A pHase III cluster randomIsed controlled, cross-over, non-inferiority Trial of a short course, High dose AntimicRobials vs conventional dose and Duration in critically ill patients

SHORT STUDY TITLE / ACRONYM

HIT-HARD

PROTOCOL VERSION NUMBER AND DATE

Protocol version number	V2.0 Date: 24 Mar 2025

RESEARCH REFERENCE NUMBERS

EU reference number	**2024-514730-21-00**
Clinical trials.gov Number / Other registry Number:	This trial will be registered at clinical.trials.gov NCTXXXXXXXX
SPONSOR Number:	ONZ-2024-0224
BeNeFIT Trials Number:	**10390082210010**
Phase of trial:	**III**
Chief investigator:	**Prof. Dr. Jan De Waele**

TABLE OF CONTENTS

■ SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in " CTR 536/2014, and any subsequent amendments, GCP guidelines and/or ISO14155, the Belgian law of May 7th 2017 regarding clinical trials with IMP, and other regulatory requirements as amended.

I confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:		
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Co- Investigator:		
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For acknowledgement on behalf of the funder (ZonMw):		
Signature:		Date: ...../...../.....
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TRIAL SUMMARY/SYNOPIS

Trial Title	A pHase III cluster randomIsed controlled, cross-over, non-inferiority Trial of a short course, high dose antimicRobials vs conventional dose and Duration in critically ill patients
Short title	HIT-HARD
Protocol version number	V2.0 24 Mar 2025
EU reference number	**2024-514730-21-00**
Clinicaltrials.gov	NCTXXXXXXXX
Sponsor	Ghent University Hospital Corneel Heymanslaan 10, 9000 Ghent Belgium
Chief Investigator	Prof. Jan De Waele
Internal reference	Sponsor: ONZ-2024-0224 / Dutch CC reference: PaNaMa 116223
BeNeFIT 3 number	10390082210010
Rationale	The HIT-HARD study addresses the dual challenge of optimizing antimicrobial use in critically ill patients and reducing antimicrobial resistance (AMR). Current treatment regimens often result in both underdosing and excessive durations, leading to suboptimal outcomes and increased AMR. Evidence suggests that shorter, high-dose antimicrobial courses can be effective and safe, reducing antimicrobial exposure, and potential adverse effects. This study will compare this innovative strategy with conventional dosing to improve patient outcomes and stewardship practices.
Objective	The primary objective is to determine the non-inferiority of a short course, high-dose antimicrobial therapy compared to conventional dose and duration in critically ill patients with pneumonia, intra-abdominal infection, or bloodstream infection, with all-cause 90-day mortality as the primary endpoint. Secondary objectives include evaluating all-cause hospital and ICU mortality, (duration of) antimicrobial exposure, total quantity antimicrobial use, number of organ support free days, emergence of antimicrobial resistance, clinical cure rates, safety, and cost-effectiveness.
Trial Design	A prospective non-inferiority, multicentre, cluster-randomized, cross-over study investigating the non-inferiority of short course, high dose antimicrobial treatment (HIT-HARD therapy) vs. conventional dose and duration antimicrobial treatment.
Trial Participants and setting	Patients in ICU, treated for Community acquired Pneumonia (CAP), Hospital acquired pneumonia (HAP), Ventilator Acquired Pneumonia (VAP) and Intra- abdominal Infection (IAI) (with adequate source control) or Bloodstream Infection (BSI) with one of the following antimicrobials: ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem.

Intervention(s)	High dose treatment with ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem (≥150-200% of conventional dosing, details below) for a short duration (3-5 days) (HIT-HARD strategy).
Control	Conventional dose and duration of ceftriaxone, cefotaxime, cefuroxime, piperacillin- tazobactam or meropenem (6-9 days) (CONTROL strategy)
Primary Endpoint	• All cause 90-day mortality
Secondary Endpoint(s)	• All-cause ICU mortality • All-cause hospital mortality • New colonization or infection with a multi-resistant organism (MRSA, VRE, MDR *P. aeruginosa*, CRE, ESBL Enterobacterales, *Acinetobacter baum*annii) or C. difficile diarrhea/infection up to 28days post inclusion • Recurrence of infection • Toxicity • Health related quality of life (EQ-5D-5L) • Exposure • Clinical cure • ICU length of stay • Hospital length of stay • Antimicrobial free days • Organ support free days • Antimicrobial days (DOT) and DDDs
Planned Sample Size	1.282 in total, 641 in each group
Treatment duration	Intervention group: 3-5 days Control group: 6-9 days
Follow up duration	Maximum 90 days after inclusion
Trial duration Estimated trial start (FPFV) Estimated trial end (LPLV) Estimated recruitment period	42 months (FPI- CSR) Q1 2025 Q4 2027 30 months
Ethical considerations	The expected benefit to individual subjects in this trial is the potential for improved health outcomes by shortening the exposure to antibiotics, which may reduce exposure to potential side effects including the development of antimicrobial resistance. Furthermore, the study could provide evidence for a more effective and efficient treatment of severe infections. The risks involve potential adverse reactions to the antibiotics and the uncertainty of whether the shorter treatment duration is as effective as standard care. Overall, the study aims to balance the potential for significant clinical benefits with the careful management of associated burdens and risks.

DOCUMENT HISTORY

Document	**Date of version**	**Summary of Changes**
Original protocol	*V2.0 24 Mar2025*	Not applicable

FUNDING AND SUPPORT IN KIND

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For the avoidance of doubt KCE or ZonMw shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and University Hospital Ghent shall make no representations whatsoever in this respect.

ROLE OF STUDY SPONSOR

Ghent University Hospital as mentioned in KEY TRIAL CONTACTS (see appendix) shall act as sponsor of the Study, as defined in the CTR536/2014 and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2017 for the Belgian participating centres. University Hospital Ghent shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Participants or the Regulatory Authorities as sponsor of the Study.

Radboudumc as mentioned in KEY TRIAL CONTACTS shall act as the Dutch coordinating centre of the study, as defined in the CTR536/2014 and shall assume all responsibilities and liabilities in connection therewith and procure the mandatory liability insurance coverage in accordance with the Law of 2017 for the Dutch participating centres. University Hospital Ghent shall ensure that it shall be mentioned in the Protocol, the Informed Consent Forms and in other relevant communication with the Study Participants or the Regulatory Authorities as sponsor of the Study.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES

Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC must also include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress, conduct, and advise on scientific credibility. The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The TSC will meet on average 3 times per year the first year and twice a year after that.

The steering committee of this trial is composed of following members:

1. Chief Investigator
2. Co-investigators
3. Project managers
4. Statistician
5. Precision dosing and pharmacometrics specialists
6. Representative of KCE
7. Representative of ZonMW
8. Representatives participating sites

Trial Management Group (TMG)

The day-to-day management of the study will be performed by the Trial Management Group (TMG) which is distinct from the TSC. The TMG consist of the chief investigator, 2 co-investigators and 3 project managers.

Patient Advisory Committee (PAC)

Representatives of SepsiBel (Belgium) and IC connect (Netherlands) are involved in the different phases of this study. Input of the patient representatives is required during study design, set up, development of patient information documentation, reporting and communication of results.

Regular meetings with the patient advisory board will be organized to discuss these various aspects of the study.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
ADE	Antimicrobial de-escalation
AMR	Antimicrobial resistance
AR	Adverse Reaction
ASR	Annual Safety Report
ATC	Anatomical therapeutic Chemical
BID	Twice a day
CA	Competent Authority
CAP	Community- acquired pneumonia
CI	Chief Investigator
CRF	Case Report Form
CSR	Clinical Study Report
CT	Clinical Trial
CTA	Clinical Trial Authorisation
CTIS	Clinical Trial Information System
CTR	Clinical Trials Regulation
DDD	Defined daily dose
DOT	Days of therapy
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FPI	First Participant In
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
HAP	Hospital acquired pneumonia
IAI	Intra-abdominal infection
ICF	Informed Consent Form
ICH	International Council on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMA	InterMutalistisch agentschap/ L'Agence InterMutualiste
IMP	Investigational Medicinal Product

ISF	Investigator Site File
ISO	International Organisation for Standardization
KCE	Belgian Healthcare Knowledge Centre
MAP	Mean arterial pressure
MDR	Multi drug resistance
MS	Member State
PI	Principal Investigator
RA	Regulatory Authority
RCT	Randomised Control Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SI	Sub- Investigator
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDM	Therapeutic Drug monitoring
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
TTP	Trusted Third Party
VAP	Ventilator associated pneumonia

TRIAL FLOW CHART

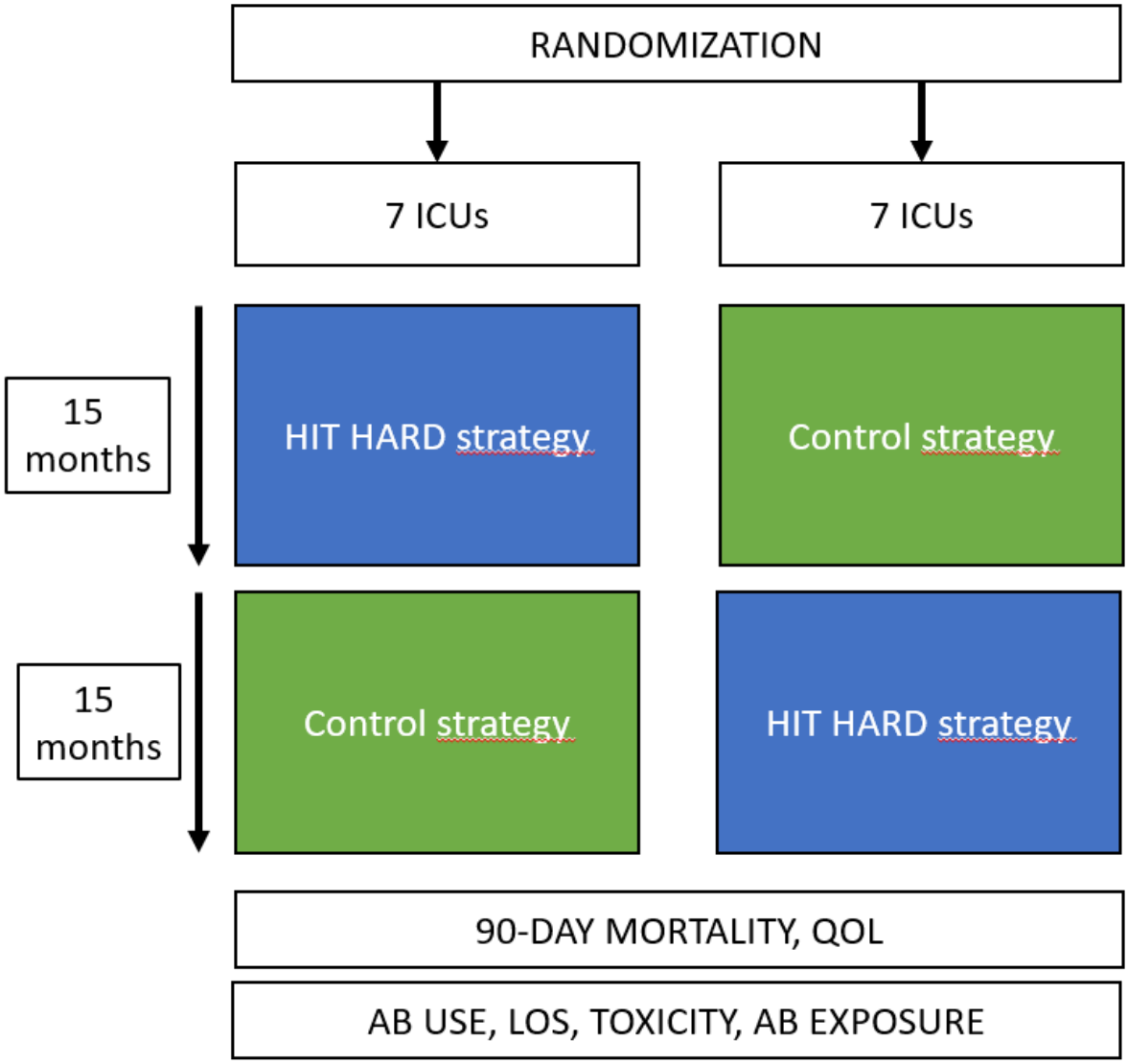

Figure 1: Trial flow chart

Legend. ICU: Intensive Care Unit; QoL: Quality of Life; AB: antibiotic; LOS: Length of Stay.

■ STUDY PROTOCOL

1 BACKGROUND

Introduction

Sepsis, defined as life threatening organ dysfunction caused by the dysregulated response to infection (1), is a continued significant clinical challenge in intensive care units (ICUs) around the world. Each year, nearly 50M patients worldwide suffer from sepsis, which is associated with high rates of morbidity and mortality (2) ; mortality is estimated to be over 10% in patients with sepsis, and when septic shock develops – a state characterised by additional circulatory and cellular/metabolic abnormalities -, it further increases to over 40% (1). In both Belgium and the Netherlands, the most commonly occurring infections in ICU settings are respiratory, abdominal, and bloodstream infections (3). Community-acquired pneumonia (CAP) and intra-abdominal infections (IAI) account for a substantial number of ICU admissions, while hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the predominant infections acquired within the ICU. As per data from Dutch NICE in 2019, before the onset of the COVID-19 crisis, 5,322 out of 39,654 medical ICU admissions across the country—or 13.4%—were for the treatment of pneumonia. The majority of these bacterial infections are treated using beta-lactam antimicrobials. Similarly, in Belgium, Sciensano's data indicates that broad-spectrum beta-lactam antimicrobials are the go-to antimicrobials in ICU settings in Belgium (3).

The rising prevalence of Antimicrobial Resistance (AMR) exacerbates these challenges, posing an especially grim threat to ICU patients suffering from severe infections, as often ICUs are the hotspots of AMR in the hospital. This is mainly due to the use of invasive devices, exposure to antimicrobials, patient vulnerability, and the intensity of care, with an inherent risk of transmission of pathogens (4).

The issue of antimicrobial (over)use in the ICU presents a complex, dual-faced challenge with both immediate and long-term consequences. On one hand, antimicrobials serve as life-saving treatments for individual patients, effectively combating bacterial infections while being weighed against potential toxic side effects. On the other hand, their usage has a broader, societal impact by contributing to the escalating problem AMR.

Inappropriate prescription practices, particularly the overuse or misuse of broad-spectrum antimicrobials, not only compromise the effectiveness of current treatments but also have far-reaching repercussions for future generations. This creates an environment in which MDR bacteria can thrive, thereby reducing the efficacy of existing antimicrobials and threaten the lives of patients who will need these treatments in the future. The magnitude of the AMR problem is huge. According to estimates, in 2019 there were roughly 4.95 million deaths globally associated with bacterial AMR, including an alarming 1.27 million deaths directly attributable to it (5). These numbers underscore the urgent need for responsible antimicrobial stewardship practices in all healthcare settings, but particularly in the ICU, where the use of antimicrobials is high.

Despite advancements in the care of critically ill patients and the introduction of new, potent, less toxic antimicrobials, the outcomes for such infections remain disappointingly poor. This reality underscores the urgent need for optimized treatment strategies in order to improve patient outcomes and combat the escalating crisis of AMR.

2 RATIONALE

Current approach to antimicrobial treatment for severe infections.

Existing treatment approaches for severe infections often involve a paradox: patients are simultaneously 'undertreated' in terms of dosing, while being 'overtreated' in terms of the duration of therapy. On the one hand, accumulating evidence has shown that conventional dosing for many antimicrobials leads to lower than expected antibiotic concentrations, frequently resulting in under-exposure of the pathogen to the antibiotic (6, 7). Not reaching a minimal concentration threshold has been associated with adverse outcomes (6). On the other hand, in current ICU settings, treatment durations frequently exceed recommendations. An international multicentre study revealed a median treatment length of 10 days for prevalent ICU infections like CAP, HAP, VAP, and IAI (with 75% of patients being treated for 7 days or longer (8). Clearly, there is a substantial opportunity for reducing treatment durations.

This dual failure does not only jeopardize individual patient outcomes but also exacerbates the development of AMR. Numerous studies have shown that extended antimicrobial courses contribute to the emergence of MDR pathogens (9, 10), and also expose patients to the risks of adverse effects such as *Clostridioides difficile* infection. Moreover, prolonged therapy causes an increase in the length of hospital stay and is associated with increased healthcare costs.

Recent evidence robustly supports shorter antimicrobial courses for various infections, a recommendation increasingly endorsed by both national (Belgian www.iggi.be and Dutch www.swab.nl) and international guidelines (11, 12). Recent studies show that for critically ill patients with VAP, antimicrobial treatment can be safely reduced to 5-7 days while safeguarding outcomes without recurrence of infection (13). Recent studies even go further, demonstrating that treatment durations can be reduced to as short as 3 - 5 days in severe infections (14-16). A prominent trial utilizing biomarkers to curtail antimicrobial duration in a patient cohort similar to the one targeted in this proposal demonstrated that a median therapy duration of 5 days was safe for most patients (17).

In addition to reducing the duration of antimicrobial therapy, another pillar of AMR prevention involves optimizing dosages to ensure a clinical effect through effective pathogen eradication to optimize outcomes and minimize the risk of strains with reduced susceptibility gaining a foothold. It is now clear that licensed dosing schemes — often derived from healthy volunteer studies—are inadequate for many critically ill patients. This is based on pharmacokinetic studies that have shown that higher doses are needed to reach adequate concentrations in critically ill patients. As a result, higher than licensed dosing regimens for antibiotics have already been used in the ICU for decades. As an example, vancomycin conventional dosing is 1000 mg BID but in ICU patients up to 5000 mg per 24h is used (18-20). Amikacin, a commonly used aminoglycoside antimicrobial, is now dosed at 25-30mg/kg whereas licensed dosing s 15 mg/kg (18, 21, 22).

Also for beta-lactam antibiotics used in critically ill patients, higher doses are deemed necessary to reach PKPD targets. This has been demonstrated for all beta-lactams included in the current study: for meropenem, (7, 23, 24, 24-28), piperacillin (29-35), ceftriaxone (7, 36, 37), cefotaxime (7), and cefuroxime (7, 38). These studies confirm that current dosing of beta-lactam antimicrobials – just like many other antibiotics - frequently fails to reach adequate therapeutic drug concentrations in ICU patients.

A recent large pragmatic RCT (39) and systematic review and meta-analysis (40) support the use of continuous infusion when administering beta-lactam antibiotics, and therefore this will be the administration method of choice in the HITHARD study.

Need for a trial

Given the current lack of evidence, a rigorously designed clinical trial is needed to compare short-course, high-dose beta-lactam therapy with the prevailing conventional strategy. Such a trial would not only address a pressing clinical question but would also have broader implications for ICU antimicrobial stewardship programs and healthcare economics, in the global fight against AMR.

We hypothesize that administering high-dose beta-lactam therapy (≥150-200% of the currently recommended dosage) for a shortened period (3-5 days instead of the conventional 6-9 days) in ICU patients admitted for a severe infection will result in reduced antimicrobial exposure without adversely affecting mortality rates. Moreover, we expect similar rates of clinical cure, re-infection and adverse effects. Possibly this intervention will lead to shorter durations of both ICU and overall hospital stay.

Rationale for a cluster-randomized design.

Cluster randomization was selected due to several factors inherent to the ICU setting and the nature of the interventions being tested.

In general, individual randomization is preferred, if it is possible. We considered individual randomization, but for this specific topic the intervention involves a treatment strategy that involves and affects a whole team in the participating ICUs. To be specific, the uniformity of all professionals acting in the same way reinforces the compliance with the treatment condition (control or HITHARD). With individual randomisation, case by case discussion and personal preferences would likely occur and this would result in breaking the randomization. Moreover, individual randomization would imply that the intended treatment is only initiated after individual randomization which always takes time, time that cannot be wasted, and in the meantime antimicrobial therapy using a conventional strategy has to be initiated. This would imply that the HITHARD concept cannot be implemented from the very start of antimicrobial therapy that – typically for our ICU patients- should be started within the first hours after admission (reference Surviving sepsis guidelines). The first hours of antimicrobial therapy are considered the most important, implying that with individual randomisation the full impact of the HITHARD strategy cannot be evaluated. Cluster randomization also helps to minimize the administrative and logistical complexities that could impact adherence to the protocol, which is particularly important in multicenter trials involving acute care settings.

Secondly, the main argument that individual randomization would be preferred, is that it leads to smaller trials. However, we use a cluster cross-over design (each cluster is exposed to the the control condition during the first period and to the intervention condition during the second period, or vice versa). This means that the clustering effect (i.e. the hospital effect) drops out in the comparison between intervention and control (within-cluster comparisons). Thus, the sample does not need to be increased compared to an individually randomized trial. There could be a time effect (i.e. a variation over time without intervention), but within the duration of a period (15 months) we do not expect that, also because we see that mortality outcomes vary little over time.

Thirdly, in an individually randomized trial, each health professional uses intermittently the intervention or the control strategy which could lead to the application of some elements of the

intervention (dose / duration) for patients randomized to control and vice versa, leading to contamination.

3 ASSESSMENT AND MANAGEMENT OF RISK

This trial is categorised as **a low-interventional clinical trial** within the scope of regulation EU No 536/2014 for the following reasons:

- The investigational medicinal products are on the market as an authorised medicine for use in adults for the intended indications and have a CE mark. They have been used for decades and their use is recommended in many guidelines for the treatment of the infections the study population is treated for (11).
- The use of the investigational medicinal products in this study is supported by published scientific evidence on the efficacy and safety, as outlined in the introduction, and based on national guidance in Belgium and the Netherlands. More specifically, following considerations have been made when designing the study:
- Short duration (5 days or less) of antimicrobial therapy is increasingly recommended for different kind of infections, also for patients with severe infections who require ICU admission, and this has shown to be safe. We refer to the introduction for a more extensive description of this aspect.
- Dosing for the HIT HARD strategy is based on (inter)national guidelines and PK studies that have consistently demonstrated failure to reach adequate targets in ICU patients when conventional dosing is used (6, 7). Below is an overview of the sources on which the proposed dosing schemes in the HITHARD strategy are based.
    - Ceftriaxone: a dose of 4g/24h is listed in European guidance from EUCAST, as the High Dosage (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_14.0_Breakpoint_Tables.pdf), and in the Dutch national guideline as the recommended dose in case of intermittent susceptibility of the pathogen (https://adult.nl.antibiotica.app/nl/node/501098), as well as PK studies (7, 36, 37)
    - Cefotaxime: a dose of 12000mg/24h is listed on the Dutch national guideline as the recommended dose in case of intermittent susceptibility of the pathogen (https://adult.nl.antibiotica.app/nl/node/1154) and in the Dutch national 'Guidelines on Antibacterial Therapy of Patients with Bacterial Central Nervous System Infections' as standard dosing regimen in central nervous system infections (https://swab.nl/nl/exec/file/download/82) and a PK study (7)
- Cefuroxim: a dose of 6000mg/24h listed on the Dutch national guideline as the recommended dose in case of intermittent susceptibility of the pathogen (https://adult.nl.antibiotica.app/nl/node/1215) and different PK studies (7, 38)
    - Piperacilline/tazobactam: a dose of 20000/2500mg/24h is recommended by on numerous PK studies (29-35) in order to reach the PKPD target
    - Meropenem: a dose of 6000mg/24h is listed in European guidance from EUCAST, as the High Dosage (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_14.0_Breakpoint_Tables.pdf), listed on the National Dutch guideline as the recommended dose in case of intermittent susceptibility of the pathogen (Dosering

bij “I” gevoeligheid | SwabID (antibiotica.app)) and recommend in several PK studies (7, 23, 24, 24-28) in order to reach the PKPD target. In the Dutch National guideline this dose is also supported https://adult.nl.antibiotica.app/node/1557

- Adverse effects with the beta-lactam antimicrobials administered in this study are widely considered to be low. The reasons for this are multiple:
  - **Targeted action:** Beta-lactam antimicrobials target the bacterial cell wall; since human cells lack this structure, the risk of harming patients' cells is minimal.
  - **Therapeutic window:** Beta-lactam antimicrobials have a broad therapeutic window which allows higher dosing strategies without exacerbating risks for adverse effects.
  - **Proven track record:** Decades of use have shown that adverse reactions to beta-lactams are rare and mild, boosting confidence in their safety.

- The additional diagnostic or monitoring procedures necessary for this study do not pose an additional risk or burden to the safety of the subjects compared to normal clinical practice in Belgium or the Netherlands
- In this study, antibiotics will be administered as continuous infusion. This has been recommended in guidelines (11) and is based on extensive clinical data. A recent systematic review and meta-analysis demonstrated an advantage for major endpoints including clinical cure and mortality over intermittent infusion (40). Many centers have already adopted this strategy – in a 2021 international survey, prolonged infusion (which included both extended infusion and continuous infusion) of beta-lactam antibiotics was around 75 percent (41).

Potential threats and how to mitigate them:

Risk	**Mitigation**
Continuous dosing may not be the preferred dosing in all hospitals.	Selection of hospitals that are willing to comply with the study protocol. Hospitals typically offer both strategies as standard of care. A recent prospective trial demonstrated no difference in continuous versus intermittent dosing (39).
Treatment duration in participating centres already short, unwillingness to use the CONTROL therapy.	Selection of hospitals that are willing to comply with the study protocol. Inventory of duration of therapy in the participating centres; willingness to use longer duration as a part of the CONTROL strategy (even if it is not ‘local practice’).
Treating physicians do not consider HIT-HARD strategy acceptable care.	The trial is positioned as a low risk intervention study to distinguish from general practice. Reduced duration is generally accepted and may mitigate the concerns with higher dosages.

Treating physicians want to de-escalate antimicrobial therapy once cultures become available.	Current de-escalation rates have shown to be low (42). Short (3-5 day) therapy will not prompt de-escalation, as the change to an alternative antibiotic for 1 –2 days will be considered unnecessary, also considering that cultures and susceptibility usually only are available after 2-3 days. In a recent similar study in Belgium centres, the BLING-III study, wish for de-escalation was not a hurdle for patient inclusion (39). Anyway, de-escalation after 3-5 five days is allowed within the study protocol as a valuable alternative in the control strategy group.
Other – non beta-lactam - antibiotics will be preferred	Unlikely in view of the central role for the included beta-lactam antimicrobials in most regimens for the studied clinical syndromes.
Switching from HIT-HARD to conventional therapy.	Expected some 20% based on previous research (SAPS 2 trial), has been corrected for in sample size calculations.
Risk of 'missing' patients during out of office hours (nights and weekends).	Cluster randomisation will facilitate effective inclusion of patients. Current participating sites have dedicated research teams who can include participants, also in the weekend. Low risk intervention helps to promote this.

4 OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

This study aims to confirm the non- inferiority of a short course, high dose antimicrobial therapy versus conventional dose and duration.

Research hypothesis

A short course, high-dose antimicrobial treatment using ceftriaxone, cefotaxime, cefuroxime, piperacillin/tazobactam or meropenem, is noninferior to conventional dose and duration of antimicrobial therapy.

4.1 Primary objective

The primary objective of this study is to determine the non-inferiority of a short course, high dose antimicrobial therapy in critically ill patients with pneumonia (CAP, HAP and VAP), intra-abdominal infection (IAI) or bloodstream infection (BSI) for all cause 90-day mortality.

Our primary hypothesis is that a short course, high dose antimicrobial therapy results in similar outcomes compared to conventional duration and dose, while it results in a lower exposure to antimicrobials.

P	Patients in ICU, treated for Community acquired Pneumonia (CAP), Hospital acquired pneumonia (HAP), Ventilator Acquired Pneumonia (VAP) and Intra-

	abdominal Infection (IAI) (with adequate source control) or Bloodstream Infection (BSI) treated with one of the following antimicrobials: ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem.
I	High-dose treatment with ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem (≥150-200% of conventional dosing, details below) for a short duration (3-5 days) (HIT-HARD strategy).
C	Conventional dose and duration of ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam or meropenem (6-9 days) (CONTROL strategy)
O	All cause 90-day mortality
T	Day 90 for the primary outcome

Antimicrobials will be administered as continuous infusion, except for ceftriaxone. Ceftriaxone is allowed to be administered via continuous or intermittent infusion.

The exact duration of antimicrobial therapy will be decided by the treating physician within the timeframes specified in the 2 strategies.

4.2 Secondary objectives

The study also has these secondary objectives:

- To determine, in critically ill patients with pneumonia, intra-abdominal infection (IAI) or bloodstream infection (BSI), if short course, high dose antimicrobial therapy is superior to conventional duration and dose for total quantity antimicrobial use, DOTs, clinical cure, number of organ support free days, and ICU length of stay.
- To compare all-cause hospital/ICU mortality, DDDs, recurrence of infection, emergence of antimicrobial resistance during and after ICU admission in critically ill patients with pneumonia, intra-abdominal infection (IAI) or bloodstream infection (BSI) between participants with a high dose antimicrobial therapy to conventional duration and dose. Antimicrobial resistance will be evaluated at day 28 based on available data obtained via routine laboratory tests and MDR pathogens identified.To assess the safety of short course, high dose antimicrobial therapy in critically ill patients with pneumonia, IAI, or BSI.
- To estimate the incremental cost-effectiveness of a short course, high dose antimicrobial therapy compared to conventional dose and duration from a medical perspective.
- To gain further insight into antibiotic exposure and inter-patient variability following higher doses of beta-lactam antibiotics and the possible relation between exposure and toxicity

4.3 Endpoints

4.3.1 Primary endpoint

All-cause mortality within 90 days after inclusion.

Relevance and rationale

Selecting mortality as a primary outcome measure holds substantial clinical significance both for healthcare professionals as well as patients and families. It is an unambiguous measure and exemplary parameter to inform medical decision-making, healthcare

policies, and resource allocation. This endpoint captures the long-term outcomes of the patients, as short-term mortality may not fully reflect the sustained impact of the antibiotic regimen, especially in critically ill patients whose recovery trajectory extends beyond the immediate treatment period.

While there is a degree of separation between the intervention and this outcome measure, the rationale is that the duration and intensity of antibiotic therapy can have lasting effects on patient health, including delayed or downstream consequences such as late-onset infections, resistance development, or other complications that could impact survival over a longer term. Additionally, the 90-day timeframe allows us to observe potential relapses or late deaths that are attributable to the initial infection or its treatment.

Specific considerations

- Measurement variable: All-cause mortality will be considered; mortality will not be limited to infection-related mortality. Mortality will be assessed at day 90 by contacting the patient via a telephone call, unless information is available in the medical records.
- Participant level analysis metric: final outcome – dead or alive.
- Summary measure: proportion of patients that died.
- Time point: mortality at Day 90 after inclusion.
- intercurrent events and their handling: 1) switch between HITHARD and CONTROL post-initiation of intended treatment. In the primary intention-to-treat (ITT) analysis, switch will be handled by the treatment policy strategy, i.e., D90 mortality as observed regardless of whether switch occurred. However, the ITT analysis may blur differences, as patients that switch from the one treatment to the other may have responses more similar to those on the other treatment. As in the context of non-inferiority, the aim of estimation is to maximise detection if HITHARD is inferior to CONTROL, a per protocol (PP) analysis is performed to put the ITT analysis in context. As the PP analysis may incur selection bias, a second and third analyses that preserve randomisation are performed to this aim (i.e., to maximise detection of non-inferority) as well. The second analysis considers switch (and death) as treatment failure (switch is handled by a composite strategy). A third aim of estimation is the effect as if switch did not occur (switch is handled with the hypothetical strategy) under the scenario that switch is not related to patient's prognosis and patients that do switch at day d in randomised treatment X are not prognostically different from those that do not switch at (or before) day d in X. Therefore, patients that switched in randomised treatment X at day *d* are multiply imputed (for day *d* onwards) from the distribution of those that did not switch in X and are alive at day d. 2) All other intercurrent events (e.g. adverse events, discontinuation of randomised treatment without switch) are handled by treatment policy strategy (i.e. death/alive is observed regardless of the occurrence of other intercurrent events). If there are few switches, the additional analyses with composite or hypothetical strategy have limited value and will be omitted.

4.3.2 Secondary endpoints

1. <u>All-cause ICU mortality</u>

Relevance and rationale

Selecting mortality as a primary outcome measure holds substantial clinical significance both for healthcare professionals as well as patients and families. It is an unambiguous measure and exemplary parameter to inform medical decision-making, healthcare policies, and resource allocation.

Specific considerations

- Measurement variable: All-cause mortality will be considered; mortality will not be limited to infection-related mortality.
- Participant level analysis metric: final outcome – dead or alive.
- Summary measure: proportion of patients that died.
- Time point: at ICU discharge.
- intercurrents events and their handling: same as all-cause mortality

2. All-cause hospital mortality

Relevance and rationale

Selecting mortality as a primary outcome measure holds substantial clinical significance both for healthcare professionals as well as patients and families. It is an unambiguous measure and exemplary parameter to inform medical decision-making, healthcare policies, and resource allocation.

Specific considerations

- Measurement variable: All-cause mortality will be considered; mortality will not be limited to infection-related mortality.
- Participant level analysis metric: final outcome – dead or alive.
- Summary measure: proportion of patients that died.
- Time point: at hospital discharge.
- intercurrents events and their handling: same as all-cause mortality

3. New colonization or infection with a multi-resistant organism (MRSA, VRE, MDR *P. aeruginosa*, CRE, ESBL Enterobacterales, *Acinetobacter baum*annii) or C. difficile diarrhea/infection up to 28 days post inclusion

Relevance and rationale

The importance of MDR pathogens causing infections in critically ill patients cannot be underestimated. In this study, the effect of the two different antimicrobial regimens is also evaluated by their ability to influence the emergence of these pathogens. Infections from resistant strains can lead to extended hospital stay, increased cost, and elevated mortality rate. Also, *C. difficile* infection or diarrhea as a potential health outcome underscores the broader implications of antimicrobials on gut flora – and is a frequent concern in critical care. Consequently, assessment of new colonization or infection caused by these specific MDR organisms provides a complete picture of the impact of an antimicrobial regimen ensuring a comprehensive comparison between the treatment strategies under study.

Specific considerations

- Measurement variable: Colonization with or infection from a multidrug resistant organism (MRSA, VRE, MDR *P. aeruginosa*, CRE, ESBL Enterobacterales, *Acinetobacter baum*annii) or C. difficile.
- Participant level analysis metric: presence or absence of
  - infection caused by...
  - colonization with...

  ... each individual pathogen listed during the 28 days after enrolment.
- Summary measure: proportion of patients with new infection or colonization with the pathogens listed.
- Time point: at Day 28 after inclusion.
- intercurrent events and their handling: similar to all-cause mortality.

4. Antimicrobial free days

Relevance and rationale

At its core, the number of days a patient remains both alive and free from antimicrobials within a 28-day window measure combines the dual imperatives of any antimicrobial therapy: ensuring patient survival and curbing antimicrobial exposure. These objectives capture the essence of contemporary antimicrobial therapy. A treatment strategy that allows more days without antimicrobials not only signifies its efficacy but also resonates with the overarching principles of antimicrobial stewardship (AMS). AMS focuses on more targeted and shorter courses, reducing the risk of antimicrobial-induced complications and enhancing a patient's overall quality of life. Beyond immediate clinical outcomes, fewer antimicrobial days also hint at economic advantages, as well as lower AMR development.

Specific considerations

- Measurement variable: Every day the patient is alive and not receiving any antimicrobial therapy (either study-related antimicrobial therapy or other antimicrobials).
- Participant level analysis metric: number of days alive and without any antimicrobial therapy in the 28 days after inclusion.
- Summary measure: median, mean.
- Time point: Day 28 after inclusion.
- intercurrent events and handling: the same as for all-cause mortality with the following clarifications. In the composite strategy for switch, days at or after switch are counted as failure days (like death and antimicrobial use). In the hypothetical strategy, the scenario that 'patients that switch at day d in randomised treatment X have the same prognosis as patients that do not switch at (or before) day d in X' translates as follows. The number of days alive and antimicrobial free for a patient that switches at day d in randomised X is multiply imputed from the distribution of patients in X that are similar up to day d, but do not switch (i.e. observations at and after switch are considered missing and multiply imputation is performed for each randomised treatment separately). If there are few switches, the additional analyses with composite or hypothetical strategy have limited value and will be omitted.

5. Recurrence of infection

Relevance and rationale

Recurrence of infection is a pivotal metric of therapeutic efficacy and microbial persistence. It may point to problems in antimicrobial exposure, both in terms of dose and duration and is therefore a particularly relevant outcome in this study. From a broader perspective, recurrent infections demand increased resource allocation, including additional diagnostics, prolonged hospitalization, and repeated therapeutic interventions contribute to escalating costs. Beyond the economic implications, recurrence rates also provide an objective measure of patient morbidity.

Specific considerations

- Measurement variable: occurrence of infection with the same pathogen at the same infection site for which the study-related antimicrobial therapy was started occurring within 7 days after cessation of the study related antimicrobial therapy, with or without acquisition of resistance against the AB used in the first treatment course.
- Participant level analysis metric: final value (absent or present).
- Summary measure: proportion of patients with at least one recurrence.
- Time point: Day 28 after inclusion.
- intercurrent events: as all-cause mortality with the following clarifications, as switch occurs before cessation of therapy. For the composite strategy for switch, switch is considered treatment failure similar as recurrence. For the hypothetical strategy for switch, patients that switched in randomised treatment X are imputed recurrence from the distribution of recurrence of those that did not switch in X. If there are few switches, the additional analyses with composite or hypothetical strategy have limited value and will be omitted.

6. Toxicity

Relevance and rationale

Toxicity is critically important as an outcome measure in this study. Evaluating toxicity allows us to ensure that the intervention does not harm the patient and allows for a comprehensive evaluation of the benefit/risk ratio of the HIT-HARD strategy. It is an endpoint that is critical for clinical decision-making.

Specific considerations

- Measurement variable: occurrence of toxicity during study-related antimicrobial therapy.
  - Toxicity will be defined as occurrence of nephrotoxicity, neurotoxicity, hepatotoxicity or haematological toxicity:
    - a) Neurotoxicity: documented seizure activity.
    - b) Nephrotoxicity: an increased serum creatinine x 1.5 or estimated glomerular filtration rate decrease > 25% or urine output < 0.5 mL/kg/hr over 6 hours.
    - c) Hepatotoxicity: liver function test ratios according to the Roussel Uclaf Causality Assessment Method.

- d) Haematological toxicity: thrombocytopenia (platelet count <50 x 109/L) or neutropenia (neutrophil count ≤0.5 x 10^9/L).

- Participant level analysis metric: final value (absent or present).
- Summary measure: proportion of patients with toxicity.
- Time point: .End of therapy + 24 hours. Intercurrent events: switch will be handled by a while on treatment strategy + 1 day (meaning that all tox that occurs up to including one day after the day of the switch will be ascribed to the originally started treatment); , all other intercurrent events will be handled by treatment policy.

7. Health related quality of life (EQ-5D-5L measured at D90)

Relevance and rationale

Measuring quality of life provides a comprehensive view of the patients' well-being, and is inherently patient-centered. It allows to gain insights into both the benefits as well as unintended consequences of any intervention. It plays a significant role in determining the health economic evaluation when combined with cost data.

Specific considerations

- Measurement variable: At baseline the EQ-5D-5L questionnaire will be used and completed by the patient or if a patient is unconscious, EQ-5D-5L questionnaire will be completed by a next of kin. If at baseline no proxy is available, this will be collected when the patient is clinically stable enough to provide a reliable response.
- At day 28 the EQ- 5D-5L will be obtained directly from the patient via a face to face meeting. If a patient has been discharged from the hospital, this will be obtained via a telephone call, unless the patient has died.
- At day 90 the EQ-5D-5L will be obtained directly from the patient via a telephone call, unless the patient has died. Participant level analysis metric: EQ-5D-5L score on day 90 post enrolment.
- Summary measure: median, mean.
- Time point: Day 90 after inclusion.
- Intercurrent events: the same as for all-cause mortality with the following clarifications given amongst others that if switch occurred, it will have occurred before the D28 or D90 measurements. In the composite strategy for switch, EQ-5D-5L at day d after switch in randomised treatment X will be multiply imputed from the 25% worst EQ-5D-5L across both treatments at day d. In the hypothetical strategy, the scenario that 'patients that switch have the same prognosis as patients that do not switch X' translates as follows. The EQ-5D-5L at day d for a patient in randomised treatment X that switched is multiply imputed from the distribution of patients in X that did not switch (i.e. observations of patients that switched are considered missing at D28 and D90 and multiply imputation is performed for each randomised treatment separately). If there are few switches, the additional analyses with composite or hypothetical strategy have limited value and will be omitted.

8. Exposure

Relevance and rationale

Measuring antibiotic exposure (by measurement of patient plasma samples) will provide insights into exposure following the used dosing regimens, and the interpatient variability in exposure.

This part of the study is not mandatory for all sites. If not feasible, the site can opt out for this element.

9. Clinical cure

Relevance and rationale

While less important than mortality, clinical cure from infection is an essential outcome for both patients and healthcare workers. Failure to cure an infection is associated with increased antimicrobial use, prolonged length of stay in the ICU and in the hospital, requiring increased resources. The definition of clinical cure used is not subjective.

Specific considerations

- Measurement variable: Clinical cure, which will be defined as follows:
    - Clinical cure will be defined as the completion of the beta-lactam antimicrobial treatment course without recommencement of antimicrobial therapy within 48 hours of cessation. For the purposes of evaluating clinical cure, change of antimicrobial therapy (i.e., either escalation or de-escalation) for the same indication for which the beta-lactam antimicrobial was commenced is considered part of the antimicrobial treatment course.
    - Participants discharged from hospital within 14 days following inclusion will be considered to meet the definition of clinical cure. However, if a participant is readmitted within 14 days of inclusion, then the participant will be assessed against the definition of clinical cure as above, using information available at readmission.
    - Participants who die while receiving study antimicrobial therapy or when study antimicrobial therapy is ceased in the setting of death being considered imminent and inevitable, will be assessed as not meeting the criteria for clinical cure.
- Participant level analysis metric: final outcome (present, absent, or indeterminate).
- Summary measure: proportion of patients with clinical cure
- Time point: End of therapy + 2 days
- intercurrent events: as recurrence of infection with the following clarifications. In the composite strategy for switch, switch is considered treatment failure similar as non-cure. In the hypothetical strategy for switch, patients that switched in randomised treatment X are imputed recurrence from the distribution of recurrence of those that did not switch in X. This will be done by category meaning: patients that switched and completed a treatment course will be imputed from the distribution of those that did not switch and completed course; patients that switched and were discharged with 14 days will be imputed from the distribution of those that did not switch and were discharged within 14 days; patients that switched and deceased are imputed from the distribution of those that did not switch and deceased. In case insufficient patients that did not switch are available in a category, the categories will be combined. If there are few switches, the additional analyses with composite or hypothetical strategy have limited value and will be omitted.

10. ICU length of stay

Relevance and rationale

LOS provides a quantitative insight into treatment efficacy: shorter durations often correlate with optimal therapeutic outcomes, whereas extended stays may indicate treatment complications or suboptimal responses. Beyond being a patient-centered outcome, LOS serves as an economic measure as well, reflecting the cost-efficiency of healthcare delivered.

Specific considerations

- Measurement variable: duration of ICU stay.
- Participant level analysis metric: number of days spent in the ICU after enrolment in the study, up to day 90 after inclusion.
- Summary measure: median, mean
- Time point: Day 90 after inclusion.
- intercurrent event: 1). switch will be handled similar to all-cause mortality with the following clarifications. In the composite strategy for switch at day d, LoS after day d will be multiply imputed from the 25% worst LoS across both treatments that are at least d days. In the hypothetical strategy for switch at day d in randomised treatment X, LoS will be multiply imputed from the distribution of LoS of patients that are at least d days in in randomised treatment X. 2). death. Death will be handled primarily by a while-alive strategy. This is motivated by the economic analysis (costs stop after death). From a clinical point of view, ICU stay cannot be interpreted in isolation and has to be interpreted together with ICU death. 3). all other intercurrent events handled via treatment policy.
  If there are few switches, the additional analyses with composite or hypothetical strategy for switch have limited value and will be omitted.

11. Hospital length of stay

Relevance and rationale

LOS provides a quantitative insight into treatment efficacy: shorter durations often correlate with optimal therapeutic outcomes, whereas extended stays may indicate treatment complications or suboptimal responses. Beyond being a patient-centered outcome, LOS serves as an economic measure as well, reflecting the cost-efficiency of healthcare delivered.

Specific considerations

- Measurement variable: duration of hospital stay.
- Participant level analysis metric: number of days spent in the hospital after enrolment in the study, up to day 90 after inclusion.
- Summary measure: median, mean
- Time point: Day 90 after inclusion.
- Intercurrent events: similar as ICU stay

12. Organ support free days

Relevance and rationale

“Days alive and free of organ support" is a particularly pertinent outcome measure in studies comparing different antimicrobial strategies, especially in critically ill populations. While survival is undeniably the ultimate desired outcome, quality of life and functional status during survival are equally vital. This metric not only quantifies survival but also the patient's independence from invasive organ support, offering a more comprehensive view of patient well-being. The need for organ support often indicates the severity of the infection or the extent of organ dysfunction. By measuring days alive and free of such support, the study effectively gauges the relative efficacies of the two antimicrobial strategies in managing severe infections or preventing their progression. Moreover, extended durations of organ support, such as mechanical ventilation or renal replacement therapy, have significant cost implications. By reducing the days on such support, an antimicrobial strategy could potentially offer cost-saving benefits, as well as reduce the risks associated with organ support intervention. Also from a patient perspective, this outcome holds great value – faster recovery and less discomfort.

Specific considerations

- Measurement variable: Every day the patient is alive and not receiving any organ support (either mechanical ventilation, kidney replacement therapy or vasopressors/inotropies).
- Participant level analysis metric: number of days alive and without any organ support in the 28 days after inclusion .
- Summary measure: median, mean.
- Time point: Day 28 after inclusion.
- intercurrent events: similar to antimicrobial free days

13. DDDs and DOTs

Relevance and rationale

DDDs and DOTs are quantitative metrics of antimicrobial use and are the most often used as standardized metrics to measure and compare populations worldwide, advocated by WHO. While they do not necessary reflect the quality of prescribing, DDDs and DOT express the antimicrobial “pressure” in a patient and in a unit (when expressed as total use per number of patient days/admissions) and are as such strongly related to the development of resistance.

Specific considerations

- Measurement variable: Defined Daily Dose; Days of Therapy.
- Participant level analysis metric: number of Defined Daily Doses of treatment received during the first 28 days after inclusion; DOT: total numbers of days of therapy during the first 28 days after randomisation (NB if a patient received two different types of antimicrobials on one day, the day counts double).
- Summary measure: median, mean per patient.

- Time point: day 28 after inclusion.
- intercurrent events: 1). switch is handled similar to all-cause mortality with the following clarifications. For switch handled by a composite strategy, days at or after switch are considered failure so as days of therapy and full DDD. In the hypothetical strategy handling of switch, DOT and DDD of a patient that switches at day d in randomised X is multiply imputed from the distribution of patients in X that are similar up to day d, but do not switch (i.e. observations at and after switch are considered missing and multiply imputation is performed for each randomised treatment separately). 2). death. Death will be handled primarily by a while-alive strategy. This is motivated by the economic analysis (cost stop after death). From a clinical point of view, DOT and DDD cannot be interpreted in isolation and have to be interpreted together with death. 3). all other intercurrent events handled via treatment policy.
  If there are few switches, the additional analyses with composite or hypothetical strategy for switch have limited value and will be omitted.

5 TRIAL DESIGN

The HIT-HARD study is a prospective, non-inferiority, multinational, multicentre, cluster-randomized, cross-over, low-intervention study investigating the efficacy of short course, high dose antimicrobial treatment (HIT-HARD strategy) for patients with pneumonia (community acquired pneumonia (CAP), hospital acquired pneumonia (HAP), ventilator associated pneumonia (VAP)), intra-abdominal infection (IAI) or bloodstream infection (BSI) with conventional dose and duration antimicrobial therapy (CONTROL strategy).

Hospitals will be randomized to the sequence: CONTROL strategy – 'HIT HARD strategy' or the reverse, in two consecutive periods of 15 months. Allocation of each hospital to start with short course, high dose or conventional treatment will be generated per computer at random.

Patients will be treated with either regimen from the start of antimicrobial therapy; a maximum of 12 hours of study antimicrobial is allowed prior to enrolment in the trial.

Dosing regimens.
The HIT-HARD and CONTROL dosing regimens are summarized in the tables below:

1. **HIT-HARD strategy empirical dosing regimen and suggested dose adaptation from day 2**

	Loading dose*	**Daily dose (immediately after loading dose) ****	**Reference for dosing regimen**	Suggested dose based on kidney function (eGFR ****) from 24h onward
Ceftriaxone	**2000mg*****	**4000mg /24h *****	- EUCAST (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_14.0_Breakpoint_Tables.pdf) - Dutch national guideline (https://adult.nl.antibiotica.app/nl/node/501098) - PK studies (7, 36, 37)	No adjustment
Cefotaxime	**4000mg**	**12000mg/24h**	- Dutch national guideline (https://adult.nl.antibiotica.app/nl/node/1154)(https://swab.nl/nl/exec/file/download/82) - PK study (7)	eGFR <10: 6000mg/24h GFR>130: 15000mg/24h
Cefuroxime	**3000mg**	**6000mg /24h**	- Dutch national guideline (https://adult.nl.antibiotica.app/nl/node/1215) - PK studies (7, 38)	eGFR 10-30: 4000mg/24h eGFR <10: 2000mg/24h GFR>130: 8000mg/24h
Piperacillin/ tazobactam	**8000/1000 mg**	**20000/2500mg/ 24h**	PK studies (29-35)	eGFR 30-50: 16000/2000mg/24h eGFR <30: 12000/1500mg/24h GFR>130: 24000/3000mg/24h
Meropenem	**2000mg**	**6000mg /24h**	- EUCAST (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_14.0_Breakpoint_Tables.pdf) - Dutch national guideline https://adult.nl.antibiotica.app/node/1557 PK studies (7, 23, 24, 24-28)	eGFR 30-50: 4000mg/24h eGFR 10-30: 2000mg/24h eGFR <10: 1000mg/24h GFR>130: 8000mg/24h

**Loading dose is the starting dose of an antibiotic that is given intermittent over 30-60 minutes.*
***Within one hour after completing the administration of the loading dose.*
****Due to the long half-life of ceftriaxone, this antimicrobial can also be administered as intermittent infusion, i.e. 2000mg q12h.*
**** eGFR calculation is done per local practice at site with preferable an 8 hours urine creatinine clearance, but if not available eGFR is deducted from serum creatinine.

2. **CONTROL strategy empirical dosing regimen and suggested dose adaptation from day 2**

	Loading dose*	**Daily dose**(immediately after loading dose) *****	Suggested dose adjustment based on kidney function (eGFR*****) from 24h onward
Ceftriaxone	**2000mg**	**2000mg/24h** ****	No adjustment
Cefotaxime	**2000mg**	**4000mg/24h**	eGFR <10: 1500mg/24h GFR>130: 4500mg/24h
Cefuroxime	**1500mg**	**4500mg/24h**	eGFR <30: 3000mg/24h eGFR <10: 1500mg/24h GFR>130: 6000mg/24h
Piperacillin/ tazobactam	**4000/500mg**	**16000/2000mg/24h**	eGFR 30-50: 12000/1500mg/24h eGFR <30: 8000/1000mg/24h GFR>130: 20000/2500mg/24h
Meropenem	**1000mg**	**3000mg/24h**	eGFR 30-50: 2000mg/24h eGFR 10-30: 1000mg/24h eGFR <10: 500mg/24h GFR>130: 4000mg/24h

**Loading dose is the starting dose of an antibiotic that is given intermittent over 30-60 minutes.*
*** Based on the licensed dose and current guidelines for the included infections.*
****Within one hour after completing the administration of the loading dose.*
*****Due to the long half-life of ceftriaxone, this antimicrobial can also be administered as intermittent infusion, i.e. 2000mg q24h.*
****** eGFR calculation is done per local practice at site with preferable an 8 hours urine creatinine clearance, but if not available eGFR is deducted from serum creatinine.*

Dose adaptation
The daily dose of the antimicrobial may be adapted after the first 24 hours based on kidney function – as decided by the treating physician. The table above summarizes the suggested dose adaptations.
Dose adaptation based on therapeutic drug monitoring is **not** allowed in the study.

Duration of the treatment
The duration of antimicrobial therapy can range from 3 to 5 days (72 hours to 120 hours of effective antimicrobial therapy) in the HIT-HARD strategy, and from 6 to 9 days (144 to 216 hours of antimicrobial therapy) in the CONTROL strategy. Exact duration will be decided by the treating physician within the timeframes specified above.

Antimicrobial de-escalation and escalation

Antimicrobial de-escalation (ADE) is not encouraged in patients enrolled in the study in order to be able to estimate the effect of the treatment in both groups. Particularly in case of the HIT-

HARD strategy, the duration of therapy is too short to justify ADE. If the treating physician wishes to perform ADE, this is allowed as detailed below:

- **Intervention group**: change therapy after at least 72h of empirically started beta lactam therapy; if a beta-lactam is chosen as de-escalation therapy (within the choice of drugs studied in this trial: ceftriaxone, cefuroxime, cefotaxime, piperacilline-tazobactam, meropenem) the HITHARD dose is to be used (e.g. switch from meropenem to ceftriaxone); for other beta-lactams, standard dosing can be used.
- **Control group**: change therapy after at least 72h of empirically started beta lactam therapy.

6 STUDY SETTING

This study will be conducted at 7 ICUs in Belgium and 7 ICUs in the Netherlands, in both university and non-university teaching hospitals.

We aim to enrol 1282 patients to include 641 patients per strategy.

Sites will be selected based on a feasibility check performed by the sponsor to determine if a site qualifies.

Sites will be invited to include patients for all antimicrobials under study but may opt to exclude up to 1 study antimicrobial. This allows study sites to participate in the study should the local PI not agree with the proposed dosing and/or duration schemes of 1 particular study antimicrobial.

The eligibility criteria for participating centres includes:

- PI and study team of the participating centre are qualified to perform all study tasks in accordance with all applicable laws and guidelines (e.g., the Belgian Law of 07/05/2017 and the ICH E6 (R2) Good Clinical Practice Guidelines).
- Commitment to include at least 3 patients per month in the study.

Patients who are admitted at the ICU will be recruited by the local PI, SI and/or another member of the study team.

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

In case a patient is incapable of giving consent, consent may be provided by a patient's legal representative or an impartial witness/interpreter.

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

- Age ≥18 years
- Patient with (suspicion of) community acquired pneumonia (CAP) or hospital acquired pneumonia (HAP) or ventilator acquired pneumonia (VAP) or intra- abdominal infection (IAI) or bloodstream infection (BSI) for which one of the following antimicrobials has been prescribed or has been commenced: ceftriaxone, cefotaxime, cefuroxime, piperacillin- tazobactam or meropenem (the study related antimicrobials) *.
    - Treatment may be empirical or targeted (I.e. based on culture results), but not prophylactic
- Patient must be admitted to the ICU and expected to be hospitalized in the ICU until at least the day after tomorrow.
- Administering study related antimicrobials using either a short course, high dose treatment or conventional dose and duration treatment, are considered appropriate for the patient **.
- One or more organ dysfunction criteria in the previous 24 hours and ongoing
    - MAP < 60mmHg for at least 1 hour.
    - Vasopressor required for > 4 hours.
    - Respiratory support using supplemental high flow nasal oxygen, continuous positive airway pressure, bilevel positive airway pressure or invasive mechanical ventilation for at least 1 hour.
    - Serum creatinine concentration > 220μmol/L or >2.49 mg/dL.

Notes

** The beta lactam antimicrobial is considered the pivotal antibiotic in a multidrug strategy: co-administration of other – non-study – antibiotics in standard dosage, e.g. to expand the spectrum of the empirical therapy (e.g. vancomycin, aminoglycosides), or because they are recommended in guidelines (e.g. macrolides) is allowed; these antimicrobials will be dosed as per local practice, and data will be collected.*

*** Patients with infections that (according to prevailing guidelines) require a higher than standard dose, or a longer duration, e.g. endocarditis, Staphylococcus aureus bacteraemia or prosthetic joint infection, osteomyelitis... (non-limitative list) are therefore not to be included. Also patients in who(m) source control is evidently not achieved, cannot be included. Patients may be included but then need to 'drop out' because one of the above-mentioned diagnoses becomes apparent during the course of therapy e.g. S. aureus is cultured from blood in a patient with CAP. This will lead to secondary exclusion of the patient ("drop out").*

7.2 Exclusion criteria

- Patient is known or suspected to be pregnant.
- Patient has received the study related antimicrobial for more than 12 hours prior to inclusion in the study.
- Patient has a proven severe allergy for one of the study antibiotics.*
- The attending physician or patient or legal representative is not committed to full active treatment. **
- The patient is treated for an infection that requires a higher than standard dose or longer than the CONTROL strategy. ***
- The patient has previously been enrolled in the HIT-HARD study.
- Use of the study related antimicrobial as *prophylactic* therapy administered as the IV component of selective digestive decontamination (SDD) strategy, without proven infection. However, oral / enteral components of SDD may be used in patients at the time of inclusion in the HITHARD study, as long as the pivotal study antibiotic is administered because of an infection as per the inclusion criteria. A patient who meets criteria for an ICU acquired (nosocomial) infection after the 4 day period of IV component of prophylactic selective digestive decontamination (SDD), is eligible for inclusion
- Patient is requiring any form of renal replacement therapy at the time of randomisation, including renal replacement therapy for chronic kidney disease.

Notes

**In case of a documented non-severe (suspected) allergy for one of the study antibiotics: choice of antibiotic according to local protocol, on discretion of the treating physician*.

*** Limitation of cardiopulmonary resuscitation (CPR) only is not an exclusion criterium.*

**** Patients with infections that require a (according to prevailing guidelines) higher than standard dose, or require a longer duration, e.g. endocarditis, Staphylococcus aureus bacteraemia or prosthetic joint infection, osteomyelitis... (non-limitative list) are therefore not to be included. Also patients in who(m) source control is evidently not achieved, cannot be included. Of course, some patients may be included but then need to 'drop out' because one of the above-mentioned diagnoses becomes apparent during the course of therapy e.g. S. aureus is cultured from blood in a patient with CAP. This will lead to secondary exclusion of the patient ("drop out").*

8 TRIAL PROCEDURES

The trial is considered started upon the first act of recruitment of a potential subject. For this trial this is considered as the date of first screening.

The start of the trial shall be notified by the sponsor in CTIS within 15 calendar days.

The first visit of the first subject (i.e. when the first subject or his/her legally designated representative signs his/her first informed consent to participate in the trial) (FVFS) will also be notified to the CA/IEC within 15 calendar days.

8.1 Trial randomisation

This is a cluster-randomised, cross over study.

Hospitals will be randomized to the sequence: regular treatment – 'HIT HARD therapy' or the reverse, in two consecutive periods of 15 months. Allocation of each hospital to start with the HIT-HARD strategy or CONTROL strategy will be generated per computer at random.

Randomisation will be done prior to the initiation of the study, and participating sites will be informed of the results of the randomisation prior to enrolling any patient.
As this is a cluster cross-over trial, the balance in site (cluster) characteristics is adjusted for by design. Nevertheless, balance on country (Belgium vs Netherlands) and type (university vs non-university) will be promoted. As stratification would restrict the randomisation too much (2 x 2 = 4 strata in which 1:1 randomisation is applied, while only 14 hospitals are available, so 2 or 3 clusters per stratum, i.e., optimally 2^4 =16 randomisation possibilities), a constrained randomisation procedure will be applied. Of the "14 choose 7" (=3432) possible randomisation of 7 hospitals to HITHARD in the first period (and the remaining 7 hospitals CONTROL in the first period), the imbalance in country plus type will be calculated and from the possible randomisations with minimal imbalance, at random one will be chosen. If number of possible randomisation with minimal imbalance is too small, type will be dropped and the imbalance minimization procedure with random choice will be repeated.
In the month preceding the transition to a new intervention, the research team will provide retraining to the participating sites. The training process is designed to ensure that study teams are fully informed and capable of effectively implementing the new study intervention when it is introduced.

Sites will be invited to attend an online training session led by the chief investigator, co-investigator(s), and project manager(s).

The study team refers to individuals responsible for conducting the study on-site, with their roles clearly documented in the delegation log. This includes the local principal investigator, sub-investigator(s), and research nurses or research coordinators.

Other stakeholders are welcome to join the training sessions; however, it is the responsibility of the local investigator to ensure that the information is further disseminated within the intensive care unit to those for whom it is relevant.

The trial management team will play a central role in organizing and overseeing the training process by preparing training slides and allowing sufficient time during the session for questions and discussions to address any uncertainties.

Given the design of the study, access to any web-based randomization system, access outside of office hours or in emergencies is not applicable.

After inclusion in the study, the study assigned regimen should start as early as possible, and always within 12 hours after initiation of the antibiotic.
The study assigned dose and administration method (continuous infusion) does no longer need to be applied after ICU discharge. However, the duration of therapy as per HIT HARD protocol should be advised to the treating physicians after discharge from the ICU.

8.2 Blinding

The PI, research nurses, research team and trial participants are unblinded to the allocation of hospital cluster randomisation.

8.3 Unblinding

Not applicable

8.4 Recruitment

There is no compensation or reimbursement of travel costs for participants in the study. Follow up visits will be done per telephone call.

8.4.1 Study participants identification

During the start-up phase of the study, the chief investigator, co-investigators, project managers and local investigator(s) will identify the most efficient workflow and personnel for eligibility screening per ICU. Personnel will be team members from the clinical and/or study nurse team, designated by the local principal investigator. The study team will discuss the patient's eligibility with the treating physician, who has the authority to review the patient's medical file.

The following data to verify eligibility will be collected before inclusion from each trial participant:

- Age
- Nationality
- Type and source of infection
- Antimicrobial treatment
- Admission details
- Organ dysfunction
- Known allergy to one of the study related antibiotics
- DNR and/or limitations of care
- Whether a patient was previously enrolled in the study
- Renal replacement therapy

The the study site Principal Investigator (PI), Sub- Investigator (SI) or delegated personof the participating ICU will check and sign off for eligibility after eligibility was discussed with the treating physician.

A poster and plastic reminders with study objectives, in- and exclusion criteria in Dutch and French will be available at the participating intensive care units. Whenever possible, this information sheet will also be communicated through banners on the ICU computers. Progress or recruitment issues will be discussed during internal ICU research meetings.

8.4.2 Screening

Screening will be done based on the eligibility criteria of the trial. There are no additional screening procedures.

8.5 Informed Consent

The local study site Principal Investigator (PI) at each participating site assumes overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice and Declaration of Helsinki. If delegation of consent is acceptable, then details should be provided in the delegation log. Only the study site Principal Investigator (PI), Sub-Investigator (SI) or delegated person is authorised to obtain informed consent.

Consent for participation to the CONTROL vs. HIT-HARD regimen does not need to be obtained prior to start of therapy (deferred consent) but must be sought at the earliest convenience. Deferred consent is only applicable for proceeding with the study intervention. No data or samples will be collected before obtaining informed consent from the patient and/or their legal representative. Consent should be obtained at the earliest opportunity, meaning as soon as the patient or legal representative is able to provide it, but no later than before the blood sample is collected.

If a patient is unconscious, inadequate or unable to provide consent due to his medical condition, illness or sedation, consent should be obtained from the legal representative. If the legal representative cannot be physically present at the hospital, informed consent may be obtained via phone with the participation of an impartial witness to the call. The impartial witness will sign the ICF until the patient regains consciousness or the legal representative is able to attend the hospital in person.

A conscious patient means a patient that is adequate to understand the information given. When a patient is unconscious or not competent to understand the given information, ICF cannot be obtained from this patient.

An impartial witness is a neutral, independent person who is not involved in the study and has no conflict of interest. This individual ensures that the informed consent process is conducted ethically and transparently. The witness can be a hospital staff member not associated with the study, a patient advocate, or another independent individual who can confirm that consent is given voluntarily.Patients, legal representatives and/or impartial witnesses from potentially eligible patients will receive an oral explanation of the study as well as a Participant Information Sheet, providing a plain language text in Dutch or French.

Subjects or their legal representative will be informed that participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorised persons without violating

the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations.

After this explanation, a written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access.

The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After having obtained the consent, a copy of the ICF must be given to the subject.

In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent. Whenever ICF has been obtained of a legal representative, PI or delegated person should inform the patient about the study as soon as she/he regains capacity in order to obtain ICF of the patient.

The following information should be added to the electronic patient dossier (EPD):

- which version of the ICF was obtained;
- date ICF was obtained;
- who signed the ICF;
- if sufficient time has been given to consider participation into the trial;
- which investigator, sub investigator or delegated person obtained ICF with the date of signature;
- if a copy was provided to the patient;

8.6 Trial assessments

Eligible patients will be enrolled in the study, and patients will be treated according to the strategy that the hospital was randomized to at the moment of patient enrolment.

Given the cluster cross-over design, the estimation is based on within-cluster comparisons (of their HITHARD period and CONTROL period) and sufficient patients in each cluster in each period are needed. Therefore, the aim is at least 20 patients per site per period with at least 630 per period in total across the sites. Once this criterion is reached in the first period, but at the latest 15 months after start of the period, the next period will start. The same criterion is used for the second and last period.

Study participants will be followed up to 90 days post- inclusion or to death, whichever is sooner.

8.6.1 screening

Patients will be screened every day and evaluated to assess eligibility for the study.

Screen failures i.e. study participants who do not meet eligibility criteria at time of screening may be eligible for rescreening from the moment a study related antibiotic therapy is prescribed for another infection, at a later stage.

A screening log will be kept in a separately REDCap database, other than the eCRF REDCap per participating site to monitor recruitment and report the size of the patient population from which eligible patients have been recruited.
Patient demographics, basic laboratory results (leukocytes, CRP, serum creatinine), severity of illness scores and information on infection site will be used to screen study participants for eligibility.

8.6.2 Baseline and baseline data

Patient characteristics, admission diagnosis and clinical information will be collected to assess baseline balance between each treatment group. Details on the site or sites of presumed or known infection will be obtained. Clinical information will allow calculation of the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores that classify illness severity in ICU patients.

The following data will be collected at baseline for all participants:

- Admission data:
  - Primary admission diagnosis
  - Date and time of admission to hospital
  - Date and time of ICU admission
  - Provenance of admission (ER, hospital ward OR (emergency or elective surgery), another hospital, another ICU
- Demographics (age, sex at birth, weight, height)
- Apache score
- Organ dysfunction criteria (SOFA score components)
  - PF ratio
  - MAP
  - Creatinine
  - Bilirubin
  - Platelet count
  - GCS
  - Received vasopressor or inotropes in the previous 24h
- Site of infection & organism(s):
  - Date and time of sample collection
  - Causative organism(s) cultured (if available)
  - Susceptibility of micro-organisms to study-related beta-lactam antimicrobial (if available)
- Antimicrobial therapy (drug name(s), dose, date and time started)
- EQ-5D-5L (evidently not at moment of admission but within the period of non-acute illness prior to admission and before current sepsis). At baseline the EQ-5D-5L questionnaire will be used and completed by the patient or if a patient is unconscious, EQ-5D-5L questionnaire will be completed by a next of kin. If at baseline no proxy is available, this will be collected when the patient is clinically stable enough to provide a reliable response.

8.6.3 Treatment phase

HIT- HARD strategy (day 0 to max day 5)

During the treatment period of up to 5 days, the following assessments will be performed daily:

- Antimicrobial therapy
- Organ support free day
- Renal replacement therapy
- Antimicrobial days (DOT and DDD's)
- Adverse events
- Serious adverse event
- Protocol deviations

Control strategy (day 0 to max day 9)

During the treatment period of up to 9 days, the following assessments will be performed daily:

- Antimicrobial therapy
- Organ support free day
- Renal replacement therapy
- Antimicrobial days (DOT and DDD's)
- Adverse events
- Serious adverse event
- Protocol deviations

At selected centers in both strategy groups a blood sample (EDTA tube of 3ml) to determine the exposure will be taken between 36 hours and 96 hours after study related antibiotic have been initiated.

8.6.4 End of therapy

HIT- HARD strategy

Patients will be treated for at least 3 days (72hours), maximum 5 days (120hours) according to the HIT- HARD strategy. At the latest the study related antimicrobial therapy must be ceased at hour 120.

Control strategy

Patients will be treated for at least 6 days (144hours), maximum 9 days (216 hours) according to the control strategy. At the latest the study related antimicrobial therapy must be ceased at hour 216.

Exact duration will be decided by the treating physician within the timeframes specified above.

A clinical cure evaluation should be performed 48hours after completion of the beta-lactam antimicrobial treatment course. End of therapy + 48hours.

At the end of therapy the following assessments will be performed:

- Antimicrobial therapy
- Toxicity
- Organ support free day
- Renal replacement therapy
- Antimicrobial days (DOT and DDD's)

- Adverse events
- Serious adverse event
- Protocol deviations
- Clinical cure

8.6.5 Follow up

Day 14

- Site of infection for which the study related beta-lactam antimicrobial therapy (at inclusion) was prescribed & causative organism(s):
  - Date and time of sample collection
  - Causative organism(s) cultured (if available)
  - Susceptibility or micro-organisms to study-related beta-lactam antimicrobial (if available)
- Antimicrobial therapy (drug name(s), dose, date and time started)
- Organ support free day
- Renal replacement therapy
- Antimicrobial days (DOT and DDD's)
- Adverse events
- Serious adverse event
- Protocol deviations

Day 28

If a patient is discharged from the hospital, this visit will be performed by a telephone call.

- Antimicrobial therapy (drug name(s), dose, date and time started)
- New colonization or infection with a multi- resistant organism or clostridioides difficile
- Recurrent infection
- Organ support free day
- Renal replacement therapy
- Antimicrobial days (DOT and DDD's)
- Antimicrobial free days
- ICU length of stay
- Hospital length of stay
- QOL EQ-5D-5L
- Adverse events
- Serious adverse event
- Protocol deviations

Day 90

If a patient is discharged from the hospital, this visit will be performed by a telephone call. Follow- up for the primary outcome will be until death or 90 days after randomisation, whichever comes first. At day 90, vital status, length of stay in the ICU; length of stay in the hospital, renal replacement therapy, date and cause of death will be recorded.

All trial assessments from screening to follow up are listed in the table of trial procedures.

8.6.6 Table of trial procedures

Procedures	**Visits**						
	Screening	**Baseline/ Inclusion**	**Treatment Phase**	**End of therapy**	**Follow Up**		
		V1: D0	V2: 48h-72h after start study related AB	V3: D3-5/6-9	V4: D14	V5: D28 (by telephone call) (+3days)	V6: D90 (by telephone call) (+3days)
Eligibility assessment	X	X					
Informed consent****		X					
ICU admission data*		X					
Demographic data*		X					
APACHE II score*		X					
SOFA score*		X					
Infection data (site and organism)*		X			X		
Antimicrobial therapy (drug and dose)		X	X	X	X	X	
All-cause mortality							X
QOL (EQ- 5D- 5L)**		X				X	X
Clinical cure				X			
New colonization or infection with a multi-resistant organism or *Clostridioides difficile**						X	

Recurrent infection*						X	
Toxicity*			X	X			
Organ support free days		X	X	X	X	X	
Renal replacement therapy			X	X	X	X	X
Antimicrobial days (DOT and DDDs)		X	X	X	X	X	
Antimicrobial free days						X	
ICU length of stay*						X	
Hospital length of stay*						X	
Adverse events and serious adverse events		X	X	X	X	X	X
Plasma exposure sample***			X				
Protocol deviations		X					

*Standard of care procedures

** At baseline the EQ-5D-5L questionnaire will be completed by the patient or if a patient is unconscious, EQ-5D-5L questionnaire will be completed by a next of kin. If at baseline no proxy is available, this will be collected when the patient is clinically stable enough to provide a reliable response. If a patient is discharged before Day 28 and/or Day 90 the EQ-5D-5L may be performed by a telephone call. (A time window of + 3 days is allowed for this visit)

***Plasma exposure sample: In selected centres one blood sample (EDTA tube of 3ml) will be obtained between 36 and 96 hours after the antibiotics have been initiated, attempt should be made to draw the blood sample as closest to 36h after antibiotics have been initiated.

****Consent for allocation to the CONTROL vs. HIT-HARD regimen does not need to be obtained prior to start of therapy (deferred consent) but must be sought at the earliest convenience.

8.7 Withdrawal criteria

Subjects are free to withdraw from participation in the trial at any time.

8.7.1 Discontinuation of trial intervention

An investigator may withdraw a subject from the trial intervention for the following reasons:

- Pregnancy
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the subject;
- Disease progression which requires discontinuation of the trial intervention;
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further trial intervention.

The participant and/or legal guardian of the patient can withdraw from trial intervention at any time. In this case, participants are asked and encouraged to still contribute to the routine-care data collection and collection of, in particular primary, endpoint data collection, However, participants are free to withdraw from data-collection all together by withdrawing from the trial (see below).

If the intervention is stopped early, the reason should be recorded in the participant's medical records and be reported on the appropriate CRF whether it is due to either the participant's, legal guardian's, or clinician's decision.

Antimicrobial de-escalation is not encouraged in the HITHARD protocol, to ensure proper comparison of the dosing strategies studied. If an excessive spectrum of antimicrobials is used, the treatment may be de-escalated. When de-escalation is used, an alternative HITHARD strategy antimicrobial may be preferred, using the relevant HITHARD dosing strategy for this antibiotic, after at least 72h of empirical therapy in both groups.

When patients are discharged from the ICU, the HITHARD dosing strategy will be stopped, and the local standard (both dose and infusion strategy) will be used for the remainder of the treatment. The duration of therapy as per the HITHARD protocol should be proposed to the treating physicians after ICU discharge.

All participants who stop randomised trial intervention will remain in the trial for follow-up unless the participant and/or legal guardian explicitly withdraws consent for data collection which should be documented in source documentation.

8.7.2 Withdrawal of consent (discontinuation of trial participation)

The participant and/or legal guardian may withdraw consent at any time during the study after inital consent was givenThe patient will receive the standard- of- care treatment from the moment of withdrawal of consent. All data collected until the moment of withdrawal will be kept in the study database and will be used in the trial analysis. No further data or samples will be collected. As written in the ICF data and/or samples already collected may be used to avoid misinterpretation of study results.

The details of withdrawal should be clearly documented in the participant's medical records and in the eCRF.

8.7.3 Refusal of deferred consent

The participant and/or legal guardian may refuse deferred consent (in this case no previous consent was received from the participant and/or legal guardian). Meaning that all randomised trial intervention will stop at the moment of refusal. No data or samples will be collected before obtaining informed consent from the patient and/or their legal representative. The patient will receive the standard- of- care treatment from the moment of refusal of deferred consent.
The detail of refusal of deferred consent should be clearly documented in the participant's medical records and through completion of the refusal of deferred consent form (if applicable).

8.7.4 Arrangements for study participants after their participation in the clinical trial ended

In case of a (serious) adverse event, every effort should be made to ensure proper follow-up within a reasonable time after in accordance with the nature and extent of the event.

Participants will be provided with the study team contact details and can reach out with any questions after the clinical trial ended.

The results of the study will be disseminated through the KCE and study website.

8.7.5 Loss to follow-up

A subject will be considered lost to follow-up if he or she is unable to be contacted by the trial site staff.

The following actions must be taken:

- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (i.e. three telephone calls and a certified letter to the subject's last known address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file;
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

8.8 End of trial

8.8.1 For an individual subject:

The subject has completed the trial when he or she has completed all phases of the study, including the last visit, as described in this protocol.

8.8.2 For the whole trial:

The end of recruitment of subjects shall be notified to the RA via the EMA (CTIS) within 15 calendar days after study completion. (End of recruitment)
Overall, the end of the trial is reached when the last visit of the last subject has occurred.

As soon as the whole trial has ended (cfr. the definition above), the RA shall be notified via the EMA (CTIS) within 15 calendar days.

A summary of the results of the trial will be submitted to the RA within 1 year from the end of the trial, irrespective of the outcome of the trial.

8.9 Trial duration

8.9.1 For an individual subject

The time that will be needed for a participant from his first visit to the last visit will be 3 months.

8.9.2 For the whole trial

The estimated time that will be needed for the whole study from the first participant's first visit until the last participant's last visit is 34 months.

9 TRIAL INTERVENTION / MEDICATION

9.1 Name and description of intervention(s)

In this study the intervention is a high dose treatment (≥150-200%) for a short duration (3-5days) with piperacillin- tazobactam, meropenem, cefotaxim, cefuroxim or ceftriaxone for treatment of patients in ICU with Community acquired Pneumonia (CAP), Hospital acquired pneumonia (HAP), Ventilator Acquired Pneumonia (VAP) and Intra-abdominal Infection (with adequate source control, IAI) or Bloodstream Infection (BSI). All used antibiotics have a marketing authorisation in the European Union and will be used within the authorised indication.

9.2 Piperacillin-tazobactam

The trial is investigating the active substance piperacillin-tazobactam (ATC-code J01CR05). Piperacillin-tazobactam has a marketing authorization and is labelled for use in children of ≥ 2 years old and adults. Vials for intravenous administration are available on the Belgian and Dutch market in 2g/250mg, 4g/500mg quantities of respectively piperacillin and tazobactam. The brand used for the study depends on the availability on site. The SmPC of piperacillin-tazobactam Fresenius Kabi© 2g/250mg (Fresenius Kabi nv – BE324073) and piperacillin-tazobactam Fresenius Kabi© 4g/500mg (Fresenius Kabi nv – BE324082) will be chosen for pharmacovigilance purposes for authorisation from the authorities.

9.2.1 General information

Also refer to	Summary of Product Characteristics (SmPC)

Name of the IMP	Piperacillin-tazobactam (ATC-code J01CR05)
Qualitative and quantitative composition	Each vials contains 2000 mg piperacillin (as the sodium salt) and 500 mg tazobactam (as the sodium salt) 4000 mg piperacillin (as the sodium salt) and 500 mg clavulanic acid (as the potassium salt)
Pharmaceutical form	Powder for solution for injection or infusion
Method of administration	intravenous
Authorised in the EU	Yes
Used within scope	No (HIT-HARD strategy uses higher dosing regimens than noted in the SmPC, yet are in line with standard of care cfr. Section 3)
Marketing authorisation holder	Depending on the brand
Marketing authorisation number(s)	
Manufacturer	
Distributor	
Responsible for batch release	

9.2.2 IMP rationale

Refer to Section 2 ‘rationale’ and Section 3 ‘Assessment and management of risk’.

9.2.3 Preparation, packaging and labeling of the IMP

As this is a low interventional trial the preparation and labelling of the antibiotics will be in accordance with the standard-of-care and in accordance with the SmPC. No additional packaging or additional labelling will be performed for this study.

9.2.4 Administration, dosage and dose frequency of the IMP

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.2.5 Permitted dose adjustments and interruption of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.2.6 Duration of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.2.7 Traceability, storage, return and destruction of the IMP

The beta-lactam therapy storage, supply, return and destruction will be according to the standard routine care of each ward. IMPs are obtained through the regular hospital pharmacy as part of the standard of care. Storage, return and destruction follow the local hospital SOP. Vials are stored at room temperature, with temperature monitoring conducted according to the local SOP. As this is a low interventional trial, no specific documentation (e.g. drug accountability) other than applicable in the routine care is required.

9.3 Meropenem

The trial is investigating the active substance meropenem (ATC-code J01DH02). Meropenem has a marketing authorization and is labelled for use in children of ≥ 3 months old and adults. Vials for intravenous administration are available on the Belgian and Dutch market in 500mg and 1g quantities. The brand used for the study depends on the availability on site. The SmPC of Meropenem Fresenius Kabi© 500mg (Fresenius Kabi nv – BE374087) and Meropenem Fresenius Kabi© 1g (Fresenius Kabi nv – BE374105) will be chosen for pharmacovigilance purposes for authorisation from the authorities.

9.3.1 General information

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Meropenem (ATC-code J01DH02)
Qualitative and quantitative composition	Each vial of powder for solution for injection or infusion contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem. Each vial of powder for solution for injection or infusion contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.
Pharmaceutical form	Powder for solution for injection or infusion
Method of administration	intravenous
Authorised in the EU	Yes
Used within scope	No (HIT-HARD strategy uses higher dosing regimens than noted in the SmPC, yet are in line with standard of care cfr. Section 3)
Marketing authorisation holder	Depending on the brand
Marketing authorisation number(s)	
Manufacturer	
Distributor	
Responsible for batch release	

9.3.2 IMP rationale

Refer to Section 2 ‘rationale’ and Section 3 ‘Assessment and management of risk’.

9.3.3 Preparation, packaging and labeling of the IMP

As this is a low interventional trial the preparation and labelling of the beta-lactam antibiotics will be in accordance with the standard-of-care and in accordance with the SmPC. No additional packaging or additional labelling will be performed for this study.

9.3.4 Administration, dosage and dose frequency of the IMP

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.3.5 Permitted dose adjustments and interruption of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.3.6 Duration of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.3.7 Traceability, storage, return and destruction of the IMP

The beta-lactam therapy storage, supply, return and destruction will be according to the standard routine care of each ward. IMPs are obtained through the regular hospital pharmacy as part of the standard of care. Storage, return and destruction follow the local hospital SOP. Vials are stored at room temperature, with temperature monitoring conducted according to the local SOP. As this is a low interventional trial, no specific documentation (e.g. drug accountability) other than applicable in the routine care is required.

9.4 Cefotaxim

The trial is investigating the active substance cefotaxim (ATC-code J01DD01). Cefotaxim has a marketing authorization in the European Union and is labelled for use in children of ≥ 0 days old and adults. Vials for intravenous administration are available on the Belgian and Dutch market in 1g quantities. The brand used for the study depends on the availability on site. The SmPC of Cefotaxim Noridem 0.5g (NORIDEM ENTERPRISES LTD - BE559884), Cefotaxim Noridem 1g (NORIDEM ENTERPRISES LTD - BE559893) and Cefotaxim Noridem 2g (NORIDEM ENTERPRISES LTD - BE559902) will be chosen for pharmacovigilance purposes for authorisation from the authorities.

9.4.1 General information

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Meropenem (ATC-code J01DD01)
Qualitative and quantitative composition	Each vial of powder for solution for injection or infusion contains cefotaxime sodium equivalent to 500mg/1g/2g of cefotaxime. Each gram of cefotaxime contains approximately 48mg (2.09mmol) of sodium.
Pharmaceutical form	Powder for solution for injection or infusion
Method of administration	intravenous
Authorised in the EU	Yes
Used within scope	No (HIT-HARD strategy uses higher dosing regimens than noted in the SmPC, yet are in line with standard of care cfr. Section 3)
Marketing authorisation holder	Depending on the brand
Marketing authorisation number(s)	
Manufacturer	
Distributor	
Responsible for batch release	

9.4.2 IMP rationale

Refer to Section 2 ‘rationale’ and Section 3 ‘Assessment and management of risk’.

9.4.3 Preparation, packaging and labeling of the IMP

As this is a low interventional trial the preparation and labelling of the beta-lactam antibiotics will be in accordance with the standard-of-care and in accordance with the SmPC. No additional packaging or additional labelling will be performed for this study.

9.4.4 Administration, dosage and dose frequency of the IMP

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.4.5 Permitted dose adjustments and interruption of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.4.6 Duration of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.4.7 Traceability, storage, return and destruction of the IMP

The beta-lactam therapy storage, supply, return and destruction will be according to the standard routine care of each ward. IMPs are obtained through the regular hospital pharmacy as part of the standard of care. Storage, return and destruction follow the local hospital SOP. Vials are stored at room temperature, with temperature monitoring conducted according to the local SOP. As this is a low interventional trial, no specific documentation (e.g. drug accountability) other than applicable in the routine care is required.

9.5 Cefuroxim

The trial is investigating the active substance cefuroxim (ATC-code J01DC02). Cefuroxim has a marketing authorization and is labelled for use in children of ≥ 0 days old and adults. Vials for intravenous administration are available on the Belgian and Dutch market in 750 mg and 1500 mg. The brand used for the study depends on the availability on site. The SmPC of Cefuroxim Fresenius Kabi 1500 mg (Fresenius Kabi nv/sa - BE343752) will be chosen for pharmacovigilance purposes for authorisation from the authorities.

9.5.1 General information

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Cefuroxim (ATC-code J01DC02)
Qualitative and quantitative composition	Each vial of powder for solution for injection or infusion contains 1578 mg of cefuroxime sodium equivalent to 1.5 g of cefuroxime. Each vial contains 81.3 mg sodium
Pharmaceutical form	Powder for solution for injection or infusion
Method of administration	intravenous
Authorised in the EU	Yes
Used within scope	No (HIT-HARD strategy uses higher dosing regimens than noted in the SmPC, yet are in line with standard of care cfr. Section 3)
Marketing authorisation holder	Depending on the brand
Marketing authorisation number(s)	
Manufacturer	
Distributor	
Responsible for batch release	

9.5.2 IMP rationale

Refer to Section 2 ‘rationale’ and Section 3 ‘Assessment and management of risk’.

9.5.3 Preparation, packaging and labeling of the IMP

As this is a low interventional trial the preparation and labelling of the beta-lactam antibiotics will be in accordance with the standard-of-care and in accordance with the SmPC. No additional packaging or additional labelling will be performed for this study.

9.5.1 Administration, dosage and dose frequency of the IMP

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.5.2 Permitted dose adjustments and interruption of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.5.3 Duration of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.5.4 Traceability, storage, return and destruction of the IMP

The beta-lactam therapy storage, supply, return and destruction will be according to the standard routine care of each ward. IMPs are obtained through the regular hospital pharmacy as part of the standard of care. Storage, return and destruction follow the local hospital SOP. Vials are stored at room temperature, with temperature monitoring conducted according to the local SOP. As this is a low interventional trial, no specific documentation (e.g. drug accountability) other than applicable in the routine care is required.

9.6 Ceftriaxone

The trial is investigating the active substance ceftriaxone (ATC-code J01DD04). Ceftriaxone has a marketing authorization and is labelled for use in children of ≥ 15 days old and adults. Vials for intravenous administration are available on the Belgian market in 1g and 2g quantities, and in the Netherlands 500mg, 1000mg and 2000mg.The brand used for the study depends on the availability on site. The SmPC of Ceftriaxone Fresenius Kabi 1g (Fresenius Kabi nv/sa - BE325735) and Ceftriaxone Fresenius Kabi 2g (Fresenius Kabi nv/sa - BE325744) will be chosen for pharmacovigilance purposes for authorisation from the authorities.

9.6.1 General information

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Ceftriaxone (ATC-code J01DD04)
Qualitative and quantitative composition	Each vial of powder for solution for injection or infusion contains 1g or 2g of ceftriaxone sodium equivalent to 1g or 2g of ceftriaxone. Each gram of Ceftriaxone contains approximately 83mg (3.6 mmol) of sodium.
Pharmaceutical form	Powder for solution for injection or infusion
Method of administration	intravenous
Authorised in the EU	Yes
Used within scope	No (HIT-HARD strategy uses higher dosing regimens than noted in the SmPC, yet are in line with standard of care cfr. Section 3)
Marketing authorisation holder	Depending on the brand
Marketing authorisation number(s)	
Manufacturer	
Distributor	
Responsible for batch release	

9.6.2 IMP rationale

Refer to Section 2 ‘rationale’ and Section 3 ‘Assessment and management of risk’.

9.6.3 Preparation, packaging and labeling of the IMP

As this is a low interventional trial the preparation and labelling of the beta-lactam antibiotics will be in accordance with the standard-of-care and in accordance with the SmPC. No additional packaging or additional labelling will be performed for this study.

9.6.4 Administration, dosage and dose frequency of the IMP

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.6.5 Permitted dose adjustments and interruption of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.6.6 Duration of treatment

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

9.6.7 Traceability, storage, return and destruction of the IMP

The beta-lactam therapy storage, supply, return and destruction will be according to the standard routine care of each ward. IMPs are obtained through the regular hospital pharmacy as part of the standard of care. Storage, return and destruction follow the local hospital SOP. Vials are stored at room temperature, with temperature monitoring conducted according to the local SOP. As this is a low interventional trial, no specific documentation (e.g. drug accountability) other than applicable in the routine care is required.

9.7 Description and justification of dosage and route of administration

Refer to Section 5 ‘Trial Design’ for detailed information about the administration, dosage and dose frequency of the beta-lactam therapy.

10 SAFETY RECORDING AND REPORTING

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to the **method of administration** of that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any **dose and duration** administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event,

which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Term	Definition
Not related	An adverse event which is not related to the **study treatment (dose and/or duration)** of the IP.
Unlikely related	An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
Possibly related	An adverse event which might be due to the **study treatment (dose and/or duration)** of the IP. An alternative explanation - e.g. concomitant drug(s) or concomitant disease(s) - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.
Probably related	An adverse event which might be due to the **study treatment (dose and/or duration)** use of the IP. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s) or concomitant disease(s).
Definitely related	An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s) or concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

An adverse event is considered associated with the use of the drug if the attribution is 'possibly', 'probably' or 'definitely related'.

10.2 Reporting of AEs, ARs, SAEs and SUSARs

Beta-lactams are widely used, generally regarded as safe and it is recognised that the patient population in the ICU will experience a number of aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard treatments in the ICU. These will not necessarily constitute adverse events or adverse reactions unless they are considered to be related to the method of administration, more specific related to IP dose and duration or in the site Principal Investigator's clinical judgement are not recognised events consistent with the patient's underlying disease and expected clinical course.

As the ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam and meropenem treatment is defined by the active substance only and locally available brands of ceftriaxone, cefotaxime, cefuroxime, piperacillin-tazobactam and meropenem at site will be administered, it is the Reference Safety Information of the relevant manufacturer's SmPC at each site that must be used when determining the expected nature of SAEs/SARs. The investigator should save a copy of this in the Investigator Site File.

In this study, reporting of adverse events will be restricted to events that are considered to be related to study treatment's dose and/or duration (possibly, probably or definitely). Events collected as study outcomes will not be reported as adverse events. Toxicity is one of the secondary outcomes in the study. Events other than the toxicity described in 4.3.2.6 may be reported as AE or SAE.

The following outcome events will be collected through the Redcap eCRF:

- All-cause mortality within 90 days after inclusion
- All-cause ICU mortality
- All-cause hospital mortality
- New colonization or infection with a multi-resistant organism (MRSA, VRE, MDR P. aeruginosa, CRE, ESBL Enterobacterales, Acinetobacter baumannii) or C. difficile diarrhea/infection up to 28 days post inclusion
- Antimicrobial free days
- Recurrence of infection
- Toxicity
- Health related quality of life (EQ-5D-5L measured at D90)
- Exposure
- Clinical cure
- ICU length of stay
- Hospital length of stay
- Organ support free days
- Antimicrobial days (DOT) and DDDs

Rationale for this procedure is to prevent expedited reporting for those events known to happen in this population frequently, without any relationship to the IP study treatment.

Adverse events and Adverse reactions

Any adverse events and/or adverse reactions thought to be related to study treatment's dose and/or duration will be reported within 7 days of discovery. The site Principal Investigator will be responsible for determining the causal relationship as either possible, probable or definitely related.
Notification will be by completing an adverse event form in the Redcap eCRF.

Serious adverse events

Serious adverse events (SAEs) are defined as any untoward medical occurrence that meets one or more of the following criteria:

1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect

The classification of an SAE is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as an SAE based on the above criteria. Given that critically ill patients are likely to meet any of the above listed criteria in the course of their ICU admission, only SAEs that are thought to be related to the study treatment's dose and/or duration will be reported.

All SAE's occurring from the time of inclusion until 48h after last administration of IP via study assigned method will be recorded in the patient his/her medical record and the Redcap eCRF and within 24 hours of participating site study staff becoming aware of the occurrence.

Reporting will be done by completing an SAE form in the Redcap eCRF. In case the Redcap eCRF is off – line or not working, a paper SAE form will be used.

For each SAE the following information will be collected:

- case description
- date of onset and end date
- seriousness criteria
- causality (i.e. relatedness to administration method of the trial drug)
- action taken
- outcome
- whether the event would be considered expected or unexpected.

Follow-up information should be provided as necessary. Assessment of seriousness, causality and expectedness must be made by the PI or another authorised physician. If an authorised physician from the reporting site is unavailable, initial reports without causality and expectedness assessment should be completed in the eCRF by a healthcare professional within 24hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter. Any change of condition or other follow-up information should be completed in the eCRF as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

In case the Chief investigator and co-investigators , in consultation with HIRUZ CTU, decide the SAE is a SUSAR, HIRUZ CTU will report the SUSAR to the EMA, through the Eudravigilance (EV) database within the timelines as defined in European legislation. In case of a fatal or life-threatening SUSAR, the sponsor should report at least the minimum information as soon as possible and in any case no later than 7 calendar days after being made aware of the case. In

case of a non-life-threatening SUSAR the reporting process must be completed within 15 calendar days.

The Trial Project Manager reports the SUSAR to the DSMB and all local PI's.

Reporting to the local ethics committee of SAEs and SUSARs remains the responsibility of the PI and should be done in accordance with the requirements of the local institution's procedure.

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes.

10.3 Responsibilities

Local Principal Investigator (PI):

1. Checking for AEs, AR's or reportable events during study period intervention and follow-up.
2. Checking protocol compliance.
3. Using medical judgement in assigning seriousness, causality and using the Reference Safety Information approved for the trial.
4. Ensuring that all required SAEs and SUSARs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
5. Coordinating role during study recruitment within the ICU.

Chief Investigator (CI):

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality, and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the safety Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs.
6. Preparing the clinical sections and final sign off of the Annual safety report (ASR)

Sponsor:

1. Central data collection and verification of reportable events in e-CRF.
2. Reporting safety information to the trial steering committee (TSC).
3. Expedited reporting of SUSARs to the Competent Authority (FAMHP) and EC within required timelines.
4. Notifying Investigators of SUSARs that occur within the trial.

5. Preparing standard tables and other relevant information for the ASR in collaboration with the CI and ensuring timely submission of ASR including safety summary and deviations to the EMA database (CTIS).

Trial Steering Committee (TSC):

1. Follow up on patient recruitment.
2. In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data.

Data Safety Monitoring Board (DSMB):

All trial medication is authorised and used in current practice. Although the safety profile of the trial medications and trial design, a DSMB will be installed.

The installation of a Data Safety Monitoring Board (DSMB) for the HIT-HARD study ensures data integrity and participant safety. The DSMB will provide independent oversight and periodic review of the data throughout the trial. This is particularly relevant in this phase III, multicenter study in critically ill patients.

Key reasons for the DSMB installation include:

1. **Participant safety**. Although the investigational antimicrobials are well-established and widely used in clinical practice, the DSMB will monitor safety data to promptly identify any unexpected adverse events.
2. **Data integrity and quality**. The DSMB will oversee the accuracy and completeness of data collection processes, ensuring the reliability and validity of the trial outcomes.

Transparency. The involvement of a DSMB increases transparency and accountability, ensuring trust in the research process.

10.4 Annual Safety reporting/periodic safety update report

The Trial management group will provide an ASR once a year throughout the entire duration of this clinical trial, or on request, to the EMA. This ASR will include all reported SAEs and SUSARs and relevant safety information regarding all investigational medicinal products, used in this trial.

The report will be submitted no later than 60 calendar days after the ASR Data Lock Point (DLP). The first DLP is 1 year after the first date of the sponsor's authorisation to conduct the clinical trial. Subsequently, the ASR will be submitted each year (+ maximum 60 days) until the trial is declared ended.

11 STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

Assuming an all-cause mortality within 90 days of 20% for both treatments obtained from the SAPS II trial (43), the number of patients for non-inferiority (NI) with 80% power, alpha 0.05 (one-sided), 7% non-inferiority margin, 20% loss to follow-up or potential treatment switching within 7 days, is 1282 patients in total.

This calculation (https://www.sealedenvelope.com/power/binary-noninferior/ with alpha=0.025 to mirror non-inferiority based on a two-sided 95%-CI) uses that in cluster randomized cross-over trials, the between-cluster effect and thus the clustering effect is removed so power is only determined by the within-cluster variance (44). The non-inferiority margin of 7% was based on different considerations: first, the project group and external experts in the field unanimously endorsed this margin, considering the benefits of lower expected toxicity based on the EMA report on choice of non-inferiority margin (EMA, Guideline on the choice of the non-inferiority margin. 2006). Second, 7% seems well balanced between what is clinically acceptable and what is feasible in terms of number of patients needed. Third, a literature search for comparable non-inferiority trials identified (PubMed, "Antibiotic AND non-inferiority", published 2016; 02-02-2023), 4 NI studies with endpoint mortality:

- MERINO-3: ceftolozane-tazobactam vs meropenem for BSI (45) 30-day mortality 5%; NIM 5%
- APEKS-NP: cefiderocol vs meropenem for nosocomial pneumonia (46) 14-day mortality 10%; NIM 12.5%
- BALANCE: length of treatment bacteremia (47); 90-day mortality: 22%; NIM 4%
- ASPECT-NP: ceftolozane-tazobactam vs meropenem for nosocomial pneumonia (48) 28-day mortality 20%; NIM 10%

11.2 Statistical analysis plan

Per cluster and overall, estimation of differences in outcome variables (means for continuous variables and percentages for categorical variables) will be reported with 95 percent confidence intervals. Median/quartiles/survival probabilities for time-to-event endpoints per randomised treatment will reported, supported by hazard ratios with 95%-CI where appropriate. Per cluster and overall, distribution of the endpoints by randomised treatment will displayed by (overlay of) histograms for continuous outcomes and bar charts for categorical outcomes.

11.2.1 Summary of baseline data and flow of participants

Baseline variables will be described per randomised treatment (HIT-HARD or CONTROL) by period (first or second) and over both periods (provided these are sufficiently similar). Continuous variables will be described by means +/- SD or median (IQR) as appropriate. Categorical outcomes will be reported with percentages.

The flow of participants will be described as recommend by the CONSORT statement.

11.2.2 Primary outcome analysis

Primary analysis will be based on the intention-to-treatment population. In particular, the intercurrent event "treatment switch" will be handled by the treatment policy strategy (ICH E9(R1): an intercurrent event is an event occuring after treatment initiation that affects either the interpretation or the existence of the outcome variable).
To test the hypothesis of non-inferiority for the pre-specified margin of 7% and estimate the risk difference between HIT-HARD and CONTROL group, we will perform an unweighted cluster-level summary regression. This model has shown to be a robust analysis model that has better

convergence rates and better protection of the type I error than models using a random effect for cluster and/or cluster-period (DOI: 10.1002/sim.7137). Specifically, proportions per cluster-period will be summarized and these will be analysed using a linear regression with fixed effects for treatment, cluster, period and normally distributed residuals. Model fit will be assessed by observed-versus predicted plots and residual plots of this regression.

In case this model would not converge or does not meet model assumptions, alternative models will be attempted. These may include logistic regression on the cluster-period proportions, and regression models on individual patient data: (parametric) survival regression models, generalized linear mixed models with fixed or random effects for clusters, identity or logit link, and binary or normal error distribution. When appropriate (e.g. same link function, same dataset, so either individual data or cluster summaries) AIC(c) will be used to guide model choice. Otherwise, leading will be which model provides the best fit to the data in terms of smallest residual variance. Model assumptions and model fit will be assessed using observed versus predicted plots and residual plots (primarily all on cluster-period level as this is a cluster randomized trial). In cases of logistic or survival regression models, the risk difference will be derived from the respective model.

- Note: the primary intention-to-treat analysis handles 'switch of therapy' by treatment-policy, but this may blur existing differences between treatments. This is because patients that switch from the one treatment to the other may have responses more similar to those on the other treatment (ICH-E9, section 5.2.3 and ICH-E9(R1) last paragraph section A.3.4).
  Therefore, the following analyses are prespecified to interpret non-inferiority:Per protocol analysis, i.e., including only patients that received the full therapy or at least 144 hours of the intended therapy in the CONTROL group and at least 72 hours in the HIT-HARD group (antimicrobial and dose) puts the primary ITT analysis in perspective.
- For the same reason, an analysis that treats switch as failure (composite strategy) and an analysis that handles switch using the hypothetical strategy will be performed (see the intercurrent event handling mentioned in 4.3). If there are few switches, these additional analyses with composite or hypothetical strategy have limited value and will be omitted.
- Additionally, a 'switched-to' analysis will be performed where switched patients are analysed according to the treatment condition they switched to. Note that this can be implemented by using the individual level analogue of the unweighted cluster-level summary regression of above. This is a linear model on patient-level data with fixed effects for treatment, cluster, period and normally distributed residuals approximating patients in clusters. Instead of normally distributed residuals, also a binary distribution could be taken, provided this generalized linear model converges.

Furthermore, the following additional analyses are prespecified:

- Between hospital variance in the same treatment condition will be reported using descriptive statistics and an analysis as the primary analysis including a random effect for cluster.
- Between hospital variance of the treatment effect will be reported using descriptive statistics and an analysis including additionally a random cluster x period interaction.
- Subgroup analyses will be performed (i) per type of infection and (ii) per antimicrobial and (iii) per type of cluster (=university or non-university teaching hospital).

- An as-treated analysis will be performed to address possible “carry-over effects”, when in some clusters/ICUs, the study team (initially) not fully transitions to the randomised intervention of the (second) period. A similar analysis model as the ‘switched-to’ analysis can be used.
- Adjustment for prognostic covariates (especially if imbalanced) and possible effect-modifiers. Prespecified prognostic covariates and effect-modifiers are: age, SOFA score and APACHE score. Other covariates may be considered based when the data are analysed (e.g. because of observed imbalance). These individual level analyses can be performed with a similar model als the ‘switched-to’ analysis.
- Other analyses may be performed post-hoc when they are considered sensible.

11.2.3 Secondary outcome analysis

Survival models for time-to-event endpoints with fixed effects for centers, linear regression for continuous endpoints on cluster-period summaries, and above linear model on cluster-period summaries for dichotomous endpoints will be applied to perform the analyses for the secundary endpoints. Similarly, the prespecified supportive and additional analyses similar as described for the primary endpoint will be performed. See also 4.3 for the specifics on how the intercurrent event switch is handled using the composite and hypothetical strategy.

These models will also be used to adjust for prognostic covariates and possible effect-modifiers. The same factors as for the primary analyses are prespecified.

If the primary endpoint meets the non-inferiority criterion, the following secondary endpoints will be tested for superiority using a fixed sequence testing procedure:

i. Antimicrobial free days
ii. DOT
ii. Clinical cure
iii. Organ support free days
iii. ICU LoS.

This means that (if D90 mortality is non-inferior) the endpoint (i) will be tested at 0.05 (two-sided) and if and only if (i) is statistically significant at that level, endpoint (ii) will be tested at 0.05 (two-sided) and so on.

11.2.4 Procedure(s) to account for missing or spurious data

Upfront, occurrence of missing data will be minimized by separating withdrawal of consent from withdrawal of data-collection (see 8.7).

Spurious outcomes will be queried.

Given that patients are measured in-hospital, the amount and therefore impact of missing data is likely limited.

Residual missing endpoint data, i.e., not due to the intercurrent event switch or death, so typically lost-to-follow-up, will be handled primarily as missing-at-random, i.e., censoring for time-to-event outcomes or mixed models/multiple imputation for continuous or binary endpoints.

Intermittent missing data in endpoints that are assessed each day such as new colonization/infection, antimicrobial free days, organ support free days will be intrapolated from surrounding days, where possible.

Sensitivity analyses for residual missing data will be performed such as responder analysis, complete case analysis. and potentially multiple imputation. Post hoc analyses will be performed as the need arises.

Other statistical considerations

Changes to the statistical analysis plan and/or protocol will be recorded with date of change, reason, and availability of outcome data. It will be stated whether changes are made before or after data lock.

11.3 Data collection for economic evaluation

Data linkage

The Belgian part of the study is funded by KCE trials. One of the goals of the KCE Trials programme is to improve the efficiency of the healthcare system. This protocol has been designed with a later possible economic analysis in mind. The planned economic analysis is briefly described below, together with the variables collected in this protocol for this purpose. For the sake of clarity, the economic analysis is not a part of this trial. The decision to conduct such economic analysis will depend on the effectiveness results of this trial.

As per KCE guidance the national number of the Belgian patients (RRN/INS) will be collected to include the possibility to collect survival data end to use billing data from RIZIV/INAMI. In that case, approval will be requested from the competent chamber of the Information Security Committee to have the relevant study data linked with IMA data by a trusted third party (TTP, eHealth platform) using this patient national number. KCE is responsible for the data linkage, while the sponsor is responsible for providing the REDCap data and informing the participants about this process.

The patient information and consent include wording that the national number will be recorded on site by the investigator for later data linkage. The national number will not be included in the trial database, available to the sponsor or any other third party. The patient information and consent will also include that in case the patient is randomized, it is planned that a trusted third party (TTP, eHealth platform) will receive and use the national number to link with IMA administrative data. This data linkage is planned to obtain a more complete data set containing costs related to health care paid by the compulsory health insurance and the patient that will be used for the analysis of effectiveness and cost-effectiveness of the intervention.

Planned HTA analysis

We anticipate showing a shorter use of antibiotics with a non-inferior outcome on all-cause mortality while there is a potential for better outcome due to reduction of risk for antimicrobial underexposure. Therefore, it might be interesting to estimate the relative cost-effectiveness of short, high dose antimicrobials compared to standard dosing alongside this clinical trial. We will

perform this economic evaluation from a medical perspective because the anticipated effect on cost will be rather small on patient level and mainly ICU care related.

The impact of both strategies on the quality of life of patients will be assessed by the EQ-5D-5L at baseline and at day 90 following randomization and the utility will be used to derive a QALY estimate for each patient according to the trapezium rule. For Dutch speaking patients we will use a validated Dutch translation and for the French speaking patients we will use a French translation. To derive the utility index value, we will use the Dutch tariff for the Dutch population and the Belgian tariff for the Belgian patients. The cost analysis consists of two main parts. First, at patient level, volumes of care related to ICU care and antimicrobial use will be subtracted from the electronic medical records. We will subtract the number of hospital days, procedures that might be performed, diagnostics and medication use. The second part of the cost analysis consists of determining the cost prices for each volume of consumption. The standard cost prices from the 'Dutch Guidelines for Cost Analyses' and www.medicijnkosten.nl will be used. For units of care where no standard prices are available real costs prices will be determined on the basis full cost pricing. For the Belgium patients we will use Belgian cost prizes where available.

We will estimate the incremental cost-utility ratio by dividing the difference in costs by the difference in QALYs between the groups. The ICER expresses how much money we need to pay extra to gain 1 QALY and can be compared to the willingness to pay. Uncertainty in the ICER will be non-parametrically determined using bootstrap techniques (1000 replications). Results from this analysis will be presented in a scatter plot and willingness to pay curve. In case data for a cluster is not available for both periods (HIT-HARD and CONTROL) then a cluster effect may be present. In that case, to correct for a relation in the data among participants within a cluster (due to the cluster randomized trial) we will also analyse the Net Monetary Benefit (QALY x WTP – Cost) on a patient level in a generalized linear model with an identity link function and gamma distribution including cluster as a co-variate. We will also analyse relevant sensitivity and scenario analyses.

12 DATA HANDLING

12.1 Data collection tools and source document identification

12.1.1 Source data & source documents

Following source documents will be consulted and/or used:

- Original hospital medical records
- Original ICU specific medical records
- Study worksheets
- Ward chart
- Operating theatre chart
- Laboratory results
- Pharmacy dispensing records
- X-rays, CT scan reports
- Standardised EQ-5D-5L questionnaire
- Data collected during screening visit, baseline visit, treatment phase until day 90

12.1.2 Case report forms

An electronic data capture (EDC) system, i.e. REDCap, will be used for data collection.

REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the Health, Innovation and Research Institute (HIRUZ). REDCap is a web-based system.

Only the data required by the protocol are captured in the eCRF. No data will be directly entered into the eCRF without corresponding source. All variables will be obtained from the patient's electronic medical record (EMR) or papers source documents.

The eCRFs and the database will be developed by the data manager based on the protocol. The final eCRF design will be approved by the Chief Investigator. The study site staff is responsible for data entry in REDCap.

12.2 Biological samples

In selected centres a blood sample (EDTA tube of 3ml) to measure antibiotic exposure will be obtained between 36 and 96 hours after the antibiotics have been initiated, attempt should be made to draw the blood sample as closest to 36h after antibiotics have been initiated.

After analysis, samples will be stored for 5 years at the Pharmacy Radboudumc, Geert Grooteplein Zuid 10, 6525 Nijmegen. These biological samples will be analyzed for objectives that fall within the scope of the study, for which Informed consent is required.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Stored samples will be pseudonymized throughout the sample storage and analysis process and will not be labeled with personal identifiers.

Refer to the study lab manual for more details on sample processing, storage and shipment.

12.3 Data handling and record keeping

The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the Ghent University Hospital campus and meets hospital level security and back-up requirements. REDCap has built-in options for univariate alerts, such as valid-value, valid-range, and missing-value alerts.

Privacy and data integrity between the user's browser and the server is provided by mandatory use of Transport Layer Security (TLS), and a server certificate issued by TERENA (Trans-European Research and Education Networking Association). All trial sites will have access to REDCap. Site access is controlled with IP restriction.

Personal data will be handled according to the European General Data Protection Regulation (GDPR, in Dutch: Algemene verordening persoonsgegevens, AVG). All personal data of participants will remain confidential. At inclusion, each participant will receive a code (unique number – not based on birthday or initials of the participant) that will be marked on all collected data and human material. The research team, the monitor and auditor of the study, and the Healthcare Inspectorate are the only people who will be able to trace data and/or human material to an individual subject by having access to the subject identification code list. On all documents submitted to the sponsor or CI, subjects will only be identified by their study number.

All study sites will have access to REDCap. Site access is controlled with IP restriction. The study site staff is responsible for data entry in REDCap. Login in REDCap is password controlled. Each user will receive a personal login name and password and will have a specific role which has predefined restrictions on what is allowed in REDCap. Futhermore, users will only be able to see data of participants of their own site. Any activity in the software is traced and transparent via the audit trail and log files.

A data management plan will be developed to document the data management process in more detail. Data validation rules will be added to maximize immediate validation of the data at entry. In addition, complex edit checks will be programmed by the data manager to check for inconsistencies within data. Any inconsistencies will be queried to the responsible persons at site. Query management and reconciliation will be carried out in Redcap. This will be documented in a data validation plan. Data analysis will be performed by a statistician.

All data entries and corrections will only be performed by study site staff, authorised by the Investigator.

No data will be entered in the study database before written informed consent is obtained.

Data will be reviewed by trained personnel (monitor, data manager) and any errors or inconsistencies will be clarified. Every effort should be made to ensure completeness of data.

Data reported on each eCRF should be consistent with the source data. If information is not known, this must be clearly indicated on the eCRF. All missing and ambiguous data will be clarified.

While in hospital, study participants will have relevant study data extracted from that routinely collected in the ICU specific medical records, ward medical record and available hospital databases.

All- cause mortality within 90 days of randomisation is the primary outcome of the study. Follow-up is performed via telephone if the patient has been discharged from the hospital. Several attempts should be made to contact each patient for follow up and ascertain their vital status and quality of life via the EQ- 5D-5L questionnaire.

The EQ-5D-5L Health Questionnaire must be completed within 14 days after the day 90 due date. If the questionnaire is not completed within this time frame it is no longer valid, therefore do not complete.

Site investigator has the responsibility to keep record of all essential documents, original signed ICF's, study related documents and ensure they are kept in a secure locked office with access limited to authorised persons.

If patient or legal guardians withdraw from the study after written consent is obtained, all data collected until the time of withdrawal will be kept in the study database. The details of withdrawal should be clearly documented in the patient's medical records and in the eCRF (see also 8.7.2).

12.4 Access to Data

The investigators and institutions involved in the trial will permit clinical trial-related monitoring, audits and regulatory inspections (including provision of direct access to source data and documents).

Login in REDCap is password controlled. Each user will receive a personal login name and password and will have a specific role which has predefined restrictions on what is allowed in REDCap. Furthermore, users will only be able to see data of subjects of their own site. Any activity in the software is traced and transparent via the audit trail.

12.5 Archiving

The investigator and sponsor specific essential documents will be retained for at least 25 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirements.

The site Principal Investigator will maintain the confidentiality of all study documentation and take measures to prevent accidental or premature destruction of these documents.

The site Principal Investigator must notify the sponsor prior to destroying any study documents following study completion or discontinuation. If the site Principal Investigator's situation is such that archiving can no longer be ensured by him/her, the site Principal Investigator will inform the sponsor and the relevant records will be transferred to a mutually agreed designee.

Essential documents are as following:

- ISF
- All study related documents
- Copy of eCRF
- TMF (only applicable for the Sponsor)

13 MONITORING, AUDIT & INSPECTION

13.1 General

Monitoring of the trial will be performed in compliance with GCP E6(R2) (GCP E6(R3) upon implementation and training completion) and the applicable regulatory requirements. The study team will be trained during an initiation visit by the monitor. A detailed description of the monitoring tasks can be found in the latest version of the (study-specific) 'Clinical Trial Monitoring Plan'.

Monitoring to check and ensure adequate study conduct with regard to ethical conduct, data collection and documentation, records of study procedures, and compliance with the approved protocol.

To address the challenges posed by staff rotations and changes, we will implement a comprehensive plan to maintain consistency and continuity across all sites and study phases:

- Training and standardization: We will provide training for all staff involved in the study, both at the onset and regularly throughout the trial. This training will cover the study protocol, data collection procedures, and the specific requirements of both the HIT-HARD and control treatments.
- Documentation and communication: Detailed documentation of study protocols and procedures will be available at each site. Moreover, we will establish clear lines of communication to ensure that new staff are fully briefed and understand the ongoing study requirements.
- Oversight and support: Together with the PIs, research coordinators at the participating sites will oversee the daily operations of the trial, serving as points of continuity regardless of staff rotations. PI and research coordinators will be responsible for ensuring that all staff, including rotational staff, adhere to the study protocol.
- Monitoring and quality assurance: We will implement regular monitoring visits, both in-person and virtual, to each site to provide support, address any issues promptly, and ensure that the study is conducted consistently across all sites and time points.

By anticipating and planning for these challenges, we aim to ensure the smooth execution of the trial and the integrity of the data collected.

13.2 Monitoring team

Monitoring services in Belgium will be provided by HIRUZ CTU. In the Netherlands monitoring will be performed by the Radboudumc IC research organisation.

All relevant contact details (e.g. primary contact person) can be found in the 'Clinical Trial Monitoring Plan'.

13.3 Scope

Monitoring services will consist of the following (non-exhaustive list):

- review of informed consents and the followed process;
- check on recruitment status;
- checking for protocol deviations/violations;
- checking GCP compatibility;
- check on safety reporting compliance;
- review of study data.

More information can be found in the Clinical Trial Monitoring Plan.

13.4 Inspection

This trial can be inspected at any time by regulatory agencies during or after completion of the trial. Therefore access to all study records, including source documents, must be accessible to the inspection representatives. Subject privacy must be respected at all times, in accordance to GDPR, GCP and all other applicable local regulations.

The investigator/study team should immediately notify the sponsor if (s)he has been contacted by a regulatory agency concerning an upcoming inspection.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Good clinical practice

The trial will be conducted in accordance with the Clinical Trials Regulation (EU No 536/2014), the study protocol and the latest version of the ICH E6 (R2) GCP guidelines (GCP E6(R3) upon implementation and training completion) , creating a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical studies that provides assurance that the data and reported results are accurate and that the rights, integrity and confidentiality of study subjects are protected.

14.2 Regulatory authorities review & reports

14.2.1 General

The protocol will be reviewed and approved by the Regulatory authorities. This trial cannot start before a favourable consolidated opinion (approval) has been obtained, a trial initiation visit has been performed by the monitor and, if applicable, all necessary agreements are finalized.

A feasibility study will be carried out to confirm which centre can participate after which a trial initiation visit will be performed by the monitor at the selected centres. The site will receive the necessary training (ICH-GCP, protocol, ICF procedure, Investigator Site File, safety follow-up…).

All correspondence with the regulatory authorities will be retained in the Trial Master File/Investigator Site File.

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

If the study is ended prematurely, the Chief Investigator will notify within 15 calendar days the RA through the EMA database (CTIS), including the reasons for the premature termination.

The Sponsor will notify within 15 calender 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. Within one year after the end of study, the Sponsor will submit a summary of results, including any publication or abstracts, it shall be accompanied by a summary written in a manner that is understandable to laypersons to the regulatory authorities through the EMA database (CTIS).

14.2.2 protocol modifications and urgent safety measures

Any substantial change or addition to the protocol can only be made in a written protocol modification that must be approved by the Ethics and Competent Authorities.

Only modifications that are intended to eliminate an apparent immediate safety threat to the participants may be implemented immediately.

Notwithstanding the need for approval of formal protocol modifications, the investigators are expected to take any immediate action, required for the safety of any subject included in this trial, even if this action represents a deviation from the protocol. These actions should always be notified to the sponsor without undue delay, in order for the sponsor to notify the Regulatory Authorities.

Submission packages and required reporting will be submitted by HIRUZ CTU through the CTIS.

14.3 Peer review

The draft version of the protocol was reviewed by the PIs of all participating centres.

14.4 Public and Patient Involvement

In Belgium, we collaborate with SepsiBEL (https://www.sepsibel.be/), a patient peer group for people who suffered from Sepsis or Septic shock.

In the Netherlands, we work with IC connect (https://www.icconnect.nl), a patient organisation for all (former) ICU patients and their family members.

A Patient Advisory Committee (PAC) has been set up, and we have been and will be in regular contact to gather input and feedback. Upon request of the patient representatives, the PAC meetings will be separate from the TSC meetings to encourage an open active discussion between the PAC and the researchers.

The PAC members have been - and will continue to be - involved in the design of the trial; the scope of the study, eligibility criteria, outcomes, use of deferred consent, the intervention, trial procedures, safety reporting and data handling have been discussed with patient representatives and no particular difficulties have been brought forward. Feedback was given by online meetings and via e-mail. A layman summary of the study protocol was provided prior to these meetings. During the trial, the PAC members will be invited to the bi-annual PAC meeting, where the conduct and progress of the study will be discussed, focusing on the priorities set by the PAC.

Patient information such as ICF's and information to be posted on the study website will reviewed by the PAC members.

After the trial has been completed and analysed, results will be presented to and discussed with the PAC. The PAC will be asked for feedback regarding the dissemination and communication of the results, targeted at patients and their caregivers.

14.5 Regulatory Compliance

The protocol states that the trial will not start until a Clinical Trial Authorisation (CTA) is obtained from the regulatory authorities.

Furthermore, the protocol and trial conduct is compliant with the Belgian Law of May 7th 2017, regarding clinical trials of medicines of human use.

14.6 Protocol compliance

Monitoring of the trial will be performed in compliance with GCP E6(R2) (GCP E6 (R3) upon implementation and the applicable regulatory requirements. (see section 13)

This trial can be inspected at any time by regulatory agencies during or after completion of the trial. (see section 13)

The Data Management plan will describe how Protocol Deviations will be identified, handled and recorded. Protocol deviations will be classified (major/minor) based on the Protocol Deviation Criteria List. Major deviations will be flagged to the trial statistician and the trial Sponsor.

Sponsor and all investigators agree to take any reasonable actions to correct protocol or other deviations/violations noted during monitoring/inspection, in consultation with the monitoring team.

All deviations must be documented on the correct deviation log by the study team that is kept available at any time for monitoring/inspection purposes. Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human subjects may take place without prior approval of the sponsor and the regulatory authorities.

14.7 Notification of Serious Breaches to Regulation, and/or the protocol

Critical issues that significantly affect patient safety, data integrity and/or study conduct should be clearly documented on the applicable deviation log and will be communicated with the Chief Investigator, HIRUZ CTU and possibly the CA/IEC.

Please contact HIRUZ CTU immediately in case of a serious breach: hiruz.ctu@uzgent.be and/or +3293320500.

Early termination of the trial (in a specific center or overall) may be necessary in case of major non-compliance.

14.8 Data protection and participant confidentiality

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules (i.e in accordance with Belgian and Dutch laws dated on 30July 2018 and 22 August 2002.

The collection and processing of personal data from subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives of the trial. Race and ethnic origin data are collected to assess possible differences in pharmacokinetics of the antimicrobial, response to treatment, and other clinical outcomes in diverse populations. There is evidence that suggests that immunological or socio-environmental factors associated with race/ethnicity may impact disease progression and the effect of the treatment in critically ill patients. As this study focuses on optimization of antimicrobial therapy, these variables must be considered to ensure inclusiveness and equity.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Appropriate technical and organisational measures to protect the personal data against unauthorised disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential. In case of data security breach, local institution's procedures will be followed.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for trial-related monitoring, audit, Ethics Committee review and regulatory inspection. This consent also addresses the transfer of the data to other entities, if applicable.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Stored samples will be pseudonymised throughout the sample storage and analysis process and will not be labeled with personal identifiers.

The sponsor is subject to the rights and obligations as data controller set forth under the Data Protection Laws in relation to the processing of personal data for the purpose of conducting the Study in accordance with the Protocol. In that respect the sponsor shall be considered as data controller of all Study Data pseudonymized for Study purposes. Participating Site is subject to the rights and obligations as “data processor” set forth under the Data Protection Laws in relation to the processing of personal data for the purpose of conducting the Study in accordance with the Protocol.

14.9 Access to the Study Data by KCE and similar institutes in the EU

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

A distinction is to be made by access by KCE (and similar institutes in Europe) and access by other parties.

Access to Study Data by KCE and similar institutes in the EU is fully defined in the contract between KCE and the Sponsor and the research agreement template is publicly available on the KCE website. Link: https://kce.fgov.be/fr/open-calls and then click on the last call open.

After the completion of the study the Sponsor will transfer the pseudonymised study data set to KCE. KCE will request approval from the competent chamber of the Information Security Committee (ISC) to have the relevant study data linked with e.g. IMA data by a trusted third party (TTP, eHealth platform) using the participant national number. This national number will be collected on the subject identification log.

The participant information and consent include wording that the national number will be recorded on site by the investigator for later data linkage, but will not be included in trial database available to the sponsor or any other third party. The participant information and consent will also include that in case the participant is randomized, it is planned that a trusted third party (TTP, eHealth platform) will receive and use the national number to link with IMA administrative data. To this end, KCE will receive the link between the study number and the national number under pseudonymised form. KCE will never be able to use the link without authorisation of the ISC and the intervention of the TTP. This data linkage is planned to obtain a more complete data set containing costs related to health care paid by the compulsory health insurance and the participant that will be used for the analysis of effectiveness and cost-effectiveness of the intervention by KCE. The processing of personal data for this analysis is necessary for the performance of a task carried out in the public interest, as specified in the law defining KCE’s missions and tasks. To the extent the personal data is related to health, the processing is necessary for scientific or statistic purposes, as specified in the law defining KCE’s missions and tasks. For all processing related to the analysis of effectiveness and cost-effectiveness of the intervention, KCE is the controller.

KCE and Sponsor have entered into a research agreement detailing the roles and responsibilities of each party, as well as other legal aspects of this collaboration, including the right to use and access of KCE to the Study Data.

Background" means any intellectual property (IP), data, materials, information owned or controlled by the Sponsor or a Site and required to run this Study. Sponsor will identify such Background including the legal restrictions of which Sponsor, or Sites are aware that may affect the use of the Background for the purpose of the Study or the rights granted to KCE under this Agreement.

The Study Data consist of this protocol, including amendments, the electronic forms for data capture, including the annotations and guidance for use, the electronic database of the pseudonymized clinical and non-clinical data collected using data capture, including the log of changes from data entry to database lock, study reports based on these pseudonymized data, and any data or reports generated at a later stage, e.g. based on exploratory analyses or stored samples.

"Foreground" means any Study Data, and any tangible biological, chemical and physical material and inventions, that are generated, acquired, discovered, conceived, developed, created, exemplified or derived as a result of carrying out the Clinical Study, whatever its form or nature, whether it can be protected or not, as well as any Foreground IP. Sponsor acknowledges that the main purpose of the research performed under this Agreement is to generate results that will serve the general public interests, and specifically the interests of the patients and public healthcare decision making bodies, and, therefore, undertakes not to exploit the Foreground in any way that is or could be detrimental to such interests.

The Sponsor owns the Study Data but provides KCE with a copy of the pseudonymized database after database lock as well as a royalty-free unrestricted license to use the Study Data for non-commercial public health related purposes as detailed in the Agreement between KCE and the sponsor. If judged appropriate, KCE will introduce the request to the competent chamber of the Information Security Committee and arrange for the data linkage. For the sake of clarity, the linked data are not part of the Study Data. However, KCE will discuss with the Sponsor the results of the analyses and the reporting of the linked data.

14.10 Access to the final trial dataset by other parties

As mentioned in 14.4 (Patient and Public Involvement) selected Patient Partners will form a PAC. These Patients will have access to the study protocol and be informed during and at the end of the trial of the study results and outcomes. They will be invited to Meetings in which the progress and/or the outcomes of the study will be discussed. They will not have access to the pseudonymized study data set itself. Nor will any other party have access to the study data.

Data access by other parties

This section needs to be in accordance with the research agreement

The information provided via the link below provides examples of data sharing statements.

http://www.journalslibrary.nihr.ac.uk/information-for-authors/data-sharing

	Example 1	Example 2	Example 3	Example 4
Will individual participant data be available (including data dictionaries)?	Yes	Yes	Yes	No
What data in particular will be shared?	All of the individual participant data collected during the trial, after deidentification	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices)	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures and appendices)	Not available
What other documents will be available?	Study protocol, statistical analysis plan, informed consent form, clinical study report, analytic code	Study protocol, statistical analysis plan, analytic code	Study protocol	Not available
When will data be available (start and end dates)?	Immediately following publication; no end date	Beginning 3 months and ending 5 years following article publication	Beginning 9 months and ending 36 months following article publication	Not applicable
With whom?	Anyone who wishes to access the data	Researchers who provide a methodologically sound proposal	Investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose	Not applicable
For what types of analyses?	Any purpose	To achieve aims in the approved proposal	For individual participant data meta-analysis	Not applicable
By what mechanism will data be made available?	Data are available indefinitely at (*link to be included*)	Proposals should be directed to xxx@yyy. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third-party website (*link to be included*).	Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our university's data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at (*link to be provided*).	Not applicable

[a] These examples are meant to illustrate a range of, but not all, data sharing options.

14.11 Liability and insurance

This study protocol is without prejudice to national and European Union law on the civil and criminal liability of the Sponsor, Chief Investigator, Principal Investigator(s) and other parties concerned.

The sponsor has entered into a no-fault insurance policy for this trial, in accordance with the relevant legislation (article 12 of the Belgian Law of 7 May 2017 and article 76 of the EU Regulation 536/2014) or all Belgian participants.

Insurance details: Allianz Global Corporate & Specialty SE, Branch Office Belgium, Uitbreidingstraat 86, BE-2600 Berchem, polisnumber BEL001889.

The Dutch coordinating center has entered an insurance policy for this trial.

Insurance details: Centramed, Maria Montessorilaan 9, 2719 DB Zoetermeer, polisnumber 624.100.021, 626.107.122

15 DISSEMINATION POLICY

15.1 Dissemination policy

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

The Sponsor of the study is committed to the unrestricted and widespread dissemination of all primary and secondary endpoint results and tertiary analyses. After trial termination, a multi-centre abstract reporting the primary results will be prepared by the chief investigator in collaboration with the members of the Trial management group, Steering Committee and others and presented at a scientific meeting. A multi-centre publication will similarly be prepared for publication in a reputable scientific journal.

The publication of the principal results from any single-centre experience within the trial is not allowed before publication of the primary results. Submission of all abstracts and publications regarding the primary and secondary endpoints from the study requires approval by the study Chief Investigator and co-investigators after review by the Steering Committee.

This trial will be registered by the sponsor at EU Clinical Trials trough Clinical Trial Information System (CTIS), and results information from this trial will be submitted by sponsor to the aforementioned website.

To guarantee correct protection and access to the data, the project will put in place the required data management structure and define a Data Management Plan (DMP) to govern the processing, storage, sharing, preservation, and archiving of those different types of data. The DMP will adhere to the relevant guidelines and regulations such as the General Data Protection Regulation (GDPR) Data Protection Act (Regulation (EU) 2016/679 of the European Parliament and of the Council) as well as the main principles of FAIR Principles (findable, accessible, interoperable, reusable).

Findability – Best efforts will be made to make the data resulting from the project findable. All types of data will be registered with community accepted metadata and unique identifiers for all units of stored information.

Accessibility – As a general rule, data underlying public reports and scientific publications will be deposited and made available immediately at the time of publication of results. All possible measures will be taken to ensure open access to research data. Restrictions to access will be applied only on account of privacy, or ethical issues, copyright, confidentiality and exploitation issues. In the DMP the partners will specify the versions or parts of the data that cannot be openly shared.

Interoperability – The project data and outputs will be described using standard descriptive metadata and, whenever possible, terms from controlled vocabularies and ontologies will be associated to the data to enhance semantic interoperability.

Reusability – Potential re-utilisation will be enabled and the quality of the data ensured by careful documentation of data collection methods as well as the contents of the datasets. To stimulate

re-use, the partners aim to convert shareable data from proprietary formats and aim to make them available in standard documented, and possibly open, formats.

15.2 Authorship eligibility guidelines and any intended use of professional writers

This section should be read in conjunction with the research agreement, which supersedes the protocol in case of contradictory statements.

Prospective trial registration in a public trial registry before recruitment of the first participant will take place and the protocol will be published.

The results of this study will be published in a scientific journal. The chief investigator and co-investigators will have the final responsibility of the main publication. Sub-analyses can be published after final publication of the main paper, co-authorship for sub-analyses will be based on the ICMJE recommendations.

15.3 Study Report

The Summary of Results will be published within 1 year from the LPLV.

Within one year after the end of the study, the investigator/sponsor will submit a final summary of results with the results of the study, including any publications/abstracts of the study, to the regulatory authorities.

16 REFERENCES

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17 APPENDICES

17.1 Risk ASSESSMENT OF THE TRIAL INTERVENTION(S)

Risks associated with trial interventions

☒ A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):

All trial medication is authorised and used in current practice.

Dosing strategy and duration are based on national and international guidelines and pharmacokinetic data justifying the dose and duration in the protocol.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Beta-lactams	Stock shortage	Detection and follow up of stock shortages	There have been shortages for many years	For each beta-lactam multiple suppliers are available in Belgian and the Netherlands.
Beta-lactams	(Serious) adverse events considered related to study assigned dose and duration of IP. (Possibly, probably, or definitely)	Standard of care assessment.	Daily clinical FU by attending physician, lab values are monitored, this supported by the PI and SC.	Sites will be trained and safety reporting is well documented in the protocol.

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

All data will be monitored. DSMB is installed and will ensure data integrity and participant safety. The DSMB will provide independent oversight and periodic review of the data throughout the trial.

Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach.

As this is **a low-interventional clinical trial** within the scope of regulation EU No 536/2014 handling, storage, temperature monitoring and IP accountability will be in accordance with the standard of care.

17.2 Safety Reporting Flow Chart

Contact persons

HIRUZ	E	hiruz.ctu@uzgent.be
	T	+32 9 332 05 00
Chief Investigator	N	Jan De Waele
	E	hithard.safety@uzgent.be
	T	+32 9 332 62 19

Flowchart reporting

Type of Adverse Event	**Action(s) be taken**
AE	Report any adverse event thought to be related to the study assigned method of administration, more specific related to IP dose and duration within 7 days of discovery.
SAE	Report any SAE thought to be related to the study assigned method of administration, more specific related to the IP dose and duration to HIRUZ CTU and chief investigator within 24 hours after becoming aware via the Redcap eCRF. Use the backup SAE form if the Redcap eCRF is not working to report the SAE within 24 hours after becoming aware to HIRUZ CTU hiruz.ctu@uzgent.be and chief investigator via the HIT HARD safety mailbox hithard.safety@uzgent.be PI should sign off the SAE entered via the Redcap eCRF or the SAE paper form in case this is used. SAEs reported will be added to a list for yearly reporting.
SUSAR	Report any SUSAR thought to be related to the study assigned method of administration, more specific related to the IP dose and duration to HIRUZ CTU hiruz.ctu@uzgent.be and chief investigator via hithard.safety@uzgent.be within 24 hours after becoming aware of the SUSAR. HIRUZ CTU submits the SUSAR to the EMA (through EV database) after communication with the CI.

Reporting to the local ethics committee of SAEs and SUSARs remains the responsibility of the PI and should be done in accordance with the requirements of the local institution's procedure

17.3 EQ-5D-5L questionnaires

Gezondheidsvragenlijst

Vlaamse versie voor België

(Flemish version for Belgium)

VERSIE VOOR AFNAME DOOR INTERVIEWER

Opmerking voor interviewer: hoewel de eigen stijl van de interviewer gerespecteerd moet worden, moet de verwoording van de instructies voor de vragenlijst zo precies mogelijk worden gevolgd. Bij het beschrijvend systeem van de EQ-5D-5L op pagina 2 van de vragenlijst moet de precieze verwoording worden aangehouden.

Als de respondent moeite heeft met het kiezen van een antwoord of om uitleg vraagt, moet de interviewer de vraag woord voor woord herhalen en de respondent vragen om zo te antwoorden dat het zijn of haar opinie over zijn of haar gezondheid vandaag zo goed mogelijk weergeeft.

INTRODUCTIE

(Opmerking voor interviewer: lees het volgende voor aan de respondent).

We willen graag weten wat u van uw gezondheid denkt. Ik zal telkens uitleggen wat u moet doen, maar u kunt me onderbreken als u iets niet begrijpt of als iets niet duidelijk is. Er zijn geen goede of foute antwoorden. We zijn alleen geïnteresseerd in uw persoonlijke mening.

Eerst lees ik een aantal vragen op. Bij elke vraag kunt u kiezen uit vijf antwoorden. Vertel me welk antwoord het beste past bij uw gezondheid van VANDAAG.

Kies bij elke groep vragen niet meer dan één antwoord.

(Opmerking voor interviewer: Lees bij elke vraag eerst alle vijf de opties. Vraag de respondent dan om te kiezen welke optie op hem/haar van toepassing is. Herhaal eventueel de vraag en opties. Vink onder elk kopje het juiste vakje aan. Wijs de respondent er eventueel regelmatig op dat de referentieperiode VANDAAG is).

EQ-5D BESCHRIJVEND SYSTEEM

MOBILITEIT

Eerst wil ik u vragen stellen over mobiliteit. Zou u zeggen dat:

1. U geen problemen hebt met rondwandelen? ❑
2. U een beetje problemen hebt met rondwandelen? ❑
3. U matige problemen hebt met rondwandelen? ❑
4. U ernstige problemen hebt met rondwandelen? ❑
5. U niet in staat bent om rond te wandelen? ❑

ZELFZORG

Nu wil ik u vragen stellen over zelfzorg. Zou u zeggen dat:

1. U geen problemen hebt om uzelf te wassen of aan te kleden? ❑
2. U een beetje problemen hebt om uzelf te wassen of aan te kleden? ❑
3. U matige problemen hebt om uzelf te wassen of aan te kleden? ❑
4. U ernstige problemen hebt om uzelf te wassen of aan te kleden? ❑
5. U niet in staat bent uzelf te wassen of aan te kleden? ❑

DAGELIJKSE ACTIVITEITEN

Nu wil ik u vragen stellen over dagelijkse activiteiten, bijv. werk, studie, huishouden, gezins- of vrijetijdsactiviteiten. Zou u zeggen dat:

1. U geen problemen hebt met uw dagelijkse activiteiten? ❑
2. U een beetje problemen hebt met uw dagelijkse activiteiten? ❑
3. U matige problemen hebt met uw dagelijkse activiteiten? ❑
4. U ernstige problemen hebt met uw dagelijkse activiteiten? ❑
5. U niet in staat bent uw dagelijkse activiteiten uit te voeren? ❑

PIJN / ONGEMAK

Nu wil ik u vragen stellen over pijn of ongemak. Zou u zeggen dat:

1. U geen pijn of ongemak hebt? ❑
2. U een beetje pijn of ongemak hebt? ❑
3. U matige pijn of ongemak hebt? ❑
4. U ernstige pijn of ongemak hebt? ❑
5. U extreme pijn of ongemak hebt? ❑

ANGST / DEPRESSIE

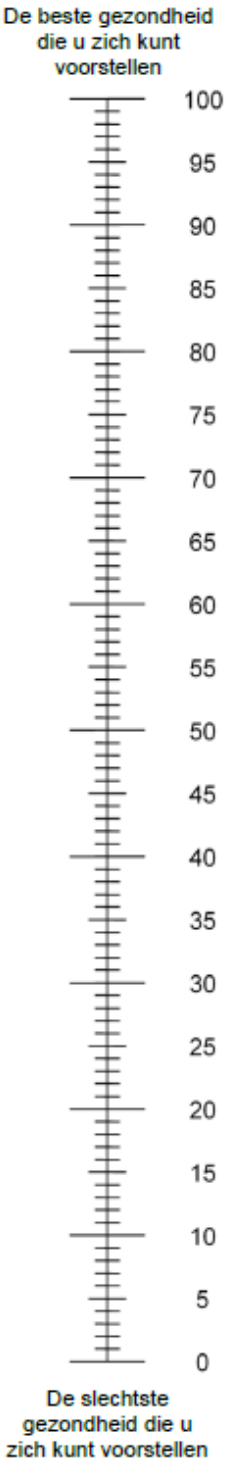
Ten slotte wil ik u vragen stellen over angst of depressie. Zou u zeggen dat:

1. U niet angstig of depressief bent? ❑
2. U een beetje angstig of depressief bent? ❑
3. U matig angstig of depressief bent? ❑
4. U erg angstig of depressief bent? ❑
5. U extreem angstig of depressief bent? ❑

EQ-5D VAS

- **Nu wil ik u graag vragen hoe goed of slecht uw gezondheid VANDAAG is.**
- **Stel u in gedachten een meetschaal voor zoals een thermometer.**
  (Opmerking voor interviewer: bij een live-gesprek laat u de persoon de VAS-meetschaal zien).
- **De beste gezondheid die u zich kunt voorstellen wordt aan de bovenkant van de meetschaal aangegeven met 100 (honderd); onderaan de meetschaal wordt de slechtste gezondheid die u zich kunt voorstellen aangegeven met 0 (nul).**
- **Geef nu het punt aan op de meetschaal dat volgens u aangeeft hoe uw gezondheid VANDAAG is.**
  (Opmerking voor interviewer: markeer de meetschaal op het punt dat de 'gezondheid vandaag' van de respondent aangeeft. Noteer dan het getal dat u op de meetschaal hebt aangegeven in het vakje hieronder).

DE GEZONDHEID VAN DE RESPONDENT VANDAAG = ☐



Dank u voor het beantwoorden van deze vragen.