**B**acteremia **A**ntibiotic **L**ength **A**ctually **N**eeded for **C**linical **E**ffectiveness (**BALANCE**) randomized clinical trial: Statistical Analysis Plan Appendix

## 1. Administrative information

### 1.1 Study identifiers

ClinicalTrials.gov registry identifier: https://classic.clinicaltrials.gov/ct2/show/NCT03005145

### 1.2 Full Protocol Reference

The BALANCE protocol is published with open access: https://bmjopen.bmj.com/content/10/5/e038300
This document is the Statistical Analysis Plan Appendix to accompany the full protocol, and includes additional definitions and details.

| 1.3 Revision History Version | Date | Details |
|---|---|---|
| 1.0 (initial) | July 27, 2023 | Initial version |
| 2.0 (final) | Aug 21, 2023 | Final version |

### 1.4 Approvals

The principal investigators and steering committee have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas of expertise and clinical practice. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner, i.e. without knowledge of the effect of the intervention(s) being assessed.

## 2. Outcome measures

### 2.1 Primary outcome measure

The primary outcome will be mortality at 90-days from the date of bacteremia. 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.[1,2]

### 2.2 Secondary outcome measures

Secondary outcomes that we hypothesize to be non-inferior with 7d vs 14d treatment include:

- hospital mortality
- ICU mortality
- relapse rates of bacteremia with the same organism within 30 days
- ICU length of stay and ICU-free days (of 28)
- hospital length of stay and hospital free-days (of 28)
- mechanical ventilation duration and mechanical ventilation-free days (of 28)
- vasopressor duration and vasopressor-free days (of 28)

Secondary outcomes that we hypothesize to be superior with 7d vs 14d treatment include:

- antibiotic allergy and adverse events in hospital
- rates of *C. difficile* infection in hospital
- rates of secondary nosocomial infection/colonization with antimicrobial resistant organisms in hospital
- antibiotic-free days (of 28)

## 3. Outcome definitions

### 3.1. Primary Outcome Definition

The primary outcome will be mortality (from any cause) at 90-days from the date of bacteremia, defined by vital status at 90 days from the date of collection of the index positive blood culture.

### 3.2. Definitions for Secondary Outcomes

**3.2.1 Hospital all-cause *mortality***: recorded as alive or dead at hospital discharge following index positive blood culture.

**3.2.2 ICU all-cause *mortality***: recorded as alive or dead at index ICU discharge following index positive blood culture, among all patients diagnosed with bacteremia during ICU admission.

**3.2.3 Relapse rate of bacteremia**: defined as the recurrence of bacteremia due to original infecting organism (same Genus and species) within 30 days after completing course of adequate antimicrobial therapy.

**3.2.4 Intensive care unit length of stay and ICU free days (of 28)**: ICU length of stay will be defined as the duration between ICU admission (and after the index blood culture) and discharge from the ICU for a consecutive 48-hour period. Durations will be calculated for all patients then separately for patients who died within ICU and those who did not die. ICU-free days (of 28) will be calculated as the cumulative days alive and not in ICU in the first 28 days from collection of the index blood culture; all patients who die within 28 days will be assigned 0 ICU-free days.

**3.2.5 Hospital length of stay and hospital-free days of (28)** – hospital length of stay will be defined as the duration between index blood culture in hospital and discharge date from hospital. Hospital-free days (of 28) will be calculated as the cumulative days alive and not in hospital in the first 28 days from collection of the index blood culture; all patients who die within 28 days will be assigned 0 hospital-free days.

**3.2.6 Duration of mechanical ventilation and ventilator-free days of (28)** – duration of mechanical ventilation will be defined as the number of consecutive days receiving invasive (via an endotracheal tube or tracheostomy) for any duration. Non-invasive ventilation, continuous positive airway pressure and high-flow oxygen therapy will not be considered in this analysis. Ventilator-free days (of 28) will be calculated as the cumulative days alive and not receiving invasive mechanical ventilation in the first 28 days from collection of the index blood culture; all patients who die within 28 days will be assigned 0 ventilator-free days.

**3.2.7 Duration of vasopressor use and vasopressor-free days of (28)-** duration of vasopressor use will be defined as the number of consecutive days receiving intravenous vasoactive medications at any dose or any duration (e.g. epinephrine, norepinephrine, vasopressin, dopamine, phenylephrine, dobutamine, milrinone). Vasopressor-free days (of 28) will be calculated as the cumulative days alive and not receiving vasopressors in the first 28 days from collection of the index blood culture; all patients who die within 28 days will be assigned 0 vasopressor-free days.

**3.2.8 Antibiotic allergy and adverse event**

**3.2.8.1. Anaphylaxis:** To be considered anaphylaxis, the patient must have had ≥1 of the following 3 criteria that a medical team member attributed to an antimicrobial:

- Acute onset of skin or mucosal tissue changes (hives, itching/flush, lip/tongue/uvula

swelling) over minutes/hours, accompanied by
  - respiratory compromise (dyspnea, wheeze, stridor, hypoxemia), AND/OR
  - reduced blood pressure or symptoms/signs of end organ dysfunction from shock
- ☐ Rapid onset of two or more of the following
  - involvement of the skin-mucosa (hives, itch, flush, swollen lips/tongue/uvula)
  - respiratory compromise
  - reduced blood pressure or associated symptoms/signs
  - persistent gastrointestinal symptoms/signs (crampy abdominal pain, vomiting)
- ☐ Reduced blood pressure after exposure to a known allergen for that patient

**3.2.8.2 Antimicrobial-associated renal injury**: To be considered Antimicrobial-associated renal injury, a medical team member must have attributed the renal injury to the Antimicrobial, and the severity of the renal injury must meet one of these (RIFLE criteria):[3]

- ☐ *Risk*: GFR decrease >25%, serum creatinine increased 1.5 times or urine production of <0.5 ml/kg/hr for 6 hours
- ☐ *Injury*: GFR decrease >50%, doubling of creatinine or urine production <0.5 ml/kg/hr for 12 hours
- ☐ *Failure*: GFR decrease >75%, tripling of creatinine or creatinine >355 µmol/l (with a rise of >44) (>4 mg/dl) OR urine output below 0.3 ml/kg/hr for 24 hours
- ☐ *Loss*: persistent AKI or complete loss of kidney function for more than 4 weeks
- ☐ *End-stage renal disease:* need for renal replacement therapy (RRT)

**3.2.8.3 Antimicrobial-associated hepatitis**: To be considered antimicrobial-associated hepatitis, a medical team member must have attributed the hepatitis to the antimicrobial, and the severity of the hepatitis must meet this FDA criteria for hepatic adverse events:

- ☐ ALT> 3x the upper limit of normal

**3.2.9 *Clostridioides difficile*** infection: defined as a positive PCR, culture or ELISA test for *Clostridioides difficile* toxin in the context of diarrhea within hospital (or 90 days, whichever occurs first) of bacteremia diagnosis.

**3.2.10 Risk of colonization/infection with antimicrobial resistant organisms in hospital**– defined as a positive culture yielding a highly resistant microbial organism (HRMO) as defined by a modification of the Dutch nosocomial infection surveillance guidelines from the date of index blood culture until 28 days or hospital discharge whichever is first. This broad definition includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci spp, extended spectrum beta-lactamase producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *Acinetobacter* spp; or Enterobacteriaceae resistant to at least two of fluoroquinolones, aminoglycosides or trimethoprim-sulfamethoxazole, *Acinetobacter* spp resistant to at least two of fluoroquinolones, aminoglycosides or ceftazidime; or non-Enterobacteriaceae resistant to at least three of fluoroquinolones, aminoglycosides, carbapenems, ceftazidime or piperacillin.[4] 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).

**3.2.11 Antibiotic-free days (of 28)** - defined as the number of days during the 28 days after the start of adequate antibiotics in which patients did not receive any dose of any antibiotic. Antifungal and antiviral therapies will not be considered in this analysis. This definition will include all antibiotics, irrespective of their activity against the pathogen(s) in the initial blood culture.

## 4. Sample size calculation

The primary analysis will assess whether 7 days of treatment is associated with a non-inferior 90-day mortality rate in comparison to 14 days of treatment. We require 1,686 patients per arm to establish a non-inferiority margin of +4% absolute increase in mortality (baseline mortality 22%)[5] 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 1.024)[6,7] for a total sample size of 3626. Recent landmark trials in with similar baseline mortality rates have used +4% as a non-inferiority margin;[8,9] the U.S. FDA has recommended a similar margin for analogous industry-sponsored trials.[10] The PneumA study of 8 vs 15 day treatment for VAP used a non-inferiority margin of 10%,[11] as have other recent prominent infectious diseases non-inferiority trials,[12,13] but we believe lower non-inferiority margins are desirable, when feasible, for the outcome of mortality.

## 5. Statistical analysis

### 5.1 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 (adherent to the intention-to-treat principle).[14] 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.[15] 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.[16] The primary analysis will examine whether 90-day mortality is non-inferior in the 7 vs. 14 day treatment group, as determined by whether the 95.7% confidence interval excludes a 4% absolute increase in mortality. Results will also be reported as relative risks with confidence intervals.

In a secondary adjusted analysis we will use generalized linear mixed models with random effects for center (which was a stratification variable) - with log-link and binomial distribution and report relative risks and confidence intervals. If this model fails to converge we will use modified Poisson regression.[17]

### 5.2 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 using the same 4% non-inferiority margin, and relapse of bacteremia using a 2% absolute margin. Continuous secondary outcomes, including ICU, hospital, ventilation and vasopressor free-days by day 28 will be summarized as means and difference in means with 95% CIs as well as medians and difference in medians using quantile regression. For ICU, hospital, ventilation and vasopressor free-days by 28, a 2-day margin will be used for assessing non-inferiority.

We hypothesize that 7 days of treatment will be superior to 14 days of treatment for: antibiotic allergy and adverse events, rates of *C. difficile* infection in hospital, rates of secondary nosocomial infection/colonization with antimicrobial resistant organisms in hospital, and antibiotic-free days (of 28). The evaluation of allergy and adverse events will be important but these analyses are likely to be underpowered due to low event rates, despite the large trial sample size. Antibiotic allergy and adverse events, *C. difficile* infection and secondary nosocomial infection/colonization with antimicrobial resistant organisms are binary outcomes, and we will examine via chi-square tests of proportions. Antibiotic-free days (of 28) will be summarized as means and difference in means with 95% CIs as well as medians and difference in medians using quantile regression.

### 5.3 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 (>48h post admission), Gram positive versus Gram negative infection, illness severity (APACHE II score of ≥25 vs. <25), vasopressor use on day of randomization and baseline Clinical Frailty Score (≥5 vs. <5).[18] We hypothesize that the non-inferiority of 7 versus 14 days of treatment will be consistent across these subgroups. The subgroup analyses will only be conducted for the primary outcome.

**5.4 Frequency of analyses**

Three interim analyses occurred for BALANCE, at 1/6 (600 patients), 1/3 (1200 patients) and 2/3 (2400 patients) of total enrollment; we planned to 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%.[6,7,15] The Data Monitoring Committee (DMC) was guided by a graphical plot indicating mortality differences which would meet futility, inferiority or superiority thresholds. We will perform both frequentist-based and Bayesian-based analyses for the primary outcome at the study's termination. Subgroup analyses were not performed for the interim analyses.

**5.5 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.[19-21] 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 we will additionally perform a companion Bayesian analysis. 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.

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