimental interventions of the CT. When revising it, it is not completely comprehensible. As commented before, does the allocation was open, single, double, triple, blinded ? Was there was a double dummy or not ?.

We have clarified that this is an open RCT, and the rationale for this design (Methods, page 7/8).

It is not completely understood why the maintaining ot the allocation concealment until the end of day no. 7 could avoid selection bias. Habitually the selection bias are avoided with the rigorous application of correct inclusion and exclusion criteria. Please explain better.

Prolonged allocation concealment helps prevent clinicians from engaging in differential practice following randomization. We have clarified this notion in the Methods (Page 8, paragraph 1).

PRIMARY AND SECONDARY FEASIBILITY OUTCOMES.

It would be correct if the authors could creat a section with the Primary- Secondary Objectives and Outcomes. Regarding the Primary Feasibility Outcomes please explain what do the authors consider as "adherence to treatment"; who has to comply this "adherence to treatment"? The patients ?, The Clincial Team?, The investigators?.

Adherence to treatment duration is not defined based on the patient or clinical team, it is defined based on whether the correct duration was actually received.

Additionally, please explain why Adherence to Treatment and Recruitment Rates were established as a primary feasible outcome in a RCT. For the purposes of the study, it is
considered that probably an analytical - observational study (cohort study) would be a more suitable study design rather than a RCT (already commented).

An observational study would not demonstrate feasibility of the main trial, because it would not be able to test recruitment rates or adherence to treatment duration protocol (the two main feasibility outcomes of interest). For example, enrolment rates would be much higher in an observational study in which clinicians and patients would not need to consent to have treatment duration fixed by study randomization assignment. Adherence to treatment duration protocol would not be meaningful if it was not being assigned in the same randomized fashion as the main trial.

Please explain better why the authors decided to include a 90 days mortality outcome only if the treatments were going to last 7 and 14 days? Which are the facts that are going to be evaluated after day No. 14 and before día No. 90? Is this outcome going to receive an appropriate analysis (Kaplan-meier analysis? Log-rank analysis) ? Do the other secondary outcomes mentioned in the text belong to this CT and are going to be analyzed within the present study? Or they are part of the future CT which the authors are willing to do? If they belong to the second CT, it is considered that they can be removed. Does the Antibiotic free days is a secondary outcome of this CT or it belongs to the "larger CT?" If it corresponds to the "larger CT" it is considered that it could be also removed. If no, please explain better the Clinical Rationale for the inclusion of an outcome, with the characteristics of this one, in the CT?

The pilot RCT has the identical study design as the main BALANCE RCT.

The pilot has served as a vanguard for the main trial. We include the secondary clinical outcomes in this manuscript because we demonstrate that they can be feasibly collected for the main RCT. We do not present group-separated results for these secondary clinical outcomes, for reasons explained in the discussion section (page 15).
MECHANISTIC SUBSTUDIES.

It is considered that this section could be removed from the text. Even though it is a substudy derived from the first one, it is about a different CT rather than the actual one.

We prefer to leave these mechanistic substudies in the manuscript, and one of the other reviewers also felt that they were a valuable contribution.

STATISTICAL ANALYSIS.

According to the text, a main descriptive analysis was performed. It is considered that this type of analysis was selected according to the type of included outcomes (Cualitative Outcomes). And because, as the authors comment, a pilot- RCT with no efficacy neither safety endpoints is not suitable to undergo a proper Clinical Investigation Statistical Analysis. Completely agree. However, didn’t the authors consider to use a more appropriate qualitative statistical test for RCTs (Chi-square test for example)? In the other hand, and regarding to the 90 day mortality outcome, what type of statistical analysis is going to undergo this outcome? : a Kaplan Meier Analysis, a Log Rank analysis, or another survival analysis? This is because this outcome (even though of being qualitative) is a mortality outcome and must be analyzed following a mortality analysis but not a merely descriptive analysis. Please explain better. It is considered that designing a correct Statistical Analysis will really avoid over-interpreting the results of the trial rather than than avoiding the underpower of the results in the Clinical Endpoints. Finally does the analysis was an "intention to treat" or a "per protocol" analysis ?.

In the BALANCE main RCT, the primary outcome will be 90-day mortality. The primary analysis will assess whether 7 days of treatment is associated with non-inferior 90-day survival rates in comparison to 14 days. We require 1,686 patients per arm to establish a non-inferiority margin of 4% absolute decrement in survival (18 power 80%, alpha 0.025, one-sided equivalence test). We have inflated this to account for 5% loss-to-follow up, and early stopping rules (coefficient 1.017) for a total requirement of 3598.
We have not evaluated group-separated clinical outcome results for the pilot RCT (please see Discussion page 15 for explanation). There is no role for chi-square testing, because we are not comparing outcomes across groups in the pilot RCT.

SAMPLE SIZE CALCULATION.

After reading the sample size calculation it is assumed that because this is a RCT with no clinical comparative objectives neither outcomes (efficacy or safety), a classical RCT sample size calculation was not done. Therefore this is why the authors do not mention the "alpha error" used, the "beta error" used, neither the magnitude nor the proportion of the expected differences between interventions, neither the expected precision. Given this, the authors do not describe if the test used for this sample size calculation was one sided or two sided. It is considered that this should be reflected in the text of the study with a brief explanation. in addition the authors should explain if in the Sample Size calculation they included the proportion of losses.

Please see above.

RESULTS

Screened, Eligible and Randomized Patients. A complete descriptive exposition of the patients Clinical characteristics has been done. Please explain better why do the authors consider as "lack of consent by the ICU physician". Does the consent was given by the treatment MD but no by the patient? Please explain in what consists the Substitute Decision Maker (SDM).

We believe this is standard terminology, but we can provide further description if the editor prefers.

In line No. 3 please change the word "me" by the word "met". Nothing else to add.

We have made this change.
Patient, Infection and Pathogen Characteristics. A descriptive exposition of the facts has been done. It would be advisable if the authors could include in the text the main patients comorbidities to make more homogenous and contrastable the information of this section.

We have described the main comorbidities in Table 1. In order to avoid repetition, we have not listed them in the text of the results.

Treatment Characteristics, Recruitment Rate and Adherence to Treatment Protocol. A descriptive exposition of the major finding results has been done. However it is recommended to make a more complete results description in the text in order to be aligned with the information included in the Tables.

We have strived to minimize repetition between the manuscript text and tables. If the editor prefers, we can repeat these results in both text and table format.

Do the adherence treatment comply the established expectatives established by the authors ?? In addition it would be advisable if the authors could separate the Adherence to Treatment Results between the 7 days regimen and the 14 days regimen. This would be more aligned and coherent with principal aims, purposes, objectives and outcomes of the study. And separating them in two different tables. This would be more clarity to the results obtained.

The BALANCE steering committee has instructed us not to present group separated results for the pilot RCT.

Clinical Outcomes. A descriptive analysis was done. Please explain the treatment underwent by patients with relapsed infection. In addition please explain better the 14-day free antibiotic period and its significance in the results of the trial. Please include what do they mean with "wide variability" and "bimodal distribution".
We measured antibiotic as the number of calendar days within 28 days after blood culture collection, on which the patient did not receive any antibiotic treatments; any patient dying within 28 days of blood culture collection was assigned zero antibiotic free days (see Methods page 8). This is analogous to the common outcome measure of ventilator-free days used in ICU patients. A median of 14 antibiotic-free days is much higher than we have observed in a retrospective observational cohort of bacteremic patients in ICU suggesting that the BALANCE trial design already reduces overall antibiotic exposure, even when only half of patients are randomized to shorter duration treatment. There was a ‘bimodal’ distribution, meaning that there were two modes at 14 and 21 free days, which is what we would expect when patients are being randomized to 7 versus 14 days of treatment. Even with imperfect protocol adherence in the trial, this indicates that we are still achieving separation in antibiotic exposure across the two treatment arms.

And please explain if the authors consider the overall mortality rate obtained as a high or low result in concordance to the expectatives of the trial regarding this fact.

The 90-day mortality rate is lower than we expected based on observational cohort data; as with all RCTs this suggests that there is selective recruitment of less sick patients.

The safety aspects are described. Please comment if the authors consider them as positive or negative results? Do they support the good pharmacologic profile of the used antibiotics and the well conduction of the interventions? Do they give support (from a safety aspect) the realization of a wider CT? Please explain.

The low rate of antibiotic side effects supports realization of the main BALANCE RCT.

Mechanistic Substudies. It is considered that they could commented elsewhere. Because these results are part of another study which is not these one. And because the measurement of the procalcitonin levels, in the included patients and derived from the interventions, are not defined as primary and secondary objectives neither outcomes.

Discussion. The discussion is aligned with the findings of the trial. The authors comment their results and analyze them adequately when commenting strengths and weaknesses. Although
interesting and promising, the pro-calcitonin results should be commented elsewhere because it is part of other substudy rather than this CT. And their use in the Clinical context of this study (bloodstream infections) has not been currently validated.

The full procalcitonin sub-study will be published following the results of the main BALANCE trial, but this will be 4-5 years down the line. In the meantime, we felt that the pilot procalcitonin results warranted inclusion in the pilot RCT manuscript, because they provide a compelling argument for the added value of a trial of fixed 7 versus 14 days of treatment (see discussion, page 16). One of the other reviewers also felt that this was an interesting and important component of the manuscript.

In addition, the discussion should be more focused with the findings of this CT rather than with the Clinical Research purposes of the BALANCE study.

One of the other reviewers requested more, rather than less, discussion of the main clinical purposes of the BALANCE study, so we have not deleted the existing content.

Conclusion. The conclusion is aligned with purposes and objectives of the Trial.

Reviewer #2: Dear authors,

you can propose a study (RCT) to compare 7 versus 14 days of antibiotic treatment for critically ill patients with bloodstream infection.

The manuscript is written sufficiently, the length is acceptable and the statistical methods are mentioned.

Please give your statement to the following points:
1. Abstract
- No problem

2. Introduction
- Please better specify the clinical message that the authors want to send

   We have now specified the clinical importance of a trial aimed at establishing non-inferiority of 7 versus 14 days of antibiotic treatment for bloodstream infection (Background, paragraph 2).

3. Materials and Methods
Ethics committee: OK; informed consent: OK; NCT: present

Please better specify if they were followed the Consort guidelines

   We have now clarified that we followed the CONSORT guideline for pilot trials (Methods, paragraph 1).

Inclusion/exclusion criteria: Well explained Primary and secondary endpoint: explained Please better specify the double-blind technique in this setting

   We have clarified that placebo controls were not feasible to use, because of variable pathogens, sources of bacteremia, mono- and combination antibiotic treatment regimens and potential for critically ill patients to develop secondary nosocomial infections requiring ongoing re-assessment of treatment choices. We have now added that as a consequence patients and clinicians were not blinded to treatment assignment (page 6, final paragraph).

Allocation/randomization: please, better specify
We have specified that randomization was accomplished via a central web-based system (http://www.randomize.net) using variable block sizes, stratified by ICU site. We have now added that patients were allocated 1:1 into 7 versus 14 day treatment arms (page 6, final paragraph).

Sample size/power calculation: Please check the calculation.

We have checked the sample size calculation.

Statistical plan: explained

4. Results
- Please better specify if there are missing data

We have specified that there was no loss to follow up, and no missing outcome data (Results page 9, paragraph 1).

5. Discussion
- Please specify the clinical message that the authors want to send

The main clinical message is specified in the final sentence of the conclusions paragraph (page 14/15). The pilot trial described in this manuscript justifies the BALANCE main trial (now underway) which will answer the clinical question of interest. If the BALANCE main trial establishes that 7 days of antibiotics are non-inferior to 14 days of antibiotics it will justify a paradigm shift in antibiotic treatment durations for these patients, with immediate global reductions in antimicrobial harms, resistance and costs.
Reviewer #3: This is a pilot RCT to assess the feasibility of conducting a large multicenter trial design based on antibiotic treatment duration in critically ill ICU patients with bloodstream infections. Durations of 7 versus 14 days of antibiotic treatment were compared among bacteremia patients from different intensive care units.

A very interesting, well written and presented pilot trial with a potential substantial impact on health care and practice.

Few points could be addressed for improvement of the manuscript.

Abstract

"conduct an RCT" should read "conduct a RCT"

We have incorporated this change (Abstract conclusion, page 2).

Background

"Given the absence of evidence, such as 7 days used by many practitioners"

This sentence is too long and could be rewritten to clarify the meaning.

We have now rewritten this sentence as two separate sentences, and we believe this helps to clarify the meaning (Background, page 4).
More information could be added here to explain the significant impact this finding could have on healthcare. For example, regarding the cost of care, side effects of extended antibiotic treatment, etc. Supporting such information with numbers and references would be helpful as well.

We have added this information (Background paragraph 4).

Brief statement regarding why a pilot study is needed prior to conducting the larger multi-center trial.

We have clarified that this was a feasibility pilot (not a mechanistic pilot)

(Background, final paragraph).

Methods

Intervention: 7 versus 14 days of Adequate Antimicrobial Treatment Details about the intervention are given here, but no information about the criteria used to define effective treatment, for e.g. how many cultures were used to confirm eradication of the bloodstream infection or any other parameters used. More details about assessment of efficacy of treatment could be added here.

Negative repeat blood cultures are not required in patients with non-

Staphylococcus aureus bacteremia, and so should not be sent as part of routine care (WiggersBMC ID 2016). There is currently no accepted test of cure for bacterial infection in critically ill patients, and so the primary measure of efficacy in the BALANCE main RCT will be 90-day mortality. Other measures of clinical efficacy will include: ICU and hospital mortality, relapse of bacteremia, ICU and hospital lengths of stay, mechanical ventilation and
vasopressor duration. We have clarified that these are measures of efficacy (Methods section page 7 paragraph 2).

Some detail regarding the follow-up is not clear such as the method of contact and assessment. This could be added under a separate section for follow-up details.

We have added a separate section for follow-up details (Methods, Page 8).

RESULTS
"patients who me the exclusion criteria" should read "who met"

We have fixed this typographic error.

Reviewer #4: Very nicely done feasibility study

Very important question and remarkable finding that PCT remained elevated in 7 and 14 day treatment groups

I am not convinced that a 70+ % adherence to the 7 and 14 day protocol really means this is a feasible study. I need more convincing from a statistician on this assertion. Non-inferiority between use of 7 or 14 day regimens when physicians only adhere to regimen in 3 of 4 patients? Escapes in 1 of four patients?

The 77% treatment adherence in the pilot RCT was lower than our initial target of 90%, but was similar to other trials of shorter versus longer treatment duration, such as the PneumoA study which has helped define treatment duration for ventilator-associated pneumonia (Chastre
Moreover, the non-adherence rate is much lower than the largest study of procalcitonin-guided treatment for infection in critically ill patients.

Our pilot RCT also elucidated some of the most common causes of treatment non-adherence, which we are now able to minimize in the main RCT. We agree with Reviewer #4 that this represents the single greatest challenge in the BALANCE main RCT.

Sounds like a third arm is needed for usual care? Some other design approach?

Based on the BALANCE Pilot RCT results we have received funding from the Canadian Institutes of Health Research (CIHR) and the New Zealand Health Research Council (NZ HRC) to conduct the BALANCE main RCT of 7 vs 14 days of treatment for bloodstream infection in critically ill patients.

We have enrolled 380 of a target 3598 patients, so we will not be able to change our design approach at this point. The design was developed and refined with iterative feedback from the Canadian Critical Care Trials Group (CCCTG). The BALANCE steering committee and broader CCCTG membership felt that a separate usual care arm was not required, given that both 7 and 14 days of treatment fall within the range of usual care as documented by the BALANCE national practice survey and multicentre observational study.