

# BMJ Open Non-inferiority trial of a shorter (7 days) compared with a longer (14 days) duration of antimicrobial therapy for the treatment of bacteraemic urinary sepsis, measured by microbiological success after the completion of therapy: a substudy protocol for the Bacteraemia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) multicentre randomised controlled trial

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## ABSTRACT

**Introduction** The BALANCE study is a randomised clinical trial (3626 participants) designed to assess the non-inferiority of 7 days (short-course) antibiotic therapy compared with 14 days of therapy for bacteraemia using the pragmatic endpoint of 90-day survival. Based on pilot study data, approximately 30% of enrollees will have a urinary tract infection (UTI) as the source of bacteraemia.

**Methods and analysis** We aim to assess the non-inferiority of short-course antibiotic therapy for patients with bacteraemia UTIs. Participating sites in four countries will be invited to join this substudy. All participants of this substudy will be enrolled in the main BALANCE study. The intervention will be assigned and treatment administered as specified in the main protocol.

We will include participants in this substudy if the probable source of their infection is a UTI, as judged by the site principal investigator, and they have a urine microscopy and culture indicative of a UTI. Participants will be excluded if they have an ileal loop, vesicoureteric reflux or suspected or confirmed prostatitis.

The primary outcome is the absence of a positive culture on a test-of-cure urine sample collected 6–12 days after cessation of antimicrobials, with a non-inferiority margin of 15%. Secondary outcomes include the clinical resolution of infection symptoms at test-of-cure.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a substudy of patients with bacteraemia from a urinary source enrolled in a large randomised trial of treatment duration for bloodstream infection.
- ⇒ This substudy will assess urinary sepsis disease-specific endpoints not captured in the main trial.
- ⇒ The endpoints selected have been used extensively in studies of antimicrobial therapy for urinary tract infection.
- ⇒ Due to COVID-19-related challenges in initiation, the study will have a limited sample size relative to the cohort of patients with urinary sepsis in the main BALANCE study.
- ⇒ The substudy is recruiting from fewer countries and sites than the main study, impacting on generalisability.

**Ethics and dissemination** The study has been approved in conjunction with the main BALANCE study through the relevant ethics review process at each participating site. We will disseminate the results through the Australasian Society for Infectious Diseases, Canadian Critical Care Trials Group, the Association for Medical Microbiology and Infectious Diseases Canada Clinical Research Network (AMMI Canada CRN) and other collaborators.

**Universal trial number** U1111-1256-0874.

**Main BALANCE trial registration** NCT03005145.

**Trial registration number** Australian Clinical Trial Register: ACTRN12620001108909.

## BACKGROUND AND RATIONALE

The BALANCE study is a randomised clinical trial comparing 7–14 days of therapy for bacteraemia.<sup>1</sup> It is designed to assess the non-inferiority of survival of those receiving short duration (7 days) as compared with longer duration (14 days) of antimicrobial therapy. In addition to survival, assessing clinical cure is important for selected foci of infection.

Pilot and preliminary data suggest approximately 30% of enrollees in BALANCE will have a urinary tract infection (UTI) as the source of bacteraemia.<sup>2</sup> UTI is a site of infection where there may be residual clinical uncertainty about the efficacy of short-course (7 day) therapy for the overall cure of infection, even if BALANCE demonstrates non-inferior survival. This uncertainty may especially apply to groups where UTI therapy has traditionally been considered less straightforward for example, males, catheter-associated UTI.

National guidelines continue to recommend extended courses of therapy (10–14 days) for non-bacteraemic UTI presentations.<sup>3</sup> Data from a clinician survey of the treatment recommendations for five bacteraemia scenarios indicate urinary sepsis presentations are recommended longer durations of therapy than other common sources of bacteraemia (pneumonia, abdominal infection, line-related infection).<sup>4 5</sup> Typically, for trials of UTI/urinary sepsis therapy, clinical and microbiological resolution of the infection are recommended as the primary endpoints.<sup>6 7</sup>

To date, the limited clinical trial data supporting the efficacy of 7 days of antimicrobial therapy for bacteraemia originating from a UTI pertain only to the fluoroquinolone class of antimicrobials. The real-world applicability of this data is limited by the safety concerns of fluoroquinolones which have led to many guidelines recommending other agents for first-line treatment of UTI.<sup>3 8</sup>

The non-inferiority of 7 compared with 14 days of ciprofloxacin in 156 women, 18 years or older with pyelonephritis, has been demonstrated in a study consisting of younger women (median age <50) mainly with uncomplicated pyelonephritis (90%). In total 27% of enrollees had bacteraemia.<sup>9</sup> Yahav *et al* demonstrated the non-inferiority of 7 compared with 14 days of therapy for bacteraemia among 604 stable patients. In this group, 68% of enrollees had a urinary source of bacteraemia and approximately 75% of all patients in the study were treated with a fluoroquinolone.<sup>10</sup>

A systematic review and meta-analysis on short versus long duration therapy for UTI identified 2515 patients in clinical trials. Microbiological failure showed a non-significant difference between short-treatment and long-treatment. Many patients received fluoroquinolones (n=1638), with a higher proportion in the short-duration therapy group. Within this analysis, the subgroup of

patients treated with beta-lactams was small (n=331) and showed high heterogeneity. The subgroup of patients with complicated UTI yielded uncertain results.<sup>11</sup> A large retrospective study compared the efficacy of oral beta-lactams compared with fluoroquinolones or trimethoprim/sulfamethoxazole for the treatment of Enterobacterales bacteraemia from a urinary source. The median duration of therapy for each group was 14 days, so conclusions could not be drawn about a shortened duration of treatment.<sup>12</sup>

Two additional randomised trials have compared 7–14 days of therapy for Enterobacterales bacteraemia. Neither of these studies offer conclusions on the treatment of UTI specifically, as subgroup analysis based on the source of bacteraemia was not presented and the endpoints were general rather than UTI specific.<sup>13 14</sup>

## Objectives

Our research hypothesis is that 7 days of antimicrobial is non-inferior to 14 days of antimicrobial for the microbiological cure of urinary sepsis with bacteraemia.

If the main BALANCE study finds non-inferiority of short course therapy, this study will address clinical uncertainty that may remain about the efficacy of short-course therapy in the treatment of urinary sepsis. The varied cohort (complicated and uncomplicated infection) treated with a range of antimicrobial classes will provide evidence to assess non-inferiority in populations including those with complicated UTI and those treated with an antimicrobial class other than a fluoroquinolone.

## Study design

This is a substudy of BALANCE (NCT03005145), an international multicentre non-inferiority trial of 7 versus 14 days of antibiotics for bloodstream infection. The study is recruiting patients in intensive care unit (ICU) and ward settings. The main study has a parallel group, open-label design with allocation of antibiotic treatment group concealed until day 7 of adequate antibiotic therapy. It uses a pragmatic primary outcome, 90-day mortality and does not include detailed clinical and microbiologic test of cure information.

The substudy does not require any additional randomisation, blinding or intervention. It involves the enhanced collection of background data, clinical symptoms, microbiological data and urine samples related to the UTI. This will allow for the assessment of UTI-specific endpoints in addition to the primary endpoints in the main BALANCE study.

## Setting

BALANCE is being conducted across a diverse range of hospitals in Canada, Australia, New Zealand, USA, Switzerland, Saudi Arabia and Israel. This substudy will invite sites in BALANCE from Australia, Canada, New Zealand and Israel to participate. A full list of sites participating in BALANCE is available at <http://balance.ccctg.ca>.

## Eligibility

All participants enrolling in this substudy will have met the inclusion and exclusion criteria specified in the BALANCE study protocol. Additional entry criteria for this substudy are outlined below. Participants can be identified as eligible for this substudy at the time of enrolment into the main BALANCE study or at any time between enrolment and unblinding of the participant's treatment allocation to the site investigators. We will maintain a master log of all patients who are eligible but not enrolled in the substudy.

### Substudy inclusion criteria

Participants must meet all three inclusion criteria.

1. The participant has been enrolled and randomised in the BALANCE study.
2. The source of bacteraemia is most likely to originate from the urinary tract as evidenced by:
  - a. The enrolling clinician believes that the urinary tract is the 'most likely' source of the bacteraemia; and
  - b. Routine clinical work-up has not identified another 'probable' source of the bacteraemia.
3. The participant has a urine microscopy and culture result on a fresh urine sample (not from the drainage bag of a urinary catheter) supporting the urinary tract as a source of bacteraemia as evidenced by the presence of a and b:
  - a. The urine culture has been collected during the same episode of acute illness associated with the bacteraemia; and
  - b. Microbiological findings are supportive of a urinary source. An acceptable supportive result is ANY of the three criteria below:
    - i. A urine culture has isolated the same bacteria (genus and species) as the blood culture. The antimicrobial resistance phenotype (antibiotic susceptibility pattern) may vary from the blood isolate; or
    - ii. A urine culture has isolated mixed bacteria for which individual species have not been characterised; or
    - iii. A urine culture collected after antimicrobial therapy demonstrates a white cell count consistent with a urinary source of sepsis, based on local interpretation guidelines.

### Substudy exclusion criteria

Participants meeting any of the criteria below are not eligible for enrolment:

1. Participants with suspected or confirmed prostatitis.
2. Participants with an ileal loop or vesicoureteric reflux.
3. Participants who are unable or unwilling to provide a follow-up urine sample for culture within the specified study timeframe.

## Intervention

Within the main trial participants are randomised to receive a shorter duration (7 days) versus a longer duration

(14 days) of adequate antimicrobial therapy. Full definitions of adequate antimicrobial treatment and treatment duration are in the main study protocol and require that the pathogen be susceptible to the prescribed agent(s).

If there is a difference in the antimicrobial susceptibility phenotype between urine and blood isolates the urine susceptibility will be used for the analysis of this substudy. If the pathogen was not cultured in the urine sample, or antimicrobial susceptibility is not available on the urine isolate, then the susceptibility of the blood isolate will be used.

Adherence to treatment duration is discussed in the main protocol. Several factors may impact on the adherence with treatment duration in this substudy relative to the whole cohort. Patients with a urinary source of bacteraemia have a lower mortality and potentially less complicated course than those with other sources of bacteraemia. This may support better adherence to the study-specified durations in hospital. In contrast, due to a potentially shorter hospital stay a higher proportion of patients in this cohort may be discharged with unsupervised oral study therapy. Because of these factors it is unknown if or how the overall adherence to treatment duration will differ from the whole-study cohort.

## Primary outcome

The primary outcome is microbiological success at the test-of-cure (TOC) urine sample collected 6–12 days after cessation of study-defined antimicrobial therapy. This is defined as the urine sample reported as having 'no-growth' OR 'no significant growth' (or the equivalent local terminology) on bacterial culture. The sample can be processed at any locally approved clinical laboratory and interpretation of culture results will be based on the standard reporting of this laboratory.

## Secondary outcomes

1. Clinical success in the treatment of the UTI at the time of TOC sample. This is defined as resolution of all the symptoms associated with the UTI at trial entry and the occurrence of no new symptoms.
2. Combined clinical and microbiological success at the time of TOC.

## Exploratory outcomes

1. Participant-reported recurrence of confirmed UTI by 90 days postrandomisation.
2. Participant-reported receipt of non-trial specified antimicrobial therapy by 90 days postrandomisation.
3. Survival at day+90.

Note the outcomes listed as exploratory outcomes were listed as secondary outcomes in the initial clinical-trial registration of this protocol.

## Non-inferiority margin for outcome

The primary and secondary outcomes in this substudy will be assessed with a non-inferiority margin of a 15% absolute difference. This was revised from 10% to 15% absolute difference after trial registration and initiation

(without any examination of outcome results). This revision was a pragmatic decision based on a potentially acceptable margin to clinicians and the feasibility of completing substudy recruitment (expected recruitment from substudy sites before the end of completion of the main study). It was undertaken due to COVID-19-related delays in initiation of the substudy and fewer sites than planned able to participate.

The 10% non-inferiority margin specified in the original clinical trial registration of this protocol was chosen to align with recommendations by the European Medicines Agency Guidance and United States Food and Drug Administration for the evaluation of new antimicrobials in the therapy of complicated UTI.<sup>6 7</sup>

### Sample size

The expected rate of microbiological success in the 14-day therapy arm is 80%–90%. This estimate is based on data outlined in US FDA guidance documents. Within this document the ‘microbiological success’ rate among 10 cohorts (from seven studies) treated for ‘complicated UTI’ ranged from 74% to 88%. The assessment time-point varied from 3 to 10 days after the end of treatment.<sup>6</sup> As our cohort will include patients with both complicated and uncomplicated UTI, we are expecting the success rate to be at or above the upper-end of these studies.

If the primary outcome rate is 90% in the 14-day group, a total of 126 assessable participants (63 patients per arm) are required to demonstrate non-inferiority in the short-duration therapy group (power of 80% and alpha of 0.025). If the primary outcome rate is 80% in the

14-day group, we require 224 assessable participants (112 patients per arm) to demonstrate non-inferiority. Based on the published data, we estimate 10% of participants will not be assessable for the primary endpoint due to non-submission of a suitable TOC sample.<sup>15 16</sup> As outlined in the main study protocol, an overall follow-up rate of 99% or greater is expected for 90-day mortality. The sample size for this substudy is not fixed. It will continue to recruit until the main study is fully recruited. Sample size calculations are provided however, to indicate feasibility.

### Participant timeline

Enrolment can occur at any time up until the unblinding of treatment duration within the main study on day 7 of adequate antimicrobial therapy. If unblinding occurs before day 7 (as specified in the main protocol) then the participant will become ineligible for the study.

Frequency and duration of follow-up is aligned with the main protocol, where possible. Substudy participants have one additional visit 6–12 days after completion of antimicrobial therapy, to assess the primary endpoint. This time window allows five full days free of antimicrobial therapy before collection of the sample and clinical symptoms. Sub-study events are outlined in [table 1](#).

### Randomisation and allocation concealment

Randomisation and allocation concealment are described in the main protocol. In brief, randomisation using variable block size with stratification by hospital site and ICU versus non-ICU location is known from a web-based platform. To minimise the potential bias introduced by the

**Table 1** Substudy events by day. (day+1 is the first day of effective antimicrobial therapy for the bacteraemia).

| Days                                                            | Days 1–6 | Day 7         | Days 8–12 | Day 13                         | Day 14         | Day 19                       | Day 20                          | Days 26                       | Day 90 |
|-----------------------------------------------------------------|----------|---------------|-----------|--------------------------------|----------------|------------------------------|---------------------------------|-------------------------------|--------|
| Sub-study Activities                                            |          |               |           |                                |                |                              |                                 |                               |        |
| Eligibility screening*                                          | X        |               |           |                                |                |                              |                                 |                               |        |
| Consent*                                                        | X        |               |           |                                |                |                              |                                 |                               |        |
| Collection of baseline data                                     | X        |               |           |                                |                |                              |                                 |                               |        |
| Unblinding of antibiotics duration (main study procedure)       |          | X             |           |                                |                |                              |                                 |                               |        |
| Cessation of antibiotics (main study procedure)                 |          | X (7-day arm) |           |                                | X (14-day arm) |                              |                                 |                               |        |
| Test of cure (collection of TOC urine sample and clinical data) |          |               |           | 7-day arm start of TOC window† |                | 7-day arm end of TOC window† | 14-day arm start of TOC window† | 14-day arm end of TOC window† |        |
| Participant reported antimicrobial use and UTI                  |          |               |           |                                |                |                              |                                 |                               | X      |

\*Eligibility screening and consent for the sub-study can occur simultaneously with enrolment in the main study OR at any time after this until the point where the antimicrobial duration allocation is unblinded. Once the antimicrobial duration has been unblinded the participant is ineligible for the sub-study

†The TOC window should be calculated to be 6–12 days after the actual stop date of antibiotic therapy. Time-windows in this table apply only to participants who take exactly 7 or exactly 14 days of therapy. TOC, test-of-cure.

open-label nature of the trial randomisation assignment is concealed until day 7 of the study. At this point the treating team is instructed to cease antimicrobials (short arm) or continue for a further 7 days (long arm).

### Data and sample collection

Substudy-specific data and variables will be collected in designated substudy case report forms. This includes enhanced details of urine microbiology results and additional clinical data. It will be collected at three time points. At substudy enrolment data will be collected by hospital-based clinical research staff (background of urinary tract abnormalities or interventions, symptoms associated with UTI presentation). Further data will be collected 6–12 days after completion of antibiotics (clinical symptoms of UTI and participant-reported antimicrobial use) and day 90 (participant-reported antimicrobial use and/or recurrence of UTI). The two later time points will be collected in-person (for participants remaining hospitalised) or via telephone (for discharged participants). A range of data quality checks are performed on all entered data and any discrepancies identified are queried with the study site.

The TOC urine sample is the only protocol-specified pathology sample required for the substudy. In non-catheterised patients a clean-catch mid-stream urine sample is required. In patients with an indwelling urinary catheter a fresh catheter specimen urine (not from the collecting bag) is required. Specimens should be collected as per the standard clinical collection protocol at the study site. Return of the TOC sample is crucial to ascertain the primary endpoint of this substudy. Study sites will develop a locally appropriate procedure to facilitate collection and return of the TOC sample to a clinical laboratory where it can be analysed and reported. The cultured pathogens are not being retained or stored.

### Analysis

This substudy will be conducted, analysed and reported according to the Consolidated Standards of Reporting Trials guidelines. The primary analysis will be by the assigned group (intention-to-treat, ITT). This group will be the equivalent of a 'microbiological intention-to-treat population' as all participants will have a microbiological sample.<sup>7</sup> Participants who have recommenced antimicrobial therapy between the cessation of trial-specified antimicrobials and the collection of the TOC sample have continued antimicrobials for 7 days or more beyond their randomised duration or have not submitted a TOC sample will be considered to not have met the primary outcome.

To support the primary analysis, a per-protocol analysis will be undertaken within the ITT population including only patients who adhered closely to the randomised duration of therapy (range 5–9 days for the 7-day group; range 12–16 days for the 14-day group) and did not have an alternative source of bacteraemia identified by the time of collection of the TOC sample. Participants

who have died before cessation of antimicrobials or have not submitted TOC sample will be excluded from this analysis.

For the primary and secondary outcomes, a 95% CI will be used to assess non-inferiority using the 15% margin. For the exploratory outcomes, a  $\chi^2$  test will be used to test for differences between groups.

Subgroup analyses will be performed for principal class of antimicrobial therapy (fluoroquinolone; beta-lactam  $\pm$  BLI), defined as participants who have received  $\leq 72$  hours of effective therapies from an alternate class of antimicrobial; complicated UTI defined as presence of indwelling catheter, urinary retention, urinary obstruction (nephrolithiasis or other causes), a neurogenic bladder ( $>100$  mL after voiding); participant sex; key pathogen groups (*Escherichia coli*; Gram-negative bacilli excluding *E. coli*). These subgroups encompass pathogens (Gram-negative bacilli other than *E. coli*) and populations (complicated UTI; male sex) who have traditionally demonstrated a relatively lower rate of cure in clinical trials of therapy for UTI.

Changes since clinical trial registration of the protocol are the inclusion of participants who do not submit a TOC sample in the ITT population and modification of the 'per-protocol' time window for the 7-day group (previously 6–8 days), to align with the main study ITT population. Additionally, the subgroup analyses have been simplified.

### Full balance cohort analysis

To supplement and contextualise the substudy, an analysis of all participants in the BALANCE study with a urinary tract source of bacteraemia will be undertaken. Participants will be included if they meet inclusion criteria 1 and 2 in this protocol (ie, the urinary tract is recorded as the 'most likely' source of infection and no other recorded 'probable' source is reported). Inclusion criteria 3 and the substudy exclusion criteria will not be applied as relevant information is not recorded for all participants (urine cell-counts and specific details on the urinary tract are only recorded for participants in this substudy).

The primary outcome will be the 'absence of indicators of recurrent UTI' occurring within 14 days after cessation of study antimicrobials. This will be indicated by the absence of: (1) recommencement of antimicrobial therapy; (2) positive cultures from the urinary tract, bloodstream or another sterile site, with the same pathogen as the index blood culture; 3) readmission to hospital (for those discharged).

ITT, per-protocol (excluding the requirement for a TOC sample) and subgroup analysis will be undertaken as outlined for this substudy. Sensitivity analysis will be undertaken (1) including only participants who can meet substudy inclusion criteria 3 and (2) on the different components of primary outcome. All analyses will be based on  $\chi^2$  test.

## Study and data monitoring

As this is an observational substudy, a separate Data Safety Monitoring Board has not been convened and there is no additional study site monitoring required for this study. No interim assessment of the data is planned. Adverse events will be managed as per the procedures outlined in the main study; this observational substudy will not have the potential to incur adverse events.

## ETHICS AND DISSEMINATION

As this sub-study involves minimal additional data collection, minimal participant burden and no additional risk, the study protocol was approved as a modification to the main BALANCE study. This was undertaken through the relevant pathway at each participating site.

We will disseminate the results through the Australasian Society for Infectious Diseases, Canadian Critical Care Trials Group, the Association for Medical Microbiology and Infectious Diseases Canada Clinical Research Network (AMMI Canada CRN) and other collaborators.

## Informed consent

All participants entering this substudy will have provided informed consent for the main study. Consent is obtained by research staff or an investigator, from the patient or a substitute decision-maker, as per the main study protocol. Informed consent for substudy participation is obtained within the main participant information and consent form. Additional explanatory text and a checkbox confirming the research team has gained consent to participate in the substudy were added to the original form (see online supplemental material).

Withdrawal from the study will be handled as described in the main study protocol. If a participant withdraws from the main BALANCE study, they will be considered as withdrawn from this urine substudy. A participant can also elect to withdraw from this sub-study alone.

## Ancillary care

As the TOC sample is not blinded and processed by a clinical laboratory, study sites are required to provide clinical follow-up of the TOC urine sample. Each site will define a locally appropriate process for this. If the TOC sample yields a positive culture, with any pathogen, the responsible clinician will assess the need for further antimicrobial therapy and/or additional clinical review required. If antimicrobial therapy is recommenced based on the results of the TOC sample this will be recorded as a protocol deviation as specified in the main protocol.

## Study progress and protocol updates

The first participant was enrolled in the substudy on 29 October 2020 in Australia. To date 69 patients have been enrolled. The main BALANCE study has recruited 3010 of a planned 3626 patients. The majority of sub-study participants are expected to come from Australia which

has recruited 327 of a planned 800 participants to the main BALANCE trial.

This study was prospectively submitted for clinical trial registration and received ethics approval based on an earlier version of this protocol (available from the authors on request). Changes from this version are outlined in the relevant text sections.

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