Safe shortening of antibiotic treatment duration for complicated Staphylococcus aureus bacteraemia (SAFE trial): protocol for a randomised, controlled, open-label, non-inferiority trial comparing 4 and 6 weeks of antibiotic treatment

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ABSTRACT

Introduction A major knowledge gap in the treatment of complicated Staphylococcus aureus bacteraemia (SAB) is the optimal duration of antibiotic therapy. Safe shortening of antibiotic therapy has the potential to reduce adverse drug events, length of hospital stay and costs. The objective of the SAFE trial is to evaluate whether 4 weeks of antibiotic therapy is non-inferior to 6 weeks in patients with complicated SAB.

Methods and analysis The SAFE-trial is a multicentre, non-inferiority, open-label, parallel group, randomised controlled trial evaluating 4 versus 6 weeks of antibiotic therapy for complicated SAB. The study is performed in 15 university hospitals and general hospitals in the Netherlands. Eligible patients are adults with methicillin-susceptible SAB with evidence of deep-seated or metastatic infection and/or predictors of complicated SAB. Only patients with a satisfactory clinical response to initial antibiotic treatment are included. Patients with infected prosthetic material or an undrained abscess of 5 cm or more at day 14 of adequate antibiotic treatment are excluded. Primary outcome is success of therapy after 180 days, a combined endpoint of survival without evidence of microbiologically confirmed disease relapse. Assuming a primary endpoint occurrence of 90% in the 6 weeks group, a non-inferiority margin of 7.5% is used. Enrolment of 396 patients in total is required to demonstrate non-inferiority of shorter antibiotic therapy with a power of 80%. Currently, 152 patients are enrolled in the study.

Ethics and dissemination This is the first randomised controlled trial evaluating duration of antibiotic therapy for complicated SAB. Non-inferiority of 4 weeks of treatment would allow shortening of treatment duration in selected patients with complicated SAB. This study is approved by the Medical Ethics Committee VUmc (Amsterdam, the Netherlands) and registered under NL8347 (the Netherlands Trial Register). Results of the study will be published in a peer-reviewed journal.

TRIAL REGISTRATION NUMBER NL8347 (the Netherlands Trial Register).

INTRODUCTION

Staphylococcus aureus can lead to a myriad of clinical infections, virtually in every organ
and ranging from mild to severe disease. S. aureus bacteremia (SAB) is one of the most feared clinical manifestations given its ability to cause metastatic complications, including infective endocarditis and bone infections. SAB accounts for a substantial proportion of all bloodstream infections and is associated with a 3-month overall mortality of around 30%.2,3

SAB is categorised as ‘complicated’ or ‘uncomplicated’, of which several definitions exist.4 In general, SAB is classified as ‘uncomplicated’ if there is a transient bacteremia without deep tissue infection and as ‘complicated’ if infective endocarditis, metastatic infection foci or deep tissue infection is present. Clinical predictors of complicated SAB include community acquisition of bacteremia, delayed start of adequate antibiotic treatment, persistent fever 72 hours after the initial positive blood culture and positive follow-up blood cultures more than 48 hours after initiation of adequate antibiotic treatment.2,5 The dichotomisation of SAB in ‘complicated’ and ‘uncomplicated’ guides diagnostic and therapeutic management and is a major determinant of clinical outcome.5 For uncomplicated SAB, 2 weeks of intravenous antibiotics are considered sufficient.6,8 International guidelines, however, vary in their recommendations for the optimal antibiotic treatment duration of complicated SAB. For S. aureus native valve endocarditis, the Infectious Diseases Society of America guidelines recommend 6 weeks of antibiotic treatment, the Working Party of the British Society for Antimicrobial Chemotherapy 4 weeks, and the European Society of Cardiology (ESC) guidelines a regimen of 4–6 weeks.9–11 The discrepancies between international guidelines reflect the lack of evidence regarding the optimal duration of antibiotic therapy for complicated SAB. A previous systematic literature review yielded only observational studies of low quality, but no randomised studies on the antibiotic treatment duration of complicated SAB.12

In the past decade, evidence has accumulated that many bacterial infections, including bloodstream infections, can safely be treated with a shorter antibiotic course than previously assumed.13–15 Unnecessary exposure to antibiotics should be avoided for prevention of adverse drug events, selection of resistant microorganisms, and catheter-associated infections and thrombosis.16–19 Furthermore, shorter courses of antibiotics could potentially reduce length of hospital stay and costs.19

The lack of evidence regarding the optimal treatment duration of complicated SAB and the major potential benefits of a shorter antibiotic regimen provide the rationale for the SAFE trial (safe shortening of antibiotic treatment duration for complicated SAB trial). This randomised controlled trial (RCT) aims to investigate whether 4 weeks of antibiotic treatment duration is non-inferior to 6 weeks in patients with complicated SAB with satisfactory clinical response to initial antibiotic treatment.

### METHODS AND ANALYSIS

#### Study design and setting

The SAFE trial is a multicentre, non-inferiority, open-label, parallel group and RCT All administrative information concerning the study is provided in online supplemental appendix A.

Participants are randomised in a 1:1 ratio to 4 weeks or 6 weeks of antibiotic treatment. The study is currently being performed in 15 hospitals in the Netherlands and is coordinated by Amsterdam UMC in Amsterdam, the Netherlands. In total, 5 university hospitals and 10 general hospitals participate. A list of all study sites can be obtained from the investigators. Inclusion of patients started in August 2020.

#### Study population

All patients with SAB will be screened for inclusion in the study. Patients with SAB treated for at least 7 days with parenteral antibiotics are eligible when they fulfill the inclusion criteria and do not meet any of the exclusion criteria as listed below. A flow diagram for study participants is displayed in figure 1.

**Inclusion criteria**

1. Adult (≥18 years).
2. At least one blood culture positive for methicillin-susceptible S. aureus.
3. Complicated SAB, defined as one of the following conditions (a and/or b):
   a. Evidence of organ involvement and/or deep-seated infection. Examples of clinical diagnoses are: endocarditis, vertebral osteomyelitis, arthritis, intravascular infection, abscess and metastatic complications. Diagnostic criteria for the most common clinical diagnoses are provided in online supplemental appendix B.
   b. One of the following predictors for complicated SAB:13:
      i. Community acquisition according to prior definitions;20
      ii. Initiation of adequate antibiotic treatment >48 hours after the initial positive blood culture;
      iii. Positive follow-up blood culture >48 hours after initiation of adequate antibiotic treatment;
      iv. Persistence of fever at 72 hours after the initial positive blood culture;
      v. Unknown primary source of infection.
4. Satisfactory clinical response to initial treatment, defined as meeting all of the following:
   a. Negative blood culture for S. aureus on day 8 of adequate antibiotic treatment, defined as intravenous administration of an antibiotic agent with in vitro activity against the cultured S. aureus. In absence of blood culture sampling on day 8, the date of the first negative blood culture is the midpoint between the last positive blood culture for S. aureus and the first negative blood culture for S. aureus. If this midpoint is later than 8 days a patient cannot be included.

**Exclusion criteria**

1. Mortality within the first 7 days of antibiotic treatment.
2. For patients randomized to 4 weeks of antibiotic treatment later than 8 days a patient cannot be included.
3. Persistent positive blood cultures sampling on day 8, the date of the first negative blood culture is the midpoint between the last positive blood culture for S. aureus and the first negative blood culture for S. aureus. If this midpoint is later than 8 days a patient cannot be included.

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b. Negative intraoperative cultures in patients with S. aureus native valve endocarditis who underwent cardiac surgery.

c. C reactive protein (CRP) decline to at least 50% of peak level or to <30 mg/L within 14 days of adequate antibiotic treatment. A high CRP due to an evident other cause, for example, an unrelated infection, is disregarded in this definition.

d. Absence of fever (temperature <38°C for two consecutive calendar days, measured at two time points with at least 24 hours interval) between 7 and 14 days of adequate antibiotic treatment. Fever due to unrelated, intercurrent infection (eg, respiratory tract infection) is disregarded in this definition.

Exclusion criteria
1. Infected prosthetic heart valve or other infected prosthetic material which is not removed within 14 days of adequate antibiotic therapy, as manifested by either one of the following:
   i. Clinical suspicion of infected prosthetic material;
   ii. Transthoracic echocardiogram or transesophageal echocardiogram positive for prosthetic valve or device endocarditis;
   iii. Positron emission tomography/computed tomography scan positive for infection of prosthetic material (including prosthetic heart valve, cardiac device, vascular prosthesis or joint prosthesis).

2. Presence of undrained abscess of 5 cm or more in one direction on imaging at day 14 of adequate antibiotic treatment. Routine diagnostics to rule out any abscess are not part of the study protocol.

3. Pregnancy or lactation.

Trial intervention
Between day 7 and day 21 of adequate antibiotic treatment participants are randomised in an open fashion to a total antibiotic treatment duration of 4 weeks (intervention group) or 6 weeks (control group). The total treatment duration is counted from the day of initiation of adequate antibiotic therapy as day 1. For patients with infective endocarditis the day of the first negative blood culture is counted as day 1 of antibiotic treatment, in accordance with the ESC guidelines. Adequate initial antibiotic therapy is defined as intravenous treatment with at least one agent with in vitro activity against the cultured S. aureus.

In the SAFE trial, intravenous antibiotics are recommended for the entire treatment duration, in accordance with the Dutch SAB guidelines. An exception can be made for patients with monoarthritis, monovertebral osteomyelitis, osteomyelitis or skin and soft tissue infections, in which case a switch to oral therapy is allowed after a minimum of 2 weeks of intravenous therapy. This is in line with recent literature on the treatment of bone and joint infections and in accordance with Dutch clinical practice. The decision whether and when a study participant will be switched from intravenous to oral antibiotics must be made and documented before randomisation to avoid selection bias.

The antibiotic regimens used in the SAFE trial are according to the Dutch SAB guidelines. The first choice agent for intravenous therapy is flucloxacillin. Cefazolin is considered equivalent to flucloxacillin as anti-staphylococcal therapy and can be administered if indicated, for example, in case of allergy or toxicity. The second intravenous alternative is vancomycin. Clindamycin is preferred agent that in vitro activity against the cultured S. aureus is demonstrated. Flucloxacillin and levofloxacin may be used as alternative oral agents. Tables 1 and 2 provide dosages of intravenous and oral antibiotics according to clinical diagnosis. After hospital discharge, study participants using intravenous antibiotics receive outpatient parenteral antimicrobial treatment. No preconceived
criteria are defined for modifying allocated interventions in case of adverse events and this decision is made by the local principal investigator in consultation with the study coordinators.

Co-interventions
Diagnostic work-up and therapeutic co-interventions are major determinants of clinical outcome in patients with SAB. We used a diagnostic and therapeutic algorithm based on the national Dutch guidelines to standardise these interventions. This algorithm is displayed in figure 2.

Trial recruitment, randomization and blinding
In all hospitals, eligible patients are identified through the local Antibiotic Stewardship Teams or Infectious Diseases consultation service. Patients are included between day 7 and 21 of adequate antibiotic therapy. Informed consent is obtained by the local principal investigator or a delegated person of the local study team. The model consent form can be found in online supplemental appendix C.

Patients are randomised after all eligibility criteria are verified and met, and informed consent has been signed. The independent central randomisation service creates a computer-generated schedule in random-sized permuted blocks of two or four patients, stratified for three determinants of clinical outcome in patients with complicated SAB:

1. Age (above or below 75 years).
2. Renal replacement therapy (yes or no).
3. Clinical manifestations of complicated SAB (endovascular infection including endocarditis, or other organ localisation, or predictors for complicated SAB only).

This is an open-label trial. Neither study participants nor care providers can be blinded, since it is considered unethical to expose patients allocated to the intervention group to prolonged presence of a venous catheter after discontinuation of antibiotics. Furthermore, use of a mock infusion precludes determination of the effect of the intervention on some of the secondary endpoints (eg, occurrence of catheter-related complications). Finally, some of the intended positive effects on secondary endpoints (eg, length of hospital stay) are affected by knowledge of the planned treatment duration.

Primary outcome measure
The primary outcome of the SAFE trial is in accordance with the consensus definition on proposed primary endpoints for bloodstream infection trials. The primary outcome is success of therapy at 180 days after randomisation, defined as follows:

1. Patient alive.
2. No evidence of microbiologically confirmed disease relapse, defined as symptoms and/or signs of infection, after initial clinical improvement, with S. aureus isolated from blood or another normally sterile site (eg, joint fluid) by conventional culture.

Secondary outcome measures
Secondary outcome measures include:

1. All-cause mortality at 180 days after randomisation.
2. Microbiologically confirmed disease relapse at 180 days after randomisation.

Table 1  Recommended dosages of intravenous antibiotic regimens in the SAFE trial, per 24 hours

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Endocarditis*</th>
<th>Other infections</th>
<th>Loading dose in case of continuous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Flucloxacillin</td>
<td>12 000 mg†</td>
<td>6000 mg</td>
</tr>
<tr>
<td>Alternative (1)</td>
<td>Cefazolin</td>
<td>6000 mg‡</td>
<td>4000 mg</td>
</tr>
<tr>
<td>Alternative (2)</td>
<td>Vancomycin§</td>
<td>40 mg/kg</td>
<td>40 mg/kg</td>
</tr>
</tbody>
</table>

Dose adjustments in case of renal impairment are made according to Dutch guidelines.

*Endocarditis, endovascular infection, or infection localized in the central nervous system.
†Dosage of flucloxacillin IV in case of endocarditis may also be based on therapeutic drug monitoring, according to local study site protocol.
‡Cefazolin not recommended in case of confirmed meningitis.
§Vancomycin dose adjusted according to plasma concentration, measured on the second day of treatment.

Table 2  Recommended dosages of oral antibiotic regimens in the SAFE trial

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Standard dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Alternative (1)</td>
<td>Flucloxacillin</td>
</tr>
<tr>
<td>Alternative (2)</td>
<td>Levofloxacin</td>
</tr>
</tbody>
</table>

Oral therapy may be considered in patients with monoarthritis, monovertebral osteomyelitis, osteomyelitis or skin and soft tissue infections.

Dosage adjustments in case of renal impairment are made according to Dutch guidelines.

Figure 2  Diagnostic and therapeutic algorithm for SAB, Staphylococcus aureus bacteremia.
3. SAB-related mortality at 180 days after randomisation, defined as death from direct complications of the infection (eg, septic brain haemorrhage) or with active infection at the time of death, defined as persistent signs of infection, positive blood cultures or a persistent uncontrolled focus of infection. Non-SAB-related mortality is defined as survival of the full length of antibiotic treatment and death from a known other cause without signs of symptoms of recurrent infection. All other deaths are scored as possibly SAB-related.

4. Antibiotic-associated adverse drug events until 90 days after randomization, defined in accordance with previous literature.

5. Catheter-related complications until 7 days after catheter removal, that is catheter-related bloodstream infection or catheter-induced thrombosis.

6. Length of hospital admission for the initial episode of SAB.

7. Perceived quality of life (PROMIS Global Health) 6 weeks after start of adequate antibiotic treatment and 180 days after randomization.

8. Societal costs, assessed at hospital discharge and at 180 days after randomization.

The primary endpoint and secondary outcomes 2–5 will be adjudicated by two independent reviewers, who will be blinded to the trial arm. If no consensus will be reached between the two reviewers the final decision will be made by a third independent reviewer.

Observational study arm

The study has an observational study arm for patients who meet the eligibility criteria, but in whom the treating physician decides to stop antibiotic treatment after 2 weeks. In line with Dutch clinical practice, patients with predictors for complicated SAB (eg, community acquisition), but without clinical manifestations of complicated SAB on relevant diagnostic studies (eg, PET-CT and echocardiogram) may be considered to have uncomplicated SAB and treated with 2 weeks of antibiotic treatment.

There is limited evidence for this therapeutic strategy.

Participants in the observational study arm are included no later than 30 days after initiation of adequate antibiotic therapy and by definition are not randomised. These patients are contacted by phone 180 days after the planned stop date of antibiotic therapy for assessment of the primary outcome.

Follow-Up

After randomisation, weekly verification of antibiotic regimen, dose and route of administration and monitoring of adverse events will be performed until the end of antibiotic treatment. If patients are discharged, they are contacted by telephone by delegated members of the study team. Laboratory monitoring for antibiotic treatment effect and toxicity (ie, haemoglobin, leukocytes, thrombocytes, CRP, creatinine, alanine-aminotransferase and plasma concentration of vancomycin, if applicable) is performed weekly until week 6 after start of adequate antibiotic therapy in all patients, irrespective of their treatment allocation. Faeces testing for *Clostridium difficile* infection is performed in case of clinical signs and symptoms of *C. difficile infection*. After cessation of antibiotic treatment, we will perform clinical follow-up by telephone at 6 weeks, 90 days and 180 days after randomisation for ascertainment of outcomes and adverse events.

Perceived quality of life is measured using two standardised surveys, that is, PROMIS Global Health and EQ-5D-5L, at three moments: at randomisation, week 6 of antibiotic treatment and 180 days after randomisation. Societal costs will be assessed using structured questionnaires based on the iPCQ (iMTA Productivity Cost Questionnaire) and iMCQ (iMTA Medical Consumption Questionnaire). The iPCQ is administered at discharge from the hospital and at 180 days after randomisation. The iMCQ is administered at 180 days after randomisation. Table 3 lists the timing of all study procedures. Participants withdrawn from the allocated treatment are asked to complete the data collection for the study as planned and will be included in the intention-to-treat analysis.

**Sample size**

In the IDISA study, in which patients with both uncomplicated and complicated SAB were included, 90-day mortality and 90-day infection relapse rate were 33% and 3%, respectively. The SAFE trial will include only patients who survived at least 7 days of adequate antibiotic treatment and who have a satisfactory clinical response to initial treatment. Therefore, we hypothesise a primary endpoint occurrence of 90% in 6 months. Assuming this frequency of treatment success, a sample size of n=396 is required in order to prove non-inferiority with a margin of 7.5%, a one-sided $\alpha$ of 0.05 and 80% power. The size of the non-inferiority margin is based on extensive discussion with experts in the field of infectious diseases and microbiology. This margin is stricter than in most non-inferiority studies, since a high frequency of treatment success is expected in the SAFE trial. Recent studies on shortening antibiotic treatment for osteomyelitis and on oral treatment for endocarditis used non-inferiority margins of 10%.

**Statistical analyses**

**Primary outcome measure**

The hypothesis of non-inferiority will be primarily tested according to the intention-to-treat principle using Cox proportional hazards models. Per-protocol analysis will only consider patients for whom the actual duration of treatment complied with the randomly allocated duration, plus or minus 4 days. To determine non-inferiority for the primary outcome, adjusted absolute risk differences will be calculated from the survival model and confidence intervals will be derived by bootstrapping. A sensitivity analysis will be performed in which patients meeting the primary endpoint between randomisation and day 28 will be excluded. In addition, we will perform Complier Average Causal Effect analysis, which corrects the bias...
inherent to per protocol analysis.\textsuperscript{32, 33} In all analyses, we will adjust for strong prognostic variables measured up to the date of randomisation. Missing data will be handled with multiple imputation, due to its nature of giving standard errors and p values that incorporate missing data uncertainty.\textsuperscript{34} Multiple imputation will be performed according to the MICE algorithm developed by van Buuren \textit{et al.}\textsuperscript{35} Missing data are assumed to be missing at random. Predictors for each imputation will be selected based on clinical knowledge and may include auxiliary variables not considered for the multivariable analyses.

**Secondary outcome measures**

Microbiologically confirmed disease relapse and length of hospital admission will be analysed using competing risks models.\textsuperscript{36} In the analysis of SAB-related mortality at 180 days after randomisation, possibly SAB-related deaths will be analysed as non-SAB-related. Adverse events (antibiotic-associated adverse drug events and catheter-related complications) will be analysed as binary variables using logistic regression analysis. In case of multiple adverse events per patient, count data will be analysed using a Poisson or negative binomial regression analysis, as appropriate based on the distribution of the counts. Health-related quality of life (PROMIS Global Health) will be analysed using a longitudinal multilevel model.

Both a cost-effectiveness analysis using the primary outcome of the trial as effect measure (CEA) and a cost-utility analysis using Quality-Adjusted Life Years (QALYs) as effect measure (CUA) will be performed from a societal and healthcare perspective, according to Dutch guidelines.\textsuperscript{37} Missing cost and effect data will be imputed using multiple imputation according to the MICE algorithm. Rubin’s rules will be used to pool the results from the different multiply imputed datasets. Linear multilevel models will be used to estimate cost and effect differences between intervention and control while adjusting for confounders if necessary. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the treatment groups by the difference in mean effects between the treatment groups. Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95\% CIs around the cost differences and statistical uncertainty surrounding the ICERs. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves will also be estimated showing the probability that the intervention is cost-effective in comparison with control for a range of different ceiling ratios thereby showing decision uncertainty.\textsuperscript{38}

**Potential harms**

The main potential risk of the SAFE trial is inferiority of 4 weeks of antibiotics compared with 6 weeks of antibiotics, that is, increased all-cause mortality and/or disease relapse after receiving 4 weeks of treatment. This risk seems limited considering the fact that some guidelines consider 4 weeks of treatment sufficient for these patients.\textsuperscript{11, 39} Furthermore, patient safety is closely monitored during the study. Antibiotic-associated adverse drug events and catheter-related complications are recorded. Serious adverse events and suspected unexpected serious adverse reactions are reported according to Dutch national law.

**Data monitoring Committee**

The SAFE trial is monitored by a Data Monitoring Committee (DMC) consisting of three independent members with extensive experience in infectious diseases, epidemiology and biostatistics. The DMC will perform an interim analysis after 50\% of the expected primary

### Table 3  Study procedures of SAFE trial

<table>
<thead>
<tr>
<th>Days since randomisation</th>
<th>7–21</th>
<th>21–28</th>
<th>28–35</th>
<th>35–42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Randomisation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up assessment of treatment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Toxicity monitoring†</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TDM for vancomycin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Follow-up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PROMIS GH, EQ-5D-5L</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPCQ</td>
<td>X‡</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IMCQ</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Treatment duration is counted from the day of initiation of adequate antibiotic therapy. The only exception is made for patients with infective endocarditis, in which case the day of first negative blood culture counts as day 1 of treatment.
† Toxicity monitoring includes the following laboratory measurements: haemoglobin, leukocytes, thrombocytes, C reactive protein, creatinine, alanine-amino transferase.
‡ At hospital discharge.
IMCQ, iMTA Medical Consumption Questionnaire; IPCQ, Productivity Cost Questionnaire; TDM, therapeutic drug monitoring.
outcome events in the intervention group or control group has occurred (ie, 10 events in either group) and will review recruitment rates, protocol violations and primary endpoint occurrence. An unbinding stopping rule for harm by shortened antibiotic therapy will be applied. The DMC will consider recommending to stop the trial if at 50% of the expected number of events in the intervention group or control group the point estimate of the absolute risk difference of success of therapy is equal or worse than the non-inferiority threshold. If the incidence of the primary endpoint in the control group substantially deviates from the expected 90% at the interim analysis, the DMC may consider adjusting the non-inferiority threshold accordingly to determine whether the trial must be stopped for harm. The DMC will also consider recommending early stopping of the trial if 50% of inclusions has not been achieved after 3 years. Any final decision to terminate the trial can only be made by the sponsor. Further details about the DMC charter can be obtained from the investigators. The conduct of the trial is monitored by the Amsterdam UMC Clinical Monitoring Center which is independent from the study and study team.

Data management
Data collection is performed by trained members of the study team. All identifiable data are only stored at the hospital where participants are being treated. All data are coded using an anonymous participant ID and collected in an electronic Case Report Form. Only data essential for evaluating the study outcomes are collected. The central study coordinators will have access to the final study dataset from all participants. Local principal investigators can only obtain access to data from participants included at their own study site. For the SAFE trial, data will be shared with investigators whose proposed use of the data has been approved by the data access committee of the trial. All individual participant data collected during the trial will be available, after deidentification. Other documents that will be available include the study protocol, statistical analysis plan and informed consent form. Data will be available beginning 1 year following article publication of the primary study results for any purpose deemed relevant by the data access committee. To gain access, data requestors will need to sign a data access agreement and data will be available at a third-party website.

Patient and public involvement
Patients were involved in the design and conduct of this trial. We established a patient panel including patients who experienced an episode of SAB and other patients. During the design phase of the trial the panel was asked to provide feedback on questionnaires and informed consents forms. During the execution of the trial regular panel meetings will be held to discuss relevant topics including participant recruitment and distribution of the trial results to the participants.

Ethics and dissemination
Ethical approval has been obtained from the Medical Ethics Committee VUmc (Amsterdam, the Netherlands). According to Dutch law, this ethical approval is valid for all participating study sites. Significant protocol modifications will be submitted to the same committee. For all participating study sites approval to start the study was granted by the board of directors. The Declaration of Helsinki, the Note for Guidance on Good Clinical Practice (ICH GCP; CPMP/ICH/135/95, step 5 consolidated guideline) and the EU Directive for clinical trials (2001/20/EG) are followed during the study.46 A central insurance is taken out for possible harm from trial participation. All results from primary and secondary outcome measures will be published in a peer-reviewed journal and authorship will be based on the ICMJE recommendations for authorship.41

DISCUSSION
The significant morbidity and mortality of SAB contrasts sharply with the lack of evidence regarding its clinical management. As a result, international guidelines vary in their treatment recommendations and patients with SAB receive diagnostic work-up and treatment mostly based on expert opinion.1 9 10 42 Only a few randomised trials specifically including patients with SAB have been performed and most studies compared the effectiveness of different antibiotic regimens.43–45 In fact, in a recent survey infectious diseases physicians and clinicians microbiologists identified optimal duration of therapy as the number one priority among different clinical research questions.46 For many bacterial infections, duration of antimicrobial therapy is based more on tradition than on solid evidence.47 In recent years, however, studies have shown that short-course antibiotic therapy is equally effective as longer traditional courses for several severe infections including community-acquired pneumonia, gram-negative bacteraemia, complicated urinary tract infections and pyogenic vertebral osteomyelitis.14 15 48 49 Shorter antibiotic therapy has multiple potential advantages, including fewer adverse events, reduction of medical costs and less antibiotic pressure on the individual and societal level.47 The benefits of shortening antibiotic therapy could be especially pronounced in SAB, since treatment-related adverse events are common in these patients.16 The SAFE trial is the first RCT investigating optimal treatment duration for complicated SAB and will provide essential insights in the advantages and disadvantages of shortening antibiotic therapy. Strengths of the study include the use of broad eligibility criteria, allowing generalisability of the trial results to clinical practice, and long follow-up. A major limitation of the study is the lack of blinding of study participants and care providers. Objective and well-defined endpoints are used to mitigate potential information bias. If non-inferiority of 4 weeks of
antibiotic therapy is shown in this study, this would allow shortening of treatment for selected patients with SAB in clinical practice.

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KCES conceived the study protocol together with MvA, MGdJB, MJMB, JBoomsma, JvdM, JMF, ES and TvdV. DTBP drafted the manuscript. KCES, JMF and HvW provided initial feedback. MvA, HB, MB, MGdJB, MJMB, JBoomsma, SD, LG, EJ, JBranger, AL, JvdM, JJO, ES, RS, JE, TvdV, Lvdv, NJV, MV and PDV critically reviewed the manuscript before providing final approval.

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Supplemental material
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