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Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) randomized clinical trial: study protocol

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Bacteremia **A**ntibiotic **L**ength **A**ctually **N**eeded for **C**linical **E**ffectiveness (**BALANCE**) randomized clinical trial: study protocol

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ABSTRACT

Introduction Bloodstream infections are a leading cause of mortality and morbidity; the duration of treatment for these infections is understudied.

Methods and Analysis We will conduct an international, multicentre randomized controlled comparative effectiveness trial of shorter (7 days) versus longer (14 days) antibiotic treatment among hospitalized patients with bacterial bloodstream infections. The trial will include 3626 patients across more than 60 hospitals and 6 countries. We will include patients with blood cultures confirming a pathogenic bacterium after being admitted to hospital. Exclusion criteria will include patient factors (severe immune compromise), infection site factors (endocarditis, osteomyelitis, undrained abscesses, infected unremoved prosthetic material) and pathogen factors (*Staphylococcus aureus, Staphylococcus lugdunensis, Candida*, and single cultures with contaminant organisms). We will leave the selection of specific antibiotic agents, doses and route of delivery to the discretion of treating physicians; no placebo control will be used given the diversity of pathogens and sources of bacteremia. The intervention will be assignment of treatment duration to be 7 versus 14 days. We will minimize selection bias via central randomization with variable block sizes, and will conceal allocation until day 7 of adequate antibiotic treatment. The primary outcome is 90-day survival; we will test whether 7 days is non-inferior to 14 days of treatment, with a non-inferiority margin of 4% absolute mortality. Secondary outcomes include hospital and intensive care unit (ICU) mortality, relapse rates of bacteremia, hospital and ICU length of stay, mechanical ventilation and vasopressor duration, antibiotic-free days, *C. difficile* infection, antibiotic allergy and adverse events, and colonization/infection with antibiotic-resistant organisms.

Ethics and dissemination The study has been approved by the Ethics review board at each participating site. We will disseminate study results via the Canadian Critical Care Trials Group and other collaborating networks, to set the global paradigm for antibiotic treatment duration for non-Staphylococcal Gram positive, Gram negative and anaerobic bacteremia, among patients admitted hospital.

Trial registration number The BALANCE Trial was registered at www.clinicaltrials.gov (registration number: NCT03005145)

Keywords: bacteremia, bloodstream infection, antimicrobial, treatment duration, mortality, antimicrobial stewardship, intensive care

Strengths and Limitations of this Study

- The BALANCE study is the largest randomized clinical trial ever conducted among patients with bloodstream infection, and should set the paradigm for antibiotic treatment duration for these patients.
- BALANCE will provide generalizable results by including a wide array of bloodstream pathogens and underlying sources of infection, examining both critically and non-critically ill hospitalized patients, and including sites across 6 countries with varying baseline antibiotic resistance rates
- If 7 days of antibiotic treatment is non-inferior to 14 days of treatment, this could lead to reductions in global antibiotic use, costs and antibiotic-related complications, including adverse events, *C. difficile* and antibiotic resistance.
- The diversity of pathogens and underlying infections that cause bloodstream infection render placebo controls infeasible. We will minimize bias through central randomization, allocation concealment until day 7, an objective primary outcome, and blinded adjudication of other outcomes such as relapse and secondary infections with antibiotic resistant organisms.

INTRODUCTION

There are more than 600,000 episodes of bloodstream infection per year in North America, and more than 1,200,000 episodes in Europe.[1] These infections affect 15% of critically ill patients, result in prolongation of hospital stay, excess health care costs, and a substantial mortality. [2-5]

Hospitals, and intensive care units (ICUs) in particular, are the location of greatest antimicrobial pressure; however, audits indicate that 30-50% of antibiotic use in acute care and critical care settings are unnecessary or inappropriate[6-8] and leads to avoidable costs and complications. Antibiotics are among the most common cause of serious adverse drug events,[9] which occur in up to 5-10% of inpatient recipients.[10] Excessive durations of antibiotic therapy are the largest contributor to inappropriate antibiotic use in acute care hospitals, long-term care facilities, and ambulatory clinics.[7, 11-13] Discontinuing antibiotics after achieving clinical cure can potentially reduce the burden of adverse events, *Clostridium difficile* infections, and selection of antibiotic resistant pathogens.[14 15]

Meta-analysis of randomized clinical trials has demonstrated that shorter duration antibiotic treatment is as effective as longer duration treatment for a range of mild to moderate infections.[16] Even in critically ill patients with ventilator-associated pneumonia, mortality rates and relapse rates were non-inferior among the 402 patients randomized to receive shorter (8 day) versus longer (15 day) courses of antibiotics.[17] However, similar high-grade evidence is lacking for the treatment of critically ill patients with bloodstream infections.[2, 18, 19] One recent study has examined 7 versus 14 days of treatment for bacteremia in non-critically ill patients, and has suggested that this may be a safe approach, but used a wide non-inferiority margin, and was limited to infections with Gram negative pathogens.[20, 21] Specific guidelines for treatment durations exist for pneumonia,[22, 23] intra-abdominal infection,[24] catheter-related bloodstream infection,[25] pyelonephritis,[26] and skin and soft tissue infection[27] but no guidelines exist for the optimal duration of treatment for the subset of bacteremic patients.

We have performed a systematic review of the existing literature,[19] practice surveys of infectious diseases and critical care physicians,[28, 29] a single-centre[30] and multicentre observational study,[31] which collectively identified gaps in current evidence, extensive practice variation, and equipoise for a randomized trial comparing shorter (7 days) versus longer (14 days) antibiotic treatment durations for bloodstream infections. Through the Bacteremia Antibiotic Length Actually Needed For Clinical Effectiveness (BALANCE) pilot randomized clinical trial (ClinicalTrials.gov, identifier: NCT02261506) we documented the feasibility of this trial design among 115 patients in intensive care units (ICUs), thereby providing a vanguard for the BALANCE main trial.[32] We have subsequently confirmed the feasibility of enrolling patients on non-ICU wards in a parallel pilot RCT (clinicaltrilas.gov identifier NCT02917551), facilitating expansion of the BALANCE trial to include non-ICU patients.[33]

The primary aim of the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) randomized clinical trial will be to determine whether 7 days (as compared to 14 days) of adequate antibiotic treatment is associated with non-inferior 90-day survival for hospitalized patients with bacteremia.

METHODS AND ANALYSIS

Study Design

We will conduct a multicentre randomized concealed allocation trial of shorter duration (7 days) versus longer duration (14 days) antibiotic treatment for patients with bacteremia admitted to hospital.

Setting

The BALANCE Trial (balance.ccctg.ca) is currently being conducted across a geographically and clinically diverse spectrum of ICUs and hospitals in Canada (currently 36 sites), Australia (6 sites), New Zealand (10 sites), United States (2 sites), Saudi Arabia (2 sites), and Israel (1 site). We commenced enrolment at the central study site, Sunnybrook Health Sciences Centre in Toronto, Canada at the beginning of the vanguard pilot (October 2014) and then added each additional site, in a staggered fashion after ethics approval, contract and site initiations were accomplished. We continue to welcome new sites into BALANCE, and anticipate approximately 60-70 active sites by the time of trial completion.

Participants

Hospitalized patients will be considered for enrolment in this study if they meet all inclusion and no exclusion criteria.

Inclusion criteria: Patient is admitted to hospital at the time a blood culture result is reported as positive with a pathogenic bacterium.

Exclusion criteria:

1) Patient already enrolled in the trial;

2) Patient has severe immune system compromise, as defined by: absolute neutrophil count $<0.5 \times 10^9$/L; *or* is receiving immunosuppressive treatment for solid organ or bone marrow or stem cell transplant;

3) Patient has a prosthetic heart valve or synthetic endovascular graft (post major vessel repair with synthetic material; coronary artery stents are not an exclusion);

4) Patient has a documented or strong suspicion of a syndrome with well-defined requirement for prolonged treatment:

i) infective endocarditis;

ii) osteomyelitis/septic arthritis;

iii) undrainable/undrained abscess;

iv) unremovable/unremoved prosthetic-associated infection (e.g. infected pacemaker, prosthetic joint infection, ventriculoperitoneal shunt infection etc.). Central venous catheters, including tunneled central intravenous catheter, and urinary catheters are not excluded.

5) Patient has a single positive blood culture with a common contaminant organism according to Clinical Laboratory & Standards Institute (CLSI) Guidelines: coagulase negative staphylococci; *or Bacillus spp.*; *or Corynebacterium spp.*; *or Propionobacterium spp.; or Aerococcus spp.; or* M*icrococcus spp;*[34]

6) Patient has a positive blood culture with *Staphylococcus aureus*[35] *or Staphylococcus lugdunensis*

7) Patient has a positive blood culture with rare bacterial pathogens requiring prolonged treatment (e.g., *Mycobacteria* spp., *Nocardia spp., Actinomyces spp., Brucella spp, Burkholderia pseudomallei*)

8) Patient has a positive blood culture with *Candida spp.* or other fungal species.

Trial intervention

We will randomize patients to receive a shorter duration of adequate antibiotic therapy (7 days) versus a longer duration (14 days) (Figure 1). Adequate antibiotic treatment will be defined as treatment with an antibiotic (or antibiotics) to which the local laboratory has reported the organism(s) responsible for the bloodstream infection as susceptible. The duration of adequate treatment will be determined as the cumulative number of days on which at least one dose of adequate treatment is delivered beyond the date of collection of the index blood culture specimen.[36] The selection of specific antimicrobial agent(s), doses and route of delivery will be at the discretion of the treating clinical team. The research team at each site will visit daily to ensure that antibiotics are stopped at the pre-specified date (end of the 7th or 14th day).

Randomization and allocation concealment

We will use web-based randomization through RANDOMIZE.NET (http://www.randomize.net/), with variable block sizes, stratified by hospital site and by ICU versus non-ICU location. After the full susceptibility results become available, the site research coordinator along with site co-investigators will determine the date for day 7 unblinding, taking into account the number of days that the patient has already received adequate antibiotics after the blood culture collection date. To avoid differentially influencing antibiotic choices and clinical decision-making, the randomization assignment will not be communicated to any clinical staff or research personnel (research coordinator, study critical care or infectious diseases investigators) - until the end of day 7. At day 7, another email will be sent with the unblinded treatment assignment for the patient to the site research coordinator. If a patient is randomized to the short (7 day) treatment arm, the treating team will be informed to stop the antibiotics at the completion of 7 days of antibiotics appropriate for the causative pathogen; if the patient is randomized to the long (14 day) arm the team will be instructed to continue the antibiotic until that date, including beyond hospital discharge if necessary.

Mechanistic sub-studies

Biomarker sub-study

Blood samples will be drawn on the randomization day and at days 7, 10 and 14 from the index blood culture collection to measure procalcitonin (PCT) levels along with other novel inflammatory and angiogenic biomarkers (s-TREM-1, S-TNFR-1, s-TNFR-2, IL-6, CHI3L1, Angiopoietin (Ang)-1, Ang-2, sTIE1, sTIE2, sFlt-1, Slt-2/ROBO). The PCT levels will be batched and measured at the end of the study for the sub-study assessing the association between PCT and clinical outcomes among patients receiving 7 versus 14 days of treatment. The results will not be made available to the treating team because this could unduly influence clinical practice and protocol adherence, and is ethical because none of the participating sites are currently using PCT routinely. Following study completion, we will compare PCT area-under-the-curve (AUC) and day 7, 10 and 14 PCT levels among patients. We will also confirm whether 7 days of antibiotics is non-inferior to 14 days of antibiotics for bacteremia, in subgroups with both normal and abnormal (>0.25ug/mL) PCT levels on day 7. We will conduct comparable analyses for the other inflammatory and angiogenic biomarkers.

Microbiome sub-study

In order to assess the effect of shortening the duration of antibiotic administration on the human gut microbiome, we will collect rectal swabs from patients on the day of randomization, and at days 7, 14, and 21 (or hospital discharge if earlier than day 21) from the start of appropriate antibiotic therapy. Flocked, sterile swabs will be inserted 2-3 cm past the anal verge, rotated 3-4 times, deposited into a room-temperature stable DNA/RNA preservative and stored at room temperature. No human sequence data will be obtained. Swabs will be transported for processing in batches, or at the end of the study, whichever is easier for the participating site.

Samples will be processed for extraction of nucleic acid for 16S rRNA microbiome sequencing and shotgun metagenomics sequencing. Participants who decline sample collection for the sub-studies will still be included in the main clinical trial.

Protecting against sources of bias

Selection bias

Selection bias (such as bias-by-indication or survival bias) will be minimized through rigorous concealed randomization procedures. Although placebo controls have been used in some RCTs of antibiotic treatment duration, such as studies examining treatment duration for cellulitis[37], pyelonephritis[38, 39], and community-acquired pneumonia,[40-43] they are not appropriate for bacteremia treatment in acutely ill patients. It is not feasible to administer placebos for each of the many antimicrobials commonly used alone or in combination to treat the many etiologies of bacteremia.[44] Even if it were possible to generate this many placebos, BALANCE patients are susceptible to developing secondary sources of nosocomial infection, and our preparatory work revealed that clinicians demand knowledge of whether a patient is receiving antibiotics or not.

Outcome misclassification bias

We have selected an objective primary outcome measure and we will use central adjudication committees blinded to treatment allocation for other outcomes including relapse, and secondary infection/colonization with antibiotic resistant organisms.[45, 46]

Withdrawal from study

If a patient is withdrawn from the study prematurely, a withdrawal form will be completed. Data will be collected under the informed consent up to the point of a consent withdrawal. Among patients who withdraw consent for continuation of the trial, we will seek their consent to ascertain vital status at ICU and hospital discharge and at 90-days from the date of bacteremia diagnosis. Anticipated reasons for withdrawal include patient not meeting inclusion criteria or having relevant exclusion criteria prior to randomization, consent withdrawn by patient or substitute-decision maker, patient's physician believes patient should be withdrawn from the study, inadvertent duplicate randomization. Detailed rationales for withdrawal will be recorded.

Protocol adherence and protocol deviations

We will define adherence to treatment duration protocol as receipt of 7 ± 2 days of adequate antibiotics in the shorter duration arm, and 14 ± 2 days in the longer duration arm; antibiotics stopped before or continued beyond these durations will be considered protocol deviations. We do not expect or aspire to achieve a 0% protocol deviation rate in this trial, given that some patients will develop persistent, recurrent or secondary infections for which antibiotics will need to be re-initiated or continued. It is appropriate for these patients to receive treatment as would occur outside of a trial. For example, in the multicenter *PneumoA* study of 8 versus 15 days of treatment for ventilator-associated pneumonia, protocol non-adherence was 18% in the 8-day treatment arm.[17] Non-adherence rates have been as high as 50% seen in some studies of PCT-guided treatment for infections in critically ill patients.[47] However, we will monitor protocol deviation rates overall and by hospital site during the trial, record rationales for the deviations, and strive to minimize unnecessary deviations.

Frequency and duration of follow-up

Patients will be reviewed daily in hospital for the first 14 days post randomization, and again at hospital discharge with extensive data collection (see case report form at balance.ccctg.ca). The research coordinator will contact the patient (or substitute decision-maker as appropriate) on day 90 by telephone to determine their

disposition and vital status. Other sources of evidence for 90 day vital status will include clinical documentation of health care visits/readmissions and testing after 90 days.

Primary outcome measure

The primary outcome will be survival at 90-days from the date of bacteremia, defined by the date of collection of the index positive blood culture. Although, most deaths from critical illness occur during hospital stay, lingering sequelae lead to a persistently elevated risk of death post-discharge. Therefore, we selected post-hospital 90 day mortality as a common vital status endpoint.[48, 49]

Secondary outcome measures

The secondary outcomes include: (a) hospital mortality (b) ICU mortality (d) relapse rates of bacteremia with the same organism (e) antibiotic allergy and adverse events (f) rates of *C. difficile* infection in hospital (g) rates of secondary nosocomial infection/colonization with antimicrobial resistant organisms in hospital (h) ICU length of stay (i) hospital length of stay (j) mechanical ventilation duration; and (k) antibiotic-free days.

Antimicrobial resistant organisms will be defined based on a positive routine culture yielding a highly resistant microbial organism (HRMO) as defined by the Dutch nosocomial infection surveillance guidelines.[50] This broad definition includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, extended spectrum beta-lactamase producing Enterobacteriaceae, carbapenem-resistant Gram negative bacilli, and multidrug resistant Gram negative bacilli (with definition of multi-drug resistance differing according to Enterobacteriaceae and non-Enterobacteriaceae species).[50] We will also conduct a sensitivity analysis limited to isolation of these organism(s) only from sterile site specimens (such as blood, cerebrospinal fluid, peritoneal fluid, synovial fluid, pleural fluid, and tissue biopsies).

Antibiotic-free days will be calculated as the number of days alive and not on any antibiotics in the time period from collection of the index blood culture to 28 days after this date; patients who die prior to day 28 will be assigned 0 antibiotic-free days.

Statistical analysis

Sample size

The primary analysis will assess whether 7 days of treatment is associated with a 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 (baseline mortality 22%)[51] power 80%, alpha 0.025, one-sided equivalence test). We have inflated this to account for a maximum of 5% loss-to-follow-up, and have incorporated early stopping rules to account for the 3 interim analyses (coefficient 1.017)[52, 53] for a total sample size of 3626. Recent landmark trials in with similar baseline mortality rates have used -4% as a non-inferiority margin;[54, 55] the U.S. FDA has recommended a similar margin for analogous industry-sponsored trials.[56] The PneumA study of 8 vs 15 day treatment for VAP used a non-inferiority margin of 10%,[17] as have other recent prominent infectious diseases non-inferiority trials,[20, 57] but we believe lower non-inferiority margins are desirable, when feasible, for the outcome of survival.[56]

Loss to follow-up

We anticipate negligible loss of patients to follow-up. The Canadian Critical Care Trials Group (CCCTG) (www.ccctg.ca) has achieved virtually 100% follow-up to hospital discharge over all of its landmark RCTs.[58-60] Although we will be following survivors to ascertain 90-day mortality and relapse rates, we also expect close to

100% follow-up based on previous CCCTG experience and our own pilot RCT experience.[32, 33] Nevertheless, we are accounting for up to 5% loss to follow-up in our sample size calculation.

Analysis of primary outcome

The BALANCE Trial will be conducted, analyzed and reported according to CONSORT guidelines, including analyzing patients in the groups to which they were assigned (intention-to-treat).[61] We will also include a per-protocol analysis. Inferences that 7 day treatment is non-inferior to 14 day treatment will be stronger if this finding is confirmed in both intention-to-treat and per protocol analyses.[62] We will also perform a modified intention-to-treat analysis (mITT), excluding patients that die before day 7 of treatment, given that these patients die prior to divergence in treatment assignment.[63] The primary analysis will examine whether 90-day survival is non-inferior in the 7 vs. 14 day treatment group, as determined by whether the 95.7% confidence interval excludes a 4% absolute decrement in survival.

Analysis of secondary outcomes

Mortality rates at other time points will be calculated in a similar manner to 90-day mortality. We hypothesize that mortality rates will be non-inferior with 7 days of treatment. Continuous secondary outcomes, including lengths of stay in ICU and hospital, durations of ventilation and vasopressor use, and antibiotic-free days will be compared by the Wilcoxon test.

Subgroup analyses

The main subgroup analysis will be based on the underlying infectious syndrome causing bacteremia (vascular catheter-related, pneumonia, pyelonephritis, intra-abdominal, skin and soft tissue, other identified source, or unknown source). We will also perform subgroup analyses based on ICU versus non-ICU enrolments, community- versus hospital-acquisition, Gram positive versus Gram negative infection, illness severity (APACHE II score of ≥25 vs. <25), and vasopressor use on day of randomization. We hypothesize that the non-inferiority of 7 versus 14 days of treatment will be consistent across these subgroups.

Frequency of analyses

Three interim analyses are planned for BALANCE at approximately 1/6 (600 patients), 1/3 (1200 patients) and 2/3 (2400 patients) of projected total enrollment; we will stop at the interim analysis for futility, inferiority or superiority using the O'Brien-Fleming spending function to generate adjusted confidence intervals for the primary endpoint, splitting the type I error at 0.0000007, 0.000452, 0.013, and 0.043 with 99.99%, 99.95% , 98.68% and 95.70% two-sided confidence intervals to give an overall type I error of 2.5%.[52, 53, 62] The Data Monitoring Committee (DMC) will be guided by a graphical plot indicating mortality differences which would meet futility, inferiority or superiority thresholds (Figure 2). We will perform both frequentist-based and Bayesian-based analyses for endpoints at the study's termination. Subgroup analyses will not be performed for the interim analyses.

Secondary Bayesian Analysis

Usual frequentist-based statistical analysis calculates the probability of obtaining data as extreme or more extreme than the observed data assuming the null hypothesis is true. Interpretations of clinical trials based on frequentist statistics using p-values and 95% confidence intervals can be challenging for clinicians for several

reasons. First, frequentist-based analyses usually consider each analysis in isolation, without an easy mechanism for quantitatively incorporating prior information and without a true measure of the probability of clinical benefit. Quantitative interpretation of new information from clinical trials can be especially challenging when either prior evidence or perception does not align with new evidence.[64-66] The interpretation of results of trials using a non-inferiority perspective can be additionally challenging; requiring interpretation of findings that may indicate non-inferiority, inferiority, superiority, equivalence, or an inconclusive estimate of effect.[67] Bayesian methods provide an alternative to null hypothesis statistical testing that allow quantification of evidence in favor of the null hypothesis, sequential testing, and comparison of strength of evidence across different studies.[68-71] In addition to our primary frequentist-based analysis of the primary 90-day mortality outcome, and secondary in-hospital and in-ICU mortality outcomes, we will additionally perform companion Bayesian analyses of each. This will be particularly informative should the study be either stopped for futility (a high likelihood of being unable to determine superiority, inferiority or non-inferiority at planned or feasible samples sizes), in order to directly estimate the *probability* of treatment benefits. We will combine the data from BALANCE with a non-informative prior to derive the posterior distribution based on which we will report the 95% Credible Intervals together with the probabilities of the difference in mortality between the two groups falling into the superiority, non-inferiority and inferiority region.

Steering Committee

The BALANCE Steering Committee is responsible for development and oversight of the BALANCE RCT procedures, rigorous and ethical trial conduct, funding applications, advising the principal applicants on responses to questions from ethics boards, the DMC or other stakeholders, and eventual interpretation and compilation of study results into reports, scholarly manuscripts and knowledge translation and exchange activities. With BALANCE expansion to additional countries, additional steering committee member(s) will be added from each country with 2 or more enrolling sites, and/or has obtained regional grant funding to support the trial.

Data Monitoring Committee (DMC)

The BALANCE DMC has multidisciplinary expertise in infectious diseases, critical care, randomized clinical trial (RCT) design and conduct, clinical epidemiology, biostatistics, interim analyses and early stopping rules. The BALANCE DMC charter (Appendix) is based on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter, and draws heavily from the charter and experience of prior landmark CCCTG studies.[58, 72] At each interim analysis the BALANCE PIs will provide the DMC with information on group characteristics, recruitment rates, adherence to treatment duration protocols, data completeness and accuracy, serious adverse events, outcome event rates and co-enrolment prevalence. Data will be presented in both one-group or two-group tables in a manner that will prevent unmasking of group allocation to the research team. The DMC will be able to request an independent (not involved in the BALANCE trial) methods centre statistician to provide the unmasked group allocation, according to the BALANCE charter (Appendix), should that be deemed necessary by the DMC to interpret the interim analysis.

Patient and Public Involvement

The CCCTG includes a Patient and Family Partnership Committee (https://cccrpf.ca/) that has been engaged throughout BALANCE development and conduct.

ETHICS AND DISSEMINATION

Ethics Approval

Ethics approval has been obtained from the research ethics board of each participating site, along with central mechanisms in the Canadian provinces of Ontario and Quebec and the Australian states of New South Wales and Victoria.

Consent

The research coordinator/site primary investigator will approach eligible patients (or their substitute decision-makers) as soon as their blood cultures are positive to obtain informed consent. Enrollment can be delayed at maximum to the 7th day of adequate antibiotic treatment. Critically ill patients are frequently unable to provide initial consent due to altered level of consciousness or comprehension, and thus the CCCTG has standard operating procedures to seek assistance from substitute-decision makers on behalf of patients. This process has been found feasible and acceptable to patients, decision-makers, and research ethics boards across Canada.[73-76] We will use this enhanced approach to consent, employing 13 previously described strategies distributed over three phases- preparation for the consent encounter, the consent encounter, and follow-up to the consent encounter.[77]

Expected Adverse Events

Short course (7 days) treatment duration could theoretically increase the risk of clinical treatment failure or relapse of the bloodstream infection or underlying focus of infection. Long course (14 days) treatment on the other hand may increase the chance of resistance to antibiotics, occurrence of new antibiotic-resistant infections, *Clostridioides difficile* infection, and adverse events like allergy, anaphylaxis, antibiotic related kidney injury, antibiotic related hepatitis, and other antibiotic related organ toxicity. Our systematic review suggests that clinical cure and survival are similar among bacteremic patients receiving shorter and longer treatment, but these represent underpowered, *post-hoc* subgroup analyses pooled from small trials.[33] Any observational study assessing the impact of duration of treatment on patient outcomes would be limited by survivor bias (patients must survive long enough to be classified as receiving longer treatment) and indication bias (clinicians select sicker patients to receive longer duration treatment). Hence, patients and clinicians require a sufficiently powered RCT dedicated to answering the question of whether shorter treatments are effective for patients with bloodstream infection.

Morbidity and mortality are expected among patients with bloodstream infections. Accordingly, mortality at 90 days, in ICU and in hospital are trial outcomes, as are episodes of C. *difficile* colitis, and antibiotic-related allergy and adverse effects. Outcomes will be reported as such, rather than as Serious Adverse Events (SAEs), Serious unexpected adverse reactions (UARs), or Suspected unexpected serious adverse reactions (SUSARs). These outcomes will be reported to the DMC at all interim analyses. We will closely monitor patient safety in the trial by recording the antimicrobial-related adverse events and serious unexpected adverse drug reactions, additionally interpreted by the Steering Committee and reported to the DMC at each interim analysis.

Knowledge Dissemination

A major mandate of the CCCTG is translating knowledge into practice and advancing the science of Knowledge Translation (KT) in critically ill hospitalized patients. The study has also been endorsed by the Association of Medical Microbiology and Infectious Diseases Canada Clinical Research Network (AMMI Canada CRN), the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) and the Australasian

Society for Infectious Diseases Clinical Research Network (ASID-CRN). The involvement of the knowledge users and leaders in these organizations will lead to rapid national and international knowledge dissemination.

DISCUSSION

Rationale for why the BALANCE Trial is urgently needed

The World Health Organization, U.S. Centers for Disease Control and Prevention, Association of Medical Microbiology and Infectious Diseases (AMMI) Canada, and Health Canada have all declared antimicrobial resistance a global threat to health, [1-4] based on rapidly increasing resistance rates and declining new drug development.[5-7] The highest rates of antimicrobial resistance occur in hospitals, and ICUs in particular, and it is crucial that we develop data-informed mechanisms to decrease antimicrobial use and selection pressure. The vulnerability of acutely ill patients, the complexity of their treatments, and the frequent uncertainty of their infectious syndromic diagnoses are all barriers to reducing antibiotic exposure in the ICU. It is very difficult to avoid initial broad-spectrum antibiotic treatment when acutely ill patients present with or develop definite or suspected infection. Multiple studies have demonstrated that early administration of effective antibiotics in the initial empiric window of antibiotic treatment is the strongest predictor of a favourable outcome in these patients. If empiric selections do not match the susceptibility profile of the isolated pathogen, the patient may be nearly twice as likely to die.[78, 79] Given that prevailing resistance rates are already high, broad-spectrum initial treatments are appropriate for many acutely ill patients. In contrast, it is much more feasible to reduce antibiotic use at the end of treatment courses, given that most patients may be treated longer than necessary, and excessive antibiotic durations are a top contributor to inappropriate antibiotic in all healthcare sectors.[7, 11-13] Shorter duration treatments have been demonstrated to be non-inferior to longer duration treatments for a range of infections.[11, 19] If BALANCE confirms this finding among critically ill patients with bacteremia it could result in effective but shorter prescribing practices for these patients. Shortening treatment durations should also reduce other adverse events, including *C. difficile* infections, and generate an estimated annual direct antimicrobial cost-savings of CAD$678-$798 million across North America and CAD$1.4-1.6 billion across Europe.[80]

Rationale for studying fixed duration therapy rather than individualized durations of treatment

Ideally antibiotic treatment duration should be individualized, and each patient should receive exactly as much antibiotic treatment as needed until their infection is cured, and not longer.[24, 81] However, an RCT based on a clinical stopping rule may not be feasible in acutely ill patients, since there are currently no proven accurate measures of cure versus persistent infection. The challenge in diagnosing and monitoring infection in ICU has sparked studies of novel biomarkers to guide antibiotic treatment duration.[43, 47] One biomarker, procalcitonin, has been used successfully to reduce average treatment durations in sepsis.[43] However, follow-up meta-analyses have indicated that the bacteremic subgroups in PCT trials have tended to receive prolonged treatment durations,[82] perhaps because of high non-adherence rates to algorithm-guided treatment.[47] Therefore, we have designed a randomized trial of fixed shorter versus longer duration antibiotic therapy, guided by our preparatory studies, as the most easily transferrable result to immediately inform clinical practice. This approach has been successful in more than two dozen randomized controlled trials of infectious diseases that are potentially complicated by bacteremia.[19] However, we appreciate the future promise of biomarkers to add nuance to individualized treatment decisions, and so in a nested substudy, we will measure procalcitonin levels and trajectory in both treatment arms to see if it could provide incremental value.[61]

TRIAL STATUS

The BALANCE pilot RCT was launched in Oct. 2014 at the central study site, Sunnybrook Health Sciences Centre, expanded to include a total of 10 CCCTG sites across Canada, and served as a successful vanguard for this BALANCE main RCT. An additional 26 Canadian sites have joined BALANCE, for a total of 36 Canadian sites in 6 provinces. A parallel BALANCE pilot RCT on medical and surgical wards was launched in October 2016 at a subset of 6 BALANCE sites, which confirmed the feasibility of recruitment and protocol adherence on non-ICU wards,[33] and enabled hospital wide expansion; approximately half of sites have now opted for hospital-wide enrolments. We have expanded BALANCE internationally to include sites in Australia (6), New Zealand (10), Saudi Arabia (2), Israel (1) and the United States (2). Therefore, there are currently 57 sites enrolling patients into BALANCE, and with continued expansion we anticipate approximately 70 sites prior to study completion (anticipated for 2022-23). The BALANCE DMC conducted the first interim analysis (n=600) on September 30, 2019 and recommended continuing enrolment. As of Feb 13, 2020, a total of 1447 patients have been recruited into BALANCE, and data from the first 1200 patients is being analyzed for the DMC review of the second interim analysis.

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Contributorship Statement

ND and RF conceived the research question. ND and RF designed the study, with crucial input from AR, RP, YA, DC, RH, SM, JM, RP, SR, BR and YS. ND and RF drafted the manuscript with important revisions provided by AR, RP, YA, DC, RH, SM, JM, RP, SR, BR and YS.

Competing Interests

None.

Patient consent for publication

Not required.

Ethics approval:

The BALANCE RCT is approved by Research Ethics Boards at all participating sites, as well as regional approval by corresponding State and Provincial ethics boards, including Clinical Trials Ontario.

Provenance and peer review: This manuscript has been reviewed by the grants and manuscript review committee of the Canadian Critical Care Trials Group. Thank you to Anand Kumar. The CCCTG is supported by a CIHR Team Grant.

Open access:

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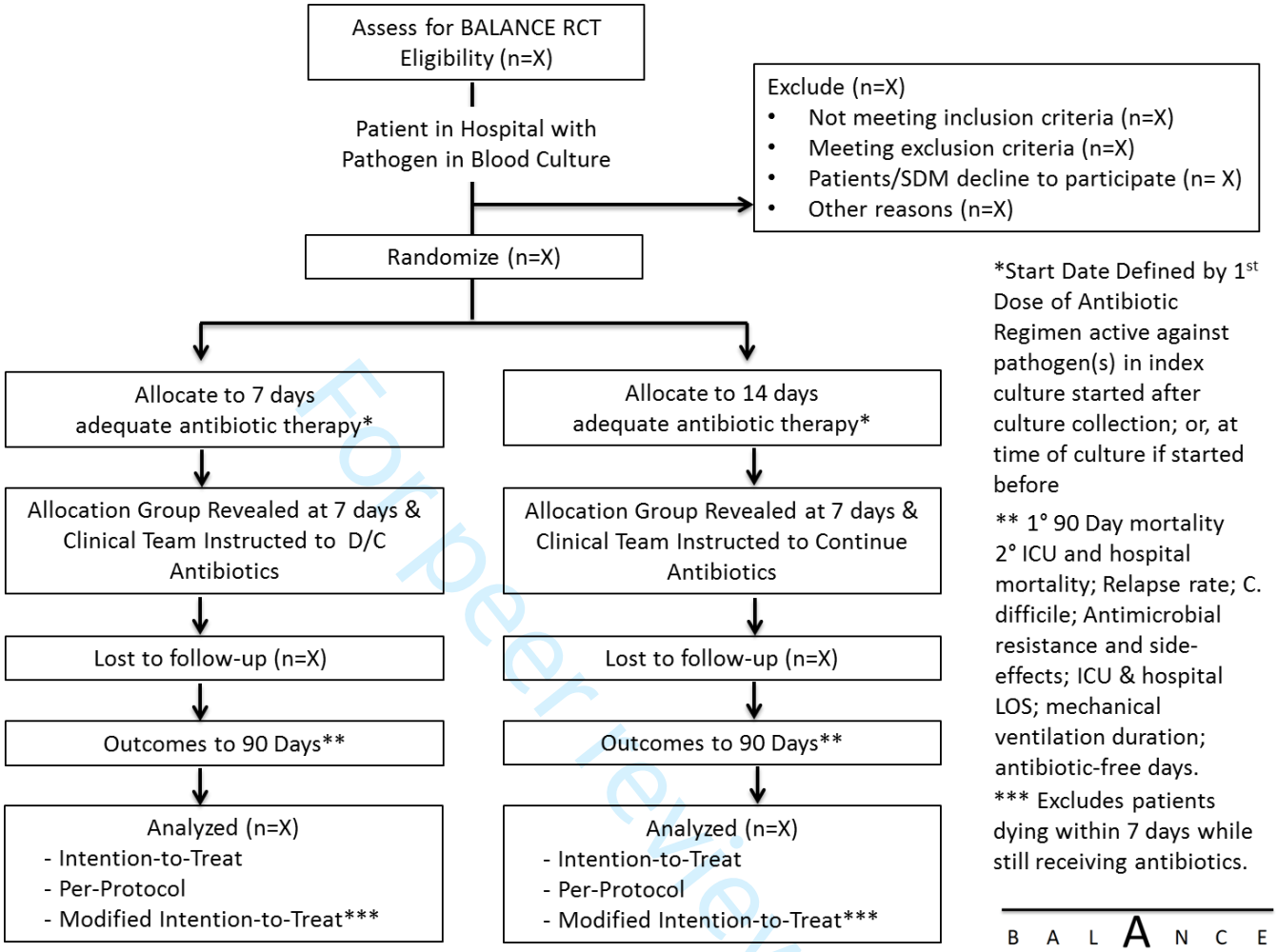
FIGURE LEGENDS

Figure 1: BALANCE Pilot RCT Intervention Flow Diagram.

Figure 2: Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates at the first interim analysis (n=600). Similar figures are available to the Data Monitoring Committee for subsequent interim analyses.

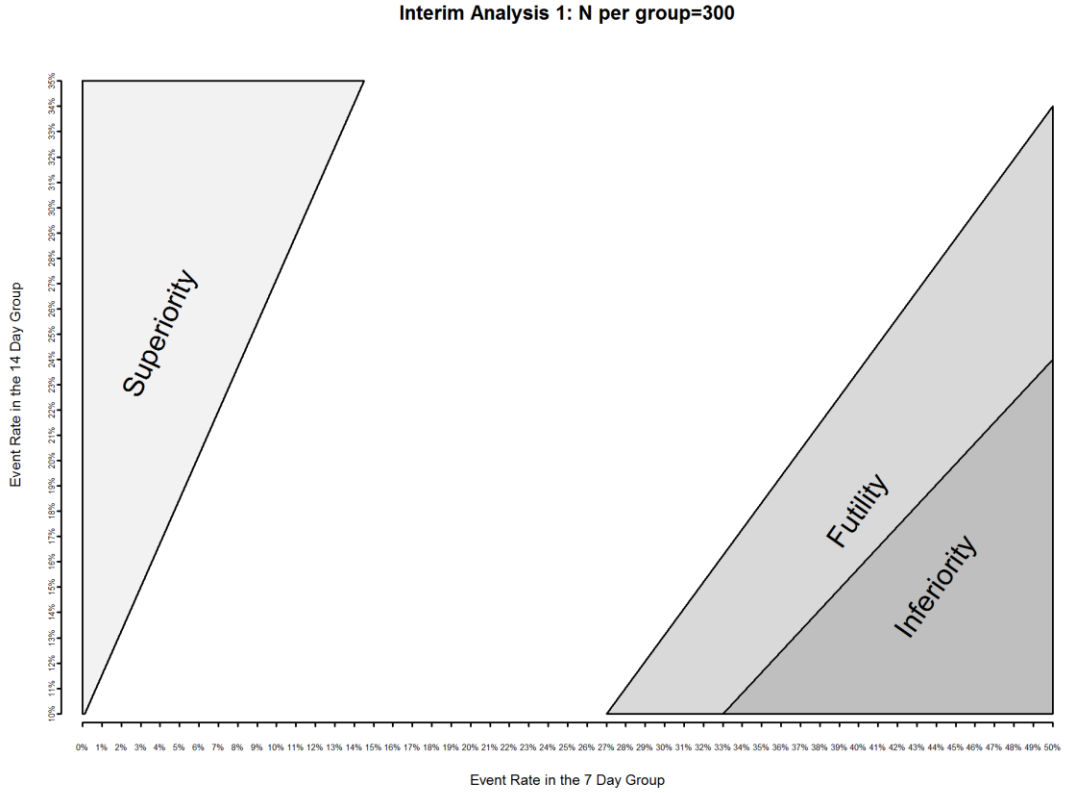


*Start Date Defined by 1st Dose of Antibiotic Regimen active against pathogen(s) in index culture started after culture collection; or, at time of culture if started before

** 1° 90 Day mortality 2° ICU and hospital mortality; Relapse rate; C. difficile; Antimicrobial resistance and side-effects; ICU & hospital LOS; mechanical ventilation duration; antibiotic-free days.

*** Excludes patients dying within 7 days while still receiving antibiotics.

B A L A N C E



Version date: April 11, 2018

Title:	Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) Randomized Controlled Trial
Protocol ID:	0796
Registration Number:	clinicaltrials.gov [NCT03005145]
Sponsor:	Sunnybrook Research Institute, Toronto, ON

BALANCE

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Data Monitoring Committee Charter

BALANCE Organization in Relation to Data Monitoring Committee:

The BALANCE Data Monitoring Committee (DMC) charter is based on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter, and draws heavily from the charter and experience of prior landmark Canadian Critical Care Trials Group studies.[1, 2] The BALANCE DMC charter outlines terms of reference for roles, responsibilities, and relationships of the DMC to the co-principal investigators (Dr. Rob Fowler, Dr. Nick Daneman), the study coordinator (Dr. Asgar Rishu), and the BALANCE steering committee (Dr. Rob Fowler, Dr. Nick Daneman, Dr. Asgar Rishu, Dr. Deborah Cook, Dr. Rick Hall, Dr. John Muscedere, Dr. Ruxandra Pinto, Dr. Steven Reynolds, Dr. Yaseen Arabi, Dr. Yahya Shehabi, Dr. Benjamin Rogers), the trial statistician (Dr. Ruxandra Pinto), investigators, trial participants, institutional research ethics boards (REBs), sponsor (the Canadian Critical Care Trials Group), and primary funding agency (The Canadian Institutes of Health Research (CIHR)).

Nominated Data Monitoring Committee Membership:

The BALANCE DMC has multidisciplinary expertise in infectious diseases, critical care, randomized clinical trial (RCT) design and conduct, clinical epidemiology, biostatistics, interim analyses and early stopping rules. The Nominated BALANCE DMC members include:

Name	Institution	Relevant Expertise
Dr. Roger Spragg	University of California, San Diego School of Medicine, San Diego, USA	Dr. Spragg has experience in the conduct and oversight of multicentre trials involving critically ill patients and will be the BALANCE DMC Chair
Dr. Taylor Thompson	Harvard University, Massachusetts General Hospital, Boston, USA	Dr. Thompson is the DMC critical care medicine content expert.
Dr. Steve Opal	Brown University, Rhode Island Hospital, Rhode Island, USA	Dr. Opal the DMC infectious diseases context expert.
Dr. David Schoenfeld	Harvard School of Public Health, Boston, USA	Dr. Schoenfeld biostatistician content expert.

Version date: April 11, 2018

Overview of Data Monitoring Committee Responsibilities:

The primary ongoing responsibilities of the DMC will be independent review of reports received directly from the BALANCE Methods Center (Sunnybrook Research Institute in collaboration with CLARITY Research, McMaster University) regarding:

1. Recruitment rates
2. Adherence rates to treatment duration protocols
3. Data completeness, accuracy and timeliness
4. Serious adverse events
5. Outcomes event rates
6. Co-enrolment prevalence, noting specific trials in which more than 20 BALANCE patients are enrolled

Sample Size Calculation:

The primary analysis will assess whether 7 days of antibiotic treatment is associated with non-inferior 90-day survival rates in comparison to 14 days of antibiotic treatment for critically ill patients with bacteremia. We require 1,686 patients per arm to establish a non-inferiority margin of 4% absolute decrement in survival (baseline mortality 22%,[3] 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 1.024)[4, 5] for a total requirement of 3626. Recent landmark trials in critically ill patient populations with similar baseline mortality rates have used 4% as a non-inferiority margin;[6, 7] the U.S. FDA has recommended a similar margin for analogous industry-sponsored trials.[8] The PneumA study of 8 vs 15 day treatment for VAP used a non-inferiority margin of 10%,[9] but we believe this to be inappropriately high for the outcome of survival; a non-inferiority margin of <4% would render a trial unfeasible.[8] We will aim to enroll approximately 2/3 of these patients in Canadian intensive care units (ICUs), and the remaining 1/3 of patients in international ICUs.

Interim Analyses:

Three interim analyses are planned for BALANCE at one-sixth, one-third and two-thirds of projected total enrollment. Non-inferiority trials with mortality end-points have traditionally been less likely to establish "early stopping rules" than superiority trials. This is in part, due to concern that mortality-based margins of difference should be very low and that early stopping likely reduces confidence that an upper margin of difference has been excluded.[4, 5] However, we will consider stopping at the interim analysis for superiority, using the O'Brien-Fleming spending function to generate adjusted confidence intervals for the primary endpoint, splitting the type I error at $7x10^{-7}$, 0.0005, 0.0132 and 0.043, with 99.99%, 99.95% and 95.70% two-sided confidence intervals to give an overall type I error rate of 2.5%.[4, 5] We have inflated the sample size to account for these 3 analyses in addition to the final analysis. We will also consider stopping at

the interim analyses on the basis of inferiority or futility, and have provided guidance for the DMC (appendix).

After each interim analysis, the BALANCE DMC will recommend either:

1. To consider continuing patient enrolment, or
2. To consider suspending enrolment until careful review by the principal investigators and steering committee, or
3. To gather more information before a recommendation can be made, or
4. To consider terminating enrolment.

Responsibilities of the Data Monitoring Committee:

1. To advise the principal investigators and steering committee about the conduct of the trial and integrity of the data, so as to protect the validity of the trial.
2. To ensure the overall safety of trial patients by protecting them from avoidable harms. The DMC should not be expected or accountable for reviewing adverse events by routine real-time transmission.

Relationship of the Data Monitoring Committee to the Principal Investigators and Steering Committee:

1. The DMC is arms-length and independent of the principal investigators and steering committee in operating and formulating recommendations, but is supportive of the aims and methods of the trial.
2. The DMC serves in an advisory role to the principal investigators and steering committee.
3. The principal investigators and steering committee receive BALANCE DMC recommendations under advisement.
4. The DMC, principal investigators and steering committee work collaboratively to ensure rigorous, valid, safe and timely conduct of the trial.

Initial Responsibilities of the Data Monitoring Committee:

1. Review the BALANCE protocol and case report forms.
2. Review, discuss, debate and approve the Methods Center operations.
3. Review, discuss, debate and approve the mechanisms for transmitting serious adverse event information to the DMC.
4. Establish guidelines for calling emergency meetings of the DMC.
5. Propose a schedule for subsequent DMC meetings, acknowledging that the DMC Chair may call for a meeting of the DMC at any time, as may the principal investigators.
6. Approve or refine template tables provided by the principal investigators and trial statistician for future review at the interim analyses.

7. Disclose any conflicts of interest such as: current honoraria or consultancies, involvement in regulatory issues relevant to the study drugs, investment in these or competing drugs, involvement with the sponsor, enrolment of patients in the trial, strong prior beliefs constituting intellectual conflict, other dual loyalties etc.

Ongoing Responsibilities of the Data Monitoring Committee:

The BALANCE DMC is responsible for helping to ensure that BALANCE patients are not exposed to unnecessary or unreasonable risks and that the trial is conducted according to the highest scientific and ethical standards.

Therefore, the BALANCE DMC will:

1. Review data from the 3 planned interim analyses provided by principal investigators and steering committee, via the Methods Centre.
2. Alert the principal investigators and steering committee about scientific, procedural or ethical concerns emerging from the interim analyses and/or final analyses.
3. Provide recommendations to facilitate rigorous, timely completion of the trial.
4. Comment on any new relevant external published data (provided by the principal investigators and steering committee) that may impact on patient safety or the efficacy of BALANCE.
5. Provide recommendations for adjustment of sample size or consideration of trial termination.
6. Read and provide suggestions for manuscript publications before submission.
7. Be acknowledged in the main report, unless requested otherwise.

Timing of Data Monitoring Committee Meetings:

The DMC will meet virtually, or if necessary in person:

1. Once initially to discuss the protocol and analysis plans, the DMC Charter, template tables, and to clarify any aspects with the principal investigators and steering committee.
2. At the first interim analysis.
3. At the second interim analysis.
4. At the third interim analysis.
5. At the end of the trial, to allow the DMC to discuss the final data with the principal investigators and steering committee to advise on data interpretation.
6. As needed, by teleconference.

Responsibilities of the Principal Investigator, Study Coordinator and Steering Committee to the Data Monitoring Committee:

1. The principal investigators and study coordinator will provide the protocol and CRFs to the DMC before their initial meeting.

2. The principal investigators and study coordinator will provide preliminary template reports of site enrolment, patient recruitment rates, patient consent rates, treatment duration protocol adherence rates, data management templates (data completeness, accuracy, timeliness and query resolution), CIHR reports, 3 interim and final analyses (baseline characteristics, primary and secondary outcomes, and serious adverse events).
3. The principal investigators and study coordinator will modify these template reports if requested, and will use to create tables for the 3 interim analyses.
4. For baseline characteristics and outcomes, the (blinded) BALANCE statistician will provide to the (blinded) DMC, data according to group A and B, including baseline characteristics (age, sex, APACHE II score, source of bacteremia, etc.), primary and secondary outcomes and serious adverse events.
5. The principal investigators and study coordinator and biostatistician will ensure that DMC members remain blinded to allocation.
6. The principal investigators and study coordinator will provide the results of any new relevant external published data for DMC consideration.

Three-Part Structure of Data Monitoring Committee Meetings:

1. First, an open session will be held with the principal investigators and study coordinator and statistician. The purpose will be to review accrual, data timeliness and quality, completeness of follow-up and adjudication, serious adverse events, problems with centres, and any proposals for changes in the trial protocol or duration. In addition, the principal investigators will report any new external evidence (especially results from other relevant ongoing studies) that bear on the conduct of the trial.
2. Second, a partially closed session will be held between the DMC and the statistician to review the primary and secondary outcomes separated by group and presented in a blinded fashion (group A and group B). These data will not be available to the principal investigators, study coordinator, steering committee, or investigators except as authorized by the DMC Chair. The principal investigators will receive data in aggregate form.
3. Third, a totally closed session for just the DMC members will be held to discuss the current results, decide on recommendations, and draft comments and recommendations for 3 reports.

Potential Unblinding of the Data Monitoring Committee:

1. During the closed session, if the DMC deems it crucial to their interpretation of the data, the DMC will request unblinding themselves to group assignment without informing the investigative team of this need.
2. A request to unblind will be very unlikely because the general scientific philosophy of modern pragmatic trials is to not unblind until completion, and this is particularly true for BALANCE which involves different two durations of antibiotic treatment that are

both a component of contemporary clinical practice, and the specific antibiotic medications, dose and route of delivery are all chosen by the treating team.
3. The request to unblind would need to be extreme, unambiguous and unanimous. The signal would be need to derive from compelling trial results such as a significantly increased risk of mortality in one arm.
4. To achieve unblinding the database manager will be authorized to provide immediate unblinding information to the DMC chair, including during a DMC meeting. An independent statistician will redo analyses if requested. The principal investigators, study coordinator and statistician will not review unblinded results, and will not be informed of the DMC decision to unblind the results unless the DMC makes a recommendation to consider terminating enrolment at an interim analysis, or at the end of the study.

Discussions of the Data Monitoring Committee:

1. Efforts should be made for the DMC to reach unanimous recommendations.
2. The role of the Chair is to summarize discussions and encourage consensus.
3. Before making any recommendations, the DMC should consider the ethical, scientific, statistical, and practical implications for the trial.

Minutes of Data Monitoring Committee Meetings:

1. Within a week of each DMC meeting, the Chair, with administrative assistance provided, will generate minutes of the open and closed sessions of the meeting.
2. The minutes will contain the major points of discussion, recommendations made, and any additional information requested for future meetings.
3. Minutes of the open session of the meeting will be for the principal investigators and study coordinator.
4. Minutes of the closed session will be for the DMC members only (until the trial is complete).

Reports of the Data Monitoring Committee:

1. After each DMC meeting, the Chair will report to the principal investigators and study coordinator. Each meeting will be summarized in 2 reports (1 short report suitable for Investigators, the CCCTG, REBs and CIHR) and 1 more detailed report for the principal investigators, study coordinator and statistician).
2. The principal investigators will circulate the DMC's short and long reports to the appropriate individuals. It is the responsibility of the principal investigators to notify the investigators, the CCCTG and participating REBs of any recommendations about trial modification or enrolment suspension or termination.

3. If the DMC recommends to continue enrolment in the trial following an interim analysis, no other information shall be provided to the principal investigators and study coordinator.
4. If the DMC recommends to consider suspending enrolment of the trial until careful review by the principal investigators and study coordinator; or whether more information is required before a recommendation can be made, or whether to consider terminating enrolment, the DMC will provide a full report of the rationale to the principal investigators, study coordinator and statistician.

Conflict Resolution:

1. DMC recommendations are advisory to the trial principal investigators, steering committee, and by extension other sponsors of the trial.
2. In the event that the principal investigators and/or study coordinator disagree with the DMC recommendation(s) to modify or to terminate the trial, a third party arbitrator may be called upon.
3. A third party arbitrator, selected by both parties, will be an individual possessing the requisite knowledge and experience (ideally both methodologic and clinical) to make a final decision.
4. The selection of the third party arbitrator will be made by mutual consent of both the principal investigators and the DMC Chair.

Confidentiality:

1. It is the duty of each member of the DMC to protect the confidentiality of the trial and the results of monitoring.
2. The members of the DMC acknowledge that the data emerging from this trial are the collective property of the principal investigators and study coordinator and investigators.
3. DMC members will not have the right to present or publish data or learnings from this trial anywhere without the explicit permission of the principal investigators and study coordinator, and not until after the trial is complete.

Reporting on the Data Monitoring Committee:

1. A brief summary of the roles, responsibilities, and recommendations of the DMC will be included in the trial manuscript.
2. DMC members will be invited to read and comment on the trial manuscript, including any statement related to the DMC.
3. DMC members will be named and their affiliations listed in the trial manuscript, unless requested otherwise.
4. Potential publications about research oversight coauthored by any of the DMC members will be deferred until the main manuscript is published.

Version date: April 11, 2018

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Appendix: **Contextual and Analytical Considerations for Stopping Considerations for each Interim Analysis of the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) Randomized Clinical Trial.**

Stopping Guidelines for Inferiority

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled) we explore the possible event rates for the 7-day group that will cause us to stop the trial for inferiority. We propose to stop the trial for inferiority of the 7-day group in comparison to the 14-day group, if the lower limit for a confidence interval for the difference between the 7-day and 14-day event rate is larger than 4% (the non-inferiority margin of error for the trial). To maintain and overall 5% type I error, at each interim analysis the confidence interval is based on the O'Brien-Fleming significance level α, corresponding to $z=Z_{OBF}*\text{sqrt}(N/n)$ where N=total sample size, n=sample size at the interim analysis, and $Z_{OBF}=2.024$

We varied the event rate in the 14-day group and used simulation to estimate the event rate in the 7-day group for which we would have enough power to determine that the event rate in the 7-day group is inferior to the 14-day group.

1. First we simulated data for the 7-day group and 14-day group from binomial distributions with event rates higher in the 7-day group.
2. Next, we calculated the confidence interval around the difference in the event rates in the 7- versus 14-day group
3. Then, we calculated the power as the proportion of simulations for which the lower confidence interval exceeded 4% (the non-inferiority margin of error for the trial).

The lowest event rate for which the power is at least 80% is the one that provides a guideline of when the trial would be stopped for inferiority.

The Figures operationalize the inferiority-based stopping guidelines for the trial at each of the three interim analyses. If the 7-day and 14-day mortality rates fall within the darkest grey shaded area, then we should consider stopping the trial for evidence of inferiority of the 7-day group.

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Stopping Guidelines for Superiority

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled), we explored the possible event rates for the 7-day group that will cause us to stop the trial for superiority. This is similar to the approach taken for the inferiority-based stopping guidance. We propose to stop the trial for superiority of the 7-day group in comparison to the 14-day group, if the upper limit for a confidence interval for the difference between the 7-day and 14-day event rate is lower than 0% (no-difference). At each interim analysis the confidence interval is based on the O'Brien-Fleming significance level α, corresponding to $z=Z_{OBF}*\text{sqrt}(N/n)$ where N=total sample size, n=sample size at the interim analysis, and $Z_{OBF}=2.024$

We varied the event rate in the 14-day group and used simulation to estimate the event rate in the 7-day group for which we would have enough power to determine that the event rate in the 7-day group is superior to 14-day group.

1. First we simulated data for the 7-day group and 14-day group from binomial distributions with event rates lower in the 7-day group.
2. Next, we calculated the confidence interval around the difference in the event rates in the 7- versus 14-day group.
3. Then, we calculated the power as the proportion of simulations for which the upper confidence interval is lower than 0%.

The lowest event rate for which the power is at least 80% is the one that provides a guideline of when the trial would be stopped for superiority.

Figures 1-3 operationalize the superiority-based stopping guidance for the trial at each of the three interim analyses. If the 7-day and 14-day mortality rates fall within the light grey shaded area then we should consider stopping the trial for evidence of superiority of the 7-day group.

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Stopping Guidelines for Futility

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled), we also explored the possible event rates for the 7-day group that will cause us to considering stopping the trial for futility, using the principle of conditional power. Conditional power is the probability that the final result will be statistically significant given the interim observed data, incorporating specific assumptions about the future data. Conditional Power was simulated for the three interim analyses under a range of conditions.

In the simulation, at the interim analysis, we assumed higher event rates (i.e. 90-day mortality) in the 7-day treatment group versus the 14-day group. For each of these event rates we can simulate samples for the remaining (future) data as follows:

1. The future event rate in the 14-day group was simulated with various scenarios:
    a. Default scenario: the same as assumed in the original sample size estimation (22% 90-day mortality); or,
    b. Alternative scenario: the same as observed at the interim analysis.
2. The future event rate in the 7-day group was simulated with various scenarios as well:
    a. Default scenario (least likely to stop early): the future event rate in the 7-day group will be the same as the future event rate in the 14-day group
    b. Alternative scenario (more likely to stop early): the future event rate in the 7-day group will be at the lower 95% confidence interval for the 7-day treatment group at the interim analysis.
    c. Alternative scenario (most likely to stop early): the future event rate in the 7-day group will be the same as the observed event rate at the interim analysis in the 7-day group.

Eventually, with a strong recommendation from the BALANCE Steering Committee and oversight of the Canadian Critical Care Trials' Group, we chose the most conservative scenario to consider for futility-based stopping considerations, namely when future data is simulated with an event rate that is the same for both groups and the same as in the original sample size calculation (1a and 2a above).

3. For each simulation, to maintain the overall type I error as stipulated by the O'Brien-Fleming stopping rule, a two-sided 95.7% confidence interval for the 7-day versus 14-day difference was calculated.
4. The conditional power is the percentage of simulations for which the upper limit of the confidence interval for the difference in 90-day mortality between 7-day group versus 14-day group is less than 4% (the non-inferiority margin of error for the trial).

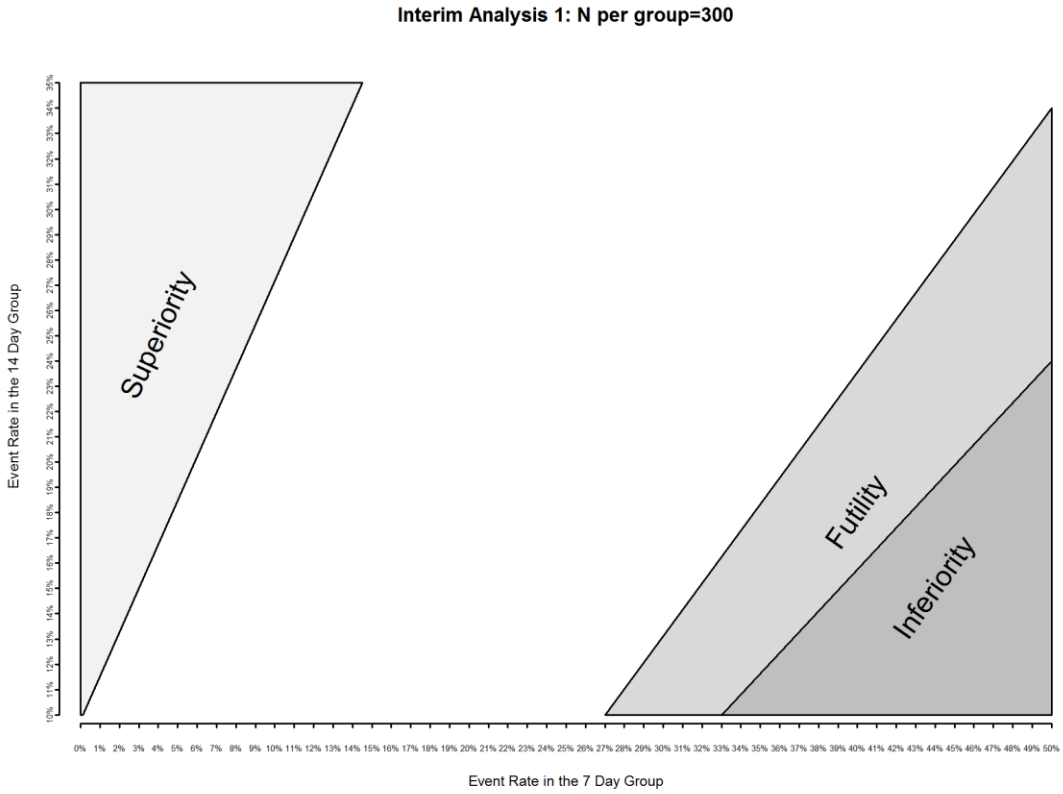
5. We specified a conditional power of ≤ 10% as a threshold for stopping the trial for futility, based on common and conservative practice from the existing medical literature.
6. We then calculated the event rate in the 7-day group at the interim analyses that will lead to a conditional power of 10% or less.

We repeated the above steps for each of the 3 interim analyses in order to derive futility stopping guidance graphs for the trial (Figures 1-3). If the event rates for the 14-day and 7-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for futility. However, given that such an interim analysis finding does not lead to an interim conclusion of a high probability of better or worse outcomes for either treatment group, and that by enrolling a greater number of patients in a non-inferiority trial, generally greater certainty will emerge on treatment effects from each group, guidance from the DMC on the issue of stopping on the basis of futility should be only positioned a consideration, and not a strong recommendation.

This position is in distinction to guidance for stopping on the basis of inferiority or superiority - where there may be a substantial clinical and statistical inference that one treatment is inferior or superior to the other. Interim analysis results indicating that there is a chance of futility (in finding that 7-days treatment is non-inferior to 14-days) does not imply a benefit to one or the other treatment strategies. Stopping the trial with fewer enrolled patients will always be associated with greater uncertainty in any true treatment-related difference in mortality than if the trial continued. An argument can be made that non-inferiority trials should not be considered for stopping on the basis of futility as doing so may not allow for effective use of the data from contributions of those patients already enrolled in the trial, and be of least value to clinicians and future patients.

Version date: April 11, 2018

Figure 1. Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 300.



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

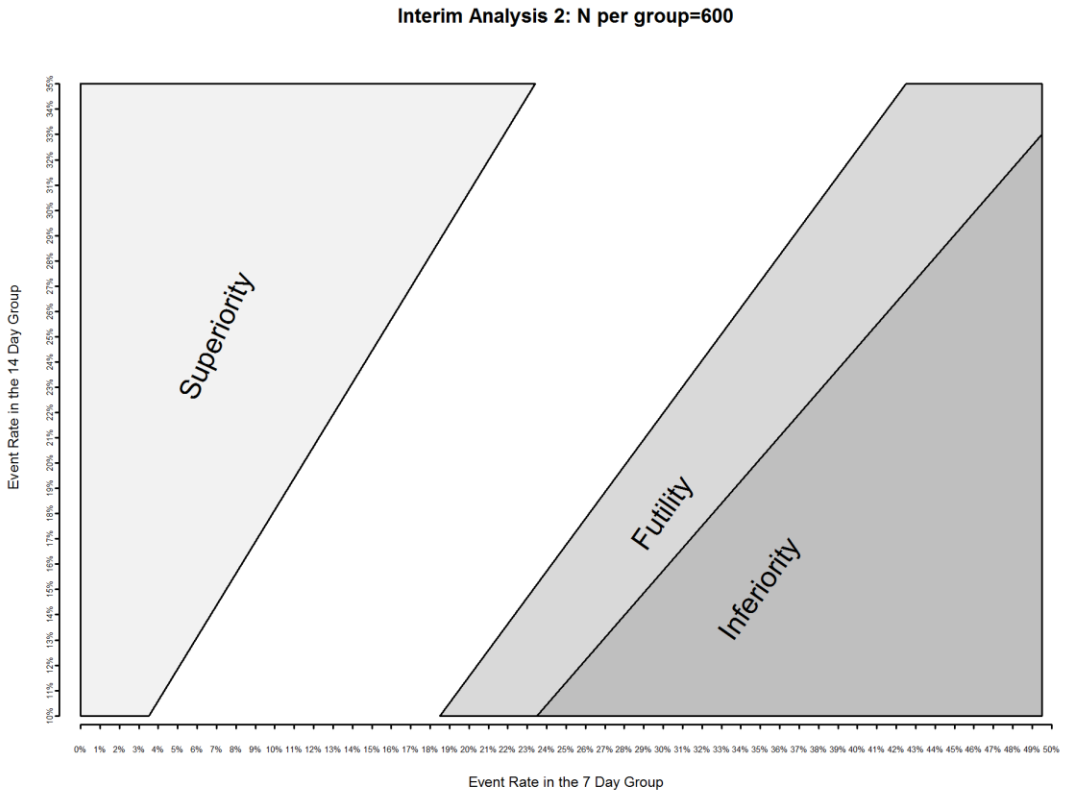
If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

Version date: April 11, 2018

Figure 2: Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 600



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

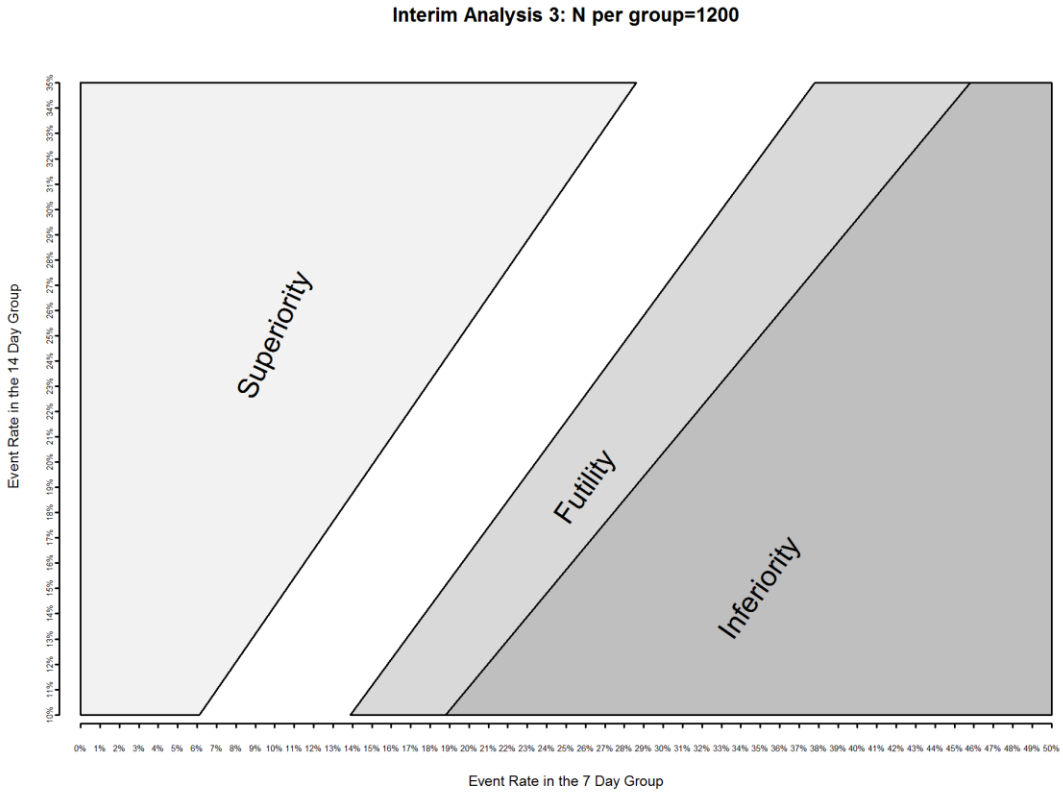
If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

Version date: April 11, 2018

Figure 3: Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 1200



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

Version date: April 11, 2018

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Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) randomized clinical trial: study protocol

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Bacteremia **A**ntibiotic **L**ength **A**ctually **N**eeded for **C**linical **E**ffectiveness (**BALANCE**) randomized clinical trial: study protocol

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ABSTRACT

Introduction Bloodstream infections are a leading cause of mortality and morbidity; the duration of treatment for these infections is understudied.

Methods and Analysis We will conduct an international, multicentre RCT of shorter (7 days) versus longer (14 days) antibiotic treatment among hospitalized patients with bloodstream infections. The trial will include 3626 patients across 60 hospitals and 6 countries. We will include patients with blood cultures confirming a pathogenic bacterium after hospital admission. Exclusion criteria will include patient factors (severe immunosuppression), infection site factors (endocarditis, osteomyelitis, undrained abscesses, infected prosthetic material) and pathogen factors (*Staphylococcus aureus, Staphylococcus lugdunensis, Candida*, and contaminant organisms). We will leave the selection of specific antibiotics, doses and route of delivery to the discretion of treating physicians; no placebo control will be used given the diversity of pathogens and sources of bacteremia. The intervention will be assignment of treatment duration to be 7 versus 14 days. We will minimize selection bias via central randomization with variable block sizes, with concealed allocation until day 7 of adequate antibiotic treatment. The primary outcome is 90-day survival; we will test whether 7 days is non-inferior to 14 days of treatment, with a non-inferiority margin of 4% absolute mortality. Secondary outcomes include hospital and ICU mortality, relapse rates of bacteremia, hospital and ICU length of stay, mechanical ventilation and vasopressor duration, antibiotic-free days, *C. difficile* infection, antibiotic allergy and adverse events, and colonization/infection with antibiotic-resistant organisms.

Ethics and dissemination The study has been approved by the Ethics review board at each participating site. Sunnybrook Health Sciences Centre is the central ethics committee. We will disseminate study results via the Canadian Critical Care Trials Group and other collaborating networks, to set the global paradigm for antibiotic treatment duration for non-Staphylococcal Gram positive, Gram negative and anaerobic bacteremia, among patients admitted hospital.

Trial registration number The BALANCE Trial was registered at www.clinicaltrials.gov (registration number: NCT03005145)

Keywords: bacteremia, bloodstream infection, antimicrobial, treatment duration, mortality, antimicrobial stewardship, intensive care

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Strengths and Limitations of this Study

- The BALANCE study is the largest randomized clinical trial ever conducted among patients with bloodstream infection, and should set the paradigm for antibiotic treatment duration for these patients.
- BALANCE will provide generalizable results by including a wide array of bloodstream pathogens and underlying sources of infection, examining both critically and non-critically ill hospitalized patients, and including sites across 6 countries with varying baseline antibiotic resistance rates
- If 7 days of antibiotic treatment is non-inferior to 14 days of treatment, this could lead to reductions in global antibiotic use, costs and antibiotic-related complications, including adverse events, *C. difficile* and antibiotic resistance.
- The diversity of pathogens and underlying infections that cause bloodstream infection render placebo controls infeasible. We will minimize bias through central randomization, allocation concealment until day 7, an objective primary outcome, and blinded adjudication of other outcomes such as relapse and secondary infections with antibiotic resistant organisms.

INTRODUCTION

There are more than 600,000 episodes of bloodstream infection per year in North America, and more than 1,200,000 episodes in Europe.[1] These infections affect 15% of critically ill patients, result in prolongation of hospital stay, excess health care costs, and a substantial mortality. [2-5]

Hospitals, and intensive care units (ICUs) in particular, are the location of greatest antimicrobial pressure; however, audits indicate that 30-50% of antibiotic use in acute care and critical care settings are unnecessary or inappropriate[6-8] and leads to avoidable costs and complications. Antibiotics are among the most common cause of serious adverse drug events,[9] which occur in up to 5-10% of inpatient recipients.[10] Excessive durations of antibiotic therapy are the largest contributor to inappropriate antibiotic use in acute care hospitals, long-term care facilities, and ambulatory clinics.[7, 11-13] Discontinuing antibiotics after achieving clinical cure can potentially reduce the burden of adverse events, *Clostridium difficile* infections, and selection of antibiotic resistant pathogens.[14 15]

Meta-analysis of randomized clinical trials has demonstrated that shorter duration antibiotic treatment is as effective as longer duration treatment for a range of mild to moderate infections.[16] Even in critically ill patients with ventilator-associated pneumonia, mortality rates and relapse rates were non-inferior among the 402 patients randomized to receive shorter (8 day) versus longer (15 day) courses of antibiotics.[17] However, similar high-grade evidence is lacking for the treatment of critically ill patients with bloodstream infections.[2, 18, 19] One recent study has examined 7 versus 14 days of treatment for bacteremia in non-critically ill patients, and has suggested that this may be a safe approach, but used a wide non-inferiority margin, and was limited to infections with Gram negative pathogens.[20, 21] Specific guidelines for treatment durations exist for pneumonia,[22, 23] intra-abdominal infection,[24] catheter-related bloodstream infection,[25] pyelonephritis,[26] and skin and soft tissue infection[27] but no guidelines exist for the optimal duration of treatment for the subset of bacteremic patients.

We have performed a systematic review of the existing literature,[19] practice surveys of infectious diseases and critical care physicians,[28, 29] a single-centre[30] and multicentre observational study,[31] which collectively identified gaps in current evidence, extensive practice variation, and equipoise for a randomized trial comparing shorter (7 days) versus longer (14 days) antibiotic treatment durations for bloodstream infections. Through the Bacteremia Antibiotic Length Actually Needed For Clinical Effectiveness (BALANCE) pilot randomized clinical trial (ClinicalTrials.gov, identifier: NCT02261506) we documented the feasibility of this trial design among 115 patients in intensive care units (ICUs), thereby providing a vanguard for the BALANCE main trial.[32] We have subsequently confirmed the feasibility of enrolling patients on non-ICU wards in a parallel pilot RCT (clinicaltrilas.gov identifier NCT02917551), facilitating expansion of the BALANCE trial to include non-ICU patients.[33]

The primary aim of the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) randomized clinical trial will be to determine whether 7 days (as compared to 14 days) of adequate antibiotic treatment is associated with non-inferior 90-day survival for hospitalized patients with bacteremia.

METHODS AND ANALYSIS

Study Design

We will conduct a multicentre randomized concealed allocation trial of shorter duration (7 days) versus longer duration (14 days) antibiotic treatment for patients with bacteremia admitted to hospital.

Setting

The BALANCE Trial (balance.ccctg.ca) is currently being conducted across a geographically and clinically diverse spectrum of ICUs and hospitals in Canada (currently 36 sites), Australia (6 sites), New Zealand (10 sites), United States (2 sites), Saudi Arabia (2 sites), and Israel (1 site). We commenced enrolment at the central study site, Sunnybrook Health Sciences Centre in Toronto, Canada at the beginning of the vanguard pilot (October 2014) and then added each additional site, in a staggered fashion after ethics approval, contract and site initiations were accomplished. We continue to welcome new sites into BALANCE, and anticipate approximately 60-70 active sites by the time of trial completion.

Participants

Hospitalized patients will be considered for enrolment in this study if they meet all inclusion and no exclusion criteria.

Inclusion criteria: Patient is admitted to hospital at the time a blood culture result is reported as positive with a pathogenic bacterium.

Exclusion criteria:

1) Patient already enrolled in the trial;

2) Patient has severe immune system compromise, as defined by: absolute neutrophil count $<0.5 \times 10^9$/L; *or* is receiving immunosuppressive treatment for solid organ or bone marrow or stem cell transplant;

3) Patient has a prosthetic heart valve or synthetic endovascular graft (post major vessel repair with synthetic material; coronary artery stents are not an exclusion);

4) Patient has a documented or strong suspicion of a syndrome with well-defined requirement for prolonged treatment:

i) infective endocarditis;

ii) osteomyelitis/septic arthritis;

iii) undrainable/undrained abscess;

iv) unremovable/unremoved prosthetic-associated infection (e.g. infected pacemaker, prosthetic joint infection, ventriculoperitoneal shunt infection etc.). Central venous catheters, including tunneled central intravenous catheter, and urinary catheters are not excluded.

5) Patient has a single positive blood culture with a common contaminant organism according to Clinical Laboratory & Standards Institute (CLSI) Guidelines: coagulase negative staphylococci; *or Bacillus spp.*; *or Corynebacterium spp.*; *or Propionobacterium spp.; or Aerococcus spp.; or* M*icrococcus spp;*[34]

6) Patient has a positive blood culture with *Staphylococcus aureus*[35] *or Staphylococcus lugdunensis*

7) Patient has a positive blood culture with rare bacterial pathogens requiring prolonged treatment (e.g., *Mycobacteria* spp., *Nocardia spp., Actinomyces spp., Brucella spp, Burkholderia pseudomallei*)

8) Patient has a positive blood culture with *Candida spp.* or other fungal species.

Trial intervention

We will randomize patients to receive a shorter duration of adequate antibiotic therapy (7 days) versus a longer duration (14 days) (Figure 1). Adequate antibiotic treatment will be defined as treatment with an antibiotic (or antibiotics) to which the local laboratory has reported the organism(s) responsible for the bloodstream infection as susceptible. The duration of adequate treatment will be determined as the cumulative number of days on which at least one dose of adequate treatment is delivered beyond the date of collection of the index blood culture specimen.[36] The selection of specific antimicrobial agent(s), doses and route of delivery will be at the discretion of the treating clinical team. The research team at each site will visit daily to ensure that antibiotics are stopped at the pre-specified date (end of the 7th or 14th day).

Randomization and allocation concealment

We will use web-based randomization through RANDOMIZE.NET (http://www.randomize.net/), with variable block sizes, stratified by hospital site and by ICU versus non-ICU location. After the full susceptibility results become available, the site research coordinator along with site co-investigators will determine the date for day 7 unblinding, taking into account the number of days that the patient has already received adequate antibiotics after the blood culture collection date. To avoid differentially influencing antibiotic choices and clinical decision-making, the randomization assignment will not be communicated to any clinical staff or research personnel (research coordinator, study critical care or infectious diseases investigators) - until the end of day 7. At day 7, another email will be sent with the unblinded treatment assignment for the patient to the site research coordinator. If a patient is randomized to the short (7 day) treatment arm, the treating team will be informed to stop the antibiotics at the completion of 7 days of antibiotics appropriate for the causative pathogen; if the patient is randomized to the long (14 day) arm the team will be instructed to continue the antibiotic until that date, including beyond hospital discharge if necessary.

Mechanistic sub-studies

Biomarker sub-study

Blood samples will be drawn on the randomization day and at days 7, 10 and 14 from the index blood culture collection to measure procalcitonin (PCT) levels along with other novel inflammatory and angiogenic biomarkers (s-TREM-1, S-TNFR-1, s-TNFR-2, IL-6, CHI3L1, Angiopoietin (Ang)-1, Ang-2, sTIE1, sTIE2, sFlt-1, Slt-2/ROBO). The PCT levels will be batched and measured at the end of the study for the sub-study assessing the association between PCT and clinical outcomes among patients receiving 7 versus 14 days of treatment. The results will not be made available to the treating team because this could unduly influence clinical practice and protocol adherence, and is ethical because none of the participating sites are currently using PCT routinely. Following study completion, we will compare PCT area-under-the-curve (AUC) and day 7, 10 and 14 PCT levels among patients. We will also confirm whether 7 days of antibiotics is non-inferior to 14 days of antibiotics for bacteremia, in subgroups with both normal and abnormal (>0.25ug/mL) PCT levels on day 7. We will conduct comparable analyses for the other inflammatory and angiogenic biomarkers.

Microbiome sub-study

In order to assess the effect of shortening the duration of antibiotic administration on the human gut microbiome, we will collect rectal swabs from patients on the day of randomization, and at days 7, 14, and 21 (or hospital discharge if earlier than day 21) from the start of appropriate antibiotic therapy. Flocked, sterile swabs will be inserted 2-3 cm past the anal verge, rotated 3-4 times, deposited into a room-temperature stable DNA/RNA preservative and stored at room temperature. No human sequence data will be obtained. Swabs will be transported for processing in batches, or at the end of the study, whichever is easier for the participating site.

Samples will be processed for extraction of nucleic acid for 16S rRNA microbiome sequencing and shotgun metagenomics sequencing. Participants who decline sample collection for the sub-studies will still be included in the main clinical trial.

Protecting against sources of bias

Selection bias

Selection bias (such as bias-by-indication or survival bias) will be minimized through rigorous concealed randomization procedures. Although placebo controls have been used in some RCTs of antibiotic treatment duration, such as studies examining treatment duration for cellulitis[37], pyelonephritis[38, 39], and community-acquired pneumonia,[40-43] they are not appropriate for bacteremia treatment in acutely ill patients. It is not feasible to administer placebos for each of the many antimicrobials commonly used alone or in combination to treat the many etiologies of bacteremia.[44] Even if it were possible to generate this many placebos, BALANCE patients are susceptible to developing secondary sources of nosocomial infection, and our preparatory work revealed that clinicians demand knowledge of whether a patient is receiving antibiotics or not.

Outcome misclassification bias

We have selected an objective primary outcome measure and we will use central adjudication committees blinded to treatment allocation for other outcomes including relapse, and secondary infection/colonization with antibiotic resistant organisms.[45, 46]

Withdrawal from study

If a patient is withdrawn from the study prematurely, a withdrawal form will be completed. Data will be collected under the informed consent up to the point of a consent withdrawal. Among patients who withdraw consent for continuation of the trial, we will seek their consent to ascertain vital status at ICU and hospital discharge and at 90-days from the date of bacteremia diagnosis. Anticipated reasons for withdrawal include patient not meeting inclusion criteria or having relevant exclusion criteria prior to randomization, consent withdrawn by patient or substitute-decision maker, patient's physician believes patient should be withdrawn from the study, inadvertent duplicate randomization. Detailed rationales for withdrawal will be recorded.

Protocol adherence and protocol deviations

We will define adherence to treatment duration protocol as receipt of 7 ± 2 days of adequate antibiotics in the shorter duration arm, and 14 ± 2 days in the longer duration arm; antibiotics stopped before or continued beyond these durations will be considered protocol deviations. We do not expect or aspire to achieve a 0% protocol deviation rate in this trial, given that some patients will develop persistent, recurrent or secondary infections for which antibiotics will need to be re-initiated or continued. It is appropriate for these patients to receive treatment as would occur outside of a trial. For example, in the multicenter *PneumoA* study of 8 versus 15 days of treatment for ventilator-associated pneumonia, protocol non-adherence was 18% in the 8-day treatment arm.[17] Non-adherence rates have been as high as 50% seen in some studies of PCT-guided treatment for infections in critically ill patients.[47] However, we will monitor protocol deviation rates overall and by hospital site during the trial, record rationales for the deviations, and strive to minimize unnecessary deviations.

Frequency and duration of follow-up

Patients will be reviewed daily in hospital for the first 14 days post randomization, and again at hospital discharge with extensive data collection (see case report form at balance.ccctg.ca). The research coordinator will contact the patient (or substitute decision-maker as appropriate) on day 90 by telephone to determine their

disposition and vital status. Other sources of evidence for 90 day vital status will include clinical documentation of health care visits/readmissions and testing after 90 days.

Primary outcome measure

The primary outcome will be survival at 90-days from the date of bacteremia, defined by the date of collection of the index positive blood culture. Although, most deaths from critical illness occur during hospital stay, lingering sequelae lead to a persistently elevated risk of death post-discharge. Therefore, we selected post-hospital 90 day mortality as a common vital status endpoint.[48, 49]

Secondary outcome measures

The secondary outcomes include: (a) hospital mortality (b) ICU mortality (d) relapse rates of bacteremia with the same organism (e) antibiotic allergy and adverse events (f) rates of *C. difficile* infection in hospital (g) rates of secondary nosocomial infection/colonization with antimicrobial resistant organisms in hospital (h) ICU length of stay (i) hospital length of stay (j) mechanical ventilation duration; and (k) antibiotic-free days.

Antimicrobial resistant organisms will be defined based on a positive routine culture yielding a highly resistant microbial organism (HRMO) as defined by the Dutch nosocomial infection surveillance guidelines.[50] This broad definition includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, extended spectrum beta-lactamase producing Enterobacteriaceae, carbapenem-resistant Gram negative bacilli, and multidrug resistant Gram negative bacilli (with definition of multi-drug resistance differing according to Enterobacteriaceae and non-Enterobacteriaceae species).[50] We will also conduct a sensitivity analysis limited to isolation of these organism(s) only from sterile site specimens (such as blood, cerebrospinal fluid, peritoneal fluid, synovial fluid, pleural fluid, and tissue biopsies).

Antibiotic-free days will be calculated as the number of days alive and not on any antibiotics in the time period from collection of the index blood culture to 28 days after this date; patients who die prior to day 28 will be assigned 0 antibiotic-free days.

Statistical analysis

Sample size

The primary analysis will assess whether 7 days of treatment is associated with a 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 (baseline mortality 22%)[51] power 80%, alpha 0.025, one-sided equivalence test). We have inflated this to account for a maximum of 5% loss-to-follow-up, and have incorporated early stopping rules to account for the 3 interim analyses (coefficient 1.017)[52, 53] for a total sample size of 3626. Recent landmark trials in with similar baseline mortality rates have used -4% as a non-inferiority margin;[54, 55] the U.S. FDA has recommended a similar margin for analogous industry-sponsored trials.[56] The PneumA study of 8 vs 15 day treatment for VAP used a non-inferiority margin of 10%,[17] as have other recent prominent infectious diseases non-inferiority trials,[20, 57] but we believe lower non-inferiority margins are desirable, when feasible, for the outcome of survival.[56]

Loss to follow-up

We anticipate negligible loss of patients to follow-up. The Canadian Critical Care Trials Group (CCCTG) (www.ccctg.ca) has achieved virtually 100% follow-up to hospital discharge over all of its landmark RCTs.[58-60] Although we will be following survivors to ascertain 90-day mortality and relapse rates, we also expect close to

100% follow-up based on previous CCCTG experience and our own pilot RCT experience.[32, 33] Nevertheless, we are accounting for up to 5% loss to follow-up in our sample size calculation.

Analysis of primary outcome

The BALANCE Trial will be conducted, analyzed and reported according to CONSORT guidelines, including analyzing patients in the groups to which they were assigned (intention-to-treat).[61] We will also include a per-protocol analysis. Inferences that 7 day treatment is non-inferior to 14 day treatment will be stronger if this finding is confirmed in both intention-to-treat and per protocol analyses.[62] We will also perform a modified intention-to-treat analysis (mITT), excluding patients that die before day 7 of treatment, given that these patients die prior to divergence in treatment assignment.[63] The primary analysis will examine whether 90-day survival is non-inferior in the 7 vs. 14 day treatment group, as determined by whether the 95.7% confidence interval excludes a 4% absolute decrement in survival.

Analysis of secondary outcomes

Mortality rates at other time points will be calculated in a similar manner to 90-day mortality. We hypothesize that mortality rates will be non-inferior with 7 days of treatment. Continuous secondary outcomes, including lengths of stay in ICU and hospital, durations of ventilation and vasopressor use, and antibiotic-free days will be compared by the Wilcoxon test.

Subgroup analyses

The main subgroup analysis will be based on the underlying infectious syndrome causing bacteremia (vascular catheter-related, pneumonia, pyelonephritis, intra-abdominal, skin and soft tissue, other identified source, or unknown source). We will also perform subgroup analyses based on ICU versus non-ICU enrolments, community- versus hospital-acquisition, Gram positive versus Gram negative infection, illness severity (APACHE II score of ≥25 vs. <25), and vasopressor use on day of randomization. We hypothesize that the non-inferiority of 7 versus 14 days of treatment will be consistent across these subgroups.

Frequency of analyses

Three interim analyses are planned for BALANCE at approximately 1/6 (600 patients), 1/3 (1200 patients) and 2/3 (2400 patients) of projected total enrollment; we will stop at the interim analysis for futility, inferiority or superiority using the O'Brien-Fleming spending function to generate adjusted confidence intervals for the primary endpoint, splitting the type I error at 0.0000007, 0.000452, 0.013, and 0.043 with 99.99%, 99.95% , 98.68% and 95.70% two-sided confidence intervals to give an overall type I error of 2.5%.[52, 53, 62] The Data Monitoring Committee (DMC) will be guided by a graphical plot indicating mortality differences which would meet futility, inferiority or superiority thresholds (Figure 2). We will perform both frequentist-based and Bayesian-based analyses for endpoints at the study's termination. Subgroup analyses will not be performed for the interim analyses.

Secondary Bayesian Analysis

Usual frequentist-based statistical analysis calculates the probability of obtaining data as extreme or more extreme than the observed data assuming the null hypothesis is true. Interpretations of clinical trials based on frequentist statistics using p-values and 95% confidence intervals can be challenging for clinicians for several

reasons. First, frequentist-based analyses usually consider each analysis in isolation, without an easy mechanism for quantitatively incorporating prior information and without a true measure of the probability of clinical benefit. Quantitative interpretation of new information from clinical trials can be especially challenging when either prior evidence or perception does not align with new evidence.[64-66] The interpretation of results of trials using a non-inferiority perspective can be additionally challenging; requiring interpretation of findings that may indicate non-inferiority, inferiority, superiority, equivalence, or an inconclusive estimate of effect.[67] Bayesian methods provide an alternative to null hypothesis statistical testing that allow quantification of evidence in favor of the null hypothesis, sequential testing, and comparison of strength of evidence across different studies.[68-71] In addition to our primary frequentist-based analysis of the primary 90-day mortality outcome, and secondary in-hospital and in-ICU mortality outcomes, we will additionally perform companion Bayesian analyses of each. This will be particularly informative should the study be either stopped for futility (a high likelihood of being unable to determine superiority, inferiority or non-inferiority at planned or feasible samples sizes), in order to directly estimate the *probability* of treatment benefits. We will combine the data from BALANCE with a non-informative prior to derive the posterior distribution based on which we will report the 95% Credible Intervals together with the probabilities of the difference in mortality between the two groups falling into the superiority, non-inferiority and inferiority region.

Steering Committee

The BALANCE Steering Committee is responsible for development and oversight of the BALANCE RCT procedures, rigorous and ethical trial conduct, funding applications, advising the principal applicants on responses to questions from ethics boards, the DMC or other stakeholders, and eventual interpretation and compilation of study results into reports, scholarly manuscripts and knowledge translation and exchange activities. With BALANCE expansion to additional countries, additional steering committee member(s) will be added from each country with 2 or more enrolling sites, and/or has obtained regional grant funding to support the trial.

Data Monitoring Committee (DMC)

The BALANCE DMC has multidisciplinary expertise in infectious diseases, critical care, randomized clinical trial (RCT) design and conduct, clinical epidemiology, biostatistics, interim analyses and early stopping rules. The BALANCE DMC charter (supplementary file) is based on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter, and draws heavily from the charter and experience of prior landmark CCCTG studies.[58, 72] At each interim analysis the BALANCE PIs will provide the DMC with information on group characteristics, recruitment rates, adherence to treatment duration protocols, data completeness and accuracy, serious adverse events, outcome event rates and co-enrolment prevalence. Data will be presented in both one-group or two-group tables in a manner that will prevent unmasking of group allocation to the research team. The DMC will be able to request an independent (not involved in the BALANCE trial) methods centre statistician to provide the unmasked group allocation, according to the BALANCE charter (supplementary file), should that be deemed necessary by the DMC to interpret the interim analysis.

Patient and Public Involvement

The CCCTG includes a Patient and Family Partnership Committee (https://cccrpf.ca/) that has been engaged throughout BALANCE development and conduct.

ETHICS AND DISSEMINATION

Ethics Approval

Ethics approval has been obtained from the research ethics board of each participating site, along with central mechanisms in the Canadian provinces of Ontario and Quebec, the Australian states of New South Wales and Victoria and New Zealand (supplementary file).

Consent

The research coordinator/site primary investigator will approach eligible patients (or their substitute decision-makers) as soon as their blood cultures are positive to obtain informed consent. Enrollment can be delayed at maximum to the 7th day of adequate antibiotic treatment. Critically ill patients are frequently unable to provide initial consent due to altered level of consciousness or comprehension, and thus the CCCTG has standard operating procedures to seek assistance from substitute-decision makers on behalf of patients. This process has been found feasible and acceptable to patients, decision-makers, and research ethics boards across Canada.[73-76] We will use this enhanced approach to consent, employing 13 previously described strategies distributed over three phases- preparation for the consent encounter, the consent encounter, and follow-up to the consent encounter.[77]

Expected Adverse Events

Short course (7 days) treatment duration could theoretically increase the risk of clinical treatment failure or relapse of the bloodstream infection or underlying focus of infection. Long course (14 days) treatment on the other hand may increase the chance of resistance to antibiotics, occurrence of new antibiotic-resistant infections, *Clostridioides difficile* infection, and adverse events like allergy, anaphylaxis, antibiotic related kidney injury, antibiotic related hepatitis, and other antibiotic related organ toxicity. Our systematic review suggests that clinical cure and survival are similar among bacteremic patients receiving shorter and longer treatment, but these represent underpowered, *post-hoc* subgroup analyses pooled from small trials.[33] Any observational study assessing the impact of duration of treatment on patient outcomes would be limited by survivor bias (patients must survive long enough to be classified as receiving longer treatment) and indication bias (clinicians select sicker patients to receive longer duration treatment). Hence, patients and clinicians require a sufficiently powered RCT dedicated to answering the question of whether shorter treatments are effective for patients with bloodstream infection.

Morbidity and mortality are expected among patients with bloodstream infections. Accordingly, mortality at 90 days, in ICU and in hospital are trial outcomes, as are episodes of C. *difficile* colitis, and antibiotic-related allergy and adverse effects. Outcomes will be reported as such, rather than as Serious Adverse Events (SAEs), Serious unexpected adverse reactions (UARs), or Suspected unexpected serious adverse reactions (SUSARs). These outcomes will be reported to the DMC at all interim analyses. We will closely monitor patient safety in the trial by recording the antimicrobial-related adverse events and serious unexpected adverse drug reactions, additionally interpreted by the Steering Committee and reported to the DMC at each interim analysis.

Knowledge Dissemination

A major mandate of the CCCTG is translating knowledge into practice and advancing the science of Knowledge Translation (KT) in critically ill hospitalized patients. The study has also been endorsed by the Association of Medical Microbiology and Infectious Diseases Canada Clinical Research Network (AMMI Canada CRN), the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) and the Australasian

Society for Infectious Diseases Clinical Research Network (ASID-CRN). The involvement of the knowledge users and leaders in these organizations will lead to rapid national and international knowledge dissemination.

DISCUSSION

Rationale for why the BALANCE Trial is urgently needed

The World Health Organization, U.S. Centers for Disease Control and Prevention, Association of Medical Microbiology and Infectious Diseases (AMMI) Canada, and Health Canada have all declared antimicrobial resistance a global threat to health, [1-4] based on rapidly increasing resistance rates and declining new drug development.[5-7] The highest rates of antimicrobial resistance occur in hospitals, and ICUs in particular, and it is crucial that we develop data-informed mechanisms to decrease antimicrobial use and selection pressure. The vulnerability of acutely ill patients, the complexity of their treatments, and the frequent uncertainty of their infectious syndromic diagnoses are all barriers to reducing antibiotic exposure in the ICU. It is very difficult to avoid initial broad-spectrum antibiotic treatment when acutely ill patients present with or develop definite or suspected infection. Multiple studies have demonstrated that early administration of effective antibiotics in the initial empiric window of antibiotic treatment is the strongest predictor of a favourable outcome in these patients. If empiric selections do not match the susceptibility profile of the isolated pathogen, the patient may be nearly twice as likely to die.[78, 79] Given that prevailing resistance rates are already high, broad-spectrum initial treatments are appropriate for many acutely ill patients. In contrast, it is much more feasible to reduce antibiotic use at the end of treatment courses, given that most patients may be treated longer than necessary, and excessive antibiotic durations are a top contributor to inappropriate antibiotic in all healthcare sectors.[7, 11-13] Shorter duration treatments have been demonstrated to be non-inferior to longer duration treatments for a range of infections.[11, 19] If BALANCE confirms this finding among critically ill patients with bacteremia it could result in effective but shorter prescribing practices for these patients. Shortening treatment durations should also reduce other adverse events, including *C. difficile* infections, and generate an estimated annual direct antimicrobial cost-savings of CAD$678-$798 million across North America and CAD$1.4-1.6 billion across Europe.[80]

Rationale for studying fixed duration therapy rather than individualized durations of treatment

Ideally antibiotic treatment duration should be individualized, and each patient should receive exactly as much antibiotic treatment as needed until their infection is cured, and not longer.[24, 81] However, an RCT based on a clinical stopping rule may not be feasible in acutely ill patients, since there are currently no proven accurate measures of cure versus persistent infection. The challenge in diagnosing and monitoring infection in ICU has sparked studies of novel biomarkers to guide antibiotic treatment duration.[43, 47] One biomarker, procalcitonin, has been used successfully to reduce average treatment durations in sepsis.[43] However, follow-up meta-analyses have indicated that the bacteremic subgroups in PCT trials have tended to receive prolonged treatment durations,[82] perhaps because of high non-adherence rates to algorithm-guided treatment.[47] Therefore, we have designed a randomized trial of fixed shorter versus longer duration antibiotic therapy, guided by our preparatory studies, as the most easily transferrable result to immediately inform clinical practice. This approach has been successful in more than two dozen randomized controlled trials of infectious diseases that are potentially complicated by bacteremia.[19] However, we appreciate the future promise of biomarkers to add nuance to individualized treatment decisions, and so in a nested substudy, we will measure procalcitonin levels and trajectory in both treatment arms to see if it could provide incremental value.[61]

TRIAL STATUS

The BALANCE pilot RCT was launched in Oct. 2014 at the central study site, Sunnybrook Health Sciences Centre, expanded to include a total of 10 CCCTG sites across Canada, and served as a successful vanguard for this BALANCE main RCT. An additional 26 Canadian sites have joined BALANCE, for a total of 36 Canadian sites in 6 provinces. A parallel BALANCE pilot RCT on medical and surgical wards was launched in October 2016 at a subset of 6 BALANCE sites, which confirmed the feasibility of recruitment and protocol adherence on non-ICU wards,[33] and enabled hospital wide expansion; approximately half of sites have now opted for hospital-wide enrolments. We have expanded BALANCE internationally to include sites in Australia (6), New Zealand (10), Saudi Arabia (2), Israel (1) and the United States (2). Therefore, there are currently 57 sites enrolling patients into BALANCE, and with continued expansion we anticipate approximately 70 sites prior to study completion (anticipated for 2022-23). The BALANCE DMC conducted the first interim analysis (n=600) on September 30, 2019 and recommended continuing enrolment. As of Feb 13, 2020, a total of 1447 patients have been recruited into BALANCE, and data from the first 1200 patients is being analyzed for the DMC review of the second interim analysis.

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Contributorship Statement

ND and RF conceived the research question. ND and RF designed the study, with crucial input from AR, RP, YA, DC, RH, SM, JM, RP, SR, BR and YS. ND and RF drafted the manuscript with important revisions provided by AR, RP, YA, DC, RH, SM, JM, RP, SR, BR and YS.

Competing Interests

None.

Patient consent for publication

Not required.

Ethics approval:

The BALANCE RCT is approved by Research Ethics Boards at all participating sites, as well as regional approval by corresponding State and Provincial ethics boards, including Clinical Trials Ontario (Supplementary file).

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Open access:

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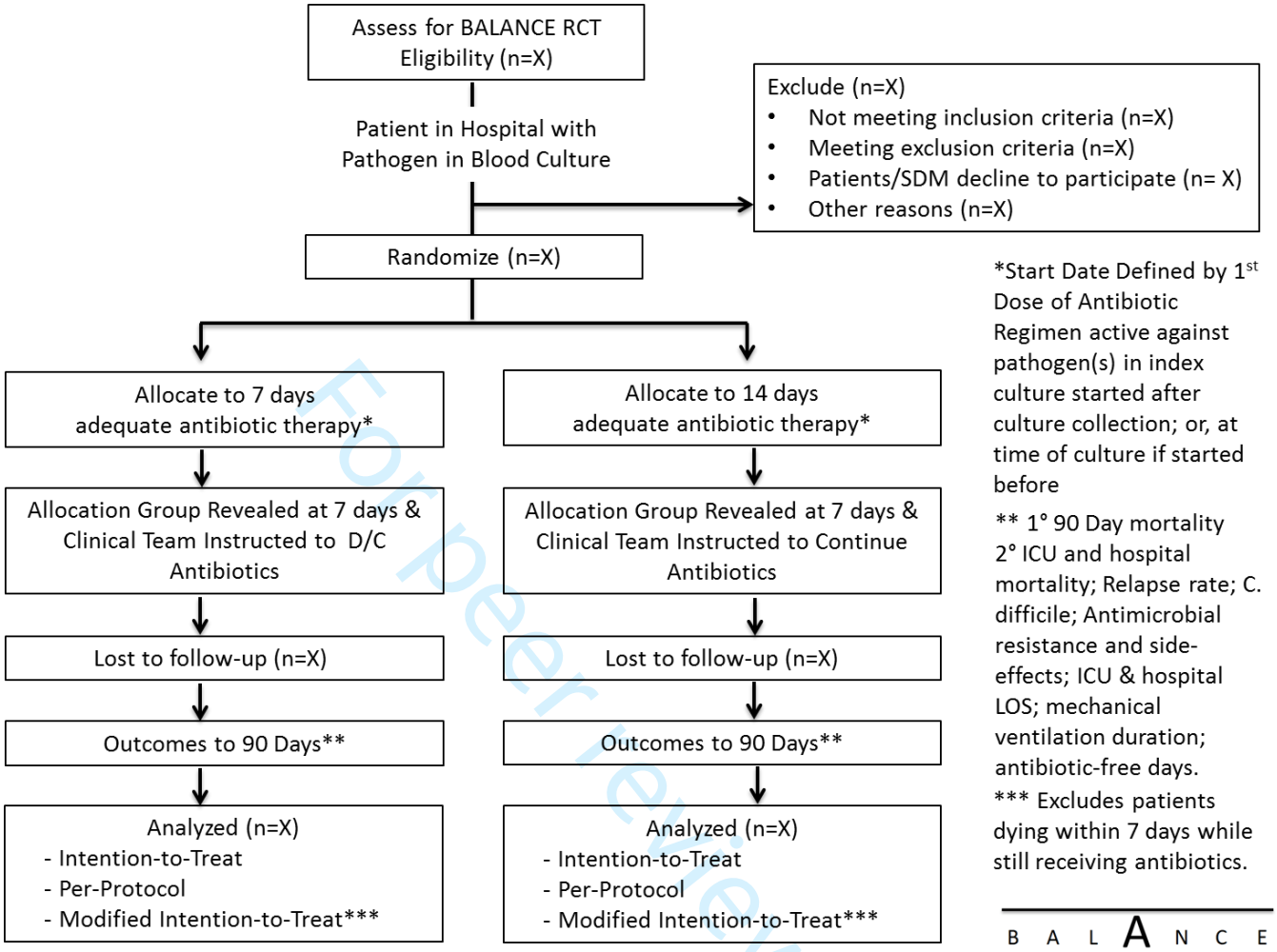
FIGURE LEGENDS

Figure 1: BALANCE Pilot RCT Intervention Flow Diagram.

Figure 2: Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates at the first interim analysis (n=600). Similar figures are available to the Data Monitoring Committee for subsequent interim analyses.

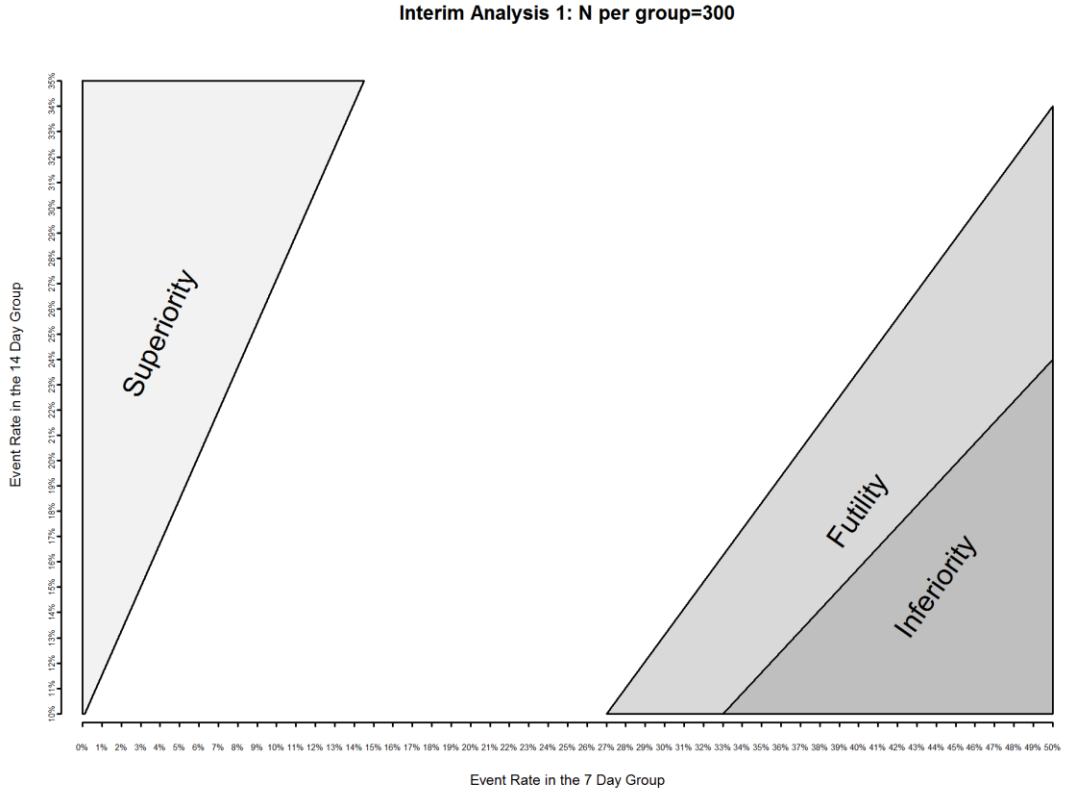


*Start Date Defined by 1st Dose of Antibiotic Regimen active against pathogen(s) in index culture started after culture collection; or, at time of culture if started before

** 1° 90 Day mortality 2° ICU and hospital mortality; Relapse rate; C. difficile; Antimicrobial resistance and side-effects; ICU & hospital LOS; mechanical ventilation duration; antibiotic-free days.

*** Excludes patients dying within 7 days while still receiving antibiotics.

B A L A N C E



Version date: April 11, 2018

Title: Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) Randomized Controlled Trial

Protocol ID: 0796

Registration Number: clinicaltrials.gov [NCT03005145]

Sponsor: Sunnybrook Research Institute, Toronto, ON

BALANCE

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Data Monitoring Committee Charter

BALANCE Organization in Relation to Data Monitoring Committee:

The BALANCE Data Monitoring Committee (DMC) charter is based on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter, and draws heavily from the charter and experience of prior landmark Canadian Critical Care Trials Group studies.[1, 2] The BALANCE DMC charter outlines terms of reference for roles, responsibilities, and relationships of the DMC to the co-principal investigators (Dr. Rob Fowler, Dr. Nick Daneman), the study coordinator (Dr. Asgar Rishu), and the BALANCE steering committee (Dr. Rob Fowler, Dr. Nick Daneman, Dr. Asgar Rishu, Dr. Deborah Cook, Dr. Rick Hall, Dr. John Muscedere, Dr. Ruxandra Pinto, Dr. Steven Reynolds, Dr. Yaseen Arabi, Dr. Yahya Shehabi, Dr. Benjamin Rogers), the trial statistician (Dr. Ruxandra Pinto), investigators, trial participants, institutional research ethics boards (REBs), sponsor (the Canadian Critical Care Trials Group), and primary funding agency (The Canadian Institutes of Health Research (CIHR)).

Nominated Data Monitoring Committee Membership:

The BALANCE DMC has multidisciplinary expertise in infectious diseases, critical care, randomized clinical trial (RCT) design and conduct, clinical epidemiology, biostatistics, interim analyses and early stopping rules. The Nominated BALANCE DMC members include:

Name	Institution	Relevant Expertise
Dr. Roger Spragg	University of California, San Diego School of Medicine, San Diego, USA	Dr. Spragg has experience in the conduct and oversight of multicentre trials involving critically ill patients and will be the BALANCE DMC Chair
Dr. Taylor Thompson	Harvard University, Massachusetts General Hospital, Boston, USA	Dr. Thompson is the DMC critical care medicine content expert.
Dr. Steve Opal	Brown University, Rhode Island Hospital, Rhode Island, USA	Dr. Opal the DMC infectious diseases context expert.
Dr. David Schoenfeld	Harvard School of Public Health, Boston, USA	Dr. Schoenfeld biostatistician content expert.

Version date: April 11, 2018

Overview of Data Monitoring Committee Responsibilities:

The primary ongoing responsibilities of the DMC will be independent review of reports received directly from the BALANCE Methods Center (Sunnybrook Research Institute in collaboration with CLARITY Research, McMaster University) regarding:

1. Recruitment rates
2. Adherence rates to treatment duration protocols
3. Data completeness, accuracy and timeliness
4. Serious adverse events
5. Outcomes event rates
6. Co-enrolment prevalence, noting specific trials in which more than 20 BALANCE patients are enrolled

Sample Size Calculation:

The primary analysis will assess whether 7 days of antibiotic treatment is associated with non-inferior 90-day survival rates in comparison to 14 days of antibiotic treatment for critically ill patients with bacteremia. We require 1,686 patients per arm to establish a non-inferiority margin of 4% absolute decrement in survival (baseline mortality 22%,[3] 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 1.024)[4, 5] for a total requirement of 3626. Recent landmark trials in critically ill patient populations with similar baseline mortality rates have used 4% as a non-inferiority margin;[6, 7] the U.S. FDA has recommended a similar margin for analogous industry-sponsored trials.[8] The PneumA study of 8 vs 15 day treatment for VAP used a non-inferiority margin of 10%,[9] but we believe this to be inappropriately high for the outcome of survival; a non-inferiority margin of <4% would render a trial unfeasible.[8] We will aim to enroll approximately 2/3 of these patients in Canadian intensive care units (ICUs), and the remaining 1/3 of patients in international ICUs.

Interim Analyses:

Three interim analyses are planned for BALANCE at one-sixth, one-third and two-thirds of projected total enrollment. Non-inferiority trials with mortality end-points have traditionally been less likely to establish "early stopping rules" than superiority trials. This is in part, due to concern that mortality-based margins of difference should be very low and that early stopping likely reduces confidence that an upper margin of difference has been excluded.[4, 5] However, we will consider stopping at the interim analysis for superiority, using the O'Brien-Fleming spending function to generate adjusted confidence intervals for the primary endpoint, splitting the type I error at $7x10^{-7}$, 0.0005, 0.0132 and 0.043, with 99.99%, 99.95% and 95.70% two-sided confidence intervals to give an overall type I error rate of 2.5%.[4, 5] We have inflated the sample size to account for these 3 analyses in addition to the final analysis. We will also consider stopping at

the interim analyses on the basis of inferiority or futility, and have provided guidance for the DMC (appendix).

After each interim analysis, the BALANCE DMC will recommend either:

1. To consider continuing patient enrolment, or
2. To consider suspending enrolment until careful review by the principal investigators and steering committee, or
3. To gather more information before a recommendation can be made, or
4. To consider terminating enrolment.

Responsibilities of the Data Monitoring Committee:

1. To advise the principal investigators and steering committee about the conduct of the trial and integrity of the data, so as to protect the validity of the trial.
2. To ensure the overall safety of trial patients by protecting them from avoidable harms. The DMC should not be expected or accountable for reviewing adverse events by routine real-time transmission.

Relationship of the Data Monitoring Committee to the Principal Investigators and Steering Committee:

1. The DMC is arms-length and independent of the principal investigators and steering committee in operating and formulating recommendations, but is supportive of the aims and methods of the trial.
2. The DMC serves in an advisory role to the principal investigators and steering committee.
3. The principal investigators and steering committee receive BALANCE DMC recommendations under advisement.
4. The DMC, principal investigators and steering committee work collaboratively to ensure rigorous, valid, safe and timely conduct of the trial.

Initial Responsibilities of the Data Monitoring Committee:

1. Review the BALANCE protocol and case report forms.
2. Review, discuss, debate and approve the Methods Center operations.
3. Review, discuss, debate and approve the mechanisms for transmitting serious adverse event information to the DMC.
4. Establish guidelines for calling emergency meetings of the DMC.
5. Propose a schedule for subsequent DMC meetings, acknowledging that the DMC Chair may call for a meeting of the DMC at any time, as may the principal investigators.
6. Approve or refine template tables provided by the principal investigators and trial statistician for future review at the interim analyses.

7. Disclose any conflicts of interest such as: current honoraria or consultancies, involvement in regulatory issues relevant to the study drugs, investment in these or competing drugs, involvement with the sponsor, enrolment of patients in the trial, strong prior beliefs constituting intellectual conflict, other dual loyalties etc.

Ongoing Responsibilities of the Data Monitoring Committee:

The BALANCE DMC is responsible for helping to ensure that BALANCE patients are not exposed to unnecessary or unreasonable risks and that the trial is conducted according to the highest scientific and ethical standards.

Therefore, the BALANCE DMC will:

1. Review data from the 3 planned interim analyses provided by principal investigators and steering committee, via the Methods Centre.
2. Alert the principal investigators and steering committee about scientific, procedural or ethical concerns emerging from the interim analyses and/or final analyses.
3. Provide recommendations to facilitate rigorous, timely completion of the trial.
4. Comment on any new relevant external published data (provided by the principal investigators and steering committee) that may impact on patient safety or the efficacy of BALANCE.
5. Provide recommendations for adjustment of sample size or consideration of trial termination.
6. Read and provide suggestions for manuscript publications before submission.
7. Be acknowledged in the main report, unless requested otherwise.

Timing of Data Monitoring Committee Meetings:

The DMC will meet virtually, or if necessary in person:

1. Once initially to discuss the protocol and analysis plans, the DMC Charter, template tables, and to clarify any aspects with the principal investigators and steering committee.
2. At the first interim analysis.
3. At the second interim analysis.
4. At the third interim analysis.
5. At the end of the trial, to allow the DMC to discuss the final data with the principal investigators and steering committee to advise on data interpretation.
6. As needed, by teleconference.

Responsibilities of the Principal Investigator, Study Coordinator and Steering Committee to the Data Monitoring Committee:

1. The principal investigators and study coordinator will provide the protocol and CRFs to the DMC before their initial meeting.

2. The principal investigators and study coordinator will provide preliminary template reports of site enrolment, patient recruitment rates, patient consent rates, treatment duration protocol adherence rates, data management templates (data completeness, accuracy, timeliness and query resolution), CIHR reports, 3 interim and final analyses (baseline characteristics, primary and secondary outcomes, and serious adverse events).
3. The principal investigators and study coordinator will modify these template reports if requested, and will use to create tables for the 3 interim analyses.
4. For baseline characteristics and outcomes, the (blinded) BALANCE statistician will provide to the (blinded) DMC, data according to group A and B, including baseline characteristics (age, sex, APACHE II score, source of bacteremia, etc.), primary and secondary outcomes and serious adverse events.
5. The principal investigators and study coordinator and biostatistician will ensure that DMC members remain blinded to allocation.
6. The principal investigators and study coordinator will provide the results of any new relevant external published data for DMC consideration.

Three-Part Structure of Data Monitoring Committee Meetings:

1. First, an open session will be held with the principal investigators and study coordinator and statistician. The purpose will be to review accrual, data timeliness and quality, completeness of follow-up and adjudication, serious adverse events, problems with centres, and any proposals for changes in the trial protocol or duration. In addition, the principal investigators will report any new external evidence (especially results from other relevant ongoing studies) that bear on the conduct of the trial.
2. Second, a partially closed session will be held between the DMC and the statistician to review the primary and secondary outcomes separated by group and presented in a blinded fashion (group A and group B). These data will not be available to the principal investigators, study coordinator, steering committee, or investigators except as authorized by the DMC Chair. The principal investigators will receive data in aggregate form.
3. Third, a totally closed session for just the DMC members will be held to discuss the current results, decide on recommendations, and draft comments and recommendations for 3 reports.

Potential Unblinding of the Data Monitoring Committee:

1. During the closed session, if the DMC deems it crucial to their interpretation of the data, the DMC will request unblinding themselves to group assignment without informing the investigative team of this need.
2. A request to unblind will be very unlikely because the general scientific philosophy of modern pragmatic trials is to not unblind until completion, and this is particularly true for BALANCE which involves different two durations of antibiotic treatment that are

both a component of contemporary clinical practice, and the specific antibiotic medications, dose and route of delivery are all chosen by the treating team.
3. The request to unblind would need to be extreme, unambiguous and unanimous. The signal would be need to derive from compelling trial results such as a significantly increased risk of mortality in one arm.
4. To achieve unblinding the database manager will be authorized to provide immediate unblinding information to the DMC chair, including during a DMC meeting. An independent statistician will redo analyses if requested. The principal investigators, study coordinator and statistician will not review unblinded results, and will not be informed of the DMC decision to unblind the results unless the DMC makes a recommendation to consider terminating enrolment at an interim analysis, or at the end of the study.

Discussions of the Data Monitoring Committee:

1. Efforts should be made for the DMC to reach unanimous recommendations.
2. The role of the Chair is to summarize discussions and encourage consensus.
3. Before making any recommendations, the DMC should consider the ethical, scientific, statistical, and practical implications for the trial.

Minutes of Data Monitoring Committee Meetings:

1. Within a week of each DMC meeting, the Chair, with administrative assistance provided, will generate minutes of the open and closed sessions of the meeting.
2. The minutes will contain the major points of discussion, recommendations made, and any additional information requested for future meetings.
3. Minutes of the open session of the meeting will be for the principal investigators and study coordinator.
4. Minutes of the closed session will be for the DMC members only (until the trial is complete).

Reports of the Data Monitoring Committee:

1. After each DMC meeting, the Chair will report to the principal investigators and study coordinator. Each meeting will be summarized in 2 reports (1 short report suitable for Investigators, the CCCTG, REBs and CIHR) and 1 more detailed report for the principal investigators, study coordinator and statistician).
2. The principal investigators will circulate the DMC's short and long reports to the appropriate individuals. It is the responsibility of the principal investigators to notify the investigators, the CCCTG and participating REBs of any recommendations about trial modification or enrolment suspension or termination.

3. If the DMC recommends to continue enrolment in the trial following an interim analysis, no other information shall be provided to the principal investigators and study coordinator.
4. If the DMC recommends to consider suspending enrolment of the trial until careful review by the principal investigators and study coordinator; or whether more information is required before a recommendation can be made, or whether to consider terminating enrolment, the DMC will provide a full report of the rationale to the principal investigators, study coordinator and statistician.

Conflict Resolution:

1. DMC recommendations are advisory to the trial principal investigators, steering committee, and by extension other sponsors of the trial.
2. In the event that the principal investigators and/or study coordinator disagree with the DMC recommendation(s) to modify or to terminate the trial, a third party arbitrator may be called upon.
3. A third party arbitrator, selected by both parties, will be an individual possessing the requisite knowledge and experience (ideally both methodologic and clinical) to make a final decision.
4. The selection of the third party arbitrator will be made by mutual consent of both the principal investigators and the DMC Chair.

Confidentiality:

1. It is the duty of each member of the DMC to protect the confidentiality of the trial and the results of monitoring.
2. The members of the DMC acknowledge that the data emerging from this trial are the collective property of the principal investigators and study coordinator and investigators.
3. DMC members will not have the right to present or publish data or learnings from this trial anywhere without the explicit permission of the principal investigators and study coordinator, and not until after the trial is complete.

Reporting on the Data Monitoring Committee:

1. A brief summary of the roles, responsibilities, and recommendations of the DMC will be included in the trial manuscript.
2. DMC members will be invited to read and comment on the trial manuscript, including any statement related to the DMC.
3. DMC members will be named and their affiliations listed in the trial manuscript, unless requested otherwise.
4. Potential publications about research oversight coauthored by any of the DMC members will be deferred until the main manuscript is published.

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Reference List

1. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 2005;365(9460):711-722.

2. Cook D, Meade M, Guyatt G et al. Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med 2011;364(14):1305-1314.

3. Daneman N, Rishu AH, Xiong W et al. Duration of Antimicrobial Treatment for Bacteremia in Canadian Critically Ill Patients. Crit Care Med 2015.

4. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35(3):549-556.

5. Jennison C, Turnbull B. Group Sequential Methods with Applications to Clinical Trials. Chapman and Hall; 2015.

6. Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340(6):409-417.

7. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350(22):2247-2256.

8. United States Deaprtment of Health and Human Services. Guidance for Industry Non-Inferiority Clinical Trials. 2010

9. Chastre J, Wolff M, Fagon JY et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290(19):2588-2598.

Version date: April 11, 2018

Appendix: **Contextual and Analytical Considerations for Stopping Considerations for each Interim Analysis of the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) Randomized Clinical Trial.**

Stopping Guidelines for Inferiority

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled) we explore the possible event rates for the 7-day group that will cause us to stop the trial for inferiority. We propose to stop the trial for inferiority of the 7-day group in comparison to the 14-day group, if the lower limit for a confidence interval for the difference between the 7-day and 14-day event rate is larger than 4% (the non-inferiority margin of error for the trial). To maintain and overall 5% type I error, at each interim analysis the confidence interval is based on the O'Brien-Fleming significance level α, corresponding to $z=Z_{OBF}*\text{sqrt}(N/n)$ where N=total sample size, n=sample size at the interim analysis, and $Z_{OBF}=2.024$

We varied the event rate in the 14-day group and used simulation to estimate the event rate in the 7-day group for which we would have enough power to determine that the event rate in the 7-day group is inferior to the 14-day group.

1. First we simulated data for the 7-day group and 14-day group from binomial distributions with event rates higher in the 7-day group.
2. Next, we calculated the confidence interval around the difference in the event rates in the 7- versus 14-day group
3. Then, we calculated the power as the proportion of simulations for which the lower confidence interval exceeded 4% (the non-inferiority margin of error for the trial).

The lowest event rate for which the power is at least 80% is the one that provides a guideline of when the trial would be stopped for inferiority.

The Figures operationalize the inferiority-based stopping guidelines for the trial at each of the three interim analyses. If the 7-day and 14-day mortality rates fall within the darkest grey shaded area, then we should consider stopping the trial for evidence of inferiority of the 7-day group.

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Stopping Guidelines for Superiority

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled), we explored the possible event rates for the 7-day group that will cause us to stop the trial for superiority. This is similar to the approach taken for the inferiority-based stopping guidance. We propose to stop the trial for superiority of the 7-day group in comparison to the 14-day group, if the upper limit for a confidence interval for the difference between the 7-day and 14-day event rate is lower than 0% (no-difference). At each interim analysis the confidence interval is based on the O'Brien-Fleming significance level α, corresponding to $z=Z_{OBF}*\text{sqrt}(N/n)$ where N=total sample size, n=sample size at the interim analysis, and $Z_{OBF}=2.024$

We varied the event rate in the 14-day group and used simulation to estimate the event rate in the 7-day group for which we would have enough power to determine that the event rate in the 7-day group is superior to 14-day group.

1. First we simulated data for the 7-day group and 14-day group from binomial distributions with event rates lower in the 7-day group.
2. Next, we calculated the confidence interval around the difference in the event rates in the 7- versus 14-day group.
3. Then, we calculated the power as the proportion of simulations for which the upper confidence interval is lower than 0%.

The lowest event rate for which the power is at least 80% is the one that provides a guideline of when the trial would be stopped for superiority.

Figures 1-3 operationalize the superiority-based stopping guidance for the trial at each of the three interim analyses. If the 7-day and 14-day mortality rates fall within the light grey shaded area then we should consider stopping the trial for evidence of superiority of the 7-day group.

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Stopping Guidelines for Futility

At each of three interim analyses (planned after 1/6, 1/3 and 2/3 of the patients have been enrolled), we also explored the possible event rates for the 7-day group that will cause us to considering stopping the trial for futility, using the principle of conditional power. Conditional power is the probability that the final result will be statistically significant given the interim observed data, incorporating specific assumptions about the future data. Conditional Power was simulated for the three interim analyses under a range of conditions.

In the simulation, at the interim analysis, we assumed higher event rates (i.e. 90-day mortality) in the 7-day treatment group versus the 14-day group. For each of these event rates we can simulate samples for the remaining (future) data as follows:

1. The future event rate in the 14-day group was simulated with various scenarios:
    a. Default scenario: the same as assumed in the original sample size estimation (22% 90-day mortality); or,
    b. Alternative scenario: the same as observed at the interim analysis.
2. The future event rate in the 7-day group was simulated with various scenarios as well:
    a. Default scenario (least likely to stop early): the future event rate in the 7-day group will be the same as the future event rate in the 14-day group
    b. Alternative scenario (more likely to stop early): the future event rate in the 7-day group will be at the lower 95% confidence interval for the 7-day treatment group at the interim analysis.
    c. Alternative scenario (most likely to stop early): the future event rate in the 7-day group will be the same as the observed event rate at the interim analysis in the 7-day group.

Eventually, with a strong recommendation from the BALANCE Steering Committee and oversight of the Canadian Critical Care Trials' Group, we chose the most conservative scenario to consider for futility-based stopping considerations, namely when future data is simulated with an event rate that is the same for both groups and the same as in the original sample size calculation (1a and 2a above).

3. For each simulation, to maintain the overall type I error as stipulated by the O'Brien-Fleming stopping rule, a two-sided 95.7% confidence interval for the 7-day versus 14-day difference was calculated.
4. The conditional power is the percentage of simulations for which the upper limit of the confidence interval for the difference in 90-day mortality between 7-day group versus 14-day group is less than 4% (the non-inferiority margin of error for the trial).

5. We specified a conditional power of ≤ 10% as a threshold for stopping the trial for futility, based on common and conservative practice from the existing medical literature.
6. We then calculated the event rate in the 7-day group at the interim analyses that will lead to a conditional power of 10% or less.

We repeated the above steps for each of the 3 interim analyses in order to derive futility stopping guidance graphs for the trial (Figures 1-3). If the event rates for the 14-day and 7-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for futility. However, given that such an interim analysis finding does not lead to an interim conclusion of a high probability of better or worse outcomes for either treatment group, and that by enrolling a greater number of patients in a non-inferiority trial, generally greater certainty will emerge on treatment effects from each group, guidance from the DMC on the issue of stopping on the basis of futility should be only positioned a consideration, and not a strong recommendation.

This position is in distinction to guidance for stopping on the basis of inferiority or superiority - where there may be a substantial clinical and statistical inference that one treatment is inferior or superior to the other. Interim analysis results indicating that there is a chance of futility (in finding that 7-days treatment is non-inferior to 14-days) does not imply a benefit to one or the other treatment strategies. Stopping the trial with fewer enrolled patients will always be associated with greater uncertainty in any true treatment-related difference in mortality than if the trial continued. An argument can be made that non-inferiority trials should not be considered for stopping on the basis of futility as doing so may not allow for effective use of the data from contributions of those patients already enrolled in the trial, and be of least value to clinicians and future patients.

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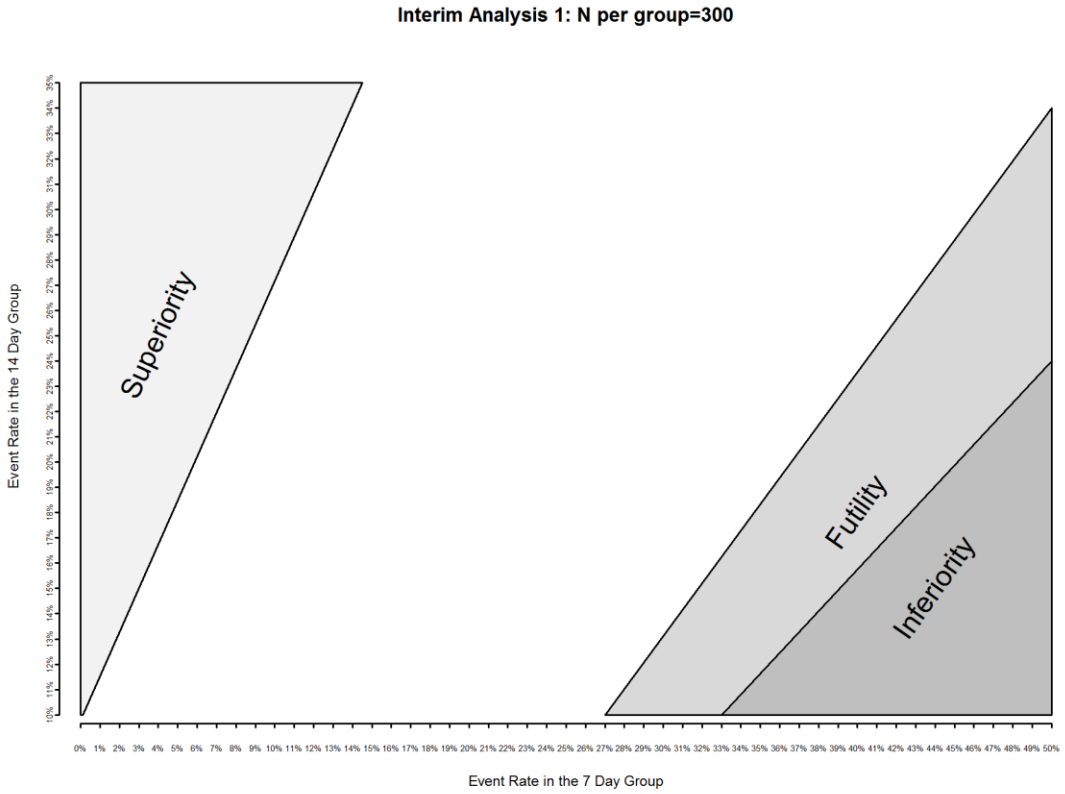
Figure 1. Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 300.



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

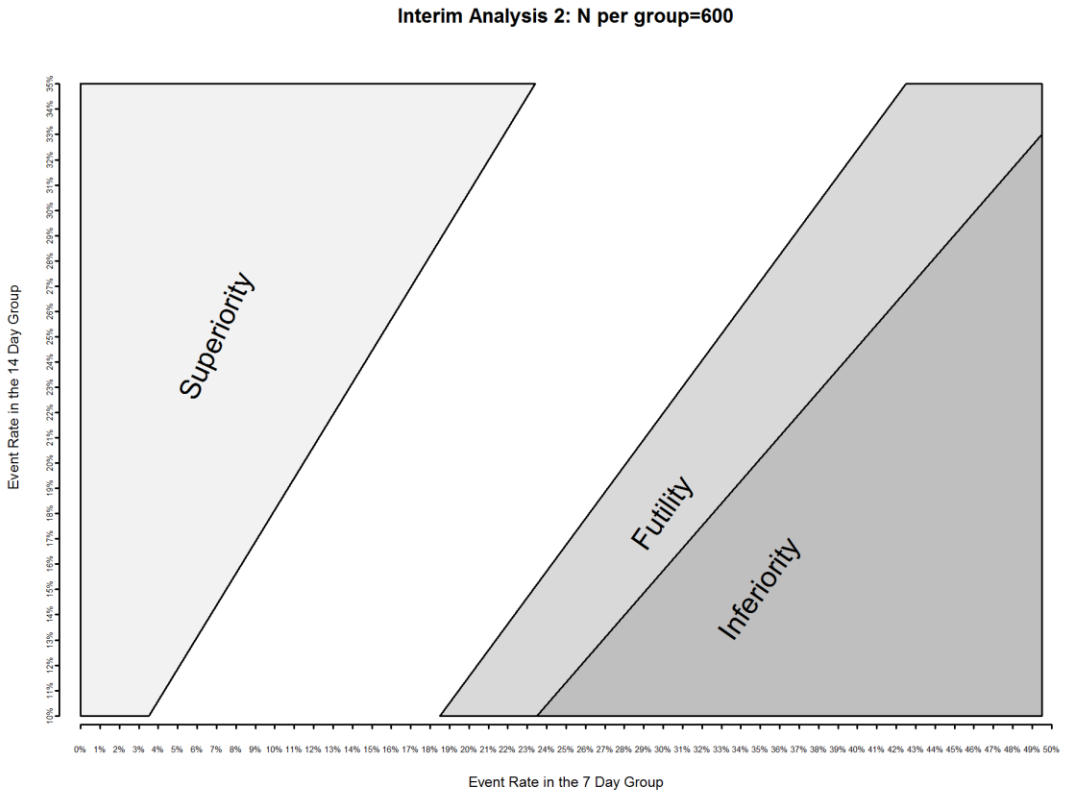
If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

Version date: April 11, 2018

Figure 2: Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 600



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

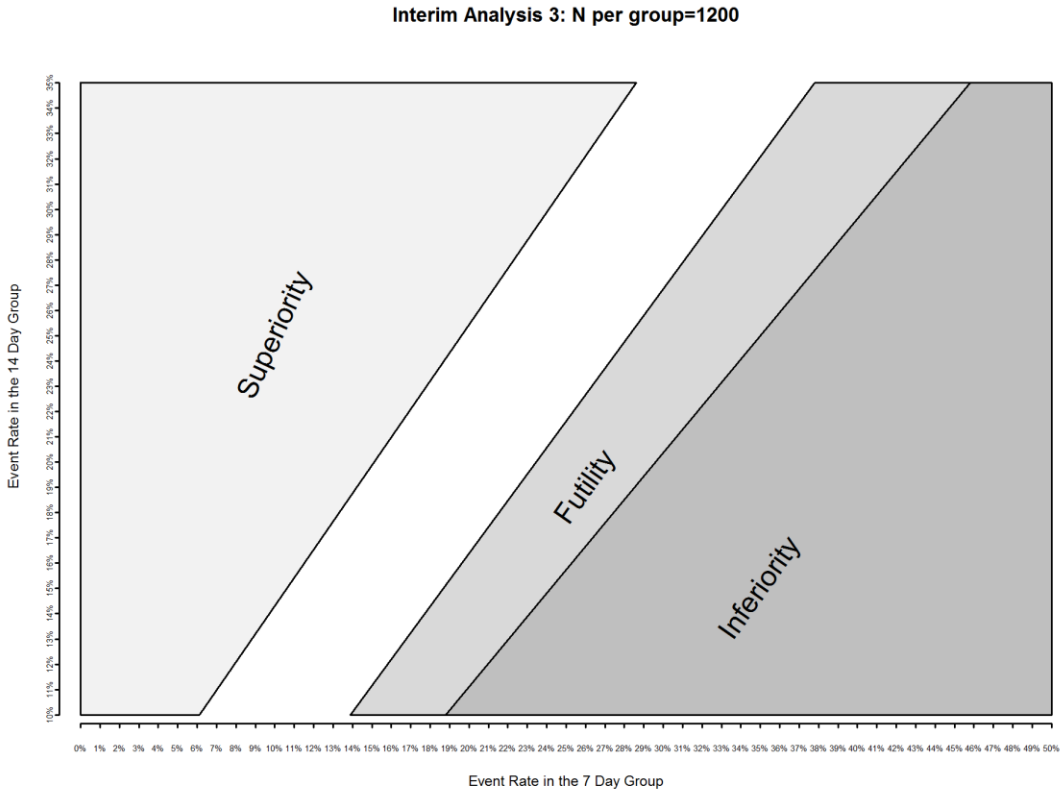
If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

Version date: April 11, 2018

Figure 3: Operationalizing stopping guidelines for inferiority (dark grey shaded area), superiority (light grey shaded area) and futility (medium grey shaded area) with interim event rates when N per group = 1200



If the 7-day and 14-day mortality rates fall within the dark grey shaded area (inferiority) then we should consider stopping the trial for evidence of **inferiority** of the 7-day treatment.

If the 7-day and 14-day mortality rates fall within the light grey shaded area (superiority) then we should consider stopping the trial for evidence of **superiority** of the 7-day treatment.

If the event rates for the 7-day and 14-day treatment groups land in the medium grey shaded area, then the conditional power is ≤ 10%, and we should consider stopping the trial for **futility**.

If the event rates for the 7-day and 14-day treatment groups fall within the white portion of the graph, then the trial should be continued.

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Appendix References:

Margaret Sullivan Pepe, Garnet L. Anderson Two-Stage Experimental Designs: Early Stopping with a Negative Result. Journal of the Royal Statistical Society. Series C (Applied Statistics), Vol. 41, No. 1(1992), pp. 181-190; http://www.jstor.org/stable/2347627.

Daniel J Bratton, Hywel C Williams, Brennan C Kahan, Patrick PJ Phillips, Andrew J Nunn. When inferiority meets non-inferiority: Implications for interim analyses CLINICAL TRIALS Clinical Trials 2012; 9: 605 –609.

Peter C. O'Brien, Thomas R. Fleming. A Multiple Testing Procedure for Clinical Trials. Biometrics, Vol. 35, No. 3 (Sep., 1979), pp. 549-556. International Biometric Society; http://www.jstor.org/stable/2530245.

Following research ethics committees approved the study for participating sites:

Clinical Trials Ontario (CTO), Toronto, ON Canada

THP Research Ethics Board, Trillium Health, Mississauga Canada

Quebec Provinccial approval through Comité d'éthique de la recherché du CIUSSS de l'Estrie – CHUS, Sherbrooke, QC Canada

Research Ethics Board, McGill University, QC Canada

University of Manitoba Health Research Ethics Board, Winnipeg, MB Canada

Research Ethics Office, University of Alberta, Edmonton, AB Canada

The Conjoint Health Research Ethics Board (CHREB), University of Calgary, AB Canada

The UBC-PHC Research Ethics Board, Vancouver, BC Canada

Clinical Research Ethics Board, Vancouver, BC Canada

Capital Health Research Ethics Board, Halifax, NS Canada

Cleveland Clinic Institutional Review Board, Ohio USA

Office of Science and Research Institutional Review, New York School of Medicine, NY USA

Institutional Review Board Committee, Jeddah KSA

Institutional Review Board Committee, (KAIMRC), Riyadh KSA

Rabin Medical Centre, Tel Aviv University, Israel

Monash Health Human Research Ethics Committee (HREC) approved following sites in Australia:

- Monash Health, Australia
- Mater Hospital, Australia
- Westmead Hospital, Australia
- Cabrini Hospital, Australia
- St Vincent's Hospital Sydney, Australia
- Bendigo Health, Australia

- Royal North Shore Hospital, Australia

- Alfred Health, Australia

- Sunshine Coast Hospital, Australia

- Logan Hospital, Australia

Northern A Health and Disability Ethics Committee, Auckland City Hospital approved study for sites in New Zealand.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry P2
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier P2
Funding	4	Sources and types of financial, material, and other support P15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors P15
	5b	Name and contact information for the trial sponsor P1
	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
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) P10
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention P4
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) P5

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 P5
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) P5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered P6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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 P8
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)
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 P8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size P13

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions P6

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned P6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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 P7
	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 P7
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 P8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) P9
	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) P8-9
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 P10

	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 P9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct P11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval P2 & 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) P11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) P11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable see item 32 (consent form)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial see item 32 (consent form)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site P15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators see item 32 (consent form)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions P11
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates uploaded as appendix file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable P6

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.