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

DTP Buis,1 CH van Werkhoven,2 MA van Agtmael,3 Hl Bax,4,5 M Berrevoets,5 MGJ de Boer,6 MMJ Bonten,2 JE Bosmans,2 J Branger,8 S Douiyeb,1 LBS Gelinck,9 E Jong,10 AJJ Lammers,11 JTM Van der Meer,12 JJ Oosterheert,13 E Sieswerda,2,14 R Soetekouw,15 JE Stalnhoef,16 TW Van der Vaart16 2,12 EA Bij de Vaate,17 NJ Verkaik,4 MGA Van Vonderen,18 PJ De Vries,19 JM Prins,1 KCE Sigaloff,1 Collaborators SAFE-trial study group

**ABSTRACT**

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 *S. aureus* 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.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

⇒ The SAFE trial is the first randomised controlled trial investigating the optimal antibiotic treatment duration for complicated *Staphylococcus aureus* bacteraemia (SAB).
⇒ The chosen combination of primary and secondary outcomes will provide essential insights in the advantages and disadvantages of shortening antibiotic therapy in these patients.
⇒ Patients with SAB with any deep-seated or metastatic infection and/or predictors of complicated SAB with satisfactory response to initial antibiotic treatment are eligible. The broad eligibility criteria and practice-based approach increase generalisability of the trial results to clinical practice.
⇒ The lack of blinding of both study participants and care providers is a limitation to the study design. Objective and well-defined endpoints and adjudication of the primary endpoint by two independent reviewers are used to mitigate potential information bias.

**INTRODUCTION**

*Staphylococcus aureus* can lead to a myriad of clinical infections, virtually in every organ
and ranging from mild to severe disease.¹ S. aureus bacteraemia (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%.²³

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 bacteraemia 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 bacteraemia, 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.²⁵ The dichotomisation of SAB in ‘complicated’ and ‘uncomplicated’ guides diagnostic and therapeutic management and is a major determinant of clinical outcome.¹ 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.¹³

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 SAB²⁰:
      i. community acquisition according to prior definitions;
      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.
Figure 1  Flow diagram study design SAFE trial. SAB, Staphylococcus aureus bacteremia.

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 (e.g., 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. In case of partial oral treatment clindamycin is the preferred agent provided 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>

Dosage 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 of skin or soft tissue infections. Dosage adjustments in case of renal impairment are made according to Dutch guidelines.
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.

**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 α 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. 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. Multiple imputation will be performed according to the MICE algorithm developed by van Buuren et al. 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. 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. 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 the 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.

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. 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>
<thead>
<tr>
<th>Table 3 Study procedures of SAFE trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days since randomisation</td>
</tr>
<tr>
<td>Treatment duration (days)*</td>
</tr>
<tr>
<td>Informed consent</td>
</tr>
<tr>
<td>Randomisation</td>
</tr>
<tr>
<td>Follow-up assessment of treatment</td>
</tr>
<tr>
<td>Toxicity monitoring†</td>
</tr>
<tr>
<td>TDM for vancomycin</td>
</tr>
<tr>
<td>Follow-up</td>
</tr>
<tr>
<td>PROMIS GH, EQ-5D-5L</td>
</tr>
<tr>
<td>IPCQ</td>
</tr>
<tr>
<td>IMCQ</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-aminotransferase.
‡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 micro-biologists 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.

Author affiliations
1Department of Internal Medicine, Division of Infectious Diseases, Amsterdam Institute for Infection and Immunity, Amsterdam UMC Locatie VUMc, Amsterdam, The Netherlands
2Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, The Netherlands
3Department of Internal Medicine, Section of Infectious Diseases, Erasmus Medical Center, Rotterdam, The Netherlands
4Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands
5Department of Internal Medicine, Elisabeth tweestenen Hospital, Tilburg, The Netherlands
6Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands
7Department of Health Sciences, Faculty of Science, Amsterdam Public Health Research Institute, VU University Amsterdam, Amsterdam, The Netherlands
8Department of Internal Medicine, Flevohospital, Almere, The Netherlands
9Department of Internal Medicine, Haaglanden Medisch Centrum, Den Haag, The Netherlands
10Department of Internal Medicine, Meander Medisch Centrum, Amersfoort, The Netherlands
11Department of Internal Medicine & Infectious Diseases, Isala Zwolle, Zwolle, The Netherlands
12Department of Internal Medicine, Division of Infectious Diseases, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands
13Department of Internal Medicine, Infectious Diseases, UMC Utrecht, Utrecht, The Netherlands
14Department of Medical Microbiology, UMC Utrecht, Utrecht, The Netherlands
15Department of Internal Medicine, Spaarne Gasthuis, Haarlem/Hoofddorp, The Netherlands
16Department of Internal Medicine, OLVG, Amsterdam, The Netherlands
17Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands
18Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands
19Department of Internal Medicine, Tergooi Hospital, Hilversum, The Netherlands

Collaborators Collaborators SAFE-trial study group: E Botman (Department of Internal Medicine, Spaarne Gasthuis Haarlem/Hoofddorp, the Netherlands), A Van den Broek (Amsterdam UMC, Universiteit van Amsterdam, Department of Internal Medicine, Division of Infectious Diseases, Amsterdam, the Netherlands), L Buitenhus (Department of Innovation & Science, Isala, Zwolle, the Netherlands), E Buitenwerf (Department of Internal Medicine & Infectious Diseases, Isala Zwolle, Zwolle, the Netherlands), A S Centis (Department of Internal Medicine, Flevohospital, Almere, the Netherlands), N Engels (Department of Internal Medicine, OLVG, Amsterdam, the Netherlands), J L J Hansen (Department of Infectious Diseases, Leiden University Medical Center, Leiden, the Netherlands), A J Meinders (Department of Internal Medicine and Intensive Care Unit, St Antonius Hospital, Nieuwegein and Utrecht, Netherlands), F P N Mollema (Department of Internal Medicine, Haaglanden Medisch Centrum, The Hague, the Netherlands), L Nagelmaker (Department of Internal Medicine, OLVG, Amsterdam, the Netherlands), M L M van Doorn-Scheeps (Department of Medical Microbiology, OLVG, Amsterdam, the Netherlands), N Roescher (Department of Microbiology and Immunology, St Antonius Hospital, Nieuwegein, the Netherlands), P Thomopoulos (Department of Medical Microbiology, Division Laboratories, Pharmacy and Biomedical Genetics (dLAB), UMC Utrecht, Utrecht University, Utrecht, the Netherlands), M Timmer (Department of Internal Medicine, Haaglanden Medisch Centrum, The Hague, the Netherlands), B van der Wiel (Department of Internal Medicine, Elisabeth tweesteden Hospital, Tilburg, the Netherlands).

Contributors KCES conceived the study protocol together with MvA, MGdJB, MJJM, JBomsans, JvdM, JMP, ES and TDV. DTPB drafted the manuscript, KCES, JMP and HvW provided initial feedback. MvA, HB, MB, MGdJB, MJJM, JBomsans, SD, LG, EJ, JBranget, AL, JvdM, JJO, ES, RS, JE, TDV, LBvdN, NV, MV and PDV critically reviewed the manuscript before providing final approval.

Funding This work was supported by The Netherlands Organization for Health Research and Development (grant number 848018006).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
DTP Buis http://orcid.org/0000-0002-0830-8670
TW Van der Vaart http://orcid.org/0000-0002-5873-0474

REFERENCES


Appendix A: Administrative information.

Trial registration number: NL8347 (the Netherlands Trial Register)

Protocol version: 12

Protocol date: April 4th, 2022

Trial sponsor: Amsterdam UMC, location VU Medical Center. De Boelelaan 1117. 1081 HV Amsterdam. The Netherlands

Funding agency: The Netherlands Organization for Health Research and Development– Goed Gebruik geneesmiddelen (GGG) programme, grant number 848018006. The study sponsor and funder will not have any role in study design; collection, management, analysis and interpretation of data; writing of the report and the decision to submit the report for publication. The coordinating center is responsible for general coordination and daily management of the trial.

WHO Trial Registration Data Set:
1) Primary Registry and Trial Identifying Number: NL8347 (the Netherlands Trial Register)
2) Date of Registration in Primary Registry: February 22, 2020.
3) Secondary Identifying Numbers: n/a.
4) Source(s) of Monetary or Material Support: The Netherlands Organization for Health Research and Development (grant number 848018006).
5) Primary Sponsor: Amsterdam UMC, location VU Medical Center.
6) Secondary Sponsor(s): n/a.
7) Contact for Public Queries: Drs. D.T.P. Buis (see page 1).
8) Contact for Scientific Queries: Drs. D.T.P. Buis (see page 1).
9) Public Title: Safe shortening of antibiotic treatment duration for severe bloodstream infections with staphylococci.
10 Scientific Title: Safe shortening of antibiotic treatment duration for complicated Staphylococcus aureus bacteremia.
12) Health Condition(s) or Problem(s) Studied: Staphylococcus aureus bacteremia.
13) Intervention(s): four weeks (intervention arm) or six weeks (control arm) of antibiotic treatment.
14) Key Inclusion and Exclusion Criteria:
   Inclusion criteria: Patients with methicillin-sensitive complicated Staphylococcus aureus bacteremia who responded well to initial treatment.
15) Study Type: Randomized controlled open-label parallel group phase IV non-inferiority trial.
17) Sample Size: Planned to enroll 396 participants. Currently enrolled: 152 participants.
18) Recruitment Status: Recruiting.
19) Primary Outcome(s): Success of therapy at 180 days after randomization, i.e. patient alive and no evidence of microbiologically confirmed disease relapse.
22) Completion date: n/a.
23) Summary Results: n/a.
24) IPD sharing statement: Undecided.
### Appendix B: Diagnostic criteria common diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
<td>Localized collection of pus, proven by:</td>
</tr>
<tr>
<td></td>
<td>A) Physical examination and/or</td>
</tr>
<tr>
<td></td>
<td>B) Radiological imaging and/or</td>
</tr>
<tr>
<td></td>
<td>C) Peroperative findings and/or</td>
</tr>
<tr>
<td></td>
<td>D) Pus culture positive for <em>S. aureus</em></td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td><em>S. aureus</em> infection heart valve according to:</td>
</tr>
<tr>
<td></td>
<td>A) Modified Duke criteria (1) and/or</td>
</tr>
<tr>
<td></td>
<td>B) Consensus by local multidisciplinary endocarditis team</td>
</tr>
<tr>
<td>Meningitis</td>
<td><em>S. aureus</em> infection of the meninges, proven by:</td>
</tr>
<tr>
<td></td>
<td>A) Cerebrospinal fluid (CSF) culture positive for <em>S. aureus</em> and/or</td>
</tr>
<tr>
<td></td>
<td>B) CSF polymerase chain reaction (PCR) positive for <em>S. aureus</em> (2)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td><em>S. aureus</em> infection, proven by:</td>
</tr>
<tr>
<td></td>
<td>A) Radiological imaging and/or</td>
</tr>
<tr>
<td></td>
<td>B) Peroperative findings and/or</td>
</tr>
<tr>
<td></td>
<td>C) Bone cultures or PCR positive for <em>S. aureus</em></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td><em>S. aureus</em> infection, proven by:</td>
</tr>
<tr>
<td></td>
<td>A) Radiological imaging and/or</td>
</tr>
<tr>
<td></td>
<td>B) Synovial fluid culture or PCR positive for <em>S. aureus</em> (3)</td>
</tr>
<tr>
<td>Septic embolism</td>
<td><em>S. aureus</em> infection embolism, proven by:</td>
</tr>
<tr>
<td></td>
<td>A) Radiological imaging and/or</td>
</tr>
<tr>
<td></td>
<td>B) Peroperative findings and (4)</td>
</tr>
<tr>
<td>Septic thrombosis</td>
<td><em>S. aureus</em> infection superficial or deep venous thrombosis, proven by:</td>
</tr>
<tr>
<td></td>
<td>A) Radiological imaging and/or</td>
</tr>
<tr>
<td></td>
<td>B) Peroperative findings and (4)</td>
</tr>
<tr>
<td>Vertebral osteomyelitis</td>
<td><em>S. aureus</em> infection of the vertebrae, proven by:</td>
</tr>
<tr>
<td></td>
<td>A) Radiological imaging and/or</td>
</tr>
<tr>
<td></td>
<td>B) Surgical findings and/or</td>
</tr>
<tr>
<td></td>
<td>C) Intraoperative or percutaneous biopsy culture or PCR positive for <em>S. aureus</em> (5)</td>
</tr>
</tbody>
</table>

PCR, polymerase chain reaction.

### References

Subject information for participation in medical research

Version 1
2022-05-04
Target group: possible participants SAFE-study

A study on safely shortening antibiotic treatment in bloodstream infections with Staphylococcal bacteria: the SAFE study.

Official title: Safe shortening of antibiotic treatment duration for complicated Staphylococcus aureus bacteremia

Introduction
Dear sir/madam,

With this letter, we would like to ask you to take part in a medical study. Participation is voluntary. Your written permission is required to participate. You have received this letter because you have a bloodstream infection with Staphylococcal bacteria, for which you are currently receiving antibiotics. Before you decide whether you want to participate in this study, you will receive an explanation of what the study entails. Read this information carefully and ask the researcher for an explanation if you have any questions. You can also ask the independent expert, named at the end of this letter, for additional information. You can also talk about it with your partner, friends or family.

General information about participating in a medical study can be found on the website of the Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek. You have at least 24 hours to decide whether you want to participate in the study.

1. General information
This research was set up by the VU Medical Center and is being carried out by doctors in various Dutch hospitals. A total of 396 subjects are needed for this study. The VUmc medical ethics review committee has approved this study. General information about the assessment of research can be found on the website of the Rijksoverheid: www.rijksoverheid.nl/mensenonderzoek.

2. What is the purpose of the study?
Subject information SAFE study

The aim of this study is to investigate whether treatment with 4 weeks of antibiotics is as good as treatment with 6 weeks of antibiotics for bloodstream infections with Staphylococcal bacteria. The results of this research will be published in a scientific article.

3. What is the background of the study?
It is important to prevent unnecessary use of antibiotics, as this can lead to adverse effects such as kidney or liver damage, prolonged hospitalization and increase of resistant bacteria. Long-term use of antibiotics can also disrupt the intestinal flora, because antibiotics kill bacteria in the gut that contribute to good health. For bloodstream infections with Staphylococcal bacteria, we currently do not know how long to treat with antibiotics. The Dutch treatment guideline recommends treating these types of infections with 4 to 6 weeks of antibiotics. In practice, most patients in the Netherlands are treated for 6 weeks. However, there are also foreign guidelines, for example in Belgium and the United Kingdom, which advise that these type of infections should always be treated for a shorter period of time, i.e. with 4 weeks of antibiotics. The two treatment times, 4 or 6 weeks of antibiotics, have never been compared in a large, well-designed scientific study.

4. What happens during the study?
If you participate, it will take about 6 months in total.

Eligibility
Pregnant women cannot participate in this study. Therefore, female patients of childbearing age (15-49 years) are asked whether they use contraception. If not, a urine pregnancy test will be taken. If you are pregnant, we will tell you. If you do not want to know this, you cannot participate in this study.

Therapy
Half of the subjects will receive 4 weeks of antibiotic treatment, the other half will receive 6 weeks of antibiotic treatment. Whether you receive 4 weeks or 6 weeks of treatment is determined by drawing lots. You and your treating doctor will be told which group you are in.

Visits and measurements
In participants treated for 4 weeks, blood samples will be drawn once a week for 2 weeks. These participants have to come to the hospital for this. If this is not possible for you, blood will be drawn at home or in the institution where you are staying.

During the examination, we want to keep a close eye on how you are doing and whether you have any physical complaints. As long as you are admitted to hospital, we can retrieve this information from your patient file. The researchers will contact you weekly by telephone when you go home. You do not have to come to the hospital for this. It concerns the following moments:

- 4 weeks after starting the antibiotics.
Subject information SAFE study

- 5 weeks after starting the antibiotics.
- 6 weeks after starting the antibiotics.
- 8 weeks after starting the antibiotics.
- 3 months after the start of the study.
- 6 months after the start of the study.

If we are unable to reach you by phone 3 times during these period, we will contact your GP to ask how you are doing.

During the study, we ask all subjects to fill in questionnaires at 4 moments. However, it is also possible to participate in the study without completing the questionnaires. It concerns the following 4 moments:

1) 2 questionnaires at the start of the study. These questionnaires are about your state of health and your quality of life. Completing these 2 questionnaires takes approximately 20 minutes in total.
2) 1 questionnaire upon discharge from hospital. This questionnaire is about the possible consequences of health problems on your work. It takes approximately 20 minutes to complete this questionnaire.
3) 2 questionnaires 6 weeks after starting antibiotics. These questionnaires are about your state of health and your quality of life. Completing these 2 questionnaires takes approximately 20 minutes in total.
4) 4 questionnaires 6 months after the start of the study. These questionnaires are about your state of health, your quality of life, your use of healthcare and the possible consequences of health problems for any work you do. Completing these 4 questionnaires takes approximately 80 minutes in total.

When you are no longer in hospital at these times, you will receive the questionnaires by email or on paper.

Appendix C lists the measurements that will take place during the study.

Different from standard care
The following matters are different in this study from usual care:
- The questionnaires that are administered at 4 moments.
- Telephone contact with the researchers

5. What agreements do we make with you?
We want the study to go well. That is why we want to make the following agreements with you.
- You do not take part in any other medical research during this study.
- You go to every appointments for blood sampling and telephone contact with the researchers.
Subject information SAFE study

- You carry the participant card of the study with you. In your wallet, for example. It states that you are taking part in this study. And who should be warned in an emergency. Show this card when you visit a doctor.
- You should contact the investigator in these situations:
  - You are hospitalised or get treatment in a hospital.
  - You no longer want to take part in the study.
  - Your telephone number, address or email address changes.

Pregnancy of you or your partner

Women who are pregnant or breastfeeding cannot take part in this study. Women should also not get pregnant during the study when treated with antibiotics. Inform your partner about this.

This study can have consequences for an unborn child. The consequences are not known. It is important to discuss this with your partner. The investigator will tell you how best to prevent pregnancy.

If you do become pregnant during the study, inform the investigator immediately. It could mean that the pregnancy needs to be monitored more closely and information about the course and outcome of the pregnancy can be requested from other healthcare providers. But only if you/your pregnant partner give separate permission for this.

6. What side effects, adverse effects or discomforts could you experience?

The antibiotics you receive may cause side effects. These possible side effects are the same for the treatment you will receive if you do not participate in the study.

You should contact your treating doctor if you experience:
- More than 3 loose stools per day.
- Nausea and/or vomiting after taking or administering the antibiotics.
- Confusion, sensory disorders or seizures.
- Newly developed skin lesions.
- Shortness of breath
- Swelling of lip and/or tongue.
- Pain, redness and/or swelling around the infusion over which you will receive antibiotics.

If you participate in the study, you will receive the package leaflet for the antibiotic, which lists all possible side effects.

7. What are the pros and cons if you take part in the study?

It is important to weigh the pros and cons, before deciding to take part in the study.
Subject information SAFE study

If you participate in the study, you will be drawn in the 4 or 6 week of antibiotic therapy group. In both cases, your participation in this study can contribute to more knowledge about the best treatment of bloodstream infections with Staphylococcal bacteria. If the draw determines that you will be treated with antibiotics for 4 weeks, a possible benefit is that you are less likely to experience side effects from the antibiotics such as kidney and liver damage and less risk of adverse effects from long-term hospitalization, such as contracting infections in the hospital and developing thrombosis. Disadvantages of participating in the study may be that 4 weeks of antibiotic treatment is less effective than 6 weeks of treatment for bloodstream infections with Staphylococcal bacteria. In this case, you may be at an increased risk of the consequences of an insufficiently treated infection. We think this risk is small. We will keep a close eye on you during the investigation to avoid this risk.

If you do not participate in the study, you will receive the standard treatment of 6 weeks. A possible advantage is that more experience has been gained with this treatment in the past. A possible disadvantage of this treatment is longer hospital stay and possibly more side effects of the antibiotics.

Participation in the study also means:
- Taking part in the study will cost you extra time.
- You have to comply with the study agreements.

All these matters have been described above under points 4, 5 and 6

8. If you stop participating in the study

It is up to you to decide if you wish to participate in the study. Participation is voluntary. If you wish not to participate, then you will receive the standard treatment for a bloodstream infection with Staphylococcal bacteria, which is 4 to 6 weeks. The researcher or treating doctor can tell you more about the available options for treatment and about the pros and cons.

If you do participate, you can always change your mind and stop anyway, even during the study. You will then receive standard of care. You don't have to say why you're stopping. You do must report this to the researcher immediately.

The data collected up to that point will be used for the research. If you wish, collected body material can be destroyed.

If there is new information about the study that is important to you, the researcher will let you know. You will then be asked if you want to continue participating

9. End of the study

Your participation in the study will end if
- all visits as described under point 4 and in Appendix C have been completed
- you choose to stop yourself
10. Use and storage of your data and body material

For this study, your personal data and blood are collected, used and stored. This concerns data such as your name, address, date of birth and data about your health. A blood sample is required for this study. The collection, use and storage of your data and your blood are necessary to answer the questions posed in this study and to publish the results.

We ask for your permission for the use of your data and blood by means of the consent form.

Confidentiality of your data and body material

To protect your privacy, your data and your body material are given a code. Your name and other information that can directly identify you are omitted. Data can only be traced back to you with the password of the code. The password to the code remains securely stored in the local research facility. The data sent to the client only contains the code, but not your name or other data with which you can be identified. Also in reports and publications about this research, the data cannot be traced back to you.

Access your data for control

Some individuals may have access to all of your data at the study site. Also to the data without code. This is necessary to be able to check whether the research has been carried out properly and reliably. Persons who have access to your data for inspection are: an inspector who works for the VUmc and national and international supervisory authorities, for example de inspectie Gezondheidszorg en Jeugd. They keep your data secret. We ask you to give permission for this inspection.

Retention period data and body material

We store your data in the hospital where you are being treated for 15 years. Your body material is not destroyed immediately after use. It will be kept in order to be able to perform additional tests related to this research in the course of this investigation.

Retention and use of data for other research

After this research, your data may also be important for other scientific research in the field of infections caused by Staphylococcal bacteria. For this purpose, your data and blood will be stored for 15 years. You can indicate on the consent form whether or not you agree to this. If you do not agree to this, you are still able to participate in this study.
Subject information SAFE study

Information about unexpected findings
During this research, something may accidentally be found that is not important for the research, but is important for you. If this is important for your health, you will be informed by your treating doctor from the hospital. You can then discuss with your treating doctor what should be done. We also ask for your permission for this by means of the consent form.

Withdraw permission
You can always withdraw your consent for the use of your personal data. This applies to this study as well as to storage and use for future research. The research data collected up to the moment you withdraw your consent will still be used in the research. Your body material will be destroyed after withdrawal of your consent. If assessment have already been taken with that bodily material, those data will still be used.

More information about your rights when processing data
For general information about your rights when processing your personal data, you can visit the website of the Dutch Data Protection Authority.

If you have any questions about your rights, please contact the person responsible for processing your personal data. For this study, that is:

drs. DTP Buis, researcher VUmc. See Appendix A for contact details.

Drs. S. Douiyeb, researcher VUmc. See Appendix A for contact details

If you have any questions about complaints about the processing of your personal data, we recommend that you first contact the research location. You can also contact the Data Protection Officer of the VUmc, see Appendix A of the Dutch Data Protection Authority.

Registration of the study
Information about this study is also included in an overview of medical scientific studies https://www.trialregister.nl. It does not contain any data that can be traced back to you. After the study, the website may display a summary of the results of this survey. You can find this study under SAFE-trial, Trial NL8347.

11. Insurance for study participants
Insurance has been taken out for everyone who takes part in this study. The insurance pays for damage caused by the study. But not for all damage. You can find more information about this insurance and any exceptions in Appendix B. It also says who you can report damage to.

12. Informing your general practitioner and treating specialist will
The investigator will send your general practitioner and treating specialist a letter to let them know that you are taking part in the study. This is for your own safety. If you do not agree with
Subject information SAFE study

this, you cannot participate in this study. We may contact your general practitioner, treating specialist or pharmacy to request information, for example about your medical history or about medication use. You must give permission for this via the permission form.

13. No compensation for participating
The extra tests and treatment for the study will not cost you anything. You will not be paid for participating in this study. You will, however, be reimbursed for your (extra) travel and parking costs. The own risk of the health insurance is not reimbursed, because you also have to pay this yourself if you do not participate in the study.

14. Do you have any questions?
If you have any questions, please contact the researcher. For independent advice about participating in this study, you can contact the independent doctor. She knows a lot about the study and your condition, but has nothing to do with this study. If you have any complaints about the study, you can discuss this with the researcher or your attending physician. If you prefer not to do this, you can contact the complaints officer of your hospital. All details can be found in Appendix A: Contact details.

15. Signing consent form
When you have had sufficient reflection time, you will be asked to decide whether to participate in this study. If you give permission, we will ask you to confirm this in writing on the accompanying informed consent form. By your written consent, you indicate that you have understood the information and agree to participate in the study. Both you and the researcher will receive a signed version of this consent form.

Thank you for your attention.
Subject information SAFE study

16. Appendices to this information
A. Contact details participating center
B. Information about the insurance
C. Overview of measurements
D. Consent form study participant
Subject information SAFE study

Appendix A: contact details for VUmc

Principal researcher VUmc:
Dr. K.C.E. Sigaloff, internist
Departement interne geneeskunde, VUmc
De Boelelaan 1117, 1118, 1081 HV Amsterdam
Email: k.sigaloff@amsterdamumc.nl

Executive researcher
Drs. D.T.P. Buis, researcher
Departement interne geneeskunde, VUmc
Email: d.t.p.buis@amsterdamumc.nl

Independent doctor:
Dr. M. Bomers, internist-infectioloog
Afdeling interne geneeskunde, VUmc
Email: m.bomers@amsterdamumc.nl

Complaints:
Complaints officer VUmc
Email: zorgsupport@vumc.nl

For more information about your rights

Data protection officer:

Email: privacy@vumc.nl
Appendix B: information about the insurance

The sponsor has taken out insurance for everyone who takes part in the study. The insurance pays for the damage you have suffered because you participated in the study. This concerns damage you suffer during the study or within 4 years after the study has ended. You must report damage to the insurer within 4 years.

The insurance does not cover all damage. At the bottom of this text is a brief description of which damage is not covered.

These conditions are set out in the ‘Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015’. This decision can be found in the government's Wettenbank (https://wetten.overheid.nl).

In the event of damage, you can contact the insurer directly via the contact details below.

<table>
<thead>
<tr>
<th>The insurer of the study is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name: Centramed</td>
</tr>
<tr>
<td>Address: Onderlinge Waarborgmaatschappij B.A., Postbus 7374, 2701 AJ Zoetermeer</td>
</tr>
<tr>
<td>Telephone number: 070 3017070</td>
</tr>
<tr>
<td>Email: <a href="mailto:schade@centramed.nl">schade@centramed.nl</a> (Policy number: …)</td>
</tr>
<tr>
<td>Polis number: 624,529,204</td>
</tr>
</tbody>
</table>

The insurance offers cover of €650,000 as a maximum per claim per participant, with a maximum of €5,000,000 for the entire study and €7,500,000 per year for all studies by the same client.

Please note that the insurance does not cover the following damage:

- Damage due to a risk about which we have given you information in this sheet. But this does not apply if the risk turned out to be greater than we previously thought. Or if the risk was very unlikely.
- Damage to your health that would also have happened if you had not taken part in the study.
- Damage that happens because you did not follow directions or instructions or did not follow them properly.
- Damage to the health of your children or grandchildren.
- Damage caused by a treatment method that already exists. Or by research into a treatment method that already exists.
Appendix C – Overview of measurements

**Time 1:** 3rd week after starting antibiotics
- Determining whether you are eligible to participate in the study.
- The lottery. This will determine whether you will receive antibiotics for 4 weeks or 6 weeks.
- 2 questionnaires: about your state of health and quality of life.

**Time 2:** 4th week after starting antibiotics
- If you are no longer in hospital, telephone contact with researchers about physical complaints and possible side effects.

**Time 3:** on discharge from hospital (time varies)
- 1 questionnaire about possible consequences of health problems for your work.

**Time 4:** 5th week after starting antibiotics
- A blood sample to determine whether the antibiotic treatment is working and whether there are any side effects.
- If you are no longer in hospital, telephone contact with researchers about physical complaints and possible side effects.

**Time 5:** 6th week after starting antibiotics
- A blood sample to determine whether the antibiotic treatment is working and whether there are any side effects.
- 2 questionnaires: about your state of health and quality of life.
- If you are no longer in hospital, telephone contact with researchers about physical complaints and possible side effects.

**Time 6:** 8th week after starting antibiotics
- Telephone contact with researchers about physical complaints and possible side effects.

**Time 7:** 3 months after the start of the study
- Telephone contact with researchers about physical complaints

**Time 8:** 6 months after the start of the study
- 4 questionnaires: about your state of health, quality of life, possible consequences of health problems for your work and your use of healthcare.
- Telephone contact with researchers about physical complaints
Appendix D - Informed consent form – subject
Versie 1
2022-05-04

A study on safely shortening antibiotic treatment in bloodstream infections with Staphylococcal bacteria: the SAFE study.

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give the investigator consent to inform my general practitioner, treating specialist and pharmacy that I am taking part in this study.
- I give consent to request information from my general practitioner, treating specialist and pharmacy about my medical history and medicine use.
- I give consent to collect and use my data and body material. The investigators only do this to answer the question of this study.
- I give permission for the storage of my data for 15 years.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- I give permission for my general practitioner and/or treating specialist to be informed of unexpected findings that are (or may be) important for my health.
- I know that if necessary I must undergo a pregnancy test, prior to participation I cannot become pregnant as long as I am being treated with antibiotics.
- The investigator discussed with me how I can best prevent becoming pregnant.

I give ☐ Yes ☐ No
consent to request information from my general practitioner if I am not available by phone 3 times

I give ☐ Yes ☐ No
consent to store my personal data longer and use it for future research into my condition.

I want to take part in this study.

My name is (subject): ………………………………..
Signature: ……………………… Date : __/__/__

Subject information SAFE study

Appendix D - Informed consent form – subject
Versie 1
2022-05-04

A study on safely shortening antibiotic treatment in bloodstream infections with Staphylococcal bacteria: the SAFE study.

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give the investigator consent to inform my general practitioner, treating specialist and pharmacy that I am taking part in this study.
- I give consent to request information from my general practitioner, treating specialist and pharmacy about my medical history and medicine use.
- I give consent to collect and use my data and body material. The investigators only do this to answer the question of this study.
- I give permission for the storage of my data for 15 years.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- I give permission for my general practitioner and/or treating specialist to be informed of unexpected findings that are (or may be) important for my health.
- I know that if necessary I must undergo a pregnancy test, prior to participation I cannot become pregnant as long as I am being treated with antibiotics.
- The investigator discussed with me how I can best prevent becoming pregnant.

I give ☐ Yes ☐ No
consent to request information from my general practitioner if I am not available by phone 3 times

I give ☐ Yes ☐ No
consent to store my personal data longer and use it for future research into my condition.

I want to take part in this study.

My name is (subject): ………………………………..
Signature: ……………………… Date : __/__/__

Subject information SAFE study

Appendix D - Informed consent form – subject
Versie 1
2022-05-04

A study on safely shortening antibiotic treatment in bloodstream infections with Staphylococcal bacteria: the SAFE study.

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give the investigator consent to inform my general practitioner, treating specialist and pharmacy that I am taking part in this study.
- I give consent to request information from my general practitioner, treating specialist and pharmacy about my medical history and medicine use.
- I give consent to collect and use my data and body material. The investigators only do this to answer the question of this study.
- I give permission for the storage of my data for 15 years.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- I give permission for my general practitioner and/or treating specialist to be informed of unexpected findings that are (or may be) important for my health.
- I know that if necessary I must undergo a pregnancy test, prior to participation I cannot become pregnant as long as I am being treated with antibiotics.
- The investigator discussed with me how I can best prevent becoming pregnant.

I give ☐ Yes ☐ No
consent to request information from my general practitioner if I am not available by phone 3 times

I give ☐ Yes ☐ No
consent to store my personal data longer and use it for future research into my condition.

I want to take part in this study.

My name is (subject): ………………………………..
Signature: ……………………… Date : __/__/__

Subject information SAFE study

Appendix D - Informed consent form – subject
Versie 1
2022-05-04

A study on safely shortening antibiotic treatment in bloodstream infections with Staphylococcal bacteria: the SAFE study.

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give the investigator consent to inform my general practitioner, treating specialist and pharmacy that I am taking part in this study.
- I give consent to request information from my general practitioner, treating specialist and pharmacy about my medical history and medicine use.
- I give consent to collect and use my data and body material. The investigators only do this to answer the question of this study.
- I give permission for the storage of my data for 15 years.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- I give permission for my general practitioner and/or treating specialist to be informed of unexpected findings that are (or may be) important for my health.
- I know that if necessary I must undergo a pregnancy test, prior to participation I cannot become pregnant as long as I am being treated with antibiotics.
- The investigator discussed with me how I can best prevent becoming pregnant.

I give ☐ Yes ☐ No
consent to request information from my general practitioner if I am not available by phone 3 times

I give ☐ Yes ☐ No
consent to store my personal data longer and use it for future research into my condition.

I want to take part in this study.

My name is (subject): ………………………………..
Signature: ……………………… Date : __/__/__

Subject information SAFE study

Appendix D - Informed consent form – subject
Versie 1
2022-05-04

A study on safely shortening antibiotic treatment in bloodstream infections with Staphylococcal bacteria: the SAFE study.

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give the investigator consent to inform my general practitioner, treating specialist and pharmacy that I am taking part in this study.
- I give consent to request information from my general practitioner, treating specialist and pharmacy about my medical history and medicine use.
- I give consent to collect and use my data and body material. The investigators only do this to answer the question of this study.
- I give permission for the storage of my data for 15 years.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- I give permission for my general practitioner and/or treating specialist to be informed of unexpected findings that are (or may be) important for my health.
- I know that if necessary I must undergo a pregnancy test, prior to participation I cannot become pregnant as long as I am being treated with antibiotics.
- The investigator discussed with me how I can best prevent becoming pregnant.

I give ☐ Yes ☐ No
consent to request information from my general practitioner if I am not available by phone 3 times

I give ☐ Yes ☐ No
consent to store my personal data longer and use it for future research into my condition.

I want to take part in this study.

My name is (subject): ………………………………..
Signature: ……………………… Date : __/__/__
Subject information SAFE study

I declare that I have fully informed this subject about the study mentioned.

If any information becomes known during the study that could influence the subject's consent, I will let this subject know in good time.

Investigator name (or their representative): ....................
Signature:........................ Date:__/__/__

-----------------------------------------------------------------------------------------------------------------
Additional information was given by:
Name:..............................
Job title:...........................
Signature:........................ Date:__/__/__

-----------------------------------------------------------------------------------------------------------------

The study subject will receive a complete information sheet, together with a signed version of the consent form.