STUDY PROTOCOL

Early intra**v**enous to **o**ral antibiotic switch in uncomplicated ***S****taphylococcus aureus* bacteraemia:

The EVOS randomized controlled trial

Protocol number	EVOS 1.3, dated 12-03-2024 (NMRR ID-23-02467-3JV)
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Sponsor	Ministry of Health Malaysia (MOH)

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Protocol amendments

No.	Date of amendment (Protocol version)	Protocol section(s) amended	Reason of amendment(s)
01	18th September 2023 (Version 1.1)	• 7.4.1 – Added case definition of uncomplicated SAB. • 7.4.2 – Clarification of body temperature 37.5℃ or below as defervescence. • 8.4.3 – Clarification on study drug accountability. • 8.9 & 9.2 – Revised criteria for stopping study drug after development of clinically significant AE.	Minor revisions based on comments and recommendation from JPP-NIH panel.
02	25th October 2023 (Version 1.2)	• 9.3, 9.5 • 10.2 • 11.1, 11.4 • 13.4.3	Minor revisions based on comments and requirements from MREC Secretariat.
03	12th March 2024 (Version 1.3)	• 8.3 –Clarified that oxacillin-susceptible staphylococci can be considered susceptible to cefazolin and cephalexin. • 9.1.4, 14.4 – Revised the minimum adherence rate to ≥ 80% for patients to be deemed adherent to study antibiotics and completed study treatment as per protocol. • 10.3 – Revised SAE reporting timeline • 14.16 – Updated Gantt Chart	For *Staphylococcus aureus*, oxacillin susceptibility predicts cefazolin and cephalexin susceptibility as per CLSI guidelines. Adherence rate of ≥ 80% is widely accepted as adherence threshold for study drugs in clinical trials. Revised SAE reporting timeline in accordance with MREC requirement. Revised study timeline after receipt of research grant in January 2024.

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1. STUDY SYNOPSIS

Study title	Early intravenous to oral antibiotic switch in uncomplicated Staphylococcus aureus bacteraemia: The EVOS randomized controlled trial
Sponsor	Ministry of Health Malaysia
Clinical Phase	Phase 3
Investigators	The principal investigators are infectious diseases (ID) physicians practicing in tertiary hospitals under the Ministry of Health Malaysia.
Study sites	12 government tertiary hospitals with ID physicians
Study period	12 months First subject enrolment: May 2024 Last subject enrolment: January 2025 Last subject to complete follow-up: April 2025
Objectives	*Primary objective* To demonstrate that early IV to oral antibiotic switch is as efficacious as standard 14-day IV antibiotic therapy for patients with uncomplicated SAB. *Secondary objectives* To evaluate the additional benefits of early IV to oral antibiotic switch for patients with uncomplicated SAB: • Duration of hospitalisation • All-cause mortality • Complications related to IV therapy • Safety of early IV to oral antibiotic switch in terms of adverse events and risk of Clostridium difficile diarrhoea.
Methodology	This is a multicentre, randomized, open-label, parallel group design trial to evaluate non-inferiority and safety of early IV to oral antibiotic switch versus standard 14-days IV antibiotic for patients with uncomplicated SAB. Eligible subjects will be randomized 1:1 into 2 groups (early oral antibiotic switch versus standard IV antibiotic therapy) following the inclusion and exclusion criteria. The study consists of 3 stages for each patient with a duration of approximately 12 weeks: screening and enrolment, open-label treatment with 7 to 11 days of study antibiotics, and follow-up until day 90 post-randomization. Phone call or inpatient follow up will be conducted at Day 7-11, Day 30, and Day 90 post-

	randomization to review patient's condition. All data will be entered electronically into REDCap.
Study outcomes	*Primary outcome:* Rate of SAB-relapse, defined as any new positive blood culture with S. aureus, and/or newly diagnosed metastatic S. aureus infection resulting from hematogenous dissemination. [Time Frame: 90 days] *Secondary outcomes:* 1. Duration of hospitalisation in days [Time Frame: 90 days] • Number of calendar days of hospitalisation after the first positive blood culture for S. aureus. 2. All-cause mortality [Time Frame: 90 days] • Rate of any death occurred within 90 days of randomization 3. Complications related to IV therapy [Time Frame: 90 days] • Rate of complications related to insertion or usage of peripheral branula or central catheter, and administration of IV drugs 4. Adverse events [Time Frame: 30 days] 5. Clostridium difficile diarrhoea [Time Frame: 90 days] • A diagnosis of diarrhoea with ⩾1 stool sample tested positive for C. difficile toxin or toxin gene.
Sample size	*Sample size and power considerations* We estimate a 4% event rate of primary outcome (SAB-relapse) among our study patients. A clinically acceptable non-inferiority margin of 8% was determined based on a consensus among infectious diseases physicians after considering the expected large gain of oral treatment (for examples, reduced hospital bed-days, saving inpatient costs, and lower risk of healthcare associated infections). Thus, a total of 256 patients are needed in this study to achieve 80% power with a one-sided 0.025 α-level. After adjustment for 10% potential dropout, the study will require 290 patients or 145 patients in each study arms. (Calculated using STATA/IC Version 13.1, Revision 16 Dec 2016).

Study Population	*Hospitalized patients who fulfil the study criteria at the time of screening will be recruited and randomized.* **<u>Inclusion criteria</u>** 1. Age 18 years old and above. 2. Blood culture positive for Staphylococcus aureus (S. aureus). 3. Received 3 to 7 days of definitive IV antimicrobial therapy, defined as: • Cloxacillin or cefazolin for methicillin-sensitive staphylococcus aureus (MSSA); Vancomycin or ceftaroline for methicillin-resistant staphylococcus aureus (MRSA). • Proven in-vitro susceptibility and adequate dosing given (as determined by the principal investigator). 4. Achieved clearance of bacteraemia, defined as at least one documented latest negative follow-up blood culture obtained within 72 hours after the initiation of definitive IV antimicrobial therapy. 5. Achieved defervescence, defined as sustained body temperature ⩽37.5°C within 48 hours before randomization. 6. Able to provide written informed consent to participate trial. **<u>Exclusion criteria</u>** 1. Evidence of metastatic infection of S. aureus: for example, infective endocarditis, intraabdominal abscess, lung empyema, and osteomyelitis. Radiological investigations such as chest X-ray, ultrasound, echocardiogram, and CT scan are not mandatory prior to enrolment, but should be done at the discretion of the treating physician if clinically indicated. 2. Septic shock, defined as hypotension requiring vasopressors to maintain MAP ≥65 mmHg despite adequate volume resuscitation. 3. Received more than 5 days of non-study antibiotics as empirical therapy prior to enrolment. 4. Polymicrobial bloodstream infection, defined as isolation of pathogens other than S. aureus from a blood culture obtained prior to randomization. Common skin contaminants such as coagulase-negative staphylococci, Bacillus spp., and diphtheroid will not be considered to represent polymicrobial infection. 5. Known history of S. aureus infection within the past 3 months.

6. Inability to tolerate oral therapy or poor absorption of oral medications, or not suitable for ongoing IV therapy (for example, difficult intravenous access)

7. No options of oral antibiotic available for patient due to:

    - In vitro resistance of S. aureus to all oral study drugs.
    - Known contraindications to receive the active oral study drugs. For example, hypersensitivity reaction to trimethoprim-sulfamethoxazole, thrombocytopenia secondary to linezolid etc.
    - Non-availability of oral study drugs at the study sites.

8. Patient is concomitantly receiving oral antibiotics which are active against S. aureus. For example, trimethoprim-sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis.

9. Presence of a non-removable foreign body such as prosthetic heart valve, vascular graft, pacemaker, automated implantable cardioverter-defibrillator, ventriculoperitoneal shunt, prosthetic joint, and fracture fixation implant

10. Failure or inability to remove intravascular catheter that is present when first positive blood culture was drawn.

11. Known comorbidity that increased the risk of complicated infections:

    - End-stage renal disease
    - Severe liver disease (Child-Pugh class C)
    - Severe immunodeficiency:
        - HIV-positive patients with CD4<200 cells/uL or AIDS
        - primary immunodeficiency disorders
        - high-dose steroid therapy (>1 mg/kg prednisone or equivalent doses given for > 4 weeks or planned during intervention)
        - immunosuppressive therapy
        - neutropenia (<500 neutrophils/µl) at randomization or neutropenia expected during intervention phase due to immunosuppressive treatment
        - solid organ or hematopoietic stem cell transplantation within the past 6 months or planned during treatment period

13. Short life expectancy < 3 months

14. Pregnancy (for women of childbearing potential)

Test treatment, dose, and mode of administration	Patients will receive either an oral or intravenous study drug, according to the treatment arm. The study drug will be selected by the site investigator from a list of study drugs as follows: **<u>Early Oral Switch (EOS) therapy:</u>** First choice for MSSA and MRSA: Tab. Trimethoprim-sulfamethoxazole 2-4 tablets BD Alternative for MSSA: Tab. Clindamycin 600mg TDS, Tab. Cephalexin 1gm QID, Tab Linezolid 600mg BD Alternative for MRSA: Tab. Linezolid 600mg BD **<u>Standard IV (SIV) therapy:</u>** First choice for MSSA: IV Cloxacillin 2g QID Alternative for MSSA: IV Cefazolin 1-2g TDS First choice for MRSA: IV Vancomycin 15-20mg/kg BD Alternative for MRSA: IV Ceftaroline 600mg TDS The choice of study drug will depend on the susceptibility of the respective isolate, expected drug interactions, contraindications, and expected side effects. Investigators will assess whether the "first-choice" regimen can be given and then consider the alternative regimen. The study drug can be switched during therapy from first choice to the respective alternative antibiotics if clinically necessary. The route of administration must be maintained according to the randomized group. Doses should be adjusted in the setting of renal dysfunction.
Duration of treatment with study medication	Patients in both groups will receive 7 to 11 days of study drugs to achieve a total course of 14 days of definitive antimicrobial therapy for SAB.
Statistical Analysis	The primary analysis for this study will be performed on the intention-to-treat (ITT) population, which consists of all randomized patients analysed as assigned. Absolute between-group difference of SAB-relapse rate and its 95% confidence interval for the oral antibiotic stepdown and the standard IV antibiotic groups will be estimated using a one-tailed z-test. If the upper limit of the 95% confidence interval falls below the 8% non-inferiority margin, early oral antibiotic switch will be deemed non-inferior to standard IV antibiotics. A second supportive analysis on the primary endpoint will be derived from the per-protocol (PP) population, which includes patients who have been treated

	according to protocol and reached a defined relapse outcome in the trial. In this analysis, we will exclude patients who do not complete the study treatment as per protocol, lost to follow-up, withdraw during the study period, or meet the criteria for protocol deviation. Secondary outcome measures expressed as proportions will be compared between control arm (SIV) and intervention arms (EOS) using chi-squared test, and risk difference as well as relative risk of the outcome measures will be calculated together with its 95% confidence interval. Mean difference and its 95% confidence interval will be provided for secondary outcome measures that are on numerical scale, and comparison between study arms will be done using independent t-test. P-value < 0.05 is considered statistically significant. Subgroup analysis of the primary endpoint may also be performed although the study power in subgroups may be low. An interim analysis will be performed on the efficacy and safety endpoints when 50% of the targeted patients have been randomized and completed 30 days follow-up. The results will be presented to the Data and Safety Monitoring Board (DSMB) to determine whether the trial should proceed as planned or be stopped early due to overwhelming non-inferiority or safety concern or undergo sample size recalculation based on conditional power.

2. INVESTIGATOR'S AGREEMENT AND DECLARATION

I hereby agree to conduct the clinical trial in compliance with the protocol with the ethical principles outlined in the Declaration of Helsinki, Malaysian Good Clinical Practice Guideline (GCP), and applicable local regulations.

I acknowledge that I am responsible for overall study conduct in my study site. I agree to personally conduct and supervise the described clinical study and maintain the appropriate records and documentation required.

I agree to ensure that all site staff involved in the conduct of the study will be appropriately trained and informed of their responsibilities and obligations.

I will ensure that all site investigators and I have no conflict of interest (COI) in this study. Any COI arises during the study shall be declared promptly.

Site Principal Investigator
Name: **Site:** **Signature:** **Date:**

Principal Investigator
Name: Dr Steven Lim Chee Loon **Signature:** **Date:**

3. LIST OF ABBREVIATIONS

AE	Adverse events
CRC	Clinical Research Center
CRF	Case Report Form
DG	Director General of Health, Ministry of Health, Malaysia
DSMB	Data and Safety Monitoring Board
EOS	Early oral switch
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICU	Intensive Care Unit
ID Physician	Infectious Diseases Physician
IDSA	Infectious Diseases Society of America
IE	Infective endocarditis
ITT	Intention-to-treat
IV	Intravenous
MSSA	Methicillin-Susceptible Staphylococcus aureus
MRSA	Methicillin-Resistant Staphylococcus aureus
MOH	Ministry of Health Malaysia
MREC	Medical Research Ethnics Committee
NIH	National Institute of Health
OPAT	Outpatient Parenteral Antimicrobial Therapy
PI	Principal Investigator
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture
SAB	Staphylococcus aureus Bacteraemia
SAE	Serious Adverse Event
SIV	Standard intravenous
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization

4. GLOSSARY OF TERMS

Arm	A group or subgroup of participants in a clinical trial that receives a specific intervention/treatment, or no intervention, according to the trial's protocol.
Baseline characteristics	Data collected at the beginning of a clinical study for all participants and for each arm or comparison group. These data include demographics, such as age, sex/gender, race and ethnicity, and study-specific measures
Collaborator	An organization other than the sponsor that provides support for a clinical study. This support may include activities related to funding, design, implementation, data analysis, or reporting.
Data and Safety Monitoring Board	A group of independent scientists who monitor the safety and scientific integrity of a clinical trial. They can recommend to the sponsor that the trial be stopped if it is not effective, is harming participants, or is unlikely to serve its scientific purpose. Members are chosen based on the scientific skills and knowledge needed to monitor the particular trial.
Definitive therapy	Targeted antibiotics administered based on the index culture and susceptibility results.
Eligibility criteria	The key requirements that people who want to participate in a clinical study must meet or the characteristics they must have. Eligibility criteria consist of both inclusion criteria (which are required for a person to participate in the study) and exclusion criteria (which prevent a person from participating).
Empirical therapy	Antibiotics administered before the index culture and susceptibility results are known.
Informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
Phase 3	A phase of research to describe clinical trials that gather more information about a drug's safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs. These studies typically involve more participants.
Primary outcome	In a clinical study's protocol, the planned outcome measure that is the most important for evaluating the effect of an intervention/treatment.
Protocol amendment	A written description of a change(s) to or formal clarification of a protocol.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Secondary outcome	In a clinical study's protocol, a planned outcome measure that is not as important as the primary outcome measure for evaluating the effect of an intervention but is still of interest.
Subject(s)	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

5. INTRODUCTION & BACKGROUND

S*taphylococcus aureus* is a common and serious cause of bloodstream infection worldwide with mortality rates ranging from 10% to 30% [1]. In the industrialized world, the population incidence of Staphylococcus aureus bacteraemia (SAB) varies from 10 to 30 per 100,000 person-years [2]. Based on a few reports from Asia on the prevalence of *Staphylococcus aureus* isolated from blood cultures, Malaysia showed a rate of 10.4%, Philippines 7.4%, Laos 19%, and India 18% [3-6].

SAB is well known for frequent relapse with distant metastatic foci such as infective endocarditis (IE), osteoarticular infection, pleuropulmonary and intrabdominal abscesses. In prospective cohort studies, 10% to 20% of SAB episodes are complicated by IE [7, 8]. To prevent these complications, most guidelines and experts recommend treating all SAB with at least 14 days of intravenous (IV) anti-staphylococcal antibiotics, albeit absence of high-quality evidence to support such practice [9, 10]. In fact, the current SAB guidelines do not cite any controlled clinical studies that established the superiority of IV-only therapy compared to oral therapy. Instead, the presumptive superiority of IV antibiotics stems from uncontrolled case series from the 1940s and 1950s, and the limited bioavailability of the few oral antibiotics available at that time [11]. To date, there are several oral antibiotics with excellent bioavailability over 90%, such as linezolid, sulfamethoxazole-trimethoprim (TMX-SMX), and clindamycin [12], all of which have not been subjected to rigorous trials in SAB.

The cornerstone in the management of SAB is the differentiation between a “complicated” and an “uncomplicated” infection. Fowler et al have ascertained 4 predictors of complicated SAB, namely community acquisition, persistent positive blood cultures at 48 to 96 hours, persistent fever at 72 hours, and skin findings suggestive of systemic infection. Patients with one of these characteristics were at approximately 35% probability for complicated SAB. In contrast, the probability of developing complications was about 16% in the absence of these risk factors [13]. The Infectious Diseases Society of America (IDSA) has published guidelines with the following criteria to define uncomplicated SAB: a) negative follow-up blood cultures obtained 2–4 days after the initial set; b) defervescence within 72 hours of initiating effective therapy; c) no prosthetic material; and d) no endocarditis and metastatic infection [14]. Patients at low risk for complications may thus benefit from an early switch to oral antibiotics through reduced length of hospital stay, fewer IV line-associated inflammation or infection, cost-saving, and improved general wellbeing.

Furthermore, in this era of antimicrobial resistance, one of the key components of antimicrobial stewardship (ASP) is a continual “review every 48–72 hours” framework for inpatient administration of antibiotics. IDSA ASP guidelines strongly recommend the timely conversion from IV to oral antimicrobials in routine clinical practices [15]. Unwarranted long courses of IV antibiotics are resource heavy and lead to prolonged hospital stay, which exposes patients to nosocomial infections with multi-resistant organisms.

There is growing evidence showing the safety and efficacy of IV to oral antibiotic switch in SAB. In a single-centre, observational study cohort of 492 patients with methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infection (BSI), Jorgensen et al found no difference

in 90-day failure between the oral-therapy group and the IV group [16]. Willekens et al compared an early switch to linezolid between Days 3 and 9 of standard IV therapy in a prospective study of 135 patients with low-risk SAB. There was no difference found in 90-day relapse between the two groups nor in 30-day all-cause mortality [17]. Recent randomized clinical trials, POET and OVIVA have shown that oral is safer than IV therapy with respect to treatment complications and has equivalent microbiological outcomes. Staphylococcus aureus has been well represented in these studies (23.4% and 36.2% in the oral treatment arms of the POET and OVIVA trials, respectively) [18, 19]. The findings of the SABATO randomized control trial were recently presented in a conference and showed that in the small group of patients at low risk of SAB complications, oral switch therapy after 5–7 days of IV treatment was not inferior compared to a complete 14-day IV course [20]. This latest evidence suggests that a more individualized treatment regimen involving oral antibiotics with good bioavailability is possible in selected patients with SAB.

Table 1: Key published studies describing non-inferiority of oral antibiotic therapy for S. aureus bacteraemia

Author/Year	Study design	Sample	Oral therapy in the study arm	Findings
Willekens et al., 2018 [17]	Prospective matched cohort study comparing the efficacy, safety, and length of hospital stay of patients receiving standard parenteral therapy (SPT) and those where SPT was switched to oral linezolid between days 3 and 9 of treatment until completion.	135 adult patients with low-risk SAB; 45 oral linezolid vs 90 SPT cases	Linezolid	No difference in 90-day relapse between the linezolid group and the SPT group (2.2% vs 4.4% respectively; P = .87).
Jorgensen et al., 2019 [16]	Single-centre, retrospective, cohort study comparing outcomes in adults completing MRSA BSI therapy with oral versus parenteral antibiotics in the outpatient setting.	492 patients with SAB; 70 received oral therapy vs 422 received IV therapy.	Oral linezolid, TMP-SMX, clindamycin, or doxycycline +/- adjuvant rifampin	Non-significant reduction in the rate of 90-day clinical failure in the oral therapy group compared with the IV therapy group [adjusted HR (aHR) 0.379, 95% CI 0.131-1.101; P = .0747)]
Iversen et al., 2019 [18]	Randomized, noninferiority, multicenter trial on patients with left-sided endocarditis treated with at least 10 days of IV antibiotics, before being randomized to continue IV treatment or to switch to oral antibiotic treatment.	400 adult patients with left-sided endocarditis; 199 patients continued IV treatment vs 201 switched to oral antibiotic treatment. 87 patients with S.	13 oral combinations for patients with S. aureus, of which the 3 most common were dicloxacillin + rifampicin, amoxicillin	The primary composite outcome (all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteraemia with the primary pathogen) occurred in 24 patients (12.1%) in the

		aureus as the causative pathogen.	+ rifampicin, and moxifloxacin + rifampicin.	intravenously treated group and in 18 (9.0%) in the orally treated group (between-group difference, 3.1 percentage points; 95% confidence interval, −3.4 to 9.6; P = .40), which met noninferiority criteria.

Overall, there is a dearth of high-quality evidence that informs appropriate management of SAB. Thus far there are no published well-designed and adequately powered RCT that evaluate the outcome of IV to oral stepdown therapy for uncomplicated SAB. The SABATO trial was completed in 2020 but has not been published in any peer-reviewed journal, for unknown reason. Robust clinical trials are needed to address this outstanding yet important clinical question in the management of SAB. We will therefore perform a national multicentre, open label, randomized clinical non-inferiority trial with the aim to assess the efficacy and safety of early IV to oral switch of antibiotics in SAB. Potentially, the study will be impactful locally and globally by providing the clinicians an essential evidence-based rationale for optimizing the treatment guidelines of SAB.

6. OBJECTIVES

6.1 Primary objective

To demonstrate that early IV to oral antibiotic switch is as efficacious as standard 14-day IV antibiotic therapy for patients with uncomplicated SAB.

6.2 Secondary objectives

To evaluate the additional benefits of early IV to oral antibiotic switch for patients with uncomplicated SAB:

- Duration of hospitalisation
- All-cause mortality
- Complications related to IV therapy
- Safety of early IV to oral antibiotic switch in terms of adverse events and risk Clostridium difficile diarrhoea.

6.3 Potential study benefit and risk

Patients who participate in this study may benefit from an early switch to oral antibiotics by shortening hospital stay, preventing nosocomial infections, and avoiding IV line-associated complications, while not compromising the treatment outcome of SAB. Literatures have consistently showed that oral stepdown therapy leads to similar if not better treatment success compared to continuing standard IV therapy. For example, Jorgensen et al. reported a much lower clinical failure rate among patients who switched

to oral therapy (7.1%) compared to patients who completed a standard course of IV therapy (14.9%) [16]. A similar trend was also observed among a selected cohort of low-risk patient with SAB in Willekens et al., in which relapse was found only in 2.2% of patients receiving linezolid as oral stepdown therapy, as opposed to 4.4% who continued with standard parenteral therapy. The mortality rate was markedly lower in the oral group as well (2.2% versus 13.3%) [17]. In this study, patients will be recruited based on strict enrolment criteria for low-risk uncomplicated SAB, hence the event rate for SAB-relapse among study patients is estimated to be 4%.

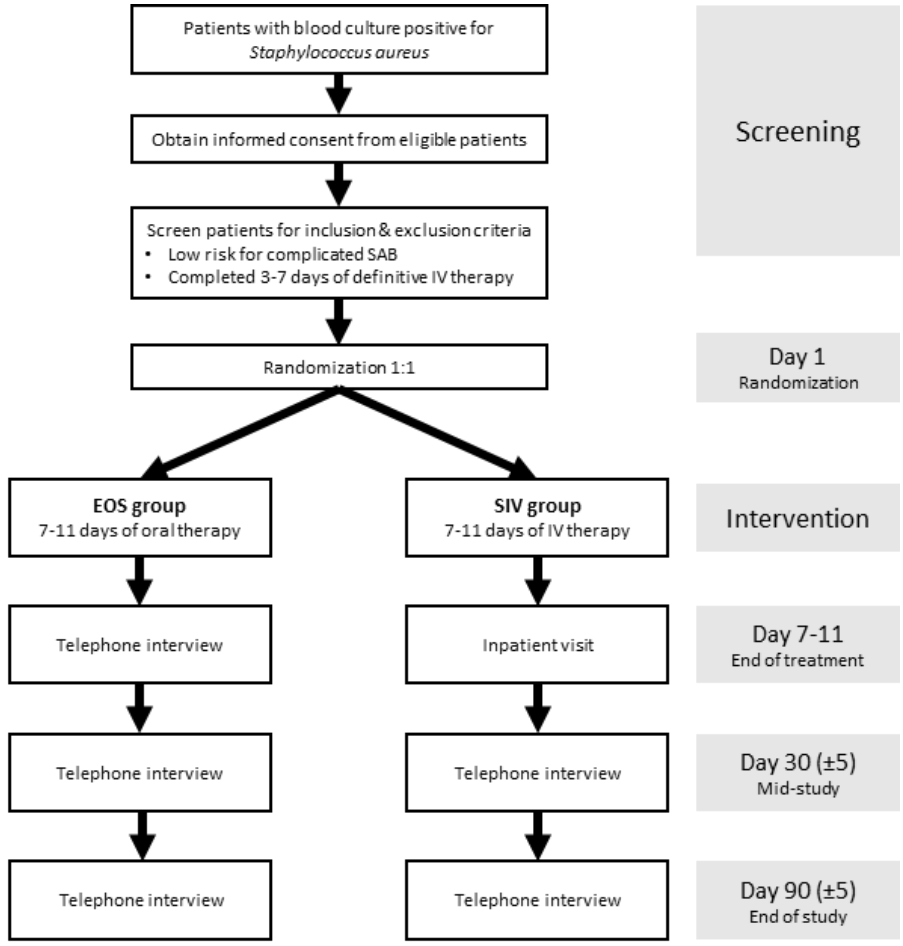
In terms of adverse events, approximately 3% of patients may experience sulfonamide allergy after taking trimethoprim-sulfamethoxazole [21]. The use of oral clindamycin, fluoroquinolones, and trimethoprim-sulfamethoxazole may also increase the incidence of Clostridium difficile-associated diarrhoea [22-24]. Nevertheless, these adverse events are well recognized and manageable by experienced treating physicians. Overall, the benefit of this study far outweighs the risk.

7. STUDY DESIGN

7.1 Overall study design

The Early Intravenous to Oral Antibiotic Switch in Uncomplicated *Staphylococcus aureus* Bacteraemia (EVOS) study is a multicentre, randomized, open-label, parallel group, Phase 3, non-inferiority trial of early intravenous to oral antibiotic switch in comparison with standard intravenous antibiotic regime among patients with uncomplicated *Staphylococcus aureus* bacteraemia. The study is based on the hypothesis that an early switch from IV to oral antimicrobial therapy is non-inferior and safe compared to conventional minimum 14-day course of IV therapy in patients with low-risk uncomplicated SAB.

7.2 Schematic diagram of study design



Follow-up will be done inpatient if patients are staying in study site hospital.

Abbreviations: EOS, Early oral antibiotic switch; SIV, Standard intravenous antibiotic

7.3 Discussion of study design

The EVOS Study is designed to evaluate non-inferiority and safety of early IV to oral antibiotic switch versus standard IV antibiotic therapy for patients with uncomplicated SAB. Considering the expected large gain of oral treatment (reduced hospital burden and improved patient wellbeing), and low incidence of SAB-related complications in selected low risk patients, a non-inferiority study design would be an appropriate initial approach to determine the benefit of oral antibiotics in the treatment of SAB with a clinically acceptable difference of 8% in efficacy compared to the standard IV therapy.

Eligible subjects will be randomized 1:1 into either early oral antibiotic switch (EOS) or standard intravenous antibiotic (SIV) groups following the inclusion and exclusion criteria. All patients will have already received 3 to 7 days of definitive IV antibiotic therapy prior to enrolment and randomization. Definitive therapy is defined as the targeted antibiotics administered based on the index blood culture and susceptibility results. In the experimental EOS group, patients will switch from definitive IV therapy to oral antibiotics.

Patients in the control SIV group will continue with IV therapy. Patients in both groups will receive 7 to 11 days of study drugs to achieve a total course of 14 (±2) days of definitive antimicrobial therapy. All patients will be followed up for 90 days from enrolment to evaluate efficacy and safety variables. Inpatient subjects will be reviewed by the site investigator clinical team in the hospital ward. Discharged patients are followed up by telephone interview with the patient or their nominated carer by designated site study investigators. Follow up assessment will be conducted at Day 7-11 (end of treatment), Day 30, and Day 90 post-randomization to review subjects' condition. All data will be entered electronically into REDCap.

7.4 Study population

Hospitalized adult patients with newly confirmed blood culture positive for S. aureus are identified by site study investigators through microbiology department. The patients are assessed for study eligibility and will be considered for enrolment when all inclusion criteria and none of the exclusion criteria are fulfilled. Strict inclusion and exclusion criteria are designed to select a group of patients with uncomplicated SAB and low risk for SAB-related complications.

Ideally, patients should be enrolled in the study before receiving any non-study antibiotic therapy. In reality, this is unachievable as patients would have been given empirical antibiotics (many of which have anti-staphylococcal activity) while awaiting blood culture results. A positive blood culture with identification of isolates and antibiotic susceptibility is typically reported by laboratory 3 to 5 days after the sample is drawn. Therefore, patients who have received 5 day or less duration of non-study antibiotic therapy (empirical therapy) are allowed to enter this study. The duration and type of non-study antibiotics before enrolment will be considered for subgroup analysis if significant difference is noted between study groups.

Patients entering the study will have already received 3 to 7 full days of definitive IV antibiotic therapy and have no evidence of complicated S. aureus infection prior to enrolment. Patients with a higher a priori risk for complicated infection are excluded (for example, severe immunodeficiency, end-stage renal disease, and presence of non-removable foreign body).

7.4.1 Case definition of uncomplicated SAB

Hospitalized adult patients with confirmed SAB who have achieved the following criteria:

- Clearance of bacteraemia, defined as negative follow-up blood culture obtained within 72 hours after the initiation of definitive IV antimicrobial therapy.
- Defervescence, defined as sustained body temperature $\leqslant$37.5°C for 48 hours.
- No evidence of metastatic infection of S. aureus.

7.4.2 Inclusion criteria

a) Age 18 years old and above.
b) Blood culture positive for Staphylococcus aureus (S. aureus).
c) Received 3 to 7 days of definitive IV antimicrobial therapy, defined as:
   - Cloxacillin or cefazolin for methicillin-sensitive staphylococcus aureus (MSSA); Vancomycin or ceftaroline for methicillin-resistant staphylococcus aureus (MRSA).
   - Proven in-vitro susceptibility and adequate dosing given (as determined by the principal investigator).
d) Achieved clearance of bacteraemia, defined as at least one documented latest negative follow-up blood culture obtained within 72 hours after the initiation of definitive IV antimicrobial therapy.
e) Achieved defervescence, defined as sustained body temperature 37.5°C or below within 48 hours before randomization.
f) Able to provide written informed consent to participate trial.

7.4.3 Exclusion criteria

a) Evidence of metastatic infection of S. aureus: for example, infective endocarditis, intraabdominal abscess, lung empyema, and osteomyelitis. Radiological investigations such as chest X-ray, ultrasound, echocardiogram, and CT scan are not mandatory prior to enrolment, but should be done at the discretion of the treating physician if clinically indicated.
b) Septic shock, defined as hypotension requiring vasopressors to maintain MAP ≥65 mmHg despite adequate volume resuscitation.
c) Received more than 5 days of non-study antibiotics as empirical therapy prior to enrolment.
d) Polymicrobial bloodstream infection, defined as isolation of pathogens other than S. aureus from a blood culture obtained prior to randomization. Common skin contaminants such as coagulase-negative staphylococci, Bacillus spp., and diphtheroid will not be considered to represent polymicrobial infection.
e) Known history of S. aureus infection within the past 3 months.
f) Inability to tolerate oral therapy or poor absorption of oral medications, or not suitable for ongoing IV therapy (for example, difficult intravenous access)
g) No options of oral antibiotic available for patient due to:
   - In vitro resistance of S. aureus to all oral study drugs.
   - Known contraindications to receive the active oral study drugs. For example, hypersensitivity reaction to trimethoprim-sulfamethoxazole, thrombocytopenia secondary to linezolid etc.
   - Non-availability of oral study drugs at the study sites.
h) Patient is concomitantly receiving oral antibiotics which are active against S. aureus. For example, trimethoprim-sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis.
i) Presence of a non-removable foreign body such as prosthetic heart valve, vascular graft, pacemaker, automated implantable cardioverter-defibrillator, ventriculoperitoneal shunt, prosthetic joint, and fracture fixation implant

j) Failure or inability to remove intravascular catheter that is present when first positive blood culture was drawn.
k) Known comorbidity that increased the risk of complicated infections:
   - End-stage renal disease
   - Severe liver disease (Child-Pugh class C)
   - Severe immunodeficiency:
     - HIV-positive patients with CD4<200 cells/uL or AIDS
     - primary immunodeficiency disorders
     - high-dose steroid therapy (>1 mg/kg prednisone or equivalent doses given for > 4 weeks or planned during intervention)
     - immunosuppressive therapy
     - neutropenia (<500 neutrophils/µl) at randomization or neutropenia expected during intervention phase due to immunosuppressive treatment
     - solid organ or hematopoietic stem cell transplantation within the past 6 months or planned during treatment period
l) Short life expectancy < 3 months
m) Pregnancy (for women of childbearing potential)

7.4.4 Study outcomes

The primary outcome of this trial is relapse of SAB, defined as any new positive blood culture with S. aureus, and/or newly diagnosed metastatic S. aureus infection resulting from hematogenous dissemination. The secondary outcomes are the all-cause mortality, length of stay in hospital after the first positive blood culture, complications related to IV therapy, Clostridium difficile diarrhoea, and adverse event (AE). All study outcomes are evaluated within 90 days of randomization, except for AE which is monitored within 30 days from randomization and treatment initiation. Any events occurred beyond 30 days are unlikely related to study treatment.

These individual outcomes will be derived from clinical evaluation, patient interviews, laboratory results, and radiological reports. The detailed definitions of each outcome measures are described in Table 2.

Adverse events (AE) and serious adverse events (SAE) are evaluated and graded according to Common Terminology Criteria for Adverse Events Version (CTCAE) version 5.0 [25].

Table 2: Definition of study outcomes

Outcomes	Definition
Relapse of SAB [Time Frame: 90 days]	Any new positive blood culture with S. aureus AND/OR Any newly diagnosed metastatic S. aureus infection resulting from hematogenous dissemination, such as infective endocarditis, liver/splenic abscess, lung empyema, osteomyelitis, or septic arthritis. Diagnosis of metastatic infection requires either imaging studies or diagnostic procedures (eg. arthroscopy) showing the presumed focus, or an isolation of S. aureus from culture samples taken from the respective site of metastatic infection. The S. aureus isolate needs to exhibit the same characteristics as the original infecting isolate based on antimicrobial susceptibility, and not to be considered by the site investigator to represent a contaminant. Catheter-related infections (from new catheter inserted during study period), superficial skin-and soft tissue, and wound infections are not regarded as metastatic infection.
All-cause mortality [Time Frame: 90 days]	Any death occurred.
Length of hospital stay [Time Frame: 90 days]	Total number of calendar days in hospital after the first positive blood culture with S. aureus. The duration includes readmission due to SAB relapse, complications related to IV therapy, adverse events, and any acute illnesses. Elective admission for procedure is excluded.
Complications related to IV therapy [Time Frame: 90 days]	Any complications related to insertion or usage of peripheral branula or central catheter, and administration of IV drugs. For examples, chemical or septic thrombophlebitis, extravasation of IV drugs, hematoma, and cellulitis.
Clostridium difficile diarrhoea [Time Frame: 90 days]	A diagnosis of diarrhoea with ≥1 stool sample tested positive for C. difficile toxin or toxin gene.
Adverse event (AE) [Time Frame: 30 days]	Any untoward medical occurrence in a patient after receiving study drugs and which does not necessarily have a causal relationship with treatment. All AE should be described in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

7.4.5 Subject withdrawal & dropout

Subjects are free to withdraw from the study at any time for any reason. Subjects may also be withdrawn from the study at any time at the discretion of the investigator due to AE or safety reasons. Reasons for withdrawn will be documented. Subjects withdrawn will not be replaced.

7.4.6 Procedures for handling withdrawal

Subjects who withdraw or are withdrawn from the study should:

- Have their reason(s) for withdrawal recorded in CRF.
- Be asked about the presence of any AEs and if so should be followed up by regular scheduled visits or telephone contact until satisfactory clinical resolution of AEs is achieved. Frequency of visits is at the discretion of the investigator.
- Be assessed by an investigator (physical visit or telephone call) and all final assessments will be performed and recorded in the CRF.
- Have at least one follow-up contact (scheduled visit or telephone contact) for safety evaluation during the 30 days following the last dose of study treatment.
- Be encouraged to participate in end of study telephone call follow up at Day 90 post-randomization.

7.4.7 Screening failures

All hospitalised adult patients with newly confirmed blood culture positive for S. aureus identified by site study investigators through microbiology department will be screened for eligibility. Patients who fail to meet the inclusion and exclusion criteria are defined as screening failures. The investigator will maintain a Screening and Enrolment Log which includes screen failures. The log will document the patient screening number, patient initials, and the reason(s) for excluding the patient from the study. This log will be kept in the Investigator Site File.

8. TREATMENT AND STUDY PROCEDURES

8.1 Description of study intervention

The study intervention involves switching to oral antibiotics after completion of at least 3 to 7 days of definitive IV antibiotics for the treatment of uncomplicated SAB. All antibiotics used this study are commercially available and commonly used in hospitals under the Ministry of Health Malaysia. Although there may be some variation in generic products used between hospitals, all individual study drugs contain the same active compounds and are approved by the National Pharmaceutical Regulatory Agency (NPRA).

The information of oral antibiotics for intervention arm is presented in Table 3. Details about individual drug's action, pharmacokinetics, adverse reactions, contraindications, and drug-drug interactions can be found in the Appendix.

Table 3: Description of oral antibiotics for intervention arm (Early Oral Switch therapy)

Study Drug	Route of administration	Formulation	Composition/ Strength	Manufacturer
Trimethoprim-sulfamethoxazole	Oral	Tablet	Each tablet contains Trimethoprim 80mg and Sulphamethoxazole 400mg	Pharmaniaga Manufacturing Berhad
Clindamycin	Oral	Capsule	Each capsule contains Clindamycin Hydrochloride 300mg	Y.S.P. Industries (M) Sdn. Bhd
Cephalexin	Oral	Capsule	Each capsule contains 250mg or 500mg of Cephalexin anhydrous	Pharmaniaga Manufacturing Berhad
Linezolid	Oral	Film-coated Tablet	Each tablet contains 600mg of linezolid	Pfizer Pharmaceutical

8.2 Description of study comparator

The study comparator involves continuation of the ongoing definitive IV antibiotics for a total of 14-day duration, as per current standard of care. The information of IV antibiotics in comparator arm is presented in Table 4. Details about individual drug's action, pharmacokinetics, adverse reactions, contraindications, and drug-drug interactions can be found in the Appendix.

Table 4: Description of IV drugs for comparator arm (Standard IV therapy)

Comparator Drug	Route of administration	Pharmaceutical form	Composition	Manufacturer
Cloxacillin	Intravenous	White crystalline powder in glass vial	Each vial contains Cloxacillin sodium BP 250mg or 500mg	Karnataka Antibiotics & Pharmaceuticals Limited
Cefazolin	Intravenous	Dry substance in glass vial	Each vial contains Cefazolin as sodium salt 1000mg	Sandoz GmbH
Vancomycin	Intravenous	White lyophilized powder in glass vial	Each vial contains Vancomycin Hydrochloride USP equivalent to Vancomycin 500mg	Gland Pharma Limited

Ceftaroline	Intravenous	Pale yellowish white to light yellow powder in glass vial	Each vial contains ceftaroline fosamil acetic acid solvate monohydrate equivalent to 600mg of ceftaroline fosamil	ACS Dobfar S.p.A.

8.3 Dosage and administration

Intervention arm (Early Oral Switch therapy):

Patients will switch to an oral antibiotic, selected by the site investigator from the following list of drugs:

- First choice for MSSA and MRSA: Tab. Trimethoprim-sulfamethoxazole
- Alternative for MSSA: Tab. Clindamycin, Tab. Cephalexin, Tab Linezolid
- Alternative for MRSA: Tab. Linezolid

Comparator arm (Standard IV therapy):

Patients will continue to receive IV antibiotics from the following list of drugs:

- First choice for MSSA: IV Cloxacillin
- Alternative for MSSA: IV Cefazolin
- First choice for MRSA: IV Vancomycin
- Alternative for MRSA: IV Ceftaroline

The choice of study drug will depend on the susceptibility of the respective isolate, expected drug interactions, contraindications, and expected side effects. Oxacillin-susceptible staphylococci can be considered susceptible to cefazolin and cephalexin [26]. Investigators will assess whether the "first-choice" regimen can be given and then consider the alternative regimen. The antibiotics can be switched from first choice to the respective alternative medication during the intervention period if clinically necessary (for example, switching to oral linezolid due to allergic reaction to sulfamethoxazole-trimethoprim). The route of administration must be maintained according to the randomized group.

Treatment of patients in this trial follows a pragmatic approach. Study medication is prescribed and administered according to local hospital practice. The recommended doses and frequency of study antibiotics in Table 5 are determined based on the National Antimicrobial Guideline 2019 [27], hospital site's clinical practice, and consideration to maximize the bioavailability of oral antibiotics for SAB. Doses should be adjusted in the setting of renal dysfunction according to the recommendations.

Study drugs will be prescribed, supplied, and dispensed to patients, whether in ward or upon discharge, in a sufficient number of doses or tablets to complete the predetermined number of treatment days from randomization Day 1 (Table 6). For example, patient who is planned to receive 8 days of Tab Linezolid 600mg bd should be supplied full 16 tablets upon discharge.

Table 5: Study drugs and dosage

Isolates	Route of administration	Drugs (Definitive therapy for SAB)	Dose in normal renal function	Renal dose adjustment*
MSSA	IV	Cloxacillin	2gm 4 hourly or 6 hourly	No
		Cefazolin	2gm tds	Yes
	Oral	Trimethoprim-sulfamethoxazole	TMP 10mg/kg/day	Yes
		Clindamycin	600mg tds	No
		Cephalexin	1gm qid	Yes
		Linezolid	600mg bd	No
MRSA	IV	Vancomycin	15-20mg/kg bd Loading dose 25-30mg is acceptable. TDM is mandatory. Aim for trough level of 15-20 ug/mL	Based on TDM
		Ceftaroline	600mg tds	Yes
	Oral	Trimethoprim-sulfamethoxazole	TMP 10mg/kg/day	Yes
		Linezolid	600mg bd	No

*Renal dose adjustment should be based on current antibiotic guidelines. Pharmacist consultation is encouraged.
Abbreviations: MSSA, methicillin-sensitive staphylococcus aureus; MRSA, methicillin-resistant staphylococcus aureus; TDM, therapeutic drug monitoring; TMP, Trimethoprim

Table 6: Determining the number of days of study treatment

	Days of treatment				
Number of days receiving definitive IV therapy before randomization (Date of last dose – Date of first dose)	3	4	5	6	7
Number of days for study treatment (IV/oral) from randomization Day 1	11	10	9	8	7
Total number of days of definitive therapy	14	14	14	14	14

8.4 Investigational product supply and handling

8.4.1 Supply, packaging, and labelling

All study medications are commercially available, commonly prescribed in hospitals, and approved by the NPRA. They will be supplied by, but not limited to, the respective manufacturers as stated in Table 3 and 4. The oral antibiotics in the intervention arm will be in blister packing of 10's x 10 while comparator IV drugs will be packaged in appropriately labelled carton box containing 10 vials each. They are labelled with the following information:

- Product identification
- Caution statement
- Direction for use
- Storage conditions
- Manufacturer's identification
- Manufacturing details (Batch Number, manufacturing date and expiry date)

8.4.2 Storage and dispensing

All the study drugs will be stored, dispensed, and administered by pharmacists and ward nurses in accordance with standard pharmacy procedures at respective study sites. Storage conditions, temperature monitoring and accountability of the study drugs will be as per hospital pharmacy policy and manufacturers' instructions.

8.4.3 Accountability

All the IV and oral study drugs are antibiotics commonly used in MOH hospitals for the treatment of *Staphylococcus aureus* infections. The investigators will ensure the study drugs are used in accordance with the protocol and dispensed to patients enrolled in the study. All study drug prescription, dispensing and administration must be accurately recorded and signed off in the patient medication charts. If there is any dispensing error or discrepancy, the PI must be notified immediately. Patient medication charts must be available for inspection by the study monitor at any time.

8.5 Treatment allocation and randomization

Patients are randomized in a 1:1 ratio to either the early oral antibiotic switch (EOS) group and standard intravenous antibiotic (SIV) group. The randomization is based on an investigator-blinded randomization list uploaded to REDCap, which allocates the patients via a central, computer-generated randomization scheme across all study sites during enrolment. The randomization list is generated independently using random permuted block sizes 2 to 6. The randomization is not stratified by site. When a patient meets the enrolment criteria, the authorized site personnel will login to the secure website to randomize the patient and receive all the relevant details on the allocated treatment. The corresponding medication will be dispensed and/or reconstituted by the designated personnel.

8.6 Baseline assessment and laboratory tests

- Social demographics, weight, and height
- Co-morbidity
- Antibiotic history
- Laboratory data
- Urine pregnancy test for women with childbearing potential

8.7 Assessment of compliance

Study drug compliance will be assessed through medication chart for inpatient and telephone interview for outpatient. The designated personnel who administered the study drugs in ward are required to fill up and sign the medication administration chart at every dose. If a subject is significantly non-compliant with the study medication, the investigators may consider withdrawing the subject from the study.

8.8 Concomitant therapy

There is no restriction of concomitant medications, except for non-study antibiotics. Protocol deviation may be considered if non-study antibiotics are given during the study period (please refer to section 14.4). Only concomitant medications taken by the patients during index admission will be documented in the CRF.

8.9 Discontinuation and interruption of treatment

The study drugs will be initiated within the same calendar day after randomization. Study drug will be discontinued after 7 to 11 days (depending on the duration of definitive antimicrobial therapy received before randomization). Patients will receive an overall course of 14 days of definitive antimicrobial therapy.

The study drug will also be terminated in case of any of the following occur:

- any relevant contraindication to study drug arises.
- eligibility criteria violation was noted after subject started study drug, when continuation of study drug would place the subject at risk.
- occurrence of clinically significant AE that renders patient unfit to continue with the study drug.
- subject requests withdrawal from the study.
- the investigator believes it is in the best interest of the subject.
- Death occurs.

8.10 Assessment of efficacy and safety

The aim of the trial is to demonstrate non-inferiority of early IV to oral antibiotic switch versus standard 14-day IV antibiotic therapy for patients with uncomplicated SAB. This will be achieved by comparing the rate of SAB relapse, defined as any new positive blood culture for S. aureus, and/or newly diagnosed metastatic S. aureus infection resulting from hematogenous dissemination within 90 days of randomization. Additional effects on

all-cause mortality, duration of hospital stay, complications related to IV therapy, and safety outcomes Clostridium difficile diarrhoea and adverse events will also be evaluated.

Assessment of efficacy and safety will be derived from patient interviews, clinical notes, laboratory reports, and clinical evaluation during intervention and follow-up schedule presented in Table 7. In addition, patients are given phone numbers to contact the designated site study investigators if they are admitted to hospital or experience adverse events during the study period.

9. STUDY CONDUCT

9.1 Study visits and procedures

9.1.1 Screening visit

- Patient with SAB from all disciplines in the hospital will be referred or notified by the primary team clinicians to the site investigator as soon as S. aureus is identified in the blood culture (reported from the microbiological department). An infographic poster (see appendix) about the trial will be disseminated among clinicians at respective study sites to help them to identify potential trial patients.
- Informed consent will be obtained from patients prior to study enrolment, and before any protocol-directed procedures are performed.
- The patient will be screened for eligibility to enter study according to the inclusion and exclusion criteria.
- A unique subject identification number (subject ID) will be assigned to each subject; this subject number will be used throughout the study.
- Women of childbearing potential should have a pregnancy test done. Study medication should not be initiated until a report of a negative pregnancy test has been obtained.
- Baseline evaluation and randomization can be performed during the screening visit or another visit.
- All patients screened for enrolment in the study will be recorded in Screening & Enrolment Log and Subject Identification Log.

9.1.2 Baseline visit

The following data will be collected at baseline:

- Subject's demography: date of birth/age, gender, ethnicity, height (cm) and weight (kg).
- Background and medical history which includes any diagnosed medical conditions within the previous 12 months, history of medication which includes list of antibiotics commenced by the primary team prior to enrolment and medical procedures within the previous 30 days of entry into the study.

- Physical examination performed by an attending physician or investigator within 24 hours before enrolment. The examination should include examination of the heart, lungs, abdomen, skin & soft tissues, joints, and spine, which aim to look for signs of complicated S. aureus infections.
- Latest vital signs recorded during screening and baseline assessment:
  - Pulse in beats/min
  - Blood pressure in mmHg
  - Temperature in ℃
- Latest laboratory tests done within 72 hours prior to enrolment and randomization:
  - WBC, Creatinine, ALT, CRP (optional)
- Imaging or diagnostic procedures done within 1 week before enrolment.

9.1.3 Eligibility verification and randomization

- Patients will be assessed for eligibility before study enrolment based on the inclusion and exclusion criteria.
- Women of childbearing potential should have a negative test (based on the pregnancy test kit used in the study site) prior to enrolment.
- All patients who are screened for eligibility will be recorded in the Screening & Enrolment Log regardless of whether the patients have been enrolled into the study or not.
- If eligible, designated personnel will enter all required data into online randomization platform where randomization result (intervention or control group) will be generated. Subject ID and randomization group will be recorded in the Patient Screening & Enrolment Log and Patient Identification List.
- If not eligible, the patient is considered as screen failure. Reasons for screen failure will be recorded in the Screening & Enrolment Log.
- As this is an open label trial, both the investigators and patient are aware of the drug/treatment given.
- The patients have equal chances to be in either intervention or control arm.
- The following information will be recorded during randomization:
  - Study ID (assigned during study initiation)
  - Site Number/ID (assigned during study initiation)
  - Patient's screening status
  - Date of informed consent signed by subject

9.1.4 Study treatment and visits

Patients randomized to intervention arm (EOS group) may either remain as inpatient or be discharged to home at the discretion of the attending physician. If they remain in hospital, the oral antibiotics will be administered to them by the ward nursing staff. If they are discharged home, they will be given a supply of oral antibiotics sufficient to complete the planned duration of therapy.

If the patient is randomized to control arm (SIV group), administration of the IV antibiotics will be continued in the ward to complete the total 14-day duration of therapy as per standard of care. Patients in SIV group can only be discharged when an outpatient antimicrobial therapy (OPAT) service is available at the local study site to administer the IV antibiotics. Alternatively, patients in SIV group can be transferred district hospital for continuation of IV therapy and will be followed by telephone interview.

All patients will be followed for 90 days from enrolment to evaluate efficacy and safety variables based on the study visit/follow-up schedule and procedures summarised in table 7. Patients in the hospital will be visited by the site investigator clinical team. Discharged patients are followed by telephone interview with the patient or their nominated carer by designated site study investigators.

At the end of therapy follow-up (Day 7 – 11), the study investigator will check for study drug adherence. For patients who are discharged home, their drug adherence will be determined by self-reported pill count during telephone interview. For patients in ward, drug adherence is determined by documentation of IV or oral study antibiotics administered in medical chart.

Patients will be assessed for study outcomes during each follow-up visits or telephone interviews: end of therapy day 7-11, mid-study day 30 (±5), and end of study day 90 (±5). All patients will be given phone numbers to contact the designated site study investigators if they are admitted to hospital or experience adverse events. If indicated, patient will be advised by investigator to visit the study site or nearest hospital for further assessment. The decisions to do investigations such as chest X-ray, ultrasound, CT scan, echocardiogram, or repeat blood culture during the study period depends on the clinical judgement of the primary treating physician in accordance with the standard of care.

Key information to be collected during follow-up assessment:

- Adherence to study antibiotics
    - Review of medication chart for inpatient or self-reported pill count during telephone interview:
    - SIV: Number of doses administered / Number of doses prescribed X 100%
    - EOS: Number of tablets taken / Number of tablets supplied X 100%
    - Patients are deemed adherent to study antibiotics and completed study treatment as per protocol only if ≥ 80% of prescribed drugs are taken.
    - Taking less than 80% of study drugs may warrant protocol deviation reporting (please refer to section 14.4).
- New positive blood culture for S. aureus
    - Date of sample(s)
- New diagnosis of metastatic S. aureus infection resulting from hematogenous dissemination
    - Date of diagnosis
    - Examples of metastatic infection include infective endocarditis, liver/splenic abscess, lung empyema, osteomyelitis, septic arthritis etc.

- Diagnosis of metastatic infection requires either imaging studies or diagnostic procedures (eg. arthroscopy) showing the presumed focus, or an isolation of S. aureus from culture samples taken from the respective site of metastatic infection.

- Duration of hospital stay
  - Total number of calendar days in hospital after the first positive blood culture (date of first positive blood culture & date of discharge)
  - The duration includes readmission due to SAB relapse, complications related to IV therapy, Clostridium difficile diarrhoea, or adverse events.
- Mortality
  - Date and cause of death.
- Clostridium difficile-associated diarrhoea
  - A diagnosis of diarrhoea with $\geqslant$1 stool sample tested positive for C.
  - Date of first stool sample tested positive for C. difficile toxin or toxin gene.
- Complications related to IV therapy
  - Any complications related to insertion or usage of peripheral branula or central catheter, and administration of IV drugs.
  - For examples, chemical or septic thrombophlebitis, extravasation of IV drugs, hematoma, and cellulitis.
- Adverse events and serious adverse events
  - Date and progress of AE or SAE
  - Classification based on the Common Terminology Criteria for Adverse Events Version (CTCAE) version 5.0.

Discharged patients are followed by telephone interview by designated site study investigators based on a structured questionnaire:

- To ascertain completion of study oral antibiotics for patients randomized in EOS group.
- To elicit symptoms suggestive of SAB relapse or adverse event, for example fever, rash, chest pain, abdominal pain, joint pain or swelling, etc.
- To document any readmission to hospital, visit to emergency department or clinic, receipt of non-study antibiotics etc. Investigator should obtain and verify key information from attending physician or hospital/clinic records.

Table 7: Study schedule of visits, follow-up, and data collection

	Screening for eligibility & baseline assessment	Randomization & study treatment initiation	End of therapy	Mid-study	End of study
Visit/Follow-up[a]	**1**	**2**	**3**	**4**	**5**
Procedures / Timeline	Within 24 hours before randomization	D1	D7-11	D30 (±5)	D90 (±5)
Check eligibility through inclusion & exclusion criteria	x				
Informed consent	x				
Demographic data & medical history	x				
Baseline characteristics	x				
Vital signs & physical examination	x				
Routine laboratory tests[b] (WBC, Creatinine, ALT, ± CRP)	X				
Imaging/diagnostic procedures done[c]	X				
Urine pregnancy test for women with childbearing potential	X				
Randomization		x			
Dispense study treatment		x			
Drug adherence check[d]			x		
Efficacy assessment[d]		x	x	x	x
Report AE and SAE		x	x	x	

[a]Discharged patients are followed by telephone interview by designated site study investigators.
[b]Latest laboratory tests done within 72 hours prior to enrolment and randomization.
[c]Any imaging or diagnostic procedures done within 1 week before enrolment
[d]Details of assessment can be found in section 9.1.4. Study treatment and visits

9.2 Criteria for stopping subject treatment

The study treatment will be discontinued prior to the protocol planned completion of study drug administration under the following circumstances:

- any relevant contraindication to study drug arises.
- any situation in which continued study participation might result in a safety risk to the patient.
- occurrence of clinically significant AE that renders patient unfit to continue with the study drug.
- patient's decision.
- the investigator believes it is in the best interest of the subject.

If discontinuation from study treatment occurs, the investigator should make reasonable effort to understand the primary reason for the patient's discontinuation and record this information.

9.3 Termination of study

The coordinating PI may choose to terminate this study prematurely after consultation with DSMB. Criteria for termination of the trial include:

- New evidence indicating early oral stepdown therapy in SAB is unsafe.
- Overwhelming non-inferiority or efficacy of oral therapy proven during interim analysis.
- Futility of study when there is statistically little or no chance of demonstrating non-inferiority of oral therapy compared to IV therapy during interim analysis.
- Unacceptable high incidence of SAB-relapse of >16% considering the study population are deemed to be low-risk with uncomplicated SAB prior to randomization.
- Increased number of unexpected serious adverse events or death due to study intervention.
- Substantial missing data that would unacceptably undermine trial conclusions.

The coordinating PI also reserves the right to terminate the trial at a study site for reasons below:

- Unsatisfactory or poor patient enrolment.
- Data recording is consistently inaccurate and/or incomplete.
- Poor supervision of study conducts by site PI.
- Lack of cooperation between local site investigators and study monitoring team.
- Deliberate violation of the approved study protocol.
- Deliberate violation of the ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline (GCP).

Should the coordinating PI decide to close the study site, all study materials including CRFs must be returned to the study central team in Hospital Raja Permaisuri Bainun. The site investigators may be informed of any additional procedures to be followed to ensure

adequate consideration is given to protect the subject's interests. The PI will be responsible for informing MREC of the early termination of the trial.

9.4 Dropouts and withdrawals

Subject may discontinue participation in the trial at any time. If a subject wishes to withdraw consent, we will use the following strategies to minimize the impact on the trial, while respecting autonomy. We will seek a better understanding of the subject's wishes and offer the following alternatives:

- Discontinue study drug but allow data collection via in-person follow-up, telephone follow-up and access to medical records
- Discontinue study drug, in-person follow-up but allow telephone follow-up and access to medical records
- Discontinue study drug, in-person and telephone follow-up, but allow access to medical records
- Discontinue study drug, all follow-up and no access to medical records (Complete withdrawal)

Subject will be considered lost to follow up if they failed to be contacted without stating to withdraw consent. The site must attempt to contact the subject (3 phone calls per day for 3 consecutive days. These contact attempts should be documented in the subject file. Subjects who withdrawn or lost to follow up will not be replaced.

9.5 Sample handling and analysis

All blood or urine specimens will be collected following acceptable laboratory procedures at the time points specified in the study schedule. The standard labels should be used to label each sample.

All biospecimens in this study will be collected, stored, and processed by designated personnel in accordance with the standard clinical practice in patient management and local laboratory procedures. There will be no additional biospecimen collected from patients solely for research purpose. This study does not involve any stored specimen used for future research. All biospecimens collected in this study is as per requirement of standard clinical management of SAB.

Laboratory tests are required at baseline before enrolment:

- White blood cell count
- Serum creatinine
- Alanine aminotransferase (ALT)
- C-reactive protein (CRP) (to be done at the discretion of the treating physician)
- Urine pregnancy test (only for female subjects of childbearing potential)

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse event (AE)

Any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have a causal relationship with treatment.

The following should be reported as AE:

- Treatment emergent symptoms which include:
  - Medical conditions or signs or symptoms that was absent before starting study treatment.
  - Medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory values or tests that induce clinical signs or symptoms or require therapy.
- For studies involving a marketed drug in an established indication, AE includes significant failure of expected pharmacological or biological action.
- Any doubtful event should be treated as an AE.
- Lack of efficacy, aggravation, relapse of current infection, or new infection are not an AE in the study and therefore also not an SAE (except death).

10.1.2 Unexpected adverse event

Any adverse event not reported in the safety section of the Investigator's Brochure or if the event is of greater frequency, specificity, or severity.

10.1.3 Serious adverse event (SAE)

An adverse event that:

- results in death
- is life threatening (places the participant at immediate risk of death)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

A hospitalisation or prolongation of a hospitalisation for reasons other than an adverse event would not be considered an SAE.

10.2 Detecting and documenting AE

As our trial intervention involves only a short course of study drugs (7 to 11 days), all study patients will be monitored for occurrence of AEs within 30 days from randomization and

treatment initiation. Any events occurred beyond 30 days are unlikely related to study treatment.

AEs that begin or worsen after treatment initiation should be recorded in the “Adverse Event” section of the CRF. Conditions that were already present or any intercurrent illnesses at the time of informed consent should be recorded in the “Co-morbidities” section of the CRF. The occurrence of AEs will be sought by non-directive questioning of the patient after study drug initiation, at the end of antibiotic therapy (between Day 7-11), and at Day 30 of randomization. AEs may also be detected via patient’s self-reporting to the study team at any time point between the scheduled follow-ups.

The investigator shall maintain and keep detailed records of all AEs in the patient files. All information about AEs, whether volunteered by the patient, discovered by the investigator during interview, or detected through physical examination, laboratory test or by other means, will be recorded on the “Adverse Event” page of the CRF and followed up as appropriate.

When eliciting experiences of AE from a subject, a standard non-leading question will be asked, for example, "Do you feel different in any way since starting the new treatment/the last visit?" This question will be put to the subject in his/her own language at each study visit or telephone interview.

Each AE should be described by:

a) Nature of AE
   The investigator should describe the AE using terminology in the Common Terminology Criteria for Adverse Events Version (CTCAE) version 5.0 [25]. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject.

b) Duration
   Start date and end dates (if the patient has recovered from the AE).

c) Assessment of causality
   The investigator should attempt to explain each AE and assess its relationship, if any, to the study treatment. Causality should be assessed and reported using the description in Table 8.

   The degree of certainty with which an AE is attributed to study treatment or alternative cause like natural history of disease or concomitant treatment should be guided by the following considerations:
   - Time relationship between treatment and occurrence of AE
   - De-challenge and re-challenge information, if applicable
   - Known pharmacology of the drug
   - Dose response relationships

- Lack of alternative explanations i.e. no concomitant drug used and no other inter-current disease
- Reaction of similar nature being previously observed with this drug or class of drug
- Reaction having often been reported in literature for similar drug

d) Severity of AE
The severity of events will be assessed and graded based on CTCAE, Version 5.0 [25] in Table 9. Grade 4 and 5 AE should be considered as SAE and need to be reported and notified to MREC.

Table 8: Causality assessment of adverse events

Causality	Description
Very likely	The AE follows a reasonable temporal sequence from study treatment administration. Abates upon discontinuation of study treatment. Reappears on repeated exposure (re-challenge).
Probable	The AE follows a reasonable temporal sequence from study treatment administration. Abates upon discontinuation of study treatment. Cannot reasonably be explained by known characteristics of the subject's clinical state.
Possible	The AE follows a reasonable temporal sequence from study treatment administration but could have been produced by the subject's clinical state or other mode of therapy administered to the subject.
Doubtful	The temporal association between study treatment and AE is such that the study treatment is not likely to have any reasonable association with the observed event.
Very unlikely	The AE is caused by the subject's clinical state or other mode of therapy administered to the subject.

Table 9: Grading of severity of adverse event

Severity	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Adopted from CTCAE version 5.0

10.3 Reporting SAE

Information about all SAEs will be recorded on the Serious Adverse Event Report Form. The investigators must assess the relationship of each SAE to the study drug and submit the completed SAE Report form to coordinating PI and MREC. For non-fatal/life-threatening SAE, initial report should be submitted within 15 calendar days from awareness of the event. For fatal/life-threatening SAE, initial report is to be submitted within 7 calendar days, followed by a follow-up report within the next 8 calendar days. Detailed instructions regarding the submission process are in the Investigator Site File provided at each site.

Follow-up information is submitted as instructed in the Investigator Site File. Each recurrence, complication or progression of the original event must be reported as a follow-up to that event, regardless of when it occurs. The follow-up information should describe whether the patient continued or withdrew from study participation. All SAEs should be followed up until resolution or permanent outcome of the event.

Where applicable, information from relevant medical records and autopsy reports should be obtained. Any death or congenital abnormality, if brought to the attention of the investigator within 6 months after cessation of study treatment, whether considered treatment related or not, should be reported.

10.4 Treatment and follow-up of AE

Treatment of any AE is at the sole discretion of the investigator who should follow up subjects with AE until the event has resolved or until the condition has stabilised. Non serious AEs considered related to the trial medication as judged by a medically qualified investigator will be followed up either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

Abnormal tests should be repeated until they return to baseline levels, or an adequate explanation of the abnormality has been found.

11. DATA MANAGEMENT

11.1 Data storage, data security and back up

This study uses the REDCap, an Electronic Data Capture (EDC) System for study data collection. The designated site clinical trial staff will enter the data into the REDCap using

electronic Case Report Forms (eCRFs), under the supervision of site-PI. The EDC system can only be accessed by designated personnel from each study site. Study personnel are only allowed access to data entry and data viewing of their own study site. Only coordinating PI and central study team members have access to view data from all sites, insert manual queries and export data from the EDC system.

Personal information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed informed consent that informs the subject of the following:

- What protected health information (study data) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to withdraw their consent or authorization for use of their personal information

(Please refer to the Patient Information Sheet and Informed Consent Form for more information)

If a subject withdraws consent to collect or use their personal information, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. Attempts will be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential subject information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Backup data from REDCap will be downloaded as both Excel file and XML File format every week. All the electronic research files will be stored within the study file in CRC HRPB server which has been located and password protected. The access is limited to designated study personnel only. The server is backed up to hard-drive every month. The hard-drive is password-locked and store in a locked cabinet which is only accessible by designated personnel only. Date format of ddmmyyyy will be used at the end of each file stored in the server for version management. At all times there will only be one current version of any document.

Paper copies of all study-related documents including subject study files and logs will be stored in locked filing cabinets in a locked office at each site. Identified data will be stored separately from de-identified data. Before archiving of data, study personnel will review existing and newer formats regarding longevity of data storage and ensure archival quality. Format changes will be approved by the PI. Should there be a sufficient risk of

obsolescence for the period in which data is to be kept, the study personnel will upgrade the format. Previous formats of the same data will be preserved with their identifiers. Newer file or data set formats will be assigned new identifiers but will link back to prior formats/ identifiers. For example, files may have the same name with the new format data having a suffix "-updated".

11.2 Data entry, checking and validation

Data entry will be done by designated personnel within the timeline based on the source documentation maintained at the clinical site. A guide for data entry will be available for all sites. REDCap used in this study has multiple automated edit checks including univariate and multivariate. In univariate alerts for multiple-choice field, REDCap provide valid-value edit check where the user is required to choose at least one checkbox from a series of different data choices. For field with "yes" and "no" options, user is required to choose only "yes" or only "no". Multivariate alerts in REDCap include user to compulsory to fill in "other, specify" when "others" is chosen. User are required to answer the queries in the REDCap. There are EDC generated queries and manual queries. EDC-generated queries are resulted from automated edit checks. Manual queries are used in cases where data is impractical to program an automatic check. Manual queries are also used during audit eCRF with source documents. Logic checks are conducted as data is entered into the EDC.

Data cleaning will be conducted monthly. Frequency tables will be created to check for invalid character values for all items, based on expected ranges and values of scales. Frequency tables will also be used to check for any missing values.

Before database lock, several checks will need to be carried out:

- All queries are answered by all sites.
- All the eCRFs are checked to ensure all expected data have been entered.
- The status of each subject in the eCRF are completed.
- Data are determined to be clean.
- Ensure absence of value formatting problems in the database.
- Ensure all expected site signed-off have been done.

11.3 Data quality assurance/quality control

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk. Continuous risk review and assessment may lead to adjustments in trial conduct, trial design and monitoring approaches.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified study site-investigators and appropriate study sites, review of protocol procedures with the study site-investigators and personnel before the study, periodic monitoring visits by Principal Coordinating Investigator or designee, and direct transmission of clinical data into the central database. Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study.

Independent personnel designated by the Principal Investigator will conduct the monitoring visits to ensure the completeness, consistency, and accuracy of the data. Periodical data monitoring visits will be initiated once first subject being enrolled into the study for each site. The designee will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the Principal Investigator; any discrepancies will be resolved with the site-investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

At the close of study, all data will be checked against the source document. Errors found during the monitoring visits will be corrected in the database before data lock.

A quality assurance audit/inspection of this trial may be conducted by independent personnel or by IRB/IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

11.4 Archiving and data destruction

Within 6 months of the completion of the research study and final publication of data, the electronic data will be stored at CRC HRPB. The paper documents will be stored at each site. Paper data will be boxed and labelled. The boxes will be transferred to the designated archival centre for archiving. Details of all archived data, including location, will be documented.

The investigator should maintain the trial documents and data as specified in Essential Documents for the conduct of the study as per regulations and guidelines. These documents will be retained for a period of not less than fifteen (15) years from the completion of the clinical trial. The investigator should take measures to prevent accidental or premature destruction of these documents.

After 15 years from the completion and publication of the study, the PI may declare that the trial documents and data are of no continuing value and will be recommended for destruction. Paper documents will be shredded, and mulched, digital data will be reformatted.

12. STATISTICAL METHODS

12.1 Sample size and power considerations

The main aim of this study is to demonstrate non-inferiority of early IV to oral switch of antibiotic therapy in preventing relapse among a selected group of low-risk patients with uncomplicated SAB.

A large prospective cohort study by Fowler et al found that low-risk patients with intravascular catheter–associated SAB with neither haemodialysis nor a permanent foreign body had a rate of 2.4% for hematogenous complications such as septic arthritis, vertebral osteomyelitis, or endocarditis [13]. Willekens et al, in a prospective cohort study of adult patients with uncomplicated SAB reported 90-day relapse rate of 4.4% for patients receiving standard IV therapy, and 2.2% for those who switched to oral linezolid [17].

In our study, the choice of oral antibiotics for the intervention arm consists of trimethoprim-sulfamethoxazole, clindamycin, cephalexin, and linezolid. Given the heterogeneity of treatment effects with each oral antibiotics, and the strict enrolment criteria for low-risk uncomplicated SAB, we estimate a 4% event rate of primary outcome (SAB-relapse) among our study patients.

A clinically acceptable non-inferiority margin of 8% was determined based on a consensus among infectious diseases physicians after considering the expected large gain of oral treatment (for examples, reduced hospital bed-days, saving inpatient costs, and lower risk of healthcare associated infections), as well as practical aspects of realistic recruitment of patients and completion of the trial.

Thus, a total of 256 patients are needed in this study to achieve 80% power with a one-sided 0.025 α-level. After adjustment for 10% potential dropout, the study will require 290 patients or 145 patients in each study arms (calculated using STATA/IC Version 13.1, Revision 16 Dec 2016).

12.2 Randomization

Patients who meet all criteria for enrolment is recruited and will undergo randomization at Day 1. Patients will be randomized into either one of the two treatment arms which is the investigational arm (Early Oral Switch therapy) or the control arm (Standard IV therapy) in a 1:1 ratio according to a site-specific randomization schedule. The randomization is based on an investigator-blinded randomization list uploaded to REDCap, which allocates the patients via a central, computer-generated randomization scheme across all study sites during enrolment. The randomization list is generated independently using random permuted block sizes 2 to 6. The randomization is not stratified by site. When consent is obtained and a patient meets the enrolment criteria, the authorized site personnel will login to the secure website to randomize the patient into the study arm according to the

randomization sequence and receive all the relevant details on the allocated treatment. The corresponding medication will be dispensed and/or reconstituted by the designated personnel. The schedule will be prepared and provided by biostatistician.

12.3 Statistical analysis plan

Baseline characteristics and therapy adherence will be summarised using counts and percentages. A one-tailed z-test will be used to compare the two observed proportions for the IV to oral antibiotic switch and the standard IV antibiotic groups based on the 8% non-inferiority margin defined in the study design. Data management and all statistical analyses will be performed using IBM Statistical Package for Social Sciences (SPSS) for Windows, version 22.0 (IBM Corp).

12.3.1 Efficacy analysis

The primary analysis for this study will be performed on the intention-to-treat (ITT) population, which consists of all randomized patients analysed as assigned. Absolute between-group difference of SAB-relapse rate and its 95% confidence interval for the oral antibiotic stepdown and the standard IV antibiotic groups will be estimated using a one-tailed z-test. If the upper limit of the 95% confidence interval falls below the 8% non-inferiority margin, early oral antibiotic switch will be deemed non-inferior to standard IV antibiotics.

A second supportive analysis on the primary endpoint will be derived from the per-protocol (PP) population, which includes patients who have been treated according to protocol and reached a defined outcome in the trial. In this analysis, we will exclude patients who do not complete the study treatment as per protocol, lost to follow-up, withdraw during the study period, or meet the criteria for protocol deviation.

Secondary outcome measures expressed as proportions will be compared between control arm (SIV) and intervention arms (EOS) using chi-squared test, and risk difference as well as relative risk of the outcome measures will be calculated together with its 95% confidence interval. Mean difference and its 95% confidence interval will be provided for secondary outcome measures that are on numerical scale, and comparison between study arms will be done using independent t-test. P-value < 0.05 is considered statistically significant. Subgroup analysis of the primary endpoint may also be performed although the study power in subgroups may be low.

12.3.2 Safety analysis

All treated patients will be included in the safety analysis. Patients will be classified according to actual treatment received. In general, safety analyses will be descriptive in nature and no hypothesis testing is planned.

Adverse events will be classified using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 [25]. For each category, we will report both the total number

of events and the proportion of participants with at least one event. Frequency, severity, and causal relationship of all AE will be tabulated by system organ class and preferred term after classification according to the CTCAE at database lock.

12.3.3 Handling of missing, unused, and spurious data

The study team will manage the data and will conduct quality control of the data following their own standard operating procedures. Missing data or suspected errors will be raised as data queries by the lead study coordinator and monitor. The missing, unused, and spurious data will be resolved prior to database lock and analysis. An audit trail will be maintained for tracking purposes.

In ITT analysis, the missing outcome data of patients who drop out from follow-up during study period will be handled based on the Last Observation Carried Forward (LOCF) imputation method. For example, if a patient was well during the end of treatment but lost to subsequent follow-up, he/she will be considered not to have met the primary outcome of 90-day SAB-relapse.

12.3.4 Procedure for deviation from original statistical plan

Any changes or deviation from the original statistical analysis plan must be approved by coordinating PI before the interim analysis and final analysis of the study.

12.3.5 Planned interim analysis

An interim analysis will be performed on the efficacy and safety endpoints when 50% of the targeted patients have been randomized and completed 30 days follow-up. The results will be presented to the Data and Safety Monitoring Board (DSMB) to determine whether the trial should proceed as planned or be stopped early due to overwhelming non-inferiority or safety concern or undergo sample size recalculation based on conditional power.

12.4 Data and Safety Monitoring Board

The members of the Data and Safety Monitoring Board (DSMB) of this trial will consist of at least 3 independent experts, namely an infectious diseases physician, an academician, and a statistician. They will be formally invited and appointed to the DSMB in their individual capacity. They will be required to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, treatment efficacy, and when appropriate, make recommendations concerning the continuation, modification, or termination of the trial.

13. ETHICS & REGULATORY CONSIDERATIONS

13.1 Independent Ethics Committee

The study protocol, case report form (CRF), Patient Information Sheet (PIS), Informed Consent Form (ICF), subject requirement procedures, and information on payments and compensation available to subjects, will be submitted to the Medical Research & Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia. Unconditional approval must be received from the MREC before commencement of this study. Approval from the MREC must be documented in a letter to the investigator specifying the study title, protocol number, the documents reviewed, the date on which the committee met and granted the approval, the name, occupation and institutional affiliation of the chairman and members of the MREC, and provisions for periodic review if any. Any amendments to the protocol, other than administrative ones, must also be approved by this committee.

The principal investigator will inform the MREC of:

- Any amendment to the protocol, informed consent changes or revisions of other documents originally submitted for review.
- Any serious and/or unexpected events occurring during the study, where required.
- Any new information that may adversely affect the safety of the subjects or the conduct of the study.
- An annual update on the progress of the study and/or request for reapproval, where required.
- Final study report when the study has been completed, where required.

All correspondence with the MREC will be filed by the principal investigator in the Master Study File.

13.2 Ethical conduct of the study

The study will be conducted after obtaining approval from the Medical Research & Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia via the National Medical Research Register (NMRR). The study will be conducted in compliance with the protocol and CRC standard operating procedures. Investigators will adhere to the ethical principles that have their origin in the "World Medical Association Declaration of Helsinki", the "Malaysian Guidelines for Good Clinical Practice" and applicable regulatory Requirements.

13.3 Informed consent and subject information

Freely given informed consent will be obtained from every subject prior to participation in this study. The investigator will inform every subject in detail about the nature of the study, its purpose, the treatments and the probability of random assignment to treatment groups, those aspects of the study that are experimental, the procedures involved including all invasive procedures and the discomfort they may entail, the possible risks including to an embryo, foetus or nursing infant where applicable, the reasonably

expected benefits the expected duration and the approximate number of subjects involved and the subject's responsibilities.

Study subjects will also be informed that:

- Participation in this study is voluntary and that he/she may withdraw from this study at any time for any reason and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.
- They will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the study.
- Alternative procedures or treatments that may be available and the important potential benefits and risks of these available alternative procedures or treatments.
- Any compensation for additional costs and/or injury caused to a subject attributable to participation in the study.
- Financial expenses, if any, to the subject for participating in the study as well as prorated payment, if any, to the subject for participating in the study.
- Any foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The person(s) to contact for further information regarding the study and whom to contact in the event of study related injury.

Written consent will be obtained from each subject involved in the study. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, stating why the patient was unable to sign the consent form. The informed consent form used to document written or oral consent in the study must be received prior to approval from the MREC. If the subject and his/her parent/guardian are unable to read, the investigator or designee will explain to the subject the content of the Patient Information Sheet and Consent Form point by point in the presence of an impartial witness. The witness should personally sign and date the consent form. The potential study subject and/or his/her parent/guardian will be given the opportunity to ask questions and time for consideration.

A copy of the Patient Information Sheet and signed Consent Form will be given to the subject. The original will be filed by the PI in the Investigator Site File.

13.4 Patient protection procedures

13.4.1 Procedures in the event of emergency

The investigators are responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. An emergency may constitute an SAE (please refer to SAE section).

13.4.2 Procedures in the event of pregnancy

Patients with childbearing potential will be instructed upon enrolment to inform the investigator if she becomes pregnant during the study treatment period. Investigator will decide on continuation or change of study treatment based on the pregnancy risk defined by the FDA pregnancy categories:

Category B: Cloxacillin, cefazolin, clindamycin, cephalexin, ceftaroline
Category C: Vancomycin, Linezolid
Category D: Trimethoprim-sulfamethoxazole

None of the study drugs is absolutely contraindicated in pregnancy. Study antibiotics in Category B and C are generally safe to be used in pregnancy. Trimethoprim-sulfamethoxazole, which is in Category D (evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits of the drug may outweigh the risks) may be switched to alternative drug in Category B or C if the patient becomes pregnant. In a rare case scenario, if a patient in EOS group taking oral trimethoprim-sulfamethoxazole becomes pregnant, investigator may consider switching her trimethoprim-sulfamethoxazole to oral linezolid while maintaining her with oral study drug as per protocol. The investigators should explain to patient regarding the risk and benefit involved.

Foetal complications are not expected since the study drugs are given over a short course. However, any study drug exposure during pregnancy must be notified to the principal investigator. If the exposure is deemed significant, the outcome of the pregnancy must be followed up and reported on the Pregnancy Monitoring Form for Clinical Studies.

13.4.3 Patient data protection

The investigator will assure that the subjects' anonymity will be maintained and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

Subjects will be identified only by their assigned identification number and initial on all CRFs and other study-related records and documents. The investigator will keep a Patient Identification List with complete identification information (name, address, contact number, IC#) on each subject. This list will be kept by Principal Investigator on site in a locked cabinet. Subject's written informed consent form will be maintained by the investigator in strict confidence by keeping them in a locked cabinet, which can only be accessed by investigators on site.

Study monitors, auditors and representatives of MREC will be granted direct access to subject medical records and other study documents for verification of study procedures and data without violating the confidentiality of the subject. The subject will be informed that by signing a written informed consent form, he/she is authorizing such access. The

subjects and their next of kin will not be given direct access to their personal study data. The subjects may be informed about study findings upon request, but only after the completion and publication of the study.

All data will be entered into an electronic database (REDCap), which only allows assigned investigators with username and password to enter and view data from respective site. Only coordinating PI and assigned personnel for data management will be granted permission to view data from all sites and export data. The electronic data will be identified by patient numbers only, thereby ensuring that patients' identity remains unknown.

13.4.4 Insurance

This clinical trial is sponsored by the Ministry of Health (MOH) Malaysia. All the investigators in this trial will conduct the trial according to the policies and guidelines set out by the MOH. The investigators will follow strict scientific standards to protect all trial participants. Investigators involved in this trial are encouraged to have professional indemnity to cover liabilities concerning clinical/professional conduct. However, all doctors in MOH are provided coverage under Section 5, Act 359. The trial investigators are responsible for managing all medical treatments for trial-related injury, directly or through referrals to related specialty departments, within the MOH facilities without any MOH hospital charges being subjected to the affected trial participants [PENGECUALIAN CAJ HOSPITAL BAGI PARA SUBJEK KAJIAN YANG TERLIBAT DALAM PENYELIDIKAN INVESTIGATOR INITIATED TRIALS; (101) DLM.KKM-58/900/69.JLD5 30 MAC 2011]. Coverage of the said treatment for trial-related injury, however, does not include monetary compensation, or treatment charges outside of MOH facilities. The trial sponsor and investigators are not liable for events unrelated to the trial procedures or the investigational product or, events due to a disease's natural progression.

14. ADMINISTRATIVE MATTERS

14.1 Notification of regulatory authority(ies)

All necessary arrangements for the registration and approval of this study with the responsible authorities and the disposition of the required data and document will be undertaken by the Principal Investigator.

14.2 Notification of primary care physician

Investigators should ask patients if they wish for their general practitioner or primary care physician to be notified about their involvement in this study. This is so that if the patients need to see their own physician for any reason, the physician will be aware that they are taking a study drug.

14.3 Study initiation

Investigators involved in this study must not enrol any patient prior to completion of a formal meeting conducted by the coordinating PI and Site Coordinator. This meeting will include an inventory of study supplies, a detailed review of the protocol and eCRF, training on study procedures and other procedures required of GCP. Investigators who are not GCP certified will undergo GCP training during the study.

14.4 Protocol deviation

Protocol deviation is any change, divergence, or departure from the study design or procedures defined in the approved protocol. For example, a patient is enrolled into trial despite having persistent SAB (non-compliance with the inclusion and exclusion criteria).

In addition, patients under the following situations during study treatment period are considered to have failed to complete study treatment as per protocol, and may warrant protocol deviation reporting:

- Any change of route of antibiotic administration
- Switching or addition of antibiotics other than those study drugs in Table 4
- Earlier discontinuation of study drugs before the study treatment duration defined in Table 6. (±2 days difference is acceptable)
- Extension of study drugs beyond the study treatment duration defined in Table 6. (±2 days difference is acceptable)
- Use of combination antibiotic therapy for SAB
- Less than 80% of study drugs are taken by patient

However, the above scenarios will not be considered protocol deviation if the following occurs during the study treatment, which may necessitate a change or escalation of antibiotic regimen and duration. This clinical decision is at the discretion of the primary treating physician:

- SAB relapse
- New infections (other than S. aureus)
- Adverse events due to study drugs
- Difficult IV access (for SIV group)
- Difficult oral administration of medications (for EOS group)
- Patient's non-adherence to study drugs (in the absence of medication dispensing or administration error)
- Clinical deterioration or failure
- Death

Any protocol deviation will be documented by the study monitor with rectification as soon as possible. The investigator should be notified immediately. Except for emergencies, no changes, or deviations in the conduct of this protocol will be permitted without prior approval from MREC. In the event of any emergency, the investigators will institute any

medical procedures deemed appropriate. All such procedures must be promptly reported to PI and MREC.

14.5 Study documentation

The investigator must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. These documents are Essential Documents and Source Documents.

14.5.1 Essential documents

These are documents that permit evaluation of the study and the quality of the data produced.

The Essential Documents are:

- Signed protocol amendments
- Sample CRFs
- MREC approval letter
- Informed consent form
- CV of investigator and co-investigator
- Correspondences with MREC, sponsor and CRC
- Interim reports to MREC
- Investigational product accountability and shipping records
- Site signature log
- Monitor visit log
- Other appropriate documents in accordance with GCP guidelines.

The coordinating PI will maintain a Master Study File. The investigator at each site will maintain an Investigator Site File (ISF). This file shall be used to facilitate and ensure filing of all relevant and Essential Documents during and after the study. The site investigator will be responsible for keeping the Investigators Site File updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

14.5.2 Source documents

These are original documents, data and records including hospital records, clinical and office charts, laboratory reports, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate, radiological films, subjects' files, and records kept at the pharmacy, at the laboratories and at medico-legal departments involved in the study. The investigator must maintain source documents for each patient in the study.

All information on CRFs must be traceable to these source documents:

- Patient identification list
- Curriculum vitae
- Site signature/authorization log

14.6 Patient identification list/enrolment log

The investigator must maintain a Subject Identification Log to record subjects' personal details including full name, date of birth, contact number and house address. The list has to show an equivocal study identification number. The investigator is also required to maintain Subject Screening and Enrolment Log to document the relevant information during screening and enrolment including the date of enrolment and randomization number. The logs will be filed in the Investigator Site File on site.

14.7 Curriculum vitae

The investigator will provide curriculum vitae showing his/her experience in the area of the proposed study. These should be filed at Master Study File as well as in the Investigator Site File at study site.

14.8 Site signature/authorization log

The investigator must maintain a Signature Log to document signatures and initials of all staff authorized to make entries and/or corrections on study related records or documents. The log will be filed in the Investigator Site File.

14.9 Study monitoring

Study monitoring and data management service will be outsourced to an independent certified, and reputable clinical research company. The scope of responsibility and activities are as follows:

Study Monitoring

- Protocol training for study sites (treatment and study procedures, safety reporting, eCRF completion guideline etc.)
- Onsite and remote monitoring of study conduct in each study sites at planned intervals during study period.
- Inspection of eCRF to verify adherence to the protocol and the completeness, consistency, and accuracy of the data in accordance with source documents.
- Maintenance of Investigator Site File (ISF) at each study sites and ensuring completion of all essential documents.

Data Management

- eCRF design start-up using REDCap or any EDC platform recommended by the clinical research company.
- Development of data management and validation plan
- Data review and quality control
- Data query resolution

The site investigators must cooperate with the study monitor to ensure that any problems detected during these monitoring visits are resolved.

14.10 Audits and inspections

The investigators should make available the various records of the trial to qualified personnel from health authority inspectors after appropriate notification. The verification of eCRFs data will be made by direct inspection of source documents.

14.11 Retention of documents

Upon study completion or study site closure, the coordinating PI shall arrange for the retention of all study documents and records for at least 15 years after completion or discontinuation of the study. The paper documents will be transferred to the designated archival centre for archiving. Details of all archived data, including location, will be documented. If the PI moves or retires, he/she must nominate someone in writing to be responsible for archiving. Archived data may be held in electronic record, provided a backup exists and a hard copy can be obtained from it if required. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

14.12 Finance

This study is funded by the Ministry of Health Malaysia.

14.13 Confidentiality

The investigator agrees that all information communicated to him/her is the exclusive property of the research team and ensure that the same will be kept strictly confidential by the investigator or any person connected with the work and shall not be disclosed to any third party without the prior written consent of the Principal Investigator.

14.14 Publication policy

All investigators are responsible for writing and reviewing the final study report and preparing the manuscript for journal submission. The first publication must be based on data from all centres, analysed as stipulated in the protocol.

Investigators in this study agree not to present data gathered from one centre or a small group of centres before the full initial publication, unless formally agreed to by all other investigators and PI.

Authorship will be determined by mutual agreement prior to the start of the study and will include lead authors for the primary presentation and publication of this study. Criteria for selection of additional authors will be agreed prior to the start of this study, based on International Committee of Medical Journal Editors (ICMJE) guideline. As it will not be possible for all investigators to be named as authors in the primary publication, other investigators who have enrolled patients and involved in data collection phase will be acknowledged as being part of the study team.

Director General (DG) of Health Malaysia's approval will be required before publishing or presenting data. Only summarized data will be presented in reports or publications. Patients' identities will not be disclosed in any publication or presentation.

14.15 Anticipated subject accrual duration

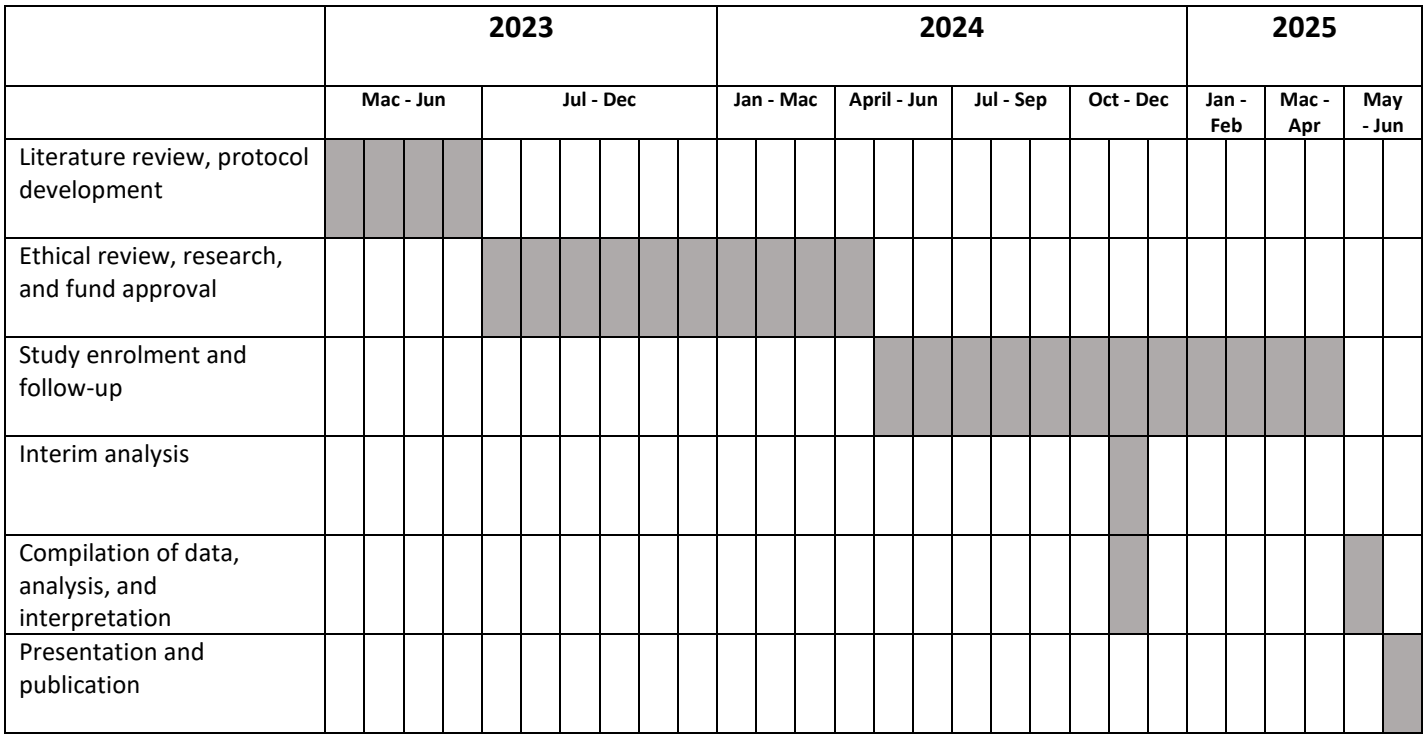
This study is expected to start in May 2024. The projected timeline for subject accrual is as follows:

- First patient enrolled is expected in May 2024
- Last patient enrolled is expected in January 2025
- Last patient expected to complete follow-up in April 2025

These accrual rates are based on reasonable planning expectations. The investigator should however continually compare the actual and expected accrual rates and make every effort to ensure that they are as closely matched as possible. If the investigator anticipates major problems with recruitment, or delay in the expected completion date, he/she should discuss this with the coordinating PI as early as possible.

14.16 Gantt Chart

The study duration is planned for 12 months, from 1st May 2024 till 30th April 2025. The study timeline is as follows:



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16. APPENDICES

- EVOS Case Report Form (CRF) Version 1.1, dated 12th March 2024
- EVOS Patient Information Sheet & Informed Consent Form (English and Bahasa Malaysia) Version 1.2, dated 12th March 2024
- EVOS Infographic Poster Version 1, dated 26th May 2023
- Investigational product labels
- Study investigators' curriculum vitae