Beta-Lactam antibiotics initiaL expoSure optimisEd in criticallY ill patients with sEpsis

“BULLSEYE”

EU_CT: 2024-512950-13-00

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DOCUMENT HISTORY

Document	Date of version	Summary of Changes
Protocol version no. 2.3	09-12-2024	Rectification of maximum antibiotic dosages Expanding research team Change definition microbiological eradication Redefine T1 Sample storage at -80 or -70^{o}
Protocol version no. 2.2	25-09-2024	Changed interim analysis
Protocol version no. 2.1	16-09-2024	Changed power calculation and statistical analysis
Protocol version no. 2.0	29-08-2024	Dosing strategy removed. Intervention duration 48 hours. Primary outcome to 28-day mortality. Added secondary outcomes. MICecoff's defined
Original protocol	*10-06-2024*	Not applicable

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

TABLE OF CONTENTS

1. ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ASZ	Albert Schweitzer Hospital
AUC	Area Under the Curve
AUROC	Area Under the Receiver Operating Curve
BID	Two times a day dose
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
ECOFF	Epidemiological cut-off breakpoints
ECMO	ExtraCorporeal Membrane Oxygenation
EDC	Electronic Data Capture
EMC	Erasmus University Medical Center
EPF	Electronic Patient File
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
HRQoL	Health-related Quality of Life
IB	Investigator's Brochure
IC	Informed Consent
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ITT	Intention to treat
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
MIC	Minimal inhibitory concentration
MSZ	Maasstad Hospital
NONMEM	Non-linear Mixed Effects Modelling
PBP	Penicillin-binding proteins
PD	Pharmacodynamic
PDMS	Patient Data Management System
PDT	Pharmacodynamic Target
PIRO	Predisposition, Infection, Response, Organ dysfunction Score
PK	Pharmacokinetic
RRT	Renal Replacement Therapy
(S)AE	(Serious) Adverse Event

SDD	Selective Digestive tract Decontamination
SIC	Subject Identification Code
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOFA	Sequential Organ Failure Assessment Score
SPC	Summary of Product Characteristics
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization, or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	Half-life
TDM	Therapeutic drug monitoring
TID	Three times a day dose
UPN	Unique Patient Identification Number, allocated by the hospital administration
Vd	Volume of distribution
VWB	Van Weel Bethesda Hospital
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

2. SYNOPSIS

EU_CT number: 2024-512950-13-00

Full title: Beta-Lactam antibiotics initiaL expoSure optimisEd in criticallY ill patients with sEpsis (BuLLSEYE)

Rationale

Severe sepsis and septic shock pose significant challenges in healthcare, with high mortality rates and a need for effective treatment strategies. In the ICU this is particularly difficult due to a highly heterogenous patient population, physiological changes and the use of extracorporeal therapies.

Patients with sepsis are commonly treated with beta-lactam antibiotics. However, recommended dose regimens are not well-defined for critically ill patients, and we therefore often fail to achieve target levels, potentially leading to underexposure.
Unlike drugs with straightforward dosing adjustments, antibiotics require careful consideration, especially since improvement may not occur for days. Previous studies suggest that higher doses and prolonged infusions improve target attainment, particularly in critically ill patients. Simulation with pharmacometric models showed that doubling the standard dosages would result in adequate target attainment. To assess this strategy a randomized trial will be carried out, researching the effect of higher dosages beta-lactam antibiotics (cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin/clavulanic acid, flucloxacillin, piperacillin/tazobactam, meropenem) in the initial treatment phase of sepsis.

Objective

To determine if using higher dosages of beta-lactam antibiotics in the initial phase of sepsis improves clinical outcome of critically ill patients.

Main trial endpoints

The main trial endpoint is all cause 28-day mortality.

Secondary trial endpoints

Secondary trial endpoints include: Hospital length of stay, ICU length of stay, microbiological eradication, time to shock reversal, Δ Lactate, Δ PCT, Δ SOFA, 90- day mortality, 365-day mortality, hospital and ICU mortality, pharmacodynamic target attainment, post study calculation of the costs in both study groups, EQ5D questionnaire 3 and 12 months after Admission, iMTA productivity questionnaire 3 and 12 months after admission, iMTA medical consumption questionnaire 3 and 12 months after admission and the number of adverse events.

Trial design

This is an open label, randomized controlled trial.

Trial population

The trial population will consist of adult patients admitted to the intensive care department with sepsis who will be treated according to protocol with beta-lactam antibiotics.

Interventions

During the trial participants in the intervention group will receive a double dose of antibiotics for the first 48 hours in comparison to the standard dose in the control group.

Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks

Based on previous research by our research group, we expect participants in the intervention group might benefit directly from the higher therapeutic antibiotic levels, resulting in more adequate treatment of sepsis. Harm could result from adverse effects of antibiotics. However, this effect is expected to be small since all antibiotics used are common practice for this indication and patients will only receive a higher dose for a short period of time. The burden of participating consists of filling in surveys three and twelve months after admission. All laboratory tests will be performed with routine blood sample drawing.

3. INTRODUCTION AND RATIONALE

3.1 Therapeutic condition and current treatment status

Severe sepsis and septic shock represent significant global healthcare challenges, annually affecting millions worldwide and ranking among the leading causes of mortality in hospitalized patients. Mortality rates for these conditions range from 20 to 54%, underscoring the critical nature of effective management strategies. (1-5) In the Netherlands, severe sepsis accounts for approximately 0.6% of hospital admissions and 11% of intensive care unit (ICU) admissions, translating to an estimated 8,000-9,000 ICU admissions annually. (6) The key to improving outcomes for severe infections, such as sepsis and septic shock, lies in the timely administration of antimicrobial therapy and individualized treatment approaches.

Patients admitted to the ICU represent a highly heterogeneous population ranging from young trauma patients to postsurgical patients and elderly medical patients. Therefore, optimizing therapeutic interventions within this context is particularly challenging. This variability contributes to the ICU population being one of the most heterogeneous and resource-intensive within the healthcare system. (7)

Beta-lactam antibiotics are amongst the most commonly used antibiotics in the ICU setting, as they are active against a broad range of bacteria including Gram positive and negative species. (8, 9) In critically ill patients treated with beta-lactams, achievement of target values is reported to occur in 40 to 60% (10, 11), suggesting that underexposure of these antibiotics in the ICU is the rule rather than the exception. To optimize dosing, the DOLPHIN study was recently carried out. (12) This study aimed to improve sepsis treatment by using Therapeutic Drug Monitoring (TDM). One of the limitations of the DOLPHIN study was, that, due to the study design and laboratory TDM availability, results and dose adjustments were available only 36 hours after antibiotic initiation. Consequently, standard dose had been administered to all patients in anticipation of dosing advice. When focusing on the “golden hour of sepsis”, and to treat as soon and as good as possible, this time window is too long. Post-hoc analysis from the DOLPHIN study confirmed this: patients with an adjustment within 24 hours after initiation, had a better positive clinical outcome (amongst all: less ICU stay) with TDM in comparison to standard dosing. (13) Therefore, it is hypothesized that optimized dosing from the start could maximize treatment efficacy may lead to better outcomes. Simulation using pharmacometrics models (using CE-approved modeling/TDM program InsightRX (13)) showed that doubling the dose would result in adequate target attainment in the EXPAT and DOLPHIN patients (10, 12), especially in the first 48 hours of treatment.

3.2 Clinical trial rationale

During patient’s time on the ICU, rapid dynamic changes in physiology occur, including augmented clearance, renal or hepatic dysfunction, changes in albumin or increased volume. (14) Significant pharmacokinetic heterogeneity was noted, with a broad, more than twofold variation of both volume of distribution and of drug clearance. (9) This is even more a problem when using supportive extracorporeal therapies, such as continuous renal replacement therapy (CRRT). (15)

Contrary to direct-acting drugs like inotropes, sedatives, and analgesics, which allow for relatively straightforward dose titration based on clinical response, antibiotics pose a unique challenge. Signs of infection resolution may not become apparent for 24–72 hours, complicating the determination of appropriate initial dosing. It is important to note that the time to achieve the desired therapeutic

target is not typically used as an effectiveness predictor. Standard practice involves establishing treatment targets within the first 24-48 hours of therapy initiation. However, in the context of severe infections treated in the ICU, it is critical to administer adequate treatment from the first dose to ensure rapid target attainment. Achieving an optimal initial dose is of considerable clinical value in managing critically ill patients effectively. Therefore, this trial aims to improve antibiotic treatment during the initial 48 hours of sepsis, leading to improved clinical outcomes.

3.3 Mechanism of action, Drug class

Beta-lactam antibiotics are bactericidal agents that interrupt bacterial cell-wall formation as a result of covalent binding to essential penicillin-binding proteins (PBPs), enzymes that are involved in the terminal steps of peptidoglycan cross-linking in both Gram-negative and Gram-positive bacteria. (16) Pharmacodynamic properties differ between specific types of antibiotics and are further described in their Dutch summery of product characteristics (SmPC). (17-26)

3.4 Rationale for Dose Regimen/Dose Justification

Antimicrobial efficacy is determined using the pharmacodynamic target (PDT). The PDT is defined as the unbound antibiotic concentration (f) above the minimal inhibitory concentration (MIC): the lowest concentration needed in order to prevent bacterial growth. In beta-lactam antibiotics the PDT is described as 100%fT>MIC (or more aggressively 100%fT>4xMIC), meaning that the unbound concentration stays above the MIC for 100% of the time (T). Previous research by our research group showed that 40% of ICU admitted sepsis patients does not reach 100%fT>MIC and even more than 75% of the patients does not reach 100%fT>4xMIC. (10) These results are in accordance with other trials. (11, 12)

The efficacy of employing higher doses and prolonged infusions as reliable predictors for achieving target antibiotic concentrations has been underscored multiple times. For instance, Imani et al. (27) and Alobaid et al. (28) provide empirical evidence supporting the association between increased dosage and improved target attainment for piperacillin, advocating for doses at least 1.5 times higher than the standard recommendations. Furthermore, Carrié et al. (29) demonstrate the safety and effectiveness of such dosing regimens in critically ill patients with augmented renal clearance, emphasizing the reduced risk of therapeutic failure. Using simulation software on previously collected data it was found that in order to reach the PDT, antibiotic dosages should be doubled.

With regards to increased dosing and toxicity, no toxicity in the DOLPHIN study was observed (12), even when the dose was increased. Furthermore, a survey was carried out in our international collaboration group (Belgium/France/Australia) and all international collaborators agreed that a double dose during a short period (of 48 hours) would lead to improved target attainment and would outbalance the possible risk of toxicity in all antibiotics.

4. STRUCTURED RISK ANALYSIS

4.1 Potential issues of concern

4.1.1 Level of knowledge about mechanism of action

In this study cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin/clavulanic acid, flucloxacillin, piperacillin/tazobactam and meropenem are researched. These are all beta-lactam antibiotics. Beta-lactam antibiotics are bactericidal agents that interrupt bacterial cell-wall formation as a result of covalent binding to essential penicillin-binding proteins (PBPs), enzymes that are involved in the terminal steps of peptidoglycan cross-linking in both Gram-negative and Gram-positive bacteria. (16) Pharmacodynamic properties differ between specific types of antibiotics and are further described in their Dutch Summary of Product Characteristics (SmPC).

4.1.2 Previous exposure of human beings

The antibiotics used in this study are registered drugs and extensively used in clinical practice.

4.1.3 Induction of the mechanism in animals and/or *ex-vivo*

In this study the effect of using higher dosages for beta-lactam antibiotics will be evaluated in ICU admitted sepsis patients.

4.1.4 Selectivity of the mechanism

Not applicable

4.1.5 Analysis of potential effect

Patients admitted to this study in the control group will receive standard care. Patients assigned to the intervention group might benefit from adequate antibiotic dosing using higher dosages as it could treat sepsis more adequately. Risks to be expected are known side effects (chapter 8), for which patients will be carefully monitored by the treating physician and coordinating investigator.

4.1.6 Pharmacokinetic considerations

Not applicable

4.1.7 Predictability of effect

In this study the choice of antibiotic will be made according to local protocol. Since all antibiotics are registered for the treatment of sepsis, the effect is very predictable.

4.1.8 Interaction with other products

Not applicable

4.1.9 Managing of effects

The expected effects of the used antibiotics are positive, namely the treatment of sepsis. In case of adverse effects, these will be treated according to local protocol. Patients admitted to the ICU are very closely monitored so it might be expected that adverse effects will be recognized and treated quickly and adequately.

4.1.10 Study population

Sepsis patients admitted to the ICU treated with beta-lactam antibiotics.

4.2 Overall synthesis of the direct risks for the research subjects

The beta-lactam antibiotics used in this study are all standard of care in the ICU. They will be used to treat and prevent infections according to their registered use. Risk and benefits are well known and can be found in the attached SmPC (chapter 8). Adverse events will be registered as described in chapter 13. Previous studies conducted by our research group showed no serious adverse events using higher dosages of the antibiotics. (12) Therefore, we consider the risks related to the intervention described in this protocol to be negligible.

5. OBJECTIVES AND ENDPOINTS

5.1 Primary objective and endpoint

To determine if using higher dosages of beta-lactam antibiotics in the initial phase of sepsis reduces mortality of critically ill patients. This will be measured as all cause 28-day mortality.

5.2 Secondary objectives and endpoints

Next to all cause 28-day mortality, 90-day mortality, 365-day, ICU, and hospital mortality will be registered.

Other clinical parameters include sequential organ failure assessment (SOFA) scores. They will be registered at baseline (T0), 24 (T1), 48 (T2) and 72 (T3) hours, or in any case, after discharge/transfer/death before T3. The SOFA scoring system is used to predict clinical outcomes of critically ill patients. The score is based on six different domains, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological system. In each domain 0-4 points are assigned based on clinical and laboratory findings, resulting in a total score ranging from 0 to 24 points. A higher total score is unfavorable. This scoring system has widely been used since 1996. (30)

Delta (Δ) SOFA score, is defined as the score on a fixed time after randomization minus the baseline score. Delta SOFA at T3 is defined as the SOFA at T3 minus SOFA at T0. In case of discharge from the ICU a SOFA of 0 points will be registered. On the opposite, in case of death of a participant 24 points will be assigned. (31) Using the delta SOFA allows to compare organ dysfunction at any time point from baseline in the trial arms. Treatment effects on delta SOFA are reliably and consistently associated with mortality in RCTs. (31)

Time to shock reversal, defined as vasopressors < 0.1 microgram/kilogram/minute for at least 4 hours, will be determined as well as daily lactate levels and procalcitonin levels.

Microbiological eradication will be defined as eradication of the causative organism from the primary source up to 30 days after therapy when confirmed by at least one repeated culture. In cases where there were no repeat cultures and the patient had resolution of the infection, microbial eradication will be presumed.

The pharmacodynamic target will be defined as 100%fT>4xMIC. For MIC the epidemiological cut-off value (ECOFF) will be used, as this is considered to be the most suitable for therapeutic drug monitoring. (32, 33) The presumed pathogen and matching MIC_{ecoff} can be found in table 1. Since antibiotic dosing will mostly take place before microorganisms can be determined, the highest MIC with a likely microorganism has been chosen.

Tabel 1 Presumed microorganism and MIC

TARGET ANTIBIOTIC	PRESUMED MICROORGANISM(S)	MIC_{ECOFF}[1] (MG/L)
CEFOTAXIM	Enterobacterales (group)	0.25
CEFTAZIDIM	Pseudomonas aeruginosa	8
CEFTRIAXON	Enterobacterales (group)	0.125[2]
CEFUROXIM	Enterobacterales (group)	8[3]
AMOXICILLINE	Enterobacterales (group)	8
AMOXICILLINE/CLAVULANIC ACID	Enterobacterales (group)	8
FLUCLOXACILLIN	Staphylococcus aureus	1
PIPERACILLIN/TAZOBACTAM	Pseudomonas aeruginosa	16
MEROPENEM	Pseudomonas aeruginosa	2

[1]European Committee on Antimicrobial Susceptibility Testing. Data from the EUCAST MIC distribution website, last accessed 12-8-2024". https://www.eucast.org

[2]between brackets in case only a tentative ECOFF is available

[3]The value of 8 mg/L is below the highest ECOFF within the group, but since the clinical breakpoint is also R> 8 mg/L it was decided to keep this value at 8 mg/L.

The safety of the intervention will be determined by comparing the number of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs).

In order to assess the economic and social effect of the intervention, hospital and ICU length of stay will be registered. Furthermore, 3 and 12 months after admission the EQ-5D-5L, iMTA productivity questionnaire and iMTA medical consumption questionnaire will be send to the participants.

6. STUDY PLAN AND DESIGN

6.1 Trial Design

This is an open label, multicenter, prospective, randomized controlled trial. Inclusion will take place over a 24-month period and will start at the Erasmus MC (EMC), Maasstad Hospital (MSZ), Van Weel Bethesda Hospital (VWB) and Albert Schweitzer Hospital (ASZ). Multiple other hospitals have expressed interest in participating and will be included as soon as possible after the start of the study based on inclusion rate.

At the start of the study period, participants will be randomized into two study arms. The control group will receive standard care. The intervention arm will receive a double starting dose of antibiotics upon admission and will continue this double dose for 48 hours. In this period the blood levels of the antibiotic are largely dependent on the distribution volume and only slightly influenced by renal clearance. Therefore, no changes based on kidney function will be made.

After 48 hours all patients will receive the standard dose according to local protocol. Data collection will continue for a total duration of 12 months, including questionnaires regarding health-related quality of life and medical consumption at 3 and 12 months after inclusion.

6.2 Number of Patients

In total 890 participants will be enrolled in this study (445 participants per study arm).

6.3 Overall study duration and follow-up

During the first three days of admission daily tests will be performed. Three and twelve months after admission, questionnaire regarding health-related quality of life and medical consumption will be sent to the participants. After returning the final questionnaire, the study period will end. It is anticipated that the study will be performed within a 48-month study period followed by 12 months of data analysis and publication of the data.

6.4 Patient participation

Active participation by ex-ICU patients (Idelette Nutma, sepsis-en-daarna) was established in our previous studies and has been continued successfully. In addition, other patient-perspective representatives are associated with an internet-forum in the Netherlands, aimed at improving continued care after treatment at an ICU and limiting post-ICU burden, such as the patient organization IC Connect (Lilian Vloet) and the organization “Family and patient Centered Intensive Care”, http://www.fcic.nl.

7. STUDY POPULATION

7.1 Population

Adult patients with sepsis, admitted to the ICU. Standard treatment must include, but is not limited to, beta-lactam antibiotics.

7.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- ≥18 years of age
- Receiving intravenous antibiotic therapy of the target drugs (including continuous infusion of beta-lactam antibiotics)
- Primary infection
- Admitted to the ICU
- Meeting the Sepsis-3 criteria for septic shock: sepsis in addition to shock requiring the start of vasopressors to maintain a mean arterial pressure 65 mm Hg or greater, and a serum lactate level greater than 2.0 mmol/L following “adequate fluid resuscitation”. (34)

7.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patient or legal representative not available to give informed consent within 72 hours after admittance
- Pregnancy
- Admittance for burn wounds
- Patients receiving target antibiotics only as prophylaxis within the context of Selective Digestive tract Decontamination (SDD)
- Enrolment in another interventional trial
- Patient received the study antibiotic for more than 24 hours before inclusion
- Patient receiving extracorporeal membrane oxygenation (ECMO)
- Patient is already treated with a double dose of antibiotics based on suspected infection

7.4 Vulnerable populations and clinical trials in emergency situations

The study will be submitted to the medical ethics committee for approval. Using the CCMO template, in the present study deferred consent is justified, as it is a therapeutic study in an acute setting in ICU patients. There is a linear correlation between the time of sepsis and start of antibiotic infusion and survival, so any research may not delay therapy. After diagnosis of sepsis, patients are directly screened for inclusion, included and randomized by using deferred consent. Afterwards, after the acute period, delayed informed consent is collected.

8. STUDY TREATMENTS

8.1 Investigational Medicinal Product(s) (IMP(s))

8.1.1 Name and description of the IMP

Table 1 Name and description IMP

Target drugs	Registered products[1] used in the participating ICUs[2]
Cefotaxime	Cefotaxim 1000 mg PCH, poeder voor oplossing voor injectie
Ceftazidime	Ceftazidim Fresenius Kabi 500, 1000 en 2000 mg, poeder voor oplossing voor injectie
Ceftriaxone	Ceftriaxon Fresenius Kabi 1 en 2 g, poeder voor oplossing voor injectie/infusie
Cefuroxime	Cefuroxim Hikma 750 en 1500 mg, poeder voor injectie I.V.
Amoxicillin	Amoxicilline CF, poeder voor oplossing voor injectie of infusie 125, 250, 500 mg en 1 g
Amoxicillin/ clavulanic acid	Amoxicilline/Clavulaanzuur Sandoz 500 mg/50 mg en 1000 mg/200 mg i.v., poeder voor oplossing voor intraveneuze infusie Amoxicilline/Clavulaanzuur 1000/200 PCH, poeder voor oplossing voor injectie
Flucloxacillin	Floxapen, poeder voor oplossing voor injectie 250 mg, 500 mg en 1 g Flucloxacilline Fresenius Kabi, poeder voor oplossing voor injectie 1000 mg
Piperacillin/ tazobactam	Piperacilline/Tazobactam Fresenius Kabi 2 g/0,25 g en 4 g/0,5 g poeder voor oplossing voor infusie
Meropenem	Meropenem CF 500 en 1000 mg, poeder voor oplossing voor injectie of infusie Meropenem Fresenius Kabi 500 mg en 1 g poeder voor oplossing voor injectie of infusie

[1] Registered products are linked to the Dutch Summary of Product Characteristics (SmPC)
[2] Products can change during the study period to similar registered products or generic medications based on availability

8.1.2 Status of development of the IMP

See attached links to SmPC in 8.1.1. (17-25)

8.1.3 Description and justification of dosage and route of administration

All antibiotics are given intravenously. Starting dosages in de SoC group are chosen in accordance with local guidelines and recommendations in the Dutch Working Party on Antibiotic Policy (SWAB). (35, 36) Dosing in the intervention group will take place using the pre-agreed dosages described in paragraph 11.3. The risk of underexposure to the antibiotic is deemed high as previous studies showed. (10, 11) In the DOLPHIN trial, where higher antibiotic dosages were administered based on blood levels, the number of adverse effects was similar between the intervention and control group. (12) None of these effects were likely to be related to the study intervention. Furthermore, higher dosing will only be applied for a short period of time.

8.2 Comparator IMP(s)

Not applicable

8.3 Placebo

Not applicable

8.4 Auxiliary Medicinal Product(s) (AxMP(s))

8.4.1 Name and description of the AxMP

Not applicable

8.4.2 Statement on authorization and justification unauthorized AxMP (if applicable)

Not applicable

8.4.3 Description and justification of dosage and route of administration

Not applicable

8.5 Additional considerations for trials involving a medical device

Not applicable

8.6 Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic

Not applicable

8.7 Preparation and labelling of the study treatment(s)

The antibiotics will be prescribed, dispensed and used in the same way as in routine clinical practice, according to (among other regulations) their marketing authorisations. No additional preparation or labelling of the antibiotics is necessary.

9. OTHER TREATMENTS AND RESTRICTIONS

9.1 Concomitant therapy

9.1.1 Permitted medication(s)

The antibiotics used in the intervention group are part of standard treatment. Therefore, all medications used in the treatment of sepsis and concomitant disease are permitted.

9.1.2 Prohibited medication(s)

There are no prohibited medications for the duration of the study.

9.2 Lifestyle restrictions

9.2.1 Contraception measures

Because of the short study period and the fact that critically ill patients on the ICU will not get pregnant during the study, contraceptive measures are not deemed necessary.

9.2.2 Other requirements

There are no other study requirements.

10. TRACEABLILITY, STORAGE, ACCOUNTABLILITY AND COMPLIANCE

10.1 Traceability and storage of the study treatment(s)?

Antibiotics used in this study are routinely used. Double dosing will take place for a short period of time (48 hours) Therefore, this is a negligible risk intervention clinical trial. The antibiotics will be provided according to local protocol and routine prescribing practice and documentation.

10.2 Accountability of the study treatment(s) and compliance

In this study, the researchers will maintain accountability for the study treatment and ensure compliance through established procedures within the participating hospital pharmacies. There is no need for additional measures to guarantee accountability, as it will always be possible to trace in the electronic patient file which participant received a specific batch of antibiotics. The beta-lactam antibiotics used, are all registered drugs commonly used in clinical practice. This information can be easily retrieved using the standard operating procedures maintained by the participating hospital pharmacies.

11. STUDY ASSESSMENTS AND PROCEDURES

11.1 Screening procedure

Local information sessions will be organized explaining the study criteria and procedures. Standard operating procedures will be provided. Eligible patients from the participating ICU departments are selected by the treating physician when antibiotic initiation is considered based on clinical suspicion of sepsis and/or cultured pathogens susceptible to the target drugs.

Patients or their legal representatives have the opportunity to ask questions and provide informed consent if they wish to participate. In case the patient or legal representative is not able to give informed consent directly, deferred consent will be used. If informed consent is not obtained within 72 hours after admission in surviving patients, the collected data will be deleted. The informed consent registration will be performed by one of the study coordinators or their delegates. Study IDs will be assigned in chronological order.

11.2 Randomization, blinding and treatment allocation

Patients will be randomly assigned in a 1:1 allocation ratio to one of the two following study arms:

1 Double dosing (intervention group) or
2 Standard of care (control group).

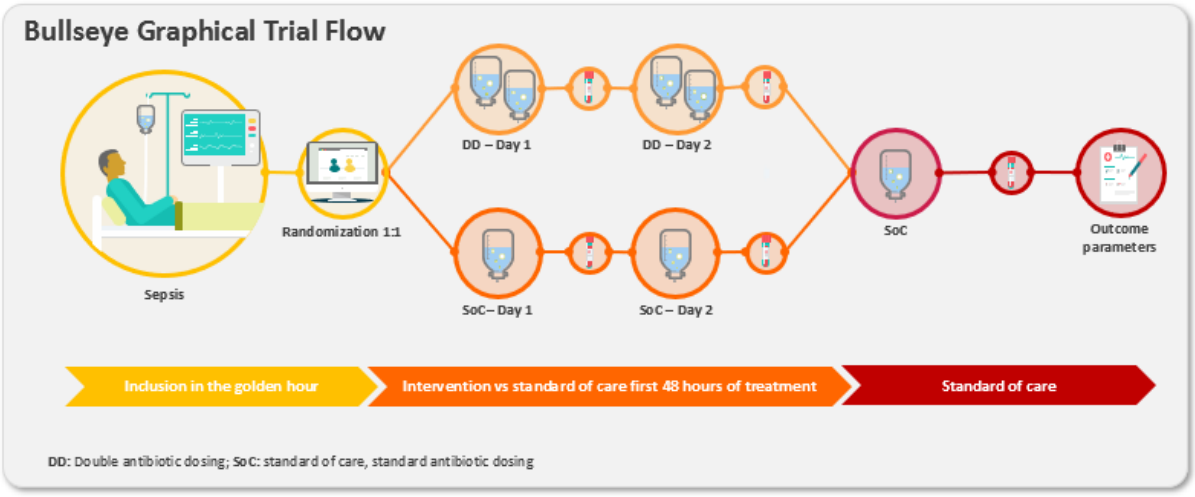
Randomization will be stratified by center. The randomization sequence is generated by a dedicated computer randomization software program (e.g. Castor EDC). The randomization will be performed by the treating physician, coordinating investigator or the local investigator.

This is an open label study.

11.3 Study procedures and assessments

Upon inclusion, participants will be randomized according to procedures described above. A graphical trial flow can be found in Figure 1. Participants randomized to the standard of care group will receive a loading dose, followed by a daily dose of the target antibiotics, chosen according to local and national guidelines. This can be an intermittent or continuous dosing scheme. Suggested loading and daily dosages can be found in table 2. Participants randomized to the double dosing group will receive a loading dose double the standard, except for ceftriaxone because of its long half-life. If patients already received a loading dose more than 2 hours prior to inclusion, a full loading dose again will be administered. In case the starting dose was administered within 2 hours prior to inclusion, only the remaining part of the loading dose will be given. This double dosing will be continued for 48 hours. Intervention dosages will not be corrected for kidney function. T1 will be defined as the first morning (8am) the day after admittance to the ICU. In order to count as T1 the patient has to be admitted (and if applicable received double dosing) for at least 8 hours. Consequently, this means T1 will be somewhere between 8 and 32 hours after admittance. Every following day will be started at 8am the morning after day 1 and day 2 respectively. This procedure has been chosen taking feasibility in mind, since most blood drawings and morning rounds are done in this time period.

Figure 1 Graphical trial flow



Tabel 2 Maximum dosages control group

	Loading dose*	Daily dose
Cefotaxime	1000mg	4000mg
Ceftazidime	1000mg	3000mg
Ceftriaxone	2000mg	2000mg
Cefuroxime	1500mg	4500mg
Meropenem	1000mg	3000mg
Flucloxacillin	1000mg	6000mg
Amoxicillin	1000mg	6000mg
Amoxicillin/clavulanic acid	1200mg	4800mg
Piperacillin/tazobactam	4500mg	18000mg

*if applicable according to local protocol

Tabel 3 Maximum dosages intervention group

	Loading dose*	Daily dose
Cefotaxime	2000mg	8000mg
Ceftazidime	2000mg	6000mg
Ceftriaxone	2000mg	4000mg
Cefuroxime	3000mg	9000mg
Meropenem	2000mg	6000mg
Flucloxacillin	2000mg	12000mg
Amoxicillin	2000mg	12000mg
Amoxicillin/clavulanic acid	1200mg Amoxicillin/clavulanic acid + 1000mg amoxicillin	4800mg Amoxicillin/clavulanic acid + 4000mg amoxicillin
Piperacillin/tazobactam	9000mg	36000mg

*if applicable according to local protocol

After 48 hours the intervention period will stop, and all patients will receive standard of care. Data collection will continue toT3. Three and twelve months after the intervention period questionnaires will be sent to the participant regarding health-related quality of life and medical consumption.

11.3.1 Efficacy assessments

Data used to determine mortality, calculate the SOFA scores, baseline characteristics and data for secondary endpoints, will be extracted from the electronic patient file (EPF) or the ICU's Patient Data Management System (PDMS) by the researcher. These include:

Demographic data

- Age
- Gender
- Height
- Weight
- Hospital and ward
- APACHE IV

Clinical data

- ICU admission diagnosis
- Comorbidity
- Presence/absence of surgery within previous 24 hours
- ICU mortality (Recorded as alive or deceased at ICU discharge)
- Hospital mortality (Recorded as alive or deceased at hospital discharge)
- 28-day mortality (Recorded as alive or deceased at 28 days after inclusion)
- 90-day mortality (Recorded as alive or deceased at 90 days after inclusion)
- 365-day mortality (Recorded as alive or deceased at 90 days after inclusion)
- ICU length of stay (Recorded as duration of ICU stay)
- Hospital length of stay (Recorded as duration of hospital stay)

Organ function and clinical chemistry data

- Presence of extracorporeal circuits (e.g. RRT (renal replacement therapy))
- Heart rate
- Mean arterial pressure or use of vasopressors including type and dosage
- Hemoglobin
- Platelet count
- Lactate
- Amount of oxygen delivery
- Mechanical ventilation including type
- Serum creatinine concentration
- Fluid balance (in the last 24 hours)
- Albumin
- Urea
- Bilirubin

Infection data

- Daily body temperature
- White blood cell count
- C-reactive protein
- Procalcitonin (where available)
- Known or presumed pathogen (positive blood culture and organisms isolated)

Antibiotic dosing data

- Indication for antibiotic therapy
- Antibiotic (also additional antibiotics)
- Start and end date of the antibiotic treatment
- Dose and frequency antibiotic therapy
- Time of dosing and sampling
- Days of antibiotic therapy (Antimicrobial days (DOT) and DDDs)
- Clinical cure

Blood samples will be drawn just before antibiotic administration at T1, T2, and T3. They will be kept on ice or in the fridge (2-8 °C) and frozen < 24 hours after withdrawal. Samples from participating hospitals, will be transported to the Pharmacy laboratory of EMC in bulk and stored at -80°C or -70°C until analysis.
The concentration of the study antibiotics in the biological samples will be determined by a validated chromatographic method (LC-MS/MS). (37)
Not all participating centra routinely measure procalcitonin. Because this parameter is indicative of severity of sepsis (38), this will be determined in bulk at the clinical chemistry from the same samples.

Health related quality of life at 3 and 12 months will be assessed using the EuroQoL 5D-5L™ (EQ5D) questionnaire. This questionnaire consists of five questions each representing a dimension of HRQoL. The dimensions are mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Patients assigned a score of no (1), slight (2), moderate (3) or severe problems (4), or are unable to (5) to each of these dimensions. Based on these five dimensions with 5 possible answers each, 3,125 health states can be discerned.

A trial-based cost-effectiveness analysis will be conducted comparing DS to the SoC following the recommendations of the Dutch guideline for conducting economic evaluations in healthcare (Dutch EE guideline). (39) The time horizon will be equal to the study follow-up period and will assume a healthcare perspective. The latter includes costs for (i) hospital admissions (ICU and other wards), drug or transfusion (ii) acquisition, and (iii) administration, (iv) laboratory diagnostics, and other healthcare resource use such as time spent by health care professionals for (iv) consultations, or (v) bedside procedures. Healthcare resource use will be valued with Dutch references pricing from the Dutch EE guideline or taken from our recent costing study. (40) Since differences in costs of informal care time, productivity losses, and travel are irrespective of the chosen strategy and hence not expected, a societal perspective is not assumed. The primary outcome of this cost analysis will be the incremental cost-effectiveness ratio (ICER) per change in SOFA of DS compared to SoC. Secondary outcomes of this cost analysis will include total costs per strategy (DS or SoC) and patient, and the ICER per quality-adjusted life years (QALYs). All costs will be expressed in Euros and indexed when necessary.

11.3.2 Safety assessments

Patients admitted on the ICU are continuously monitored. No further assessments or examinations are undertaken than those routinely performed or deemed necessary by the treating physician.

12. STUDY DISCONTINUATION AND COMPLETION

12.1 Definition End of Trial

The trial will end when the required data of the last participant has been collected. This is either after the final questionnaires have been filled in or with passing away of the final participant.

12.2 Criteria for temporary halt and early termination of the clinical trial

If there is a need to temporarily halt the study for reasons of subject safety, the sponsor will promptly report this in the Clinical Trials Information System (CTIS), ensuring that the notification is made within 15 days without undue delay. The report will include clear and detailed reasons for taking such action and outline the follow-up measures implemented to address the safety concerns adequately.

1. Severe or unexpected adverse events in study participants that raise safety concerns.
2. Identification of new safety risks or significant safety signals not previously observed.
3. Issues related to the investigational product's quality, safety, or efficacy that require immediate investigation.
4. Safety concerns arising from interim analyses indicating potential harm to participants.

Upon identifying the need for a temporary halt, the sponsor will take immediate action to protect the well-being of the participants. The appropriate regulatory authorities and ethics committees will be informed as required by applicable regulations. Once the safety concerns have been addressed and resolved, and the necessary corrective actions have been taken, the study may resume, subject to approval from the relevant authorities and ethics committees.

12.3 Discontinuation/withdrawal of individual subjects

Participants have the right to withdraw from the study without any adverse consequences, regardless of the reason. In cases of urgent medical necessity or disease progression, participants may be withdrawn from the trial, with the decision adequately justified by the investigator and treating physician to prioritize participant safety.

12.4 Arrangements for subjects after their participation in the clinical trial ended

Upon the conclusion of their involvement in the clinical trial, participants will continue the standard of care treatment as per the decision of the treating physician.

13. SAFETY REPORTING

13.1 Definitions

13.1.1 Adverse events (AEs)

Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

13.1.2 Serious adverse events (SAEs)

Serious adverse event is any untoward medical occurrence in a patient or trial subject that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect

13.1.3 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious;
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the SmPC.

13.2 Recording of AEs/SAEs/SUSARS

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC and competent authority.
The investigator shall record and document all AEs, unless the protocol provides differently. Include the list of AEs which do not require recording in this section, if relevant (CTR: Article 4). The investigator must record and document AEs or laboratory anomalies that are critical to safety evaluations and report them to the sponsor (CTR: Article 41 (1).

This safety report consists of:

- A list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- A report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

13.3 Reporting of AEs and SAEs

13.3.1 Reporting of SAEs by the investigator to the sponsor

Common toxicities observed for progressive disease and events secondary to progressive disease are generally excluded from reporting. However, in cases where the attribution to progressive disease in equivocal, the event should still be reported.

13.3.2 List of SAEs which do not require immediate reporting and procedure for reporting

1. Mild to Moderate Adverse Events: SAEs that fall within the CTCAE grade 1 or 2 and are considered mild to moderate in severity, without any immediate life-threatening implications.
2. Known and Expected Side Effects: SAEs that are well-documented in the literature, SmPC and the IB as common and anticipated side effects of cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin/ clavulanic acid, flucloxacillin, piperacillin/tazobactam or meropenem.
3. Pre-existing Medical Conditions: SAEs related to pre-existing medical conditions of the participant that were known before the administration of cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin/ clavulanic acid, flucloxacillin, piperacillin/tazobactam or meropenem and do not worsen significantly during the trial.
4. Events with Established Causality: SAEs that have a clear and established cause unrelated to cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin/ clavulanic acid, flucloxacillin, piperacillin/tazobactam or meropenem administration.
5. Events Managed Successfully: SAEs that have been promptly managed and resolved with appropriate medical interventions, and no further immediate action is required.
6. Expected Laboratory Abnormalities: SAEs involving laboratory abnormalities that are expected as known effects of cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin/ clavulanic acid, flucloxacillin, piperacillin/tazobactam or meropenem and have no clinical implications.

Justification:
These SAEs do not require immediate reporting as they are either known and expected effects of cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin/ clavulanic acid, flucloxacillin, piperacillin/tazobactam or meropenem, related to pre-existing conditions, or have already been appropriately addressed and managed. Continuous monitoring and documentation of these events will be carried out as per the study protocol for further evaluation and safety assessment.

Procedure for reporting these SAEs to the sponsor:
The investigator will include these SAEs in regular safety updates, following the protocol's specified intervals. The safety update will provide a comprehensive overview of all SAEs, their nature, severity, and outcomes. The sponsor will review the safety update to assess the investigational product's overall safety profile and take appropriate actions if necessary.

13.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

13.5 Reporting of SUSARs by the sponsor to EudraVigilance

The sponsor will keep detailed records of all AEs which are reported to him/her by the investigator or investigators.

The sponsor will report electronically and without delay to EudraVigilance all relevant information about any SUSAR.

The period for the reporting of SUSARs by the sponsor to EudraVigilance will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction.
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction.
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report.

13.6 Annual safety report

Regarding investigational medicinal products other than placebo, the sponsor shall submit annually through CTIS to all Member States concerned a report on the safety of each investigational medicinal product used in a clinical trial.

13.7 Unblinding procedures for safety reporting

Not applicable.

13.8 Temporary halt for reasons of subject safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will submit the notification through CTIS without undue delay of a temporary halt but not later than in 15 days of the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state. The investigator will take care that all subjects are kept informed.

13.9 Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the subjects. In addition, the sponsor will notify the Member States concerned, through CTIS, of the event and the measures taken. That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken.

13.10 Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

An independent data safety monitoring board will be installed.

14. STATISTICAL ANALYSIS

14.1 Description of statistical methods

In general, p-values< 0.05 are considered to indicate statistical significance (2-tailed test). The p-values for the secondary endpoints will be presented but considered descriptive and hypothesis generating rather than confirmatory. Both R studio and Graphpad software will be used for statistical analysis and making graphs, respectively. A p-value below 5% will be the threshold for statistical significance.

14.2 Analysis sets

All analyses will be performed according to the intention-to-treat (ITT) principle. The ITT population will consist of all patients who have been randomized, irrespective of withdrawals, dropouts or other reasons for failing to complete the study. A per-protocol analysis will be performed as a sensitivity analysis.

14.3 Participant demographics and other baseline characteristics

Descriptive statistics will be used to describe the baseline characteristics. Continuous variables will be described using means (SDs) or medians (interquartile range) depending on the normality of the distribution. Categorical variables will be described using numbers (percentages).

14.4 Randomization and blinding

Patients will be randomized in a 1:1 ratio by the local (sub)investigator(s) and/or his delegates using Castor EDC, a single electronic clinical data management platform with an integrated randomization module. Randomization will take place using random block size and will be stratified by hospital site. This is an open label study, so no blinding will take place.

14.5 Sample size, trail power and level of significance used

The power calculation was based on the available mortality data from the DOLPHIN trial. (12) The primary outcome was set at 28-day mortality. It was hypothesized that the 28-day mortality will decrease from 28% to 20%. Furthermore, it was assumed to have an 80% power, 5% two-sided alpha level and 5% loss-to-follow up. Therefore, the final sample requires 988 patients (494 patients in each treatment arm). The power calculation was performed using G*Power. The 8% mortality decrease is relevant and is feasible in early intervention sepsis studies. (41)

14.6 Planned analysis

14.6.1 Analysis primary endpoint

The primary endpoint, 28-day mortality, will be analyzed using a mixed-effects binary logistic regression. (42) This regression will include treatment effect and source of sepsis as fixed effects and site as random effect. For these regression Odds Ratios (OR) and 95% confidence intervals (95% CI) will be reported. Crude proportions by treatment arm will also be reported with an unadjusted OR (95% CI), absolute risk difference (95% CI) and associated p-values.

14.6.2 Analysis secondary endpoint(s)

Secondary outcomes are ICU and hospital mortality, 3 months and 1 year mortality, hospital and ICU mortality, length of stay, microbiological eradication, time to shock reversal, cost of treatment, resolution of infection, quality of life, side effects, Delta PCT (Baseline – Day 3), Delta lactate (Baseline – Day 3), SOFA day 3, Delta SOFA (Baseline – Day 3) and target attainment. A similar analyses approach will be taken for the secondary outcomes as for the primary outcome, while for continuous and/or count variables multivariate linear or Poisson regressions will be used, respectively. Missing data, where applicable, will be imputed with the use of multiple imputation under the missing-at-random assumption with chained equations. In the case of missing baseline data, they will be imputed based on baseline characteristics (age, sex, APACHE IV). (43) The outcome values are not imputed as per convention.

14.6.3 Analysis other study parameters/endpoints

Not applicable.

14.7 Interim analysis

For the interim analysis at half of the anticipated sample (N = 494 patients), an alpha < 15% estimated power to demonstrate a significant effect at full enrollment (988 patients), was defined as non-binding threshold to stop early for futility. Other parameters should be considered too such as recruitment speed, funding parameters and/or external events that prohibit the completion of the trial.

14.8 (Statistical) criteria for termination of the trial

1. Safety Concerns: If there is a significant increase in adverse events or serious adverse events in the treatment group or if there are any unexpected safety issues that pose risks to participants' health.
2. Ethical Considerations: If new information emerges during the trial that makes the study unethical to continue, such as the emergence of more effective treatment options or other compelling reasons.

14.9 Procedure for accounting for missing, unused and spurious data

Missing data will be identified and the reasons for missing or unused data will be documented.

14.10 Procedure for reporting any deviation(s) from the original statistical plan

In the event of any deviation from the original statistical plan, a detailed description and justification for the deviation will be documented in the protocol and/or the final report, as appropriate. The reasons for the deviation will be thoroughly explained, and any impact on the study results and conclusions will be assessed. Transparency and full disclosure of the deviations will be maintained to ensure the integrity and validity of the study findings. The deviation(s) will be appropriately addressed during data analysis and interpretation, and steps will be taken to mitigate any potential biases introduced by the deviation(s).

15. ETHICAL CONSIDERATIONS

15.1 Declaration of Helsinki

The investigator will ensure that this study is conducted to the standards of Good Clinical Practice, in full conformance with the "Declaration of Helsinki" (latest amendment http://www.wma.net/en/30publications/10policies/b3/), the Dutch laws and regulations with the W.M.O. ("Wet Medisch-wetenschappelijk Onderzoek met mensen") in particular.

15.2 Recruitment and informed consent procedures

Deferred consent is necessary in this patient group, followed by the request for patient's (deferred subject consent) or representative's (deferred proxy consent) informed consent in a later phase. The investigator or his/her representative will explain the nature of the study to the subject or his or her legally designated representative and answer all questions regarding this study. In the interview it will be verified that the subject has understood the information. The subject or, where the subject is not able to give informed consent, his or her legally designated representative will be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent will be documented. To prevent unauthorized use of the obligation to obtain consent, a time limit of 72 hours (after start of study procedures) is used to obtain consent. Given privacy-respecting handling of data and thorough confidentiality, patient's interests are not harmed by using the data.

15.3 Benefits and risks assessment, group relatedness

This study has the potential to offer more effective treatment to ICU admitted sepsis patients. As a result, individual patients may experience significant benefits from their participation. Throughout the study daily blood samples will be collected from each patient, posing low risks. Depending on the result of randomization, standard care or higher antibiotic dosages will be administered. Based on our previous research and clinical experience the overall risk associated with this approach is considered to be negligible. Patient safety and well-being will be closely monitored throughout the study to mitigate any potential risks and ensure the best possible outcomes for all participants.

15.4 Compensation for injury

The sponsor has an insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO, under 1). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

The sponsor/investigator has a liability insurance that is in accordance with article 7, under 9, of the WMO.

15.5 Compensation for subjects

Subjects participating in the clinical trial will not receive any special incentives or financial compensation.

15.6 Compensation for investigators

There will be no additional financial compensation for the investigators.

15.7 Other ethical considerations

Not applicable

16. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY

The study will be conducted in compliance with the protocol, Clinical Trials Regulation No 536/2014, and good clinical practice principles.

16.1 Approval initial application and substantial modifications

The trial protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other documents required by the Regulation will be submitted for the regulatory approval before the clinical trial is started via CTIS.

The sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS.

A 'substantial modification' is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

16.2 Monitoring

Monitoring will be performed in accordance with applicable law and regulation, and the NFU Guideline "Quality assurance of research involving human subjects".

This trial has been assessed as Negligible risk in regard to the NFU risk classification.
Based on the negligible risk of the intervention and the negligible risk of the quality of the data, the trial will be monitored every year. The procedures of the monitoring are according to standard Erasmus MC monitoring procedures for studies with low to negligible risk. The monitor will have an independent role in relation to the study: the monitor will not have any involvement in the set-up of the study, the conduct of the study or interpretation of the results. Monitoring is executed according to Erasmus MC standard operating procedures for monitoring. At the beginning of the study a study specific monitoring plan will be written and approved by the sponsor. The principal investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. Prior to subject recruitment an initiation meeting will be held with all participating sites to discuss the protocol and procedures and to train the site. After data collection is complete, all eCRF queries have been answered and closed, a close out visit will be conducted. Some monitoring activities may be conducted remotely. This will be specified in the monitoring plan.

The investigator should be made aware that trial – and source documents for this study should be readily made available to regulatory authority or health authority inspectors (see paragraph 15.4).

16.3 Recording, handling and storage of information

Each patient will be given a unique patient study number. EDC will be performed in Castor. Castor is a program validated and compliant with the WBP and therefore guarantees the privacy of the participants of the study.

16.3.1 Handling of data and data protection

This trial will collect both already existing (personal) data from participants' treating physicians or medical specialists and new personal data. All data will be analyzed and stored in a pseudonymized

format within the clinical site, ensuring participant privacy and confidentiality. The sponsor confirms compliance with the General Data Protection Regulation (EU) 2016/679, protecting personal data at all times. Access to the data will be restricted to authorized individuals directly involved in the research, including the research safety monitoring committee members, monitor, and regulatory authorities.
The principal investigator and coordinating researcher will safeguard the key linking samples to participants. Participants' consent will be obtained, and their data rights will be upheld throughout the trial.

16.3.2 Source documents and case report forms (CRF)

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.
All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code.

16.3.3 Clinical trial master file and data archiving

The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated.

The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other EU law requires archiving for a longer period. The medical files of subjects shall be archived in accordance with national law.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request.

16.3.4 Collection and storage of biological samples

The samples will be stored within the sponsor’s organization for a period of 5 years, and during this time, they will be securely maintained and preserved to ensure their integrity and usefulness for research purposes. The stored samples may potentially be used for future research within the scope of related studies. Informed consent will include the provision for patients to give permission for the use of their samples in future research. Patients will have the autonomy to decide whether they grant permission for future use of their samples or not. They can still participate if they don’t give permission.

16.4 Audits and inspections and direct access to source data/documents

This trial may be subject to internal or external monitoring, auditing, or inspections procedure to ensure adherence to GCP. Access to all trial-related documents including direct access to source data will be given at that time.

16.5 Reporting of serious breaches

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **seven days** of becoming aware of that breach.

16.6 Notification of the start and the end of the recruitment

The sponsor will notify within 15 days each Member State concerned of the start of a clinical trial in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the first visit of the first subject in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU.

16.7 Temporary halt/(early) termination

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS.

16.7.1 Temporary halt/early termination for reasons not affecting the benefit-risk balance

The sponsor will notify with 15 days each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through CTIS.

When a temporarily halted clinical trial for reasons not affecting the benefit-risk balance is resumed the sponsor will notify each Member State concerned through CTIS.

The sponsor will notify to the EU portal CTIS of early termination of the clinical trial for reasons not affecting the benefit-risk balance through CTIS. The reasons for such action and, when appropriate, follow-up measures for the subjects will be provided as well.

16.7.2 Temporary halt/early termination for reasons of subject safety

In accordance to article 38 of the CTR, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance will be notified to the Member States concerned through the EU portal CTIS without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorization procedure laid down in Chapter III of the CTR.

16.8 Summary of the results

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V.

16.9 Public disclosure and publication policy

After obtaining ethical approval, the trial will be registered on ClinicalTrials.gov for transparency and accessibility to the scientific community. Positive outcomes will be locally implemented and integrated into routine clinical practice to improve patient care. Adherence to ethical and regulatory guidelines will be ensured to uphold study integrity. Trial results will be submitted for open-access publication in a peer-reviewed scientific journal. Data from the clinical trial will be submitted to the EU portal CTIS, meeting the requirement for publicly accessible registration.

17. REFERENCES

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