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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.
BACKGROUND and RATIONALE

The BALANCE study is a randomised clinical trial comparing 7–14 days of therapy for bacteraemia. 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 enrolles in BALANCE will have a urinary tract infection (UTI) as the source of bacteraemia. 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. 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). Typically, for trials of UTI/urinary sepsis therapy, clinical and microbiological resolution of the infection are recommended as the primary endpoints.

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.

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 enrolles had bacteraemia. 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 enrolles had a urinary source of bacteraemia and approximately 75% of all patients in the study were treated with a fluoroquinolone.

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. 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.

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.

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.cccctg.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 post-randomisation.
2. Participant-reported receipt of non-trial specified antimicrobial therapy by 90 days post-randomisation.
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.6 7

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 5 to 10 days after the end of treatment.6 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.13 14 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>
<thead>
<tr>
<th>Table 1</th>
<th>Substudy events by day. (day+1 is the first day of effective antimicrobial therapy for the bacteremia).</th>
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<tbody>
<tr>
<td>Days</td>
<td>Days 1–6</td>
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<td>---------</td>
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<tr>
<td>Sub-study Activities</td>
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<tr>
<td>Eligibility screening*</td>
<td>X</td>
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<td>Consent*</td>
<td></td>
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<tr>
<td>Collection of baseline data</td>
<td>X</td>
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<tr>
<td>Unblinding of antibiotics duration (main study procedure)</td>
<td>X</td>
</tr>
<tr>
<td>Cessation of antibiotics (main study procedure)</td>
<td>X (7-day arm)</td>
</tr>
<tr>
<td>Test of cure (collection of TOC urine sample and clinical data)</td>
<td>7-day arm start of TOC window†</td>
</tr>
<tr>
<td>Participant reported antimicrobial use and UTI</td>
<td>X</td>
</tr>
</tbody>
</table>

*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. 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 ± BLI), defined as participants who have received ≤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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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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REFERENCES


Participant Information Sheet/Consent Form – Participant

[Insert site name]

Title
Bacteraemia Antibiotic Length Actually Needed for Clinical Effectiveness

Short Title
BALANCE

Protocol Number
Version 1.4

Project Sponsor
Canadian Institute of Health Sciences, National Health and Medical Research Council

Coordinating Principal Investigator/Principal Investigator

Associate Investigator(s)
(if required by institution)

Location (where CPI/PI will recruit)

Part 1 What does participation involve?

1 Introduction
You are invited to take part in this research project. This is because you have a bloodstream infection and are being treated with antibiotics in the hospital. The research project is to determine the optimum duration for treatment of bloodstream infection that will allow doctors in the future to make informed decisions about how long to give the antibiotics for.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not you want to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don’t wish to take part, you do not have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read
• Consent to take part in the research project
• Consent to having the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The purpose of this study is to determine whether in patients with bloodstream infection, shorter duration antibiotic treatment (7 days) is associated with the same survival rates at 90 days to those achieved with longer duration antibiotic treatment (14 days).

The current study is designed to find the best possible duration of antibiotic treatment in patients with bloodstream infections and will answer the question of whether patients with bloodstream infection can be treated with a shorter duration of antibiotic therapy (7 days). The goal is to make cure rates as high as possible, while making antibiotics side effects and complications (including antibiotic resistance) as low as possible.

There are no guidelines for doctors as to how long to treat patients with bloodstream infection, and so there is no standard of care for treatment of patients with bloodstream infections. Doctors treat these patients based on their personal experience and choice. There is wide variation in treatment duration; some patients are treated for a few days while others are treated for many days due to lack of evidence. The most common treatment choices by hospital doctors are 14, 10 and 7 days. Therefore, there is a need to do a research study to determine the best antibiotic treatment duration in these patients.

The study is funded by the Canadian Institute of Health research & National Health and Medical Research Council and is a collaboration between the Australia and New Zealand Intensive Care Society clinical trials group and the Canadian Critical Care Trials Group.

3 What does participation in this research involve?

You will be participating in a randomised controlled research project. You will be required to sign the consent form before any study assessments are performed.

Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random).

As part of routine care, patients suspected of having an infection have a blood sample sent to the laboratory by the treating team to see if there is any infection and to find the bacteria causing it. These blood tests are screened by the research team to see if the participant is eligible to be included in the study.

We then randomise you into one of the groups described below. Randomisation means that you are put into a group by chance (Like flipping a coin). There is no way to predict which group you will be assigned to. There is a 50% chance of receiving 7 days and 50% chance of receiving 14 days of treatment. Neither the study staff, nor the study doctors choose what group you will be in.

Group 1: short course (7 days) of antibiotic treatment

If you are randomised to this group you would receive antibiotics for a total of 7 days. The treating team will stop the antibiotics after the last dose is received on day 7. The treating team has full
authority to refuse to stop antibiotics at this stage if they strongly feel the need to continue antibiotics beyond day 7 for the same infection or if a new infection has developed meanwhile.

Group 2: long course (14 days) of antibiotic treatment

If you are randomised to this group you would receive antibiotics for 14 days. The treating team will stop the antibiotics after the last dose is received on day 14. The treating team has full authority to refuse to stop antibiotics at this stage if they strongly feel the need to continue antibiotics beyond day 14 for the same infection or if a new infection has developed meanwhile.

The selection of antibiotics, doses and route is initially done by the treating doctor. As soon as preliminary blood test results are available, the study team review the antibiotics to make sure you are receiving the right antibiotics for the bacteria causing the infection. After the blood test results are finalised, the team re-reviews the antibiotic to ensure that you are still getting the best possible antibiotic. If the antibiotic was not adequate, the treating team changes the antibiotic to adequate ones.

You will be followed by the research team in the hospital to collect study related data like age, sex, hospital admission dates, severity of disease, reason for hospital admission and underlying disease etc. We will also collect data regarding signs and symptoms of any new infections, blood test results, any side effects, and status at the time of hospital discharge. If you are discharged from hospital within 90 days of bloodstream infection, we will contact you by telephone to see how you are 90 days later.

As you have been in the hospital when the antibiotics are given, you would be closely monitored and treated immediately if problems arise.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. There are no additional costs associated with participating in this research project, nor will you be paid.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

Urinary tract infection sub-study

If your bloodstream infection was caused by a urinary tract infection you will be invited to participate in this sub-study. If you are willing to participate we will ask you to submit a urine sample for culture 6-12 days after you complete your antibiotics. This test is to confirm that the bacteria that caused your infection does not remain in your urine. This sample can go to a local pathology laboratory (you will not receive a bill for this). Our research staff will also be contacting you at this time to confirm that your symptoms have resolved.

4 Other relevant information about the research project

In total there will be 3,622 participants taking part in the study in countries like New Zealand, Canada, Australia, USA, Saudi Arabia, Israel and possibly other countries too around the world.

The study involves researchers from Canadian institute of Health Sciences and Australia and New Zealand Intensive care society working in collaboration with each other.

5 Do I have to take part in this Research Project?
Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your relationship with those treating you or your relationship with the hospital you are being treated in.

6 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. If you decide to participate, you will be receiving antibiotics for either 7 days or 14 days, depending upon which arm you get randomised in. If you decide not to take part, you will continue to receive antibiotics as determined by your treating team.

7 What are the possible benefits of taking part?

You may or may not benefit directly from participating in this study. Your participation may or may not help other people with bloodstream infection in the future but by participating in this research, you may contribute to the knowledge and development of new treatment strategies for bloodstream infections in the future. We hope the information learned from this study will help other people with similar infections in the future.

8 What are the possible risks and disadvantages of taking part?

The treatment you will receive while participating in this research project is the same treatment you may receive as part of standard care. The only difference is that how long you receive the antibiotics for will be determined by which group you are assigned to. This can be changed by the treating team if they strongly feel they need to, therefore there are no extra risks from participation.

9 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw from the study, the study doctor will make arrangements for your regular health care to continue. If you decide that you wish to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, the study doctor might consider it to be in your best interests to be withdrawn from the research project. If this happens, the doctor will explain the reasons and arrange for your regular health care to continue.

10 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow you or the research supervisor to further discuss any health risks or special requirements linked to withdrawing.

If you do withdraw during the research project, the study doctor and relevant study staff will not collect additional personal information, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form
part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

If you are participating in the urine sub-study you can elect to withdraw only from this study or from the whole project.

11 What happens when the research project ends?

If you give us your permission by signing the consent document, we plan to discuss and publish the results from this study in peer-reviewed journals, conference presentations on the internet and a public lay press release. In any publication, information will be provided in such a way that you cannot be identified.

Part 2 How is the research project being conducted?

12 What will happen to information about me?

Your medical information resulting from participation in this study will be recorded by the study staff and stored on a secure database. Your study results will be coded for confidentiality and a Master code that identifies codes with the participants will only be accessible by site investigators and only where necessary by law, will the names be accessed. Only coded study information will be securely transferred to the data management centre (The Sunnybrook Institute for Research) for evaluation. Your original medical records may be reviewed by study monitors, the Ethics Review Committee, and regulatory authorities for the purpose of verifying clinical trial procedures and accuracy of data where necessary. For this reason, study data will be stored for 15 years after study completion. Study data in this de-identified format may be used or given to regulatory authorities if required but individual participants will not be identifiable. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to participation in this research project.

13 Can I access my information/data?

In accordance with relevant Australian and/or State privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information with which you disagree be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

14 Who is organising and funding the research?

The study has been designed by a group of intensive care researchers and infectious diseases physicians from Canada. The study is being carried out in collaboration with Canadian and Australia and New Zealand Intensive care and infectious diseases physicians. The study is being funded by the Medical Research Council of Canada.

15 Is this research project approved?
The ethical aspects of this research project have been approved by the Monash Health Human Research Ethics Committee.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

16 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on [Contact phone number] or any of the following people:

Clinical contact person

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<th>Name</th>
<th>[Name]</th>
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<td>Position</td>
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<td>Email</td>
<td>[Email address]</td>
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Complaints contact person

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If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

<table>
<thead>
<tr>
<th>Reviewing HREC name</th>
<th>Monash Health Human Research ethics Committee</th>
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<tbody>
<tr>
<td>HREC Executive Officer</td>
<td>Deborah Dell</td>
</tr>
<tr>
<td>Telephone</td>
<td>95944605</td>
</tr>
<tr>
<td>Email</td>
<td><a href="mailto:Deborah.dell@monashhealth.org">Deborah.dell@monashhealth.org</a></td>
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Local HREC Office contact (Single Site - Research Governance Officer)

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Consent Form – Adult Providing Own Consent

Title
Bacteraemia Antibiotic Length Actually Needed for Clinical Effectiveness

Short Title
BALANCE

Protocol Number
Version 1.4

Project Sponsor
Canadian Institute of Health Sciences, National Health and Medical Research Council

Coordinating Principal Investigator/
Principal Investigator

Associate Investigator(s)
(if required by institution)

Location (where CPI/PI will recruit)

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the research project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to [Name of Institution] concerning my disease and treatment for the purposes of this research project. I understand that such information will remain confidential.

I am willing to participate in the urine sub-study (cross if not relevant)

NO □ YES □ 

Participant Initials……………………

Declaration by Participant – for participants who have read the information

Name of Participant (please print) 

Signature of Participant ____________________________ Date__________
Declaration - for participants unable to read the information and consent form

Name (please print) __________________________________________________________

Signature _______________________________ Date ______________________________

* Witness is not to be the Investigator, a member of the study team or their delegate. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/Senior Researcher† (please print) __________________________________________

Signature _______________________________ Date ______________________________
Form for Withdrawal of Participation – Participant

Title
Bacteraemia Length Actually Needed for Clinical Effectiveness

Short Title
BALANCE

Protocol Number
Version 1.4

Coordinating Principal Investigator/
Principal Investigator

Associate Investigator(s)
(if required by institution)

Location (where CPI/PI will recruit)

Declaration by the participant

I wish to withdraw from taking part in the above research project and understand that such withdrawal will not affect my routine treatment, relationship with those treating me or my relationship with [Institution].

<table>
<thead>
<tr>
<th>Name of Participant (please print)</th>
<th>Signature of Participant</th>
<th>Date</th>
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| Name of Study Doctor/
Senior Researcher (please print) | Signature | Date |
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Note: All parties signing the consent section must date their own signature.