The Intensive Care Platform Trial (INCEPT)

Core protocol

Protocol version and date
Version 1.3, 2025-02-13

Website
www.incept.dk

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1 | Abstract

Background
Randomised clinical trials (RCTs) are the gold standard for evaluating intervention effects, however, conventional RCTs are bureaucratic, costly, inflexible, and often inconclusive. Adaptive platform trials are increasingly used as they can reduce barriers and are more flexible, and thus come with a higher probability of obtaining conclusive results faster at lower costs.

Objectives
This core protocol describes the methodological framework for the *Intensive Care Platform Trial (INCEPT)*, which will be used to assess the effects of interventions used in adults acutely admitted to the intensive care unit (ICU).

Design
INCEPT is an investigator-initiated, pragmatic, randomised, embedded, multifactorial, domain-based, international, adaptive platform trial. *INCEPT* uses adaptive stopping and arm-dropping rules, as well as fixed and response-adaptive randomisation.

Domains and interventions
Comparable groups of interventions will be nested in domains, which have conceptual similarities with stand-alone randomised trials. Specific domains may be either open label or blinded. Domains will continuously be added to *INCEPT* and conducted following domain-specific appendices to the core protocol. Domains will be *closed*, i.e., arms will not be added to domains once started.

Inclusion and exclusion criteria
Adults acutely admitted to the ICU will be screened if they are eligible for at least one active domain. The only platform-level exclusion criteria are 1) informed consent after inclusion expected to be unobtainable and 2) patients admitted under coercive measures. Additional inclusion and exclusion criteria will be domain-specific.

Stakeholder involvement
Stakeholder involvement is central in *INCEPT* and ensured through a central advisory board comprising various key stakeholder and national and international research panels consisting of ICU survivors, family members, clinicians, and researchers. Stakeholders have been involved in the development of the overall platform trial and continued involvement is planned with pre-specified minimum requirements for involvement in *INCEPT* and all domains.

Outcomes

The following core outcomes will be evaluated in all *INCEPT* domains:

- All-cause mortality at 30, 90, and 180 days
- Days alive without life support at 30 and 90 days
- Days alive and out of hospital at 30 and 90 days
- Days free of delirium at 30 days
- Health-related quality of life at 180 days evaluated using EQ-5D-5L index values and EQ VAS
- Cognitive function at 180 days evaluated using the Mini MoCA test
- One or more domain-specific safety outcomes

Each domain will use one of the core outcomes as the primary outcome and the *guiding* outcome driving all adaptations.

Statistical methods

Primary analyses will generally be conducted in the intention-to-treat population of each domain. *INCEPT* primarily uses Bayesian statistical methods with neutral priors conveying either minimal information or some scepticism, although specific domains may use conventional, frequentist statistical methods. Outcomes will generally be analysed using logistic and linear regression models adjusted for pre-specified anticipated prognostic baseline characteristics, followed by calculation of sample-average estimates and intervention effects using G-computation. Results will be presented for each intervention and comparisons presented on both the absolute (risk differences and mean differences) and relative (risk ratios and ratios of means) scales with 95% credible intervals and probabilities of superiority. *INCEPT* will generally use constant, symmetric stopping rules for superiority/inferiority based on the guiding outcome; domains may use stopping rules for practical equivalence or futility based on the posterior distribution of the guiding outcome on the absolute scale. All stopping rules will be binding. Response-adaptive randomisation, either with or without restrictions, may be used based on the posterior distribution for the guiding outcome. Missing data will be multiply imputed. Additional secondary analyses (e.g., per-protocol analyses), sensitivity analyses, and analyses of heterogeneity in intervention effects according to pre-defined baseline characteristics may be specified for each domain and undertaken once a domain has stopped. Domains will be designed and evaluated using statistical simulation.

Estimated timeline

We expect that *INCEPT* will launch and include the first participant in the first quarter of 2025. *INCEPT* has been designed to run perpetually with domains continuously added and stopped and without a planned stopping date for the overall platform.

Funding
INCEPT is funded by the *Novo Nordisk Foundation* and *Sygeforsikringen 'danmark'*, with additional support from *Savværksejer Jeppe Juhl og hustru Ovita Juhls Mindelegat*, *Grosserer Jakob Ehrenreich og Hustru Grete Ehrenreichs Fond*, and *Dagmar Marshalls Fond*.

2 | Administrative information

2.1 | Sponsor and management committee

Sponsor

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INCEPT management committee

The *INCEPT* management committee will consist of key persons at the coordinating centre, representatives of all partners in *INCEPT*, and all participating countries and Danish regions. In addition, the sponsor (or a delegate) of each active domain will be included in the platform management committee. If domain sponsors have conflicts of interest with regards to other domains or the general management (e.g., in case of partnerships with industry or commercial actors), they will only hold an advisory role. The complete management committee will be made available on the *INCEPT* website before the first inclusion and continuously updated as relevant.

2.2 | Coordinating and methodological centres

A list of key persons at the coordinating and methodological centres will be made available on the *INCEPT* website before the first inclusion and continuously updated as relevant.

Central coordinating centre

Department of Intensive Care 4131, Copenhagen University Hospital – Rigshospitalet
Blegdamsvej 9, DK-2100, Copenhagen, Denmark
Phone: +45 3545 7450
Mail: contact@incept.dk
Website: www.incept.dk

Methodological and statistical centres

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Blegdamsvej 9, DK-2100, Copenhagen, Denmark

Section of Biostatistics, Department of Public Health, University of Copenhagen
Østre Farimagsgade 5, DK-1014, Copenhagen, Denmark

Data management centre
Department of Intensive Care 4131, Copenhagen University Hospital – Rigshospitalet
Blegdamsvej 9, DK-2100, Copenhagen, Denmark

Advisory board, research panels, and independent data monitoring and safety committees
A central advisory board and multiple research panels consisting of key stakeholders including ICU survivors and family members, clinicians, trialists, methodologists/biostatisticians, and other relevant stakeholders (e.g., representatives of hospital management, legal units, and health economists) will advise the platform and domain management committees on central aspects related to the conduct of *INCEPT* or specific domains (section 11). In addition, independent data monitoring and safety committees (IDMSCs) will be established for each domain (section 17).

2.3 | Investigators and clinical trial sites

A list of all investigators (including all national and local investigators) and clinical trial sites will be available with the registration in the *Clinical Trials Information System (CTIS)* prior to initiation of *INCEPT* and subsequently continuously updated by the platform management committee. An overview of the participating sites in each domain will be available and continuously updated at the *INCEPT* website.

2.4 | Protocol contributors

The following persons have contributed to the *INCEPT* core protocol:

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3 | Abbreviations

ACT EU: *Accelerating Clinical Trials in the EU*
AE: *adverse event*
API: *application programming interface*
AR: *adverse reaction*
ATC: *Anatomical Therapeutic Chemical (drug classification system)*
CAM-ICU[-7]: *Confusion Assessment Method for the Intensive Care Unit [7]*
CONSERVE: *CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances statement*
CONSORT-ACE: *Adaptive designs CONSORT Extension*
CONSORT: *Consolidated Standards of Reporting Trials statement*
CrI: *credible interval*
CRIC: *Collaboration for Research in Intensive Care*
CRP: *C-reactive protein*
CT: *computer tomography (scan)*
CTIS: *Clinical Trials Information System*
ECG: *electrocardiogram*
eCRF: *electronic case report form*
EMPRESS: *Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis trial*
EPR: *electronic patient record*
EQUATOR: *Enhancing the QUAlity and Transparency of health Research*
EU: *European Union*
EUCT number: *European Union Clinical Trials Information System (CTIS) number*
FDA: *United States Food and Drug Administration*
FHIR: *Fast Healthcare Interoperability Resources standard*
GCP: *Good Clinical Practice*
GCS: *Glasgow Coma Scale*
GDP: *gross domestic product*
GDPR: *General Data Protection Regulation*
HRQoL: *health-related quality of life*
ICDSC: *Intensive Care Delirium Screening Checklist*
ICH: *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*
ICH-GCP: *International Council for Harmonisation on Good Clinical Practice*
ICMJE: *International Committee for Medical Journal Editors*
ICU: *intensive care unit*
IDMSC: *independent data monitoring and safety committee*
IL: *interleukin*

INCEPT: *the Intensive Care Platform Trial*
IQR: *interquartile range*
ITT: *intention-to-treat*
kg: *kilogram*
L: *litre*
m: *meter*
MAE: *median absolute error*
MAAS: *Motor Activity Assessment Scale*
MD: *mean difference*
MI: *multiple imputation*
Mini MoCA: *Montreal Cognitive Assessment test, 5-minute version*
mmHg: *millimetres of mercury*
mmol: *millimoles*
NIHR: *National Institute for Health and Care Research*
OR: *odds ratio*
PaO_2: *arterial partial pressure of oxygen*
PP: *per-protocol*
Pr: *probability*
RASS: *Richmond Agitation-Sedation Scale*
RCT: *randomised clinical trial*
RD: *risk difference*
REMAP-CAP: *Randomized Embedded Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia*
RLS85: *Reaction Level Scale*
RMSE: *root mean squared error*
ROBUST: *Reporting of Bayes Used in clinical STudies guideline*
RoM: *ratio of means*
RR: *relative risk*
RRT: *renal replacement therapy*
RSS: *Ramsay Sedation Scale*
SAE: *serious adverse event*
SAR: *serious adverse reaction*
SAS: *Sedation Agitation Scale*
SmPC: *Summary of Product Characteristics*
SMS-ICU: *Simplified Mortality Score for the Intensive Care Unit*
SPIRIT: *Standard Protocol Items: Recommendations for Interventional Trials statement*
SUSAR: *suspected unexpected serious adverse reaction*
UCPH: *University of Copenhagen*
WHO: *World Health Organization*
YYYY-MM-DD*: year, month, day*

μmol: *micromoles*

4 | Core protocol structure and overview

The latest and previous versions of the core protocol will be made publicly available on the *INCEPT* website (www.incept.dk) prior to trial initiation and a manuscript describing the rationale and key design features will be submitted to a peer-reviewed, international medical journal. Similarly, the latest and previous version of all protocol appendices (including domain-specific appendices and national/local appendices) will be made publicly available on the *INCEPT* website before they become effective.

4.1 | Core protocol

This core protocol describes the overarching methodological and organisational aspects of the *INCEPT* platform trial. In several sections, the protocol includes multiple methodological options; different choices and combinations thereof will be chosen for specific domains on the platform as described in the domain-specific appendices.

4.2 | Appendices

Separate domain-specific appendices describe each domain including backgrounds/rationales, interventions, and methodological choices for each domain. National/local appendices describe any adaptations of *INCEPT* necessary in specific countries or regions. Additional appendices may be developed as necessary. The following appendices are included as part of the core protocol document (with all other appendices being separate documents, available at the *INCEPT* website):

- Appendix 1 (section 21.1): completed reporting checklists
- Appendix 2 (section 21.2): frequent serious adverse events in intensive care patients
- Appendix 3 (section 21.3): example domain inclusion flowchart
- Appendix 4 (section 21.4): example baseline and outcome data tables
- Appendix 5 (section 21.5): variable definitions

5 | Objectives and lay description

5.1 | Objectives

Randomised clinical trials (RCTs) are essential for comparing intervention effects [1]. However, conventional RCTs come with challenges related to both the chances of obtaining conclusive and clinically useful results and to regulatory burden, infrastructure, data collection, timeliness, and costs [2]. The primary objective of the *Intensive Care Platform Trial (INCEPT)* research programme is to establish an investigator-initiated adaptive platform trial to overcome or mitigate these challenges. *INCEPT* will facilitate efficient and rigorous assessment of interventions used in critically ill adults by establishing a broad intensive care unit (ICU) based platform trial with regulatory frameworks, including protocols and contracts; flexible and improved methodology; substantial involvement of relevant stakeholders including ICU survivors and members of the public; and automated data capture through integration with electronic patient records (EPRs) and registers. *INCEPT* will primarily focus on interventions in common use where practice differs among clinicians, but other interventions may similarly be assessed on the platform.

The *INCEPT* core protocol describes the central platform trial features and methods and outlines the necessary choices when preparing *domains*, in which specific interventions are compared. Domains are conceptually comparable stand-alone 'trials' running on the platform. In addition, the *INCEPT* research programme aims to solve methodological and practical issues related to trial conduct in the critically ill and to provide guidance to fellow trialists on the conduct of adaptive trials including adaptive platform trials. Further, the core protocol describes involvement of key stakeholders (including patient and public involvement) in *INCEPT* through a central advisory board and multiple research panels, including involvement in the development of a core outcome set for general ICU patients [3,4]. In addition, we are developing tools and guidance that will help other researchers understand and conduct similar platform trials, which is identified as a pressing need by the *World Health Organization* (*WHO*) [1]. We are also establishing a solid and lasting integration between trial infrastructure, EPRs, and clinical databases and registers to automate data collection. Finally, as part of *INCEPT* we aim to later establish additional biobanking infrastructure and a framework for conducting health economic analyses.

The overall objectives of the *INCEPT* programme are, thus, to establish an adaptive platform trial that will facilitate better, more efficient, faster, and cheaper comparisons of interventions used in critically ill ICU patients with higher probabilities of conclusive results. This will lead to faster improvements in the quality of care provided to ICU patients; development of infrastructure that will support this and decrease laborious, error-prone, and time-consuming manual data entry; and increased involvement of patients, public and other relevant stakeholder in the research progress to maximise relevance and value for patients and their family members, hospitals, and society.

5.2 | Lay description

Among critically ill patients, many die, and many of the survivors and their family members struggle for years with reduced quality of life [5]. Critically ill patients are treated in intensive care units (ICUs). Here, they receive life support, e.g., mechanical ventilation and advanced support of the circulation (heart and blood vessels) and kidneys. In addition, ICU patients receive many other treatments. It is, however, uncertain if all the treatments provide value for the patients [6]. The desirable effects of many treatments are uncertain, and some may be wasteful or even harmful [7,8].

Clinical trials are essential to validly assess the desirable and undesirable effects of different treatments [1]. However, conventional clinical trials have limitations [2]:

- They typically only assess a single question related to a single comparison of treatments at a time.
- They are often not very flexible, including with regards to the number of participants needed, and this increases the risk that a trial will end up as inconclusive.
- There is no or limited re-use or sharing of infrastructure across trials, leading to duplicate work and resource use.
- Trial participants do usually not benefit from the obtained knowledge before the trial concludes.
- Involvement of patients, family members, and other stakeholders is typically limited, which may decrease the relevance of the questions addressed [9].

With the *Intensive Care Platform Trial (INCEPT)*, we aim to tackle these challenges by establishing a flexible platform trial that continuously learns from the obtained results. The platform trial may run forever with simultaneous and continuous assessment of many treatments. *INCEPT* will continuously learn from the accrued data and use these to improve the treatment of both participating and future patients. With *INCEPT*, we are also building a framework for thorough and extensive involvement of key stakeholders, including patients and family members. *INCEPT* will improve the way clinical trials are done and increase the probabilities that treatments are improved. This will:

- Directly improve outcomes for ICU patients.
- Relieve a strained healthcare system by discarding inefficient or harmful treatments.
- Ensure that new treatments are beneficial or cost-effective before implementation.
- Lower the costs and burdens of assessing more treatments in the critically ill.

Finally, as part of the *INCEPT* research programme, we are developing tools and guidance to help researchers implement adaptive platform trials in other clinical settings or diseases.

6 | Background

6.1 | Clinical trials in acutely admitted ICU patients

The most critically ill patients are admitted to intensive care units (ICUs) for life supportive treatments, e.g., advanced respiratory support, advanced circulatory support, and renal replacement therapy (RRT). Approximately 25,000-30,000 patients are admitted to Danish ICUs each year [10,11], a number that is expected to increase in coming years due to demographic changes [12].
The overall mortality in general ICU patients in Denmark is approximately 20% after 30 days [11], and survivors suffer from long hospital stays and recovery periods, and decreased health-related quality of life (HRQoL) [13,14]. Further, ICUs consume vast amounts of healthcare and financial resources, e.g., up to 1% of the gross domestic product (GPD) in the United States [15]. Thus, critical illness is a huge burden on patients, their family members, and society [5]. Only approximately 10% of ICU interventions are supported by evidence of high certainty [6], with the rest based on physiological rationales, tradition, and evidence of lower certainty, including results from non-randomised studies. Lack of clinically relevant effects or even harm has been shown alarmingly often for interventions that *have* been assessed in RCTs, and increased mortality has been shown almost as often as reduced mortality [7,8]. Consequently, multiple recent RCTs have led to several interventions no longer being used routinely [16–19]. RCTs of common and new interventions (*before* implementation in clinical practice) are hence essential to ensure optimal care of critically ill patients and optimal use of resources in healthcare systems.

While RCTs are essential [1], conventional RCTs (i.e., parallel group, 2-arm RCTs with fixed allocation profiles and sample sizes, analysed using frequentist statistical methods) come with limitations [2]. Most RCTs conducted in the intensive care setting have been unable to firmly show superiority of the interventions assessed [7,20], with uncertainty precluding firm conclusions about small-to-moderate clinically relevant effects. There are likely multiple reasons for this. First, the effects of most interventions used in the ICU are likely relatively small. While small differences in intervention effects may be important when used for many patients world-wide [1], they are difficult to substantiate in an average-sized RCT. Second, over-optimistic assumed effect sizes and incorrect assumed baseline outcome distributions (e.g., control group event rates) have frequently been used in previous RCTs conducted in the ICU [21–25]. This may lead to uncertain results [25], making RCT unable to firmly refute or confirm clinically relevant effect sizes, with the risk that results are erroneously interpreted as if there are no differences between interventions [22,26]. Third, conventional RCTs are inflexible with predefined sample sizes and no or few interim analyses with very strict criteria for stopping before the full sample size has been reached. Thus, there is not only a risk of inconclusiveness despite inclusion of the planned number of participants, but also a risk that trials continue *longer* than necessary, thereby wasting limited research

resources and potentially exposing participants to potential harm while delaying benefit for other patients from the trial results [2]. Finally, involvement of relevant stakeholders (including ICU survivors and family members) is essential to keep research focused on the questions most relevant to patients [1]. While stakeholder involvement seems on the rise [27,28] and is increasingly recommended [29], it is still relatively uncommon in the ICU setting [9,30] where research agendas are primarily set by academic and industry researchers [31].

6.2 | Adaptive platform trials

Adaptive trials

Adaptive trials use results from pre-defined adaptive (interim) analyses of data to modify the ongoing trial [32]. To ensure the integrity of the trial and the validity of the results, this is done according to clear, pre-specified adaptations rules [32–34]. Many large RCTs conducted in critically ill patients are technically adaptive due to the use of conventional (frequentist) group sequential designs with pre-planned interim analyses and stopping rules [32], however, the extent of adaptivity is typically limited. Increasingly, more complex adaptive designs (with more adaptive analyses and multiple types of adaptations) are used, including adaptive platform trials which are complex, flexible designs with multiple adaptive elements [35,36].

Adaptive trials may use several adaptive features, including adaptive stopping, adaptive arm-dropping, response-adaptive randomisation, and adaptive enrichment [2,37,38] as illustrated in **Figure 1**.

Figure 1. Adaptive trial flow

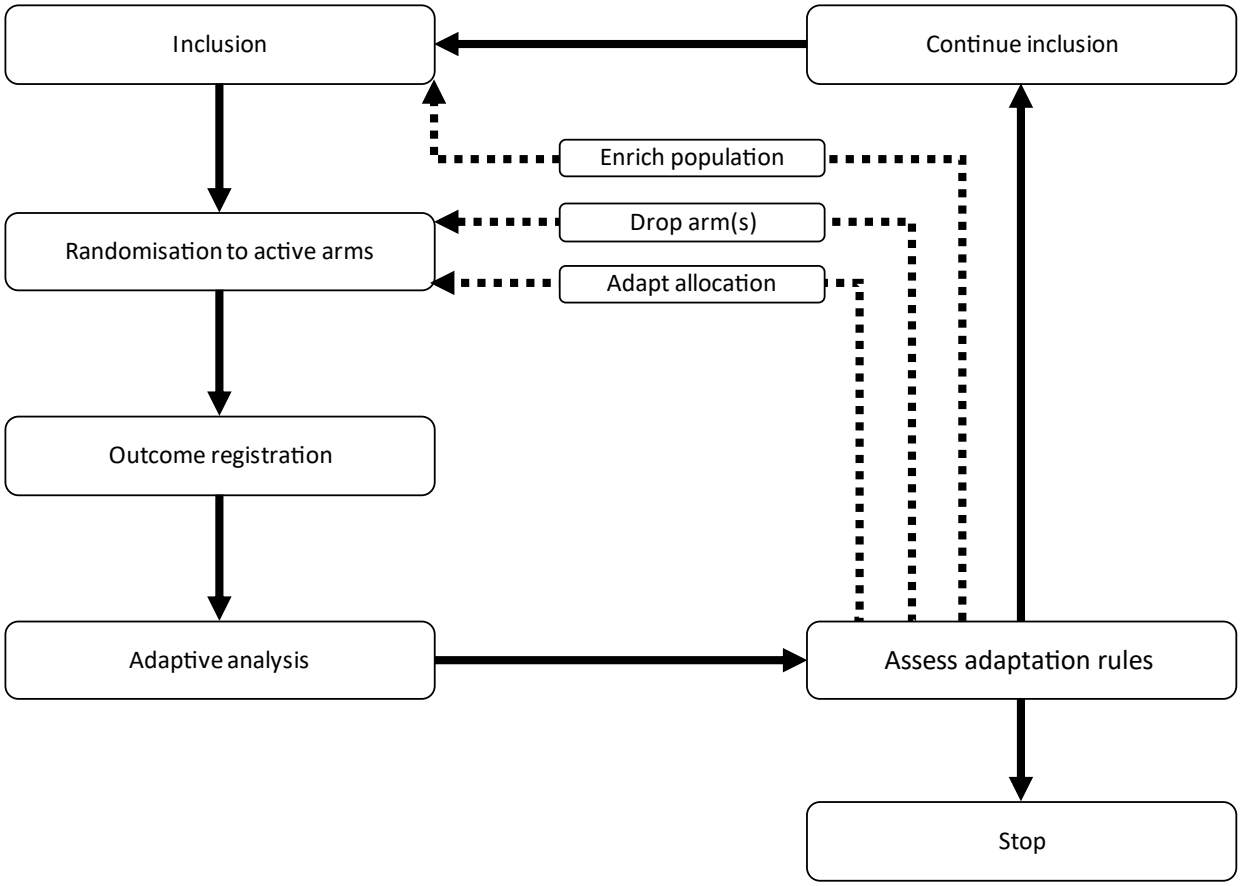


Illustration of the flow in an adaptive trial with adaptive stopping, arm-dropping, allocation, and enrichment as described in the text. Not all adaptive features are used in every adaptive trial (or adaptive platform trial domain).

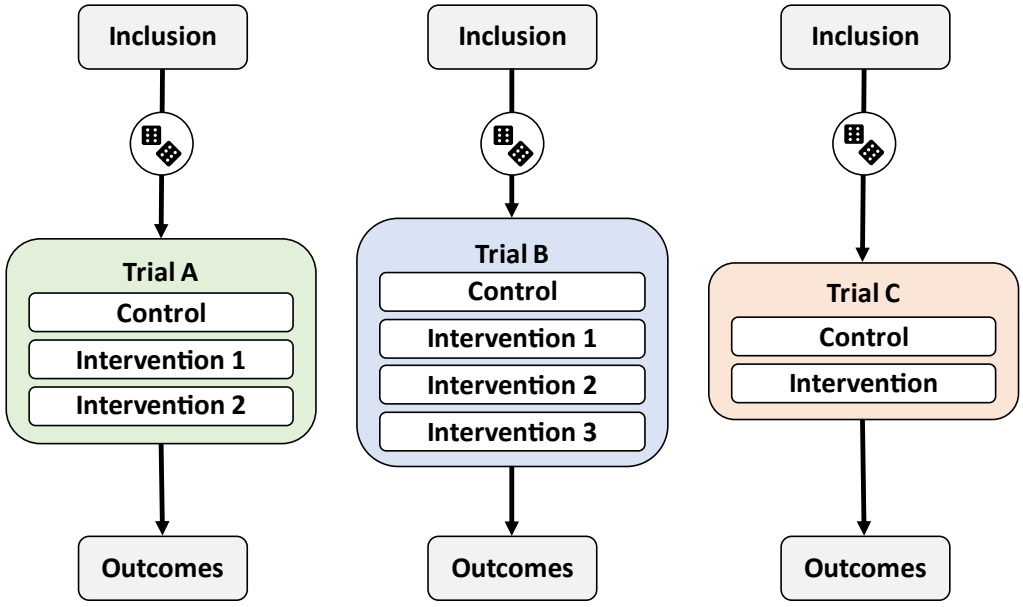
Adaptive stopping and arm-dropping rules make trials flexible and limit the influence of the assumptions used to estimate fixed sample sizes. This can increase trial efficiency (i.e., decrease sample sizes) and the chance of conclusive results [2,39–42], especially if inferior arms are dropped early in multi-arm trials (>2 arms), leading to increased allocation to better-performing arms. While concerns have been raised about slight inflation of effect estimates in trials stopped early, the likelihood, magnitude, and implications of this are limited in realistic scenarios, especially in larger trials and when constant stopping thresholds are used throughout [43–46]. This potential downside is outweighed by the benefits of allowing early stopping according to pre-specified and adequately evaluated rules (section 9.4 and section 9.9). Stopping rules for superiority, inferiority, practical equivalence, and/or futility may be used, typically in combination with a pre-specified maximum number of participants [2,38]. Response-adaptive randomisation may be used to adapt allocation profiles based on adaptive analyses of outcome data, leading to more participants allocated to more promising interventions and thus increasing the benefit for participants (i.e., *internal* patients) [2,35,38,47]. Depending on the exact trial design, response-adaptive randomisation may increase trial efficiency (by lowering the total sample sizes) and

power compared to fixed randomisation. However, it may also decrease trial efficiency and power in other cases, including some 2-arm trials and some multi-arm trials without a common control group [39,48–53], depending on the type of outcome and whether there are between-arm differences, which is unknown at trial initiation. Finally, using adaptive enrichment, trials may update or restrict inclusion criteria to those more likely to benefit [2,37,54]. Overall, these adaptive features may confer ethical benefits and make adaptive trials more compelling to patients, clinicians and other stakeholders [55], just as they have been highlighted as ethically favourable for participants in ongoing adaptive trials in the ICU setting [47,56].

Adaptive platform trials

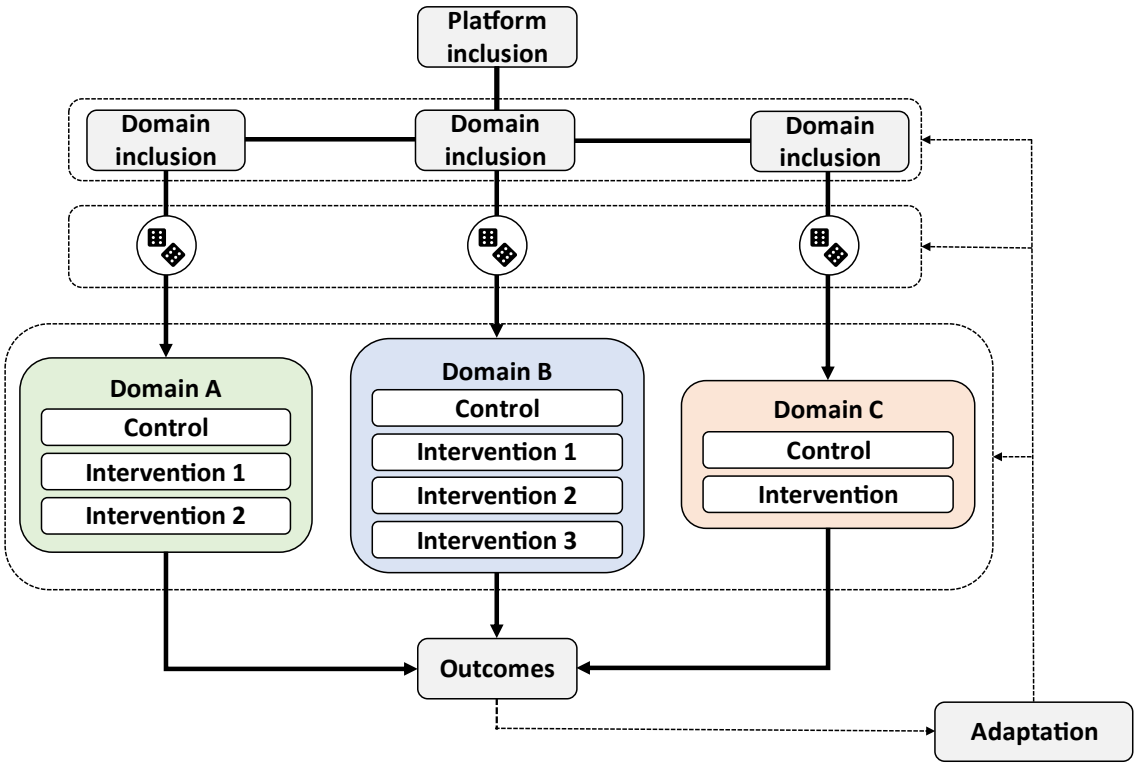
Adaptive platform trials may remedy some of the challenges with conventional RCTs [2,35] and are increasingly used across medical specialties [36,57], including critical and intensive care [58]. Adaptive platform trials extend adaptive trials by using a core protocol not focusing on specific *interventions* but on studying multiple interventions in a *population* defined by a specific disease, condition, or setting [1,2,35,59,60]. In *INCEPT*, the population will be adults who are acutely admitted to the ICU. Comparable groups of *interventions* may be nested in *domains*, which conceptually are comparable to separate conventional RCTs (**Figure 2** and **Figure 3**). This structure will be used throughout *INCEPT*. New interventions or domains can be added to platform trials as they progress or as old interventions are dropped or old domains are stopped [2,35]. Hence adaptive platform trials may run perpetually, assessing many different interventions using the same trial framework, infrastructure, methodology, and core protocol. Once up and running, adaptive platform trials will likely increase efficiency and lower the costs and workload associated with the assessment of additional interventions compared with multiple stand-alone trials [2,35,61,62].

Figure 2. Multiple stand-alone trials



Multiple stand-alone example trials with a control arm in each and one or more interventional arms. Approvals, inclusion, randomisation, outcome registration, and trial infrastructure are separate for each trial.

Figure 3. Multiple domains in a single adaptive platform trial



Multiple domains consisting of comparable interventions within a single adaptive platform trial (in this example, all domains include a control arm and at least one interventional arm; of note, domains to not need to include a control arm, similar to how this is not required in stand-alone trials). All domains use the same overall trial infrastructure, overall eligibility criteria (with additional domain-specific enrolment criteria possible), and data collection framework.

Based on accumulating outcome data, each domain may adapt continuously with regards to stopping/arm-dropping, allocation profiles (response-adaptive randomisation), and/or domain eligibility criteria (enrichment).

6.3 | Rationale and ethical justification

The rationale behind the *INCEPT* platform trial is motivated by the benefits of adaptive platform trials and substantial stakeholder involvement, and ethically justified by the direct improvements in treatment and quality of care (including for participants in the trial) and for the indirect improvements or other patients associated with increased trial efficiency, high probabilities of conclusive results, lower costs, and research infrastructure re-use [2,35,55,62].

First, platform trials can decrease costs and time to initiation of assessment of interventions compared to multiple stand-alone trials once the platform is up and running due to standardisation and re-use of trial infrastructure [61,62], including the approval of domain-specific protocol appendices, contracts, and data agreements. This will make participation and enrolment easier and simplify trial procedures compared to multiple independent stand-alone trials. As research funding and resources are limited, lower costs and efficiency gains are ethically desirable, as it allows more research questions to be answered using the limited resources available and avoids or limits waste due to inconclusive results. Thus, platform trials ultimately have the potential to improve patient care faster and with higher certainty.
Relatedly, platform trials have the potential to harmonise and ease procedures related to informed consent (section 8.5) not only for clinicians and researchers, but also for participants and their next of kin compared to separate informed consent procedures in multiple stand-alone trials. Further, platform trials – due to longer durations, potentially running perpetually – may make it more feasible to establish extensive integration into clinical practice and embedding of the platform trial in EPRs and existing registries, including automatic data capture. This will ease trial conduct, reduce barriers between research and clinical practice through tighter integration (e.g., by automatic alerts on eligible patients or relevant clinical events through the EPRs), and further decrease costs if data collection is partially or fully automated within the platform trial [2,35,47,63]. In addition, integration with EPRs will make it easier to monitor protocol adherence and separation in platform domains and enable quicker detection of outliers (e.g., sites with less separation between arms than expected), which may increase quality and validity of the trial results and serve as continuous quality assurance of trial procedures and delivery.

Second, adaptive platform trials may be more attractive than conventional stand-alone RCTs to patients and family members. Results from conventional RCTs in the ICU will primarily benefit future patients *external* to the trial. Thus, participation in conventional RCTs is fundamentally altruistic. Adaptive platform trials may directly benefit participants, i.e., *internal* patients, for multiple reasons. For multi-arm comparisons, early dropping of inferior arms increases allocation to better performing interventions [2,35]. Further, when response-adaptive randomisation is used,

adaptive platform trials *learn* prior to conclusion and this increases the individual participants' chances of being allocated to interventions that are more likely to be better [2,35,47]. Thus, participation in adaptive platform trials may be more attractive to individual patients [55] and their family members, and may accelerate implementation of results in clinical practice, which is otherwise a complex and lengthy process [64,65]. Further, in multi-arm trials and platform trials with multi-arm domains with a control group, participants are more likely to be allocated to a non-control intervention, which may be desirable to potential participants as interventional arms *a priori* are generally expected to be better than usual care. This has the potential to increase recruitment rates [66].

Third, adaptive stopping rules in combination with large maximum sample sizes limit the risk of trials being both too large (and more costly and taking longer time to complete than necessary) and too small (and at risk of being inconclusive) if assumptions used in sample size calculations do not hold, and make it more feasible to focus not only on large effects, but also smaller but clinically relevant effects [2]. Compared to multiple stand-alone 2-arm trials, multi-arm trials and platform trial domains can be faster and more efficient, require lower total sample sizes, and may thus be preferable both economically and for participants, clinicians, and researchers [35,41,67,68].

Fourth, platform trials with simultaneous enrolment to multiple domains have advantages compared to multiple stand-alone RCTs with co-enrolment due to standardisation of trial procedures, enrolment procedures and data collection; limitation of competition and exclusions due to non-aligned enrolment criteria; and by facilitating easier and more efficient assessment of interactions [47].

Fifth, if new interventions or groups of interventions emerge after trial initiation or if the number of relevant (groups of) interventions is larger than what is considered simultaneously feasible based on logistics or expected recruitment rates, additional interventions or domains may be added in platforms trials when they emerge or when previous arms are dropped or previous domains conclude [2,35,59].

Sixth, developing lasting frameworks for involvement of relevant stakeholders throughout the different research phases may be more feasible in large platform trials compared to separate stand-alone trials, and this ensures relevancy to the end-users of the generated evidence.

Finally, patients eligible for INCEPT in general and specific domains will be unable to consent due to their critical illness, which constitutes a medical emergency requiring immediate intervention with the interventions assessed in the trial. Consequently, INCEPT will use the applicable consent procedures for emergency research as the interventions cannot be delayed. Informed consent will be obtained according to the applicable laws for emergency research in the participating

countries. Additional ethical justification for each individual domain will be provided in the domain-specific appendices. Compared to multiple individual stand-alone trials, the informed consent procedure in a single platform trial with multiple domains is simplified and expected to be easier for participants and proxies than comparable procedures in multiple individual stand-alone trials.

Together, these benefits of adaptive platform trials provide the rationale and ethical justification for *INCEPT*.

7 | Trial conduct

7.1 | General trial conduct

The *INCEPT* core protocol describes all required items included in the *Standard Protocol Items: Recommendations for Interventional Trials* (*SPIRIT*) *2013 statement* [69] and the relevant items from the *Consolidated Standards of Reporting Trials (CONSORT) Adaptive designs CONSORT Extension (ACE) checklist* [34] (completed checklists included in appendix 1, section 21.1). As *CONSORT-ACE* was developed for trial reports and not protocols, all items are not applicable, but as no counterpart for adaptive trial protocols exist, we considered both *SPIRIT* and *CONSORT-ACE* when preparing this core protocol. *INCEPT* will comply with the core protocol and all relevant appendices, including domain-specific appendices, which will be approved by the competent authorities before enrolment starts and before domains are added to the platform.

INCEPT will comply with the latest version of the Declaration of Helsinki [70], the *WHO* guidance for best practices for clinical trials [1], the *International Council for Harmonisation on Good Clinical Practice (ICH-GCP)* guidelines [71], the *General Data Protection Regulation (GDPR)*, and applicable national laws (including the *Danish Data Protection Act*). Trial conduct will be overseen by the platform and domain management committees, advised by the advisory board and research panels (section 11), and with involvement of domain-specific independent data monitoring and safety committees (IDMSCs; section 17). *INCEPT* has been prepared according to recommendations and guidance from the *Accelerating Clinical Trials in the EU (ACT EU*) initiative for complex clinical trials [72] and the United States *Food and Drug Administration (FDA)* [55]. Finally, *INCEPT* has been designed considering guidance based on practical experiences from other platform trial groups [73] and designed to ensure integrity and validity of the results while using adaptive features, as described throughout the core protocol.

7.2 | Approval and oversight by the competent authorities

INCEPT will be approved by the competent authorities and registered in the *European Union Clinical Trials Information System (CTIS)* and at *ClinicalTrials.gov* before enrolment of the first participant. These registrations will be updated continuously as *INCEPT* progresses and as intervention arms/domains are added, dropped, or concluded.

Following the annual IDMSC meetings for each domain (section 17), reports of domain progress and preliminary results will be shared with the competent authorities. These reports will include the open and closed IDMSC meeting reports as well as the IDMSC minutes described in the IDMSC section (section 17). In combination, these reports and minutes include data on recruitment, consent, protocol adherence, feasibility and separation (where relevant), data on the

primary/guiding outcome and safety outcomes, and results of adaptive analyses conducted including updated allocation profiles where relevant. In addition, the reports to the competent authorities will describe if the platform or domain has been inspected by the competent authorities, any relevant findings from the external monitoring (section 14.5), and a summary or conclusion of the full report.
Importantly, contents of the open reports and IDMSC minutes will be available to the competent authorities and the platform and domain sponsors and management committees, whereas the closed reports are kept confidential from the platform and domain sponsors and management committees and may only be seen by the IDMSC, the methodological-statistical team preparing the reports, and the competent authorities.

All *INCEPT* domains will be paused or stopped for inclusion and randomisation if deemed necessary by the competent authorities.

7.3 | Protocol modifications

No substantial changes to or deviations from the core protocol or the domain-specific appendices will be implemented before review and approval by the competent authorities, except where necessary to eliminate a potential, immediate hazard to the trial participants. Should this happen (e.g., due to unexpected safety outcomes; see section 8.10), the deviation will be reported within 7 days to the competent authorities (15 days if the deviation leads to pausing of *INCEPT* as a whole or a specific domain). If necessary, the information to platform/domain participants will be changed and approved accordingly. Upon approval, notifications about relevant modifications will be sent to all relevant parties, including primary investigators and monitors.

7.4 | Serious breaches

In case of any serious breaches, the platform sponsor will notify the competent authorities via *CTIS* without undue delay, within seven days of becoming aware of the breach. A serious breach is defined as any breach of the European Union (EU) clinical trials regulation (EU regulation (No 536/2014) [74]) or of the currently applicable version of the protocol, including the core protocol and all domain-specific appendices, that are likely to significantly affect the safety and rights of a participant or the reliability and robustness of the trial data [74]. For participating countries outside the EU, serious breaches will be reported as required in those countries.

8 | Platform trial design

8.1 | Overall design

INCEPT is an investigator-initiated, pragmatic, randomised, embedded, multifactorial, international, adaptive platform trial with interventions nested in domains (**Figure 2** and **Figure 3** in section 6.2). *INCEPT* features adaptive stopping and arm-dropping, as well as fixed and response-adaptive randomisation. Specific domains may be either open label or blinded. The core design features and general methodology of *INCEPT* are described in this section of the protocol; section 9 details the statistical methodology.

8.2 | Eligibility criteria

The general eligibility criteria below apply to *INCEPT* as a whole and thus to all domains. Domains may impose domain-specific eligibility criteria that *restrict* the population eligible for that domain further, but domains are not allowed to *broaden* the general eligibility criteria. Domain-specific eligibility criteria always apply to all arms in a domain.

Inclusion criteria:

- Adult patient (≥18 years old) acutely admitted to the ICU. This includes ICU admissions after emergency surgery, unplanned ICU admissions after elective surgery, and prolonged ICU admissions due to complications after elective surgery (i.e., admissions occurring or being prolonged due to an unexpected, worsened condition, but excluding planned ICU admissions after elective surgery without clinical deterioration).
- Eligible for at least one active domain.

Exclusion criteria:

- Informed consent following inclusion expected to be unobtainable (e.g., known previous objections to participation).
- Patient is under coercive measures (e.g., ongoing involuntary hospital stay or under the jurisdiction of correctional authorities).

Patients who have previously been included in *INCEPT* may be included again during new ICU admissions but may only be randomised to domains in which they have not previously been randomised.

8.3 | Domains and interventions

Interventions assessed in *INCEPT* will be nested in *domains* [35] consisting of interventions (arms) comparable to what would normally be assessed in a stand-alone trial (**Figure 2** and **Figure 3** in section 6.2). Although interventions will be mutually exclusive, different interventions may consist of, e.g., different combinations of similar drugs or different doses of the same drug. First-in-human investigational medicinal products or combinations with very limited clinical experience and advanced therapy medicinal products without EU marketing authorisations will not be assessed on *INCEPT*. All domains and interventions will constitute emergency medical research (described in detail in section 8.5), i.e., the research questions cannot be meaningfully answered in populations where this does not apply, including mixed populations. Domain-specific appendices will detail the specific interventions and methodological choices made for each domain (i.e., randomisation/allocation schemes, outcome selection/prioritisation, exact adaptation rules, and statistical analysis plan), with the overall methodological aspects covered in and adhering to the core protocol.

Domain-specific appendices require approval by the platform management committee and the competent authorities. Domains will be prioritised, and domain-specific protocols developed, considering input from key stakeholders, when relevant (section 11). Each domain will have a domain sponsor and domain management committee responsible for the conduct and day-to-day management of that domain. There is no limit per se on the number of active domains on *INCEPT*. However, the platform sponsor and management committee will continuously evaluate the complexity of *INCEPT* with regards to the number of active domains permitted on the platform.

For each domain, the exact number of intervention arms will be specified, including whether all arms are compared against each other or if one arm will be used as a common control against which the other arms are compared separately and pairwise (section 9.2). Either option may be chosen if one arm can be considered to represent standard of care/usual care, in which case the decision will be based on statistical evaluation of domain design performance with both options section 9.9). The first option (i.e., no common control arm) will always be used when no arm can reasonably be considered to represent usual care. *INCEPT* uses *closed* domains [41], i.e., arm-adding and staggered entry within domains is not supported from the outset due to the increased complexity [38,75]. This may be added later, in which case an update to the core protocol will be made. Consequently, while *INCEPT* may potentially run perpetually, domains will continuously be added and closed. Of note, following closure of a specific domain, a new domain may assess similar or identical interventions in comparison with other interventions.

INCEPT will allow enrolment in multiple domains (section 12). Exceptions will be some cases where domains considered highly likely to interact with interventions in another domain or otherwise

affect enrolment, protocol adherence, or outcome assessment in another domain [76]. These decisions will be made on a case-by-case basis, involving the platform and specific domain management committees, as the platform trial setup enables formal assessment of potential interactions between domains, and thus co-enrolment between domains considered likely to interact may appropriate be permitted where relevant and scientifically and ethically appropriate.

INCEPT generally allows and encourages co-enrolment with other trials (section 12). Concomitant/co-interventions not assessed in active domains in *INCEPT* will be given at the discretion of the treating clinicians unless otherwise specified or given according to randomisation in a separate trial with co-enrolment with *INCEPT* permitted (section 12). Domain-specific recommendations or requirements are not allowed to interfere with other active domains allowing simultaneous enrolment; instead, specific exclusion criteria between domains may be used.

8.4 | Trial sites and personnel

Trial sites

Trial sites will be ICUs in hospitals in Denmark and other participating countries. Trial sites may decide to only actively participate in selected domains, i.e., only include patients in selected domains and only delivering the interventions in those domains (in case of transfers from one site participating in *INCEPT* to another, the receiving site will continue data collection and the consent procedure for the entire platform trial, including domains in which the site is not active). Sites participating in a domain must allow inclusion into all active arms in that domain. Participating trial sites will be listed in the *CTIS* registration, which will be continuously updated as relevant. An overview of countries and trial sites participating in *INCEPT* and each domain will be made available and continuously updated at the trial website.

Trial personnel

All clinical staff caring for included participants will generally be eligible to care for and deliver the interventions to trial participants, except where specifically restricted in a domain-specific appendix. Trial personnel may consist of multiple staff groups including but not limited to medical doctors, nurses, and medical or nursing students. All trial personnel will be trained and certified in the relevant trial procedures according to *Good Clinical Practice (GCP)* guidelines [71]. Screening to domains will be done by trained trial staff and informed consent procedures will be handled by trained trial staff with thorough knowledge of the platform trial and any relevant domains and following the applicable legislation for clinical trials conducted in emergency situations (justification provided in section 8.5) in each participating country (described separately for each country in a national appendix prior to commencement of enrolment in each country). Participating trial sites will receive written and oral instructions about the trial procedures and

training, and (a) 24-hour hotline(s) will be staffed and available for trial-related questions, including questions to the enrolment and informed consent procedures.

8.5 | Screening, inclusion, and informed consent procedures

Screening and inclusion

Screening and inclusion of participants will be done by trained trial staff (trial investigators) (section 8.4) followed by obtainment of informed consent according to the applicable laws. The process is illustrated in **Figure 4**.

Figure 4. Screening and informed consent in INCEPT

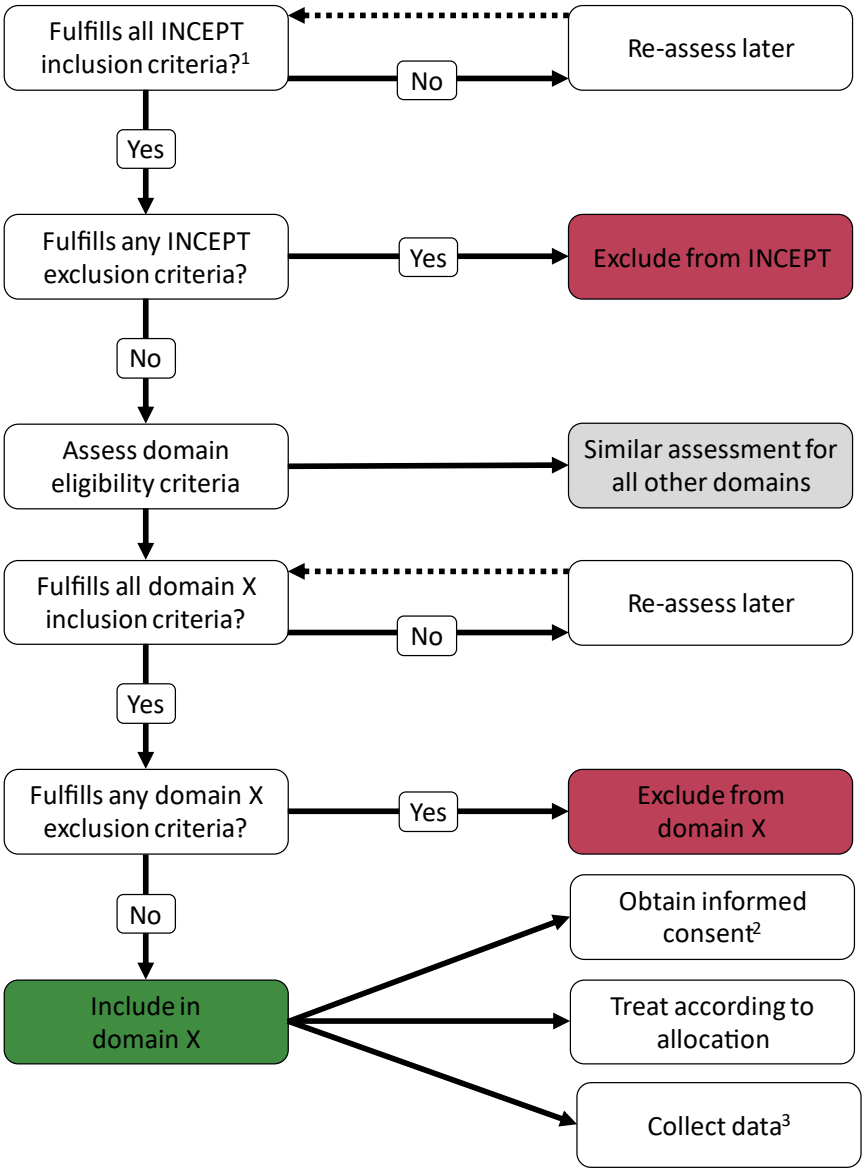


Illustration of screening, inclusion, and obtainment of informed consent in *INCEPT*; the screening/consent flow for a single domain (*domain X*) is illustrated in the lower part of the figure; this is a separate but otherwise identical process for each additional domain.
[1] The general INCEPT inclusion criteria include the patient being eligible for at least one active domain; for simplicity, this is not illustrated in the figure.
[2] The informed consent process is common and simultaneous for all domains that the patient is included into *and* all domains that the patient may potentially be included to later during the ICU stay (described in detail below). Of note, as *INCEPT* constitutes emergency medical research, inclusion and randomisation to *INCEPT* will take place before obtainment of informed consent. Subsequent inclusion to all additional domains will also constitute medical emergencies.
[3] Data collection includes generic *INCEPT* baseline data and core outcomes (overlapping between domains) and domain-specific data.

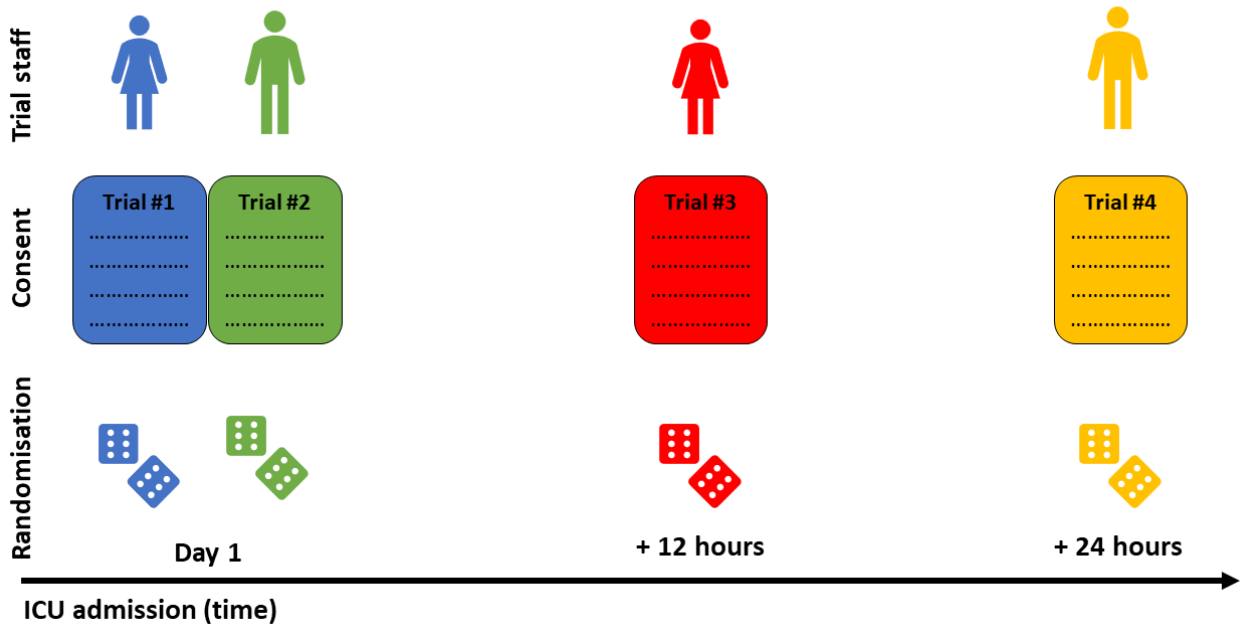
Screening will occur as soon as possible when a patient admitted to a participating ICU fulfils all the general *INCEPT* inclusion criteria (including eligibility in at least one domain). If at least one *INCEPT* exclusion criterion is fulfilled, the patient will be excluded from *INCEPT* in general; otherwise, formal assessment of eligibility in all domains active at the ICU where the patient is admitted will take place. The patient will be screened in all active domains where the domain-specific inclusion criteria are fulfilled; if at least one domain-specific exclusion criterion is fulfilled, the patient will be excluded from that domain. Similarly, if a domain is not active at the screening site, the patient cannot be included to that domain during that particular ICU stay, even in case of transfers to other *INCEPT* sites participating actively in that domain. Patients who have been excluded from either the entire platform or a single domain during one ICU stay, may be screened again for the platform (if excluded from the platform overall during the last ICU stay) or specific domains (if excluded from specific domains during the last ICU stay) during a new, separate ICU stay if the general and domain-specific inclusion criteria are then fulfilled. ICU stays will be considered separate if the patient has been discharged to any non-ICU location followed by admission to the same or a different ICU. This procedure is similar to current practice in separate, stand-alone RCTs and necessary as *INCEPT* is expected to run for a substantially longer period than conventional RCTs. If patients do not fulfil the *INCEPT* or domain inclusion criteria (and have not been excluded from *INCEPT* or a particular domain during the current ICU stay), inclusion criteria may be re-assessed at any time. For each domain, a flowchart illustrating screening and inclusion process will be presented as exemplified in **Figure S1** (appendix 3, section 21.3).

Inclusion and allocation across multiple domains

INCEPT is a multifactorial, domain-based, adaptive platform trial [35] with sets of interventions nested in domains. Domains may be seen as sets of interventions according to separate factors in a conventional factorial trial. As such, the inclusion, allocation, and informed consent procedures largely resemble the procedures in conventional factorial trials. Whenever a patient is eligible for the platform and at least 1 domain, the patient will be included without prior informed consent (due to *INCEPT* being conducted as an emergency trial, due to the rationale provided below). Informed consent will be obtained according to the applicable laws as soon as possible afterwards.

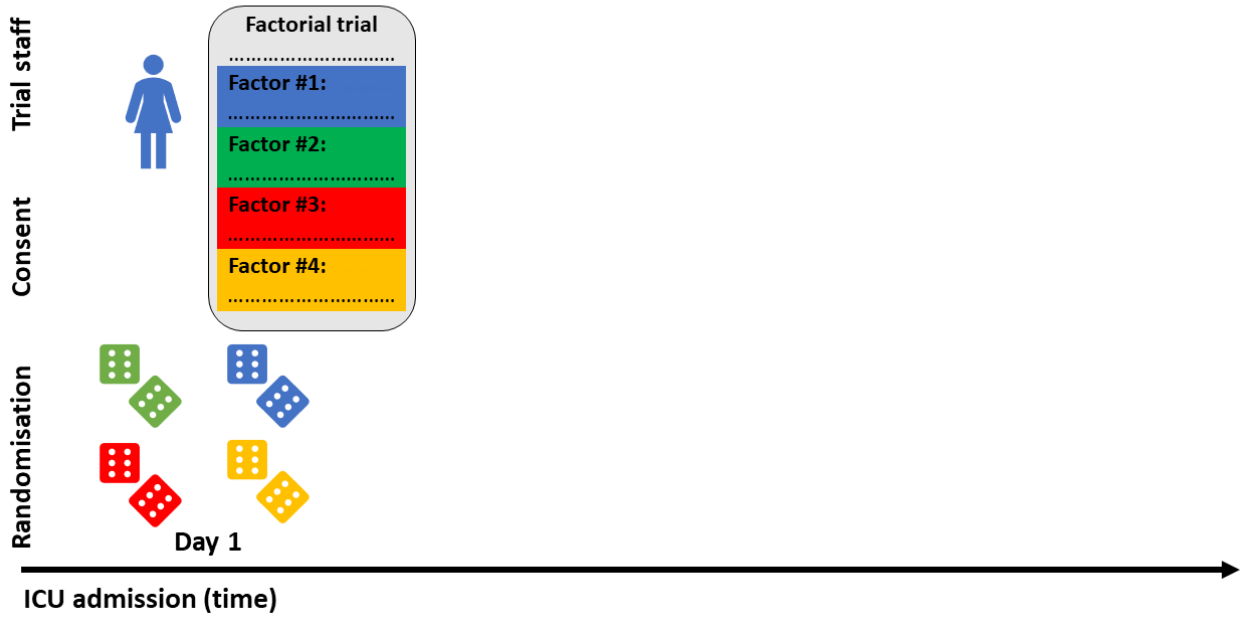
Informed consent for domains that a patient has not already been included to will be obtained once per ICU stay (informed consent given to any domains during previous ICU stays will still be valid during new ICU stays, except if withdrawn), with a common and simultaneous informed consent process for all domains that a patient is included to *and* all active domains that the participant may be eligible for later during the same ICU stay. Importantly, subsequent inclusion to additional domains during the same ICU stay will always constitute medical emergencies (due to, e.g., changes in the clinical condition requiring additional interventions) and may thus occur without prior informed consent, as detailed later in this section. Information about domains that a patient cannot become eligible for during the current ICU stay will be omitted (i.e., when patients fulfil at least one domain-specific exclusion criterion that cannot change during the same ICU stay or if the patient is included at a site where a domain is not active). Importantly, informed consent may be denied or withdrawn on a domain-by-domain basis. Actual *inclusion* and *random allocation* in a specific domain occur once eligibility criteria are fulfilled, and inclusion to different domains during the same ICU stay may thus occur at separate time points; importantly, each additional domain inclusion and randomisation always constitute a medical emergency and all domains will thus be conducted according to the applicable laws for emergency medical research. When new domains are added to the platform, patients already included in one or more domains during their current ICU stay may not be screened to the new domains during their current ICU admission (but this is permitted during a new ICU admission). The procedures in multiple conventional stand-alone trials, in conventional factorial trials, and in domain-based adaptive platform trials like *INCEPT* are illustrated and compared in **Figure 5**, **Figure 6**, and **Figure 7**.

Figure 5. Inclusion, consent, and randomisation in multiple conventional stand-alone trials



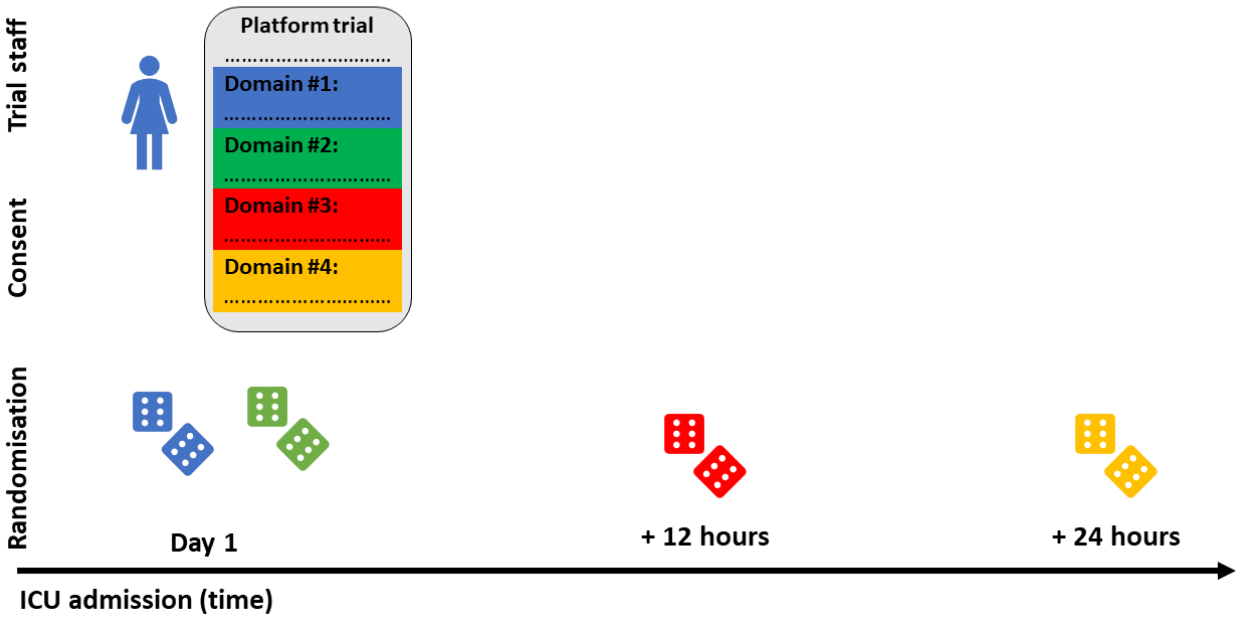
This figure illustrates the inclusion, consent, and randomisation process in multiple stand-alone trials during an ICU stay (horizontal axis). In brief, inclusion, informed consent, and randomisation is completely separate, with different trial staff handling inclusion, random allocation (which occurs immediately following inclusion), and the obtainment of informed consent.

Figure 6. Inclusion, consent, and randomisation in a conventional factorial trial



This figure illustrates the inclusion, consent, and randomisation process in a conventional (multi-)factorial trial during an ICU stay (horizontal axis). In brief, inclusion, informed consent, and randomisation is a single process for all factors in the factorial trial, with randomisation for each factor occurring simultaneously (and immediately following inclusion) and all parts of the process handled by the same trial staff. Eligibility and consent to all comparisons for each factor is generally required, i.e., it is typically not possible to consent to specific comparisons only.

Figure 7. Inclusion, consent, and randomisation in a domain-based adaptive platform trial



This figure illustrates the inclusion, consent, and randomisation process in a domain-based (multifactorial) adaptive platform trial during an ICU stay (horizontal axis). In brief, inclusion in the platform and one or more domains occurs initially, with screening and informed consent procedures handled by the same trial staff. Informed consent is simultaneously obtained for all domains a patient is eligible for or may become eligible for during the current ICU stay using the same procedure and written informed consent materials using a modular structure describing both *INCEPT* and specific domains. Inclusion and randomisation to separate domains occurs initially or once a participant becomes eligible for additional domains, with randomisation handled at the time of domain inclusion. Importantly, subsequent inclusion to additional domains during the same ICU stay will always constitute medical emergencies (due to, e.g., changes in the clinical condition requiring additional interventions) as described later in this section. It is possible to separately consent to and withdraw consent to specific domains.

Of note, the procedure outlined above and used in *INCEPT* is similar to the procedure used in other domain-based adaptive platform trials, including the *Randomized Embedded Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP)* domain-based, adaptive platform trial conducted in adult ICU patients and approved and conducted within the EU and elsewhere [47]. Importantly, the inclusion and informed consent procedure has been discussed with ICU survivors and relatives (section 11), who were very supportive of this approach, as it reduces information burden (and potential information overload) and is simpler than the procedures in multiple stand-alone trials, where separate informed consent procedures for multiple trials handled by different trial staff members was seen as overly complex and time-consuming.

Informed consent procedures

The procedure for obtaining verbal and written informed consent in *INCEPT* will be based on the

applicable legislation for clinical trials conducted in emergency situations in the participating countries, e.g., the European and Danish legislation [74,77], with adaptations to the legislation in other participating countries as necessary, and additional domain-specific adaptations if required according to the applicable legislation. Detailed recruitment and informed consent procedures for each participating country will be described in national appendices and submitted for approval by the relevant competent authorities and subsequently be made available on the trial website (www.incept.dk) prior to commencement of enrolment in each participating country. *INCEPT* will use a modular approach with regards to the informed consent procedure. The written information material will consist of a section describing *INCEPT* in general followed by separate information sheets about each domain. Information about domains that participants cannot be included in during the current ICU admission (e.g., due to domains not being active in a particular site or country or due to participants fulfilling one or more domain-specific exclusion criteria) will be omitted from the informed consent procedure for that specific participant.

Justification for the use of emergency situation clinical trial procedures

Enrolment in *INCEPT* including all domains will occur without prior informed consent according to the criteria in the applicable EU regulation (No 536/2014) [74]:

- Critical illness requiring acute ICU admission constitutes a medical emergency requiring urgent treatment, including treatment with the interventions assessed in the domains in *INCEPT*.
- Participation in the trial and each domain has the potential to produce a direct clinically relevant benefit for the participant, as described for each domain in the domain-specific appendices.
- It is not possible to supply adequate information and obtain prior informed consent from the patient's proxy or legally designated representative within the therapeutic window, as the interventions assessed are required to be initiated urgently, as delays may negatively affect patient outcomes.
- It is required that the investigator(s) assessing eligibility are not aware of any previously expressed objections to trial participation; if so, the patient will be excluded according to the *"Informed consent following inclusion expected to be unobtainable"* exclusion criterion (section 8.2).
- The platform trial and all relevant domains directly relate to the patient's medical condition (i.e., acute critical illness requiring ICU admission), because of which it is not possible to obtain prior informed consent from the patient or the patient's proxy/legally designated representative within the therapeutic window, and the platform trial and all relevant domains are of such a nature that they can only be conducted in emergency situations due to the clinical condition under study will always constitute an medical emergency.
- The platform and all relevant domains will generally pose minimal risk and burden on the patient in comparison with standard treatment of acute critical illness; if specific domains

deviate from this criterion, this will be included and discussed in the domain-specific appendices.

All domains will be approved according to the applicable regulation for emergency situations described above, as all interventions assessed are used in medical emergencies requiring urgent treatment with the interventions assessed. If inclusion to a domain occurs after the initial inclusion to *INCEPT* and other domains during an ICU stay, it will be due to acute changes in the participant's condition (e.g., clinical deterioration) leading to the requirement for urgent treatment with the interventions assessed in that domain and where delaying this treatment may negatively affect outcomes.

8.6 | Randomisation and allocation concealment

Randomisation and allocation will take place centrally using an electronic system integrated in the electronic case report form (eCRF). For unblinded domains, allocation will be concealed for all clinicians and researchers involved in the screening and randomisation process until a patient has been randomised; for domains with blinded interventions, allocation will remain concealed from clinicians, participants, family members, and research personnel involved in screening, obtainment of informed consent, care of the patient, or data collection.

Randomisation will be completely independent in each domain; thus, participants may be assigned to the control arm (if any) in one domain and to non-control intervention arms in other domains, which may make participation more attractive to patients and their legal surrogates [66]. The exact randomisation scheme will be specified for each domain in the domain-specific protocol appendices; the possible options and general principles are described below with the statistical details outlined in section 9.5.

INCEPT supports both fixed and (restricted) response-adaptive randomisation and combinations hereof [2,35]. As response-adaptive randomisation may have different effects in different trial designs (section 6.2) [39,48–53], use of response-adaptive randomisation in a given domain will depend on pertinent considerations [38].

In domains with fixed allocation profiles, stratified block randomisation will generally be used [78]. Stratification variables will always include site and may include important anticipated prognostic baseline characteristics (specified in the domain-specific appendices). If arms are dropped from such domains, participants will only be randomised to remaining arms but the remaining allocations to remaining arms in the current blocks will be used.

In domains with response-adaptive randomisation, allocation profiles are updated after adaptive analyses (section 9.5). In these domains, we will generally use stratified block randomisation (as described above) until the first adaptive analysis that may change allocation profiles, followed by simple, unstratified randomisation for the rest of the conduct of the domain. This is chosen as stratified block randomisation on one hand protects against major imbalances for important baseline characteristics, which is mostly important initially in a domain. On the other hand, stratified block randomisation is difficult to implement when response-adaptive randomisation is used, as allocation lists would have to be updated with every adaptive analysis, and as the matching of block sizes with highly variable allocation profiles is difficult [38,78]. Separate, different randomisation profiles and separate response-adaptive randomisation in different strata (i.e., different subsets of patients in a domain) are not supported in the initial version of *INCEPT*. If response-adaptive randomisation is used, updated allocation profiles will not be revealed to clinicians or investigators randomising patients or others, except those performing the adaptive analyses and directly implementing the randomisation profiles and the IDMSCs (section 9 and section 17). The updated allocation profile will be directly implemented in the electronic randomisation system to avoid treatment decisions or decisions to randomise further patients to be influenced by knowledge of the current allocation profiles, which may introduce bias [34,47,55]. Although clinicians and investigators randomising patients or other research staff members may theoretically be able to infer changes to the allocation profiles for unblinded domains, the influence of this is expected to be minimal as distinguishing changes to the allocation profiles from random fluctuations will be difficult at single sites, especially when response-adaptive randomisation is restricted.

Patients will be randomised immediately when included in a domain, i.e., we will not use *randomisation with delayed reveal* as done elsewhere [47] as this would interfere with the stratified block randomisation when used.

8.7 | Blinding and unblinding

The use of blinding will be decided for each specific domain. The use of blinding or placebo in multi-arm adaptive trials, including adaptive platform trials, comes with additional challenges compared to conventional, fixed-size trials, and may thus be omitted in some cases as a trade-off with the benefits of the adaptive platform trial design [35,79]. First, if routes of administration or frequency of administration matter, it may be necessary to use multiple placebos, which complicates practical trial or domain conduct. Second, production of dedicated placebos is expensive and time-consuming, which is further complicated or unfeasible in adaptive trials with flexible sample sizes or with adaptive allocation. This may be remedied by the use of shelf medication as previously done [80–83], with trial staff not otherwise participating in inclusion, clinical care, or outcome registration preparing the blinded interventions. In general, the costs of

using blinding will be weighed against the potential risk of bias due to lack of blinding. Previous meta-epidemiological studies have been unable to show firm associations between blinding and mortality in RCTs [84,85] or have indicated slightly larger intervention effects in unblinded trials without being able to rule out confounding by other trial design characteristics or small-study effects [86]. As such, the potential influence of blinding is likely negligible for harder (i.e., more objective) outcomes such as mortality and may not be worth the costs or practical/logistical issues, especially if these are likely to make domains more expensive and laborious to implement, potentially affecting inclusion rates negatively. For HRQoL outcomes and cognitive function at day 180, outcome assessors will always be blinded to the allocated intervention(s), even when respondents are not, to minimise the risk of bias for these outcomes [87] (section 8.9).
If domains are blinded, we will specify adequate procedures for emergency unblinding for treatment or safety reasons (e.g., if there is clinical suspicion of unexpected serious adverse reactions [SUSARs]) and general unblinding when relevant adaptive decisions are made (e.g., arm-dropping or domain closure) in the domain-specific appendices.

We will generally not blind the statistical team or the IDMSCs as it will not be possible in a substantial proportion of the cases (e.g., when allocation ratios are different for control arms or when running the analyses, this will *de facto* lead to unblinding and as the actual comparator group must be known to correctly specify priors when running analyses) and as the cost of doing so unlikely are worth the additional added protection.

8.8 | Follow-up, discontinuation and withdrawals, and data completeness

Follow-up
Follow-up will be conducted during hospital stay (including re-admissions within the first 90 days) and after 30, 90 and 180 days after randomisation, regardless of the localisation of participants. An overview is provided in **Table 1**.

Table 1. Schedule of activities

Tasks	Screening	Inclusion	Baseline	Consent	Day 1 to 30	Day 31 to 90	Day 180
Assessment of eligibility	X						
Registration of stratification and adjustment variables		X					
Randomisation		X					
Intervention delivery and registration of protocol adherence[1]		X	X		(X)	(X)	
Baseline data registration			X				
Obtainment of informed consent				X			
Day 30 outcome data registration					X		
Day 90 outcome data registration						X	
Day 180 outcome data registration							X

Overview of the schedule of activities in *INCEPT*, including all domains. Following initial screening and inclusion, participants may later be included in additional domains as described in section 8.5. When this occurs, tasks listed under *Screening*, *Inclusion* and *Baseline* will be repeated as necessary. The *Informed consent* procedure will continue. Registration of outcome data will be extended/repeated as described in section 8.9 and 8.10 when inclusion to additional domains occurs after initial inclusion to *INCEPT*.

[1] Intervention durations will vary between domains and will be detailed in the domain-specific appendices. Interventions will generally be delivered while in participating ICUs for a maximum of either 30 or 90 days, except where specified otherwise in the domain-specific appendices.

[2] X in parenthesis indicates that the intervention delivery may not continue for the full period indicated.

Follow-up will be conducted by the site investigators, except for 180-day follow-up which may be done centrally or by investigators from other sites. Where possible, we plan to automate outcome data collection by establishing integrations with EPRs and existing registers (e.g., the *Danish Intensive Care Database* [10] and the *Danish National Patient Register* [88]), supplemented with manual data entry and contact to participants and proxies by phone, mail or secure electronic post (e.g., for HRQoL outcomes, which will be obtained by proxies for participants unable to respond themselves). For patient-reported outcomes (section 8.9), we will collect data by phone, physical mail, secure electronic post or later through integration with existing healthcare data systems. Data on safety outcomes (section 8.10) will be collected using EPRs and by contact to the treating clinicians if further details are necessary once reported. When initiated, we expect that all data entry in *INCEPT* will be manual, but we are preparing integration with EPRs and registers to later allow (partially) automated data capture. Additional details on data collection and management are provided in section 14.

Discontinuation and withdrawals

The following procedure for handling discontinuation and withdrawals will be used in *INCEPT*; this procedure follows applicable Danish regulations. If required in other participating countries, adaptations to this procedure to comply with national regulations will be described in national appendices.

Discontinuation and withdrawal at the choice of the participant or proxy

Participants that no longer wish to participate in the platform trial may withdraw consent at any time without the need for explanation and with no consequences for further treatment (section 8.5). Similarly, consent may be withdrawn at any time prior to the participant being able to decide for themselves by person(s) giving proxy consent. Participants may decide to withdraw from the entire platform trial or only from specific domains, and we will specifically ask about this if participants or proxies decide to withdraw. To minimise missing data, we will ask participants who withdraw from the intervention or their proxies if they allow continued data collection and follow-up. In previous trials by our group, the proportion of participants or proxies not giving/withdrawing consent for both the allocated intervention and the continued collection/use of data has been minimal (approximately 1% of participants) [89–92].

Discontinuation and withdrawal at the choice of the investigator

A participant may have the allocated intervention(s) stopped by the treating clinician or an investigator at any time if one of the following events occurs:

- The participants experience intolerable serious safety outcomes suspected to be related to a trial intervention.
- The clinician decides it to be in the interest of the participant after conference with a coordinating investigator of the domain.
- Withdrawal of active therapy.
- Use of coercive measures.

If any of these events lead to withdrawal from interventions, data collection and follow-up will continue, and the participant will remain in the intention-to-treat (ITT) population. Whenever possible, participants will be withdrawn from active intervention specific domains only and continue in other domains.

Discharge

Generally, interventions in *INCEPT* will discontinue once participants are discharged or transferred to a non-participating hospital department (including ordinary wards and non-participating ICUs), except if explicitly described otherwise in a domain-specific appendix. The participant will be followed through EPRs, registers, and contact as described above. If a participant is readmitted to

a participating site within the intervention period, the allocated intervention(s) will generally resume.

Data completeness
In addition to continuing data collection after intervention discontinuation or withdrawal from a domain (where permitted), we aim to minimise the amount of missing data by (over time) implementing automatic collection of as much data as possible by using EPRs and registers, and by communication with participants and their proxies. The amount of missing data will be centrally monitored with local site investigators alerted as necessary. The handling of missing data in the analyses is described in section 9.8.

8.9 | Outcomes

Table 2 lists the *core outcomes* of *INCEPT*. These must be collected and reported for all participants in all domains. All core outcomes are considered directly patient-important and critical for clinical decision making [93,94], and are based on a recently developed *core outcome set* for adult general adult ICU patients developed as part of *INCEPT* with extensive stakeholder involvement (section 11) [3,4]. Of note, the core outcome set defines the outcomes on an overall, conceptual level, and the development of a *core outcome measurement set* determining the exact definitions, tools used, and durations is planned, but not yet conducted [3,4]. Thus, the exact definitions and operationalisations below were decided for the *INCEPT* core protocol based on the core outcome set. Once the core outcome measurement development process concludes, the *INCEPT* core outcomes and their definitions will be revised as necessary to correspond to the outcome measurement sets to the extent possible. Deviations from the final core outcome measurement set may occur due to implementation, data registration, and feasibility considerations within the *INCEPT* context; all deviations will be decided by the platform management committee after discussion with relevant members of the advisory board and research panels (including ICU survivors, family members, clinicians, and researchers not part of the daily management of *INCEPT* or any *INCEPT* domains) supplemented with clear rationales.

Table 2. INCEPT core outcomes (continues on the next pages)

Outcome	Definition/operationalisation	Remarks
All-cause 30-day mortality	All-cause, fixed-time mortality. Binary.	Event day/censoring secondarily collected, but not included in primary analyses.
All-cause 90-day mortality		
All-cause 180-day mortality		
Days alive without life support at day 30	Days alive without the use of life support, with life support defined as invasive mechanical ventilation (≥1 hour of ventilation through a cuffed tube), continuous (i.e., ≥1 hour) use of vasopressors/inotropes, use of RRT (including any form of in-hospital RRT [e.g., haemodialysis, haemofiltration, or haemodiafiltration], continuously or intermittently, and including days in between intermittent RRT; pauses between RRT of up to three days will be considered as days receiving intermittent RRT) at hospitals. Integer (0-30 or 0-90 overall; 0-29 or 0-89 in domains with life support at baseline as an eligibility criterion).	These outcomes will be reported in two versions with the primary version always specified in the domain-specific appendices: A) Participants who die within the time-frame will be assigned the worst possible value (0), as frequently done and originally recommended for these types of outcomes [94–97]. B) Using the actual values without penalising mortality. These outcomes are preferred to similar time-to-event outcomes as participants may get on/off life support or be discharged/readmitted to the hospital multiple times during the follow-up period [97–99]. <u>For days free of delirium at day 30:</u> systematic, daily screening using a validated tool is recommended at participating sites but not mandated. The outcome will be registered similarly at participating and non-participating sites (including the use of registered delirium/coma scores where available, but without mandating this). Coma defined using any of the following scales (modified from a previous definition [92]): Richmond Agitation-Sedation Scale (RASS) [100] -3 to -5; Ramsay Sedation Scale (RSS) [101] 4 to 6; Motor Activity Assessment Scale (MAAS) [102] 0 to 1; Glasgow Coma Scale (GCS) [103] 3 to 8; Reaction Level Scale (RLS85) [104] 4 to 8; or Riker Sedation-Agitation Scale (SAS) [105] 1 to 2.
Days alive without life support at day 90		
Days alive out of hospital at day 30	Days alive and out of hospital. Rehabilitation facilities and nursing homes [106,107] do not count as hospitals. Integer (0-29 or 0-89).	
Days alive out of hospital at day 90		
Days free of delirium at day 30	Days free of delirium. Days are *not* considered free of delirium in case of any of the following: a) any registered positive delirium score with a validated screening tool (Confusion Assessment Method for the Intensive Care Unit [CAM-ICU] [108], CAM-ICU-7 [109], or Intensive Care Delirium Screening Checklist [ICDSC] [110]) b) new treatment with antipsychotics (any administration of haloperidol, olanzapine, or quetiapine in participants not receiving either of these at the time of index hospital admission) c) delirium status not evaluable due to mortality or registered coma. Integer (0-30 overall; 0-29 in domains with delirium at baseline as an eligibility criterion).	

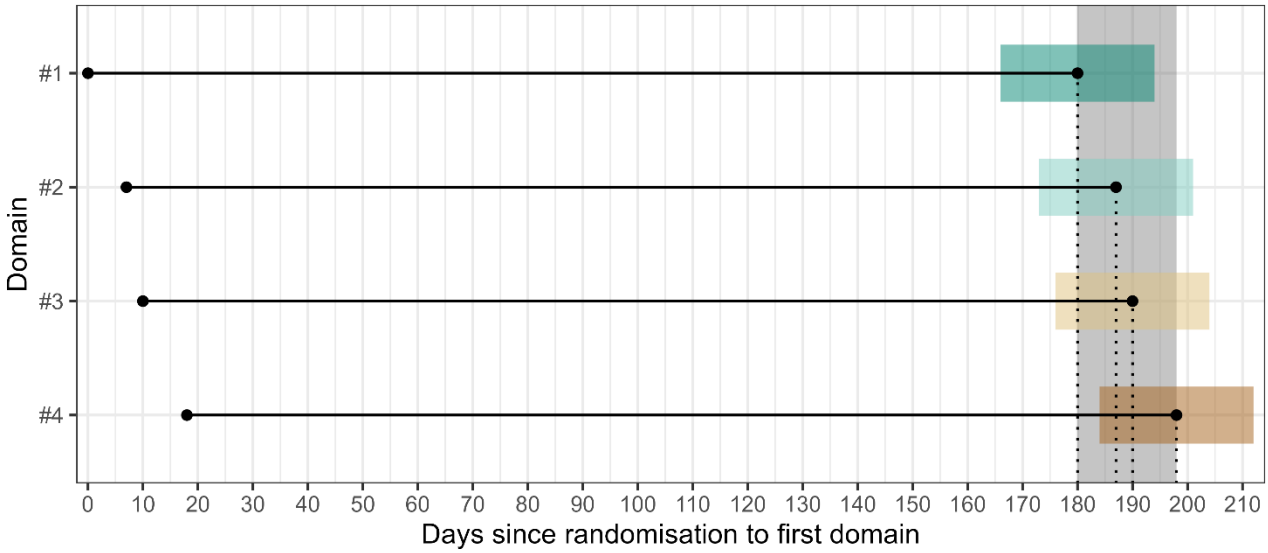
Outcome	Definition/operationalisation	Remarks
EQ-5D-5L index values (HRQoL) at day 180	EQ-5D-5L instrument [111] with responses across five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with five response levels each. Used with a value set to calculate index values anchored at 1 (perfect health) and 0 (a health state considered as bad as being dead) with index values below 0 representing health states worse than death. Preferably completed by participants, but completed by proxies if participants are unable to answer (using the proxy-participant perspective, i.e., the proxy will answer from the participant's perspective as the limited, indirect data available indicates that this perspective may better correspond to the participant's own response, if available [112]). Decimal number (minimum values depend on value sets used, e.g., -0.758 with the Danish value set [113]; maximum value: 1.000).	Primarily analysed in all participants with non-survivors assigned 0 (corresponding to the weighting of being dead) [94,114,115] and secondarily analysed in survivors only. Primarily analysed using applicable national value sets (specified in national/local appendices); where no national value set exists, the most appropriate value set will be chosen by the platform management committee and the national investigator(s), defaulting to the Danish value set [113] if no other value set seems more appropriate. Secondarily, a sensitivity analysis will be conducted in all participants using the national value set applicable to most participants [116]. Responses to the separate EQ-5D-5L domains will be presented numerically and graphically without formal analysis except if otherwise specified.
EQ VAS (HRQoL) at day 180	A visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) [111].	Primarily analysed in all participants with non-survivors assigned the value 0 (worst possible value) [94,114,115] and secondarily analysed in survivors only. Of note, no specific EQ VAS value corresponds to being dead, and assigning the worst possible value to non-survivors is a pragmatic choice to avoid bias and potentially misleading results and ensure that the results have a valid causal interpretation when the intervention(s) may affect mortality [114,115]. This approach is similar to previous trials [117–120].
Cognitive function at day 180	Montreal Cognitive Assessment test 5-minute version, v2.1 ("Mini MoCA") [121,122], ranging from 0 points (worst) to 15 points (best).	Primarily analysed in all participants with non-survivors assigned the value 0 (worst possible value) [94,114,115] and secondarily analysed in survivors only. Of note, no specific Mini MoCA value

Outcome	Definition/operationalisation	Remarks
		corresponds to being dead, and assigning the worst possible value to non-survivors is a pragmatic choice to avoid bias and potentially misleading results and ensure that the results have a valid causal interpretation when the intervention(s) may affect mortality [114,115]. This approach is similar to a previous trial [118].
One or more domain-specific safety outcomes	The number of participants with one or more safety outcomes specified in the domain-specific appendices, using the follow-up time point specified in each domain. The follow-up period must cover at least the interventional period.	Detailed in section 8.10. Separate data on each safety outcome will secondarily be reported descriptively in each intervention arm. If the primary or guiding outcome is registered after shorter follow-up than the maximal intervention period, this outcome will be reported both with the same follow-up duration as the primary/guiding outcome and after the full follow-up period covering at least the interventional period.

As seen in **Table 2**, outcomes collected at multiple time points are considered separate outcomes. Follow-up time points will be relative to time of randomisation in each specific domain in *INCEPT*, i.e., if a participant is randomised in multiple domains on different days, the final day of follow-up for each outcome will differ accordingly to ensure the specified follow-up duration. Where between-domain interactions are planned to be assessed, the relevant domain-specific appendices will specify how potential differences in the follow-up periods for the same outcome in the different domains will be handled. For day 180 patient-reported outcomes (HRQoL and cognitive function), outcome assessors will be blinded to the interventions received to minimise the risk of bias when collecting these outcome data [87], although respondents will not necessarily be blinded and it thus cannot be guaranteed that respondents will not reveal their allocation(s) to the outcome assessor in all cases. For cognitive function, outcome assessors will be trained and certified in the administration of the MoCA tests, as required [121]. For EQ-5D-5L, EQ VAS, and cognitive function, we aim for registration as close as possible to 180 days post-domain inclusion but within 14 , as we expect this to have minimal influence on the actual values and as this will limit the number of times participants (or their proxies) will be asked thus potentially reducing the proportions of missing data (**Figure 8**). Vital status on the day of assessment of HRQoL and cognitive function will also be collected (as this may not be the same day as the all-cause 180-day mortality outcome in a particular domain) and used in the analyses of these outcomes solely. If

HRQoL or cognitive function is collected prior to day 180 post-randomisation to a domain but within the allowed 14-day period, these values will be used regardless of vital status at day 180. If multiple HRQoL or cognitive function measurements are available within the allowed period of 14 days before or after day 180, the measurements closest to day 180 in each domain will be used.

Figure 8. Follow-up for health-related quality of life and cognitive function in INCEPT



Participants in *INCEPT* may be enrolled in different domains (vertical axis) at different relative time-points (horizontal axis). This figure illustrates the periods from domain inclusion to 180 days after domain inclusion (black horizontal lines). We aim to collect health-related quality of life outcomes (EQ-5D-5L index values and EQ VAS) and cognitive function (Mini MoCA) at 180 days after domain inclusion +/- 14 days, illustrated by the coloured boxes. The points and vertical dotted lines indicate day 180 after inclusion in each domain. Overall, the figure provides an example of when these outcomes may be collected and used in multiple domains, and when it is necessary to collect them again – e.g., if collected 180 days after inclusion in domain #1, the same data may be used in domains #2 and #3, but not #4, whereas the same data may be used for all four domains if collected, e.g., 180 days after inclusion in domain #2 or #3. In practice, inclusion to most domains during the same ICU stay is expected to occur simultaneously and we aim to collect these data as close as possible to day 180, except when already collected data can be used for additional domains. The grey shade illustrates the period starting from 180 days after inclusion to the first domain and ending 180 days after inclusion to the last domain in the example.

The prioritisation of outcomes will vary between domains and will be specified in the domain-specific appendices. For all domains, the primary outcome(s) must be one of the *INCEPT* core outcomes. In each domain, a single *guiding* outcome must be specified for adaptive analyses, and this outcome will, generally, be the primary outcome as well. This guiding outcome must be one of the *INCEPT* core outcomes, with the following exceptions: 1) domain-specific safety outcomes, as automating cross-domain data collection is central to efficiency and data quality of *INCEPT*, and 2) the HRQoL and cognitive function outcomes due to their relatively long follow-up, typically moderate data missingness, and the methodological and interpretational challenges related to the handling of non-survivors [94,114]. In specific cases, a non-guiding core outcome may be the

primary outcome if high correlation between the primary and guiding outcomes is expected *a priori* [2], e.g., for similar outcomes with different durations of follow-up or good proxy outcomes.

8.10 | Safety outcomes and risk assessment

This section outlines the handling of safety outcomes in *INCEPT* domains based on EU regulations [123] for the assessment of safety outcomes for pharmacological interventions (investigational medicinal products); this procedure may be adapted in domain-specific appendices for non-pharmacological domains. Country-specific adaptations of safety outcome data registration and reporting may be required for countries outside the EU. In these instances, the procedures for collecting and reporting additional safety data will be specified in national appendices.

Definitions
The following definitions adapted from the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH) [124] to fit both domains assessing pharmacological and non-pharmacological interventions are used in *INCEPT*:

Adverse event (AE)
Any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with an intervention.

Adverse reaction (AR)
An unintended and noxious response to an intervention occurring when normally used.

Serious adverse event (SAE)
Any AE that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious adverse reaction (SAR)
Any SAE assessed to be related to the intervention. SARs will be specifically defined in domain-specific appendices for all included interventions; for pharmaceutical interventions, these will be based on the Danish Summary of Product Characteristics (SmPCs) and other relevant SmPCs where relevant (e.g., national SmPCs for other countries than Denmark if, e.g., the domain sponsor is located in another country) for the relevant drugs and may include additional clinically relevant events.

Suspected unexpected serious adverse reaction (SUSAR)
Any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with those defined as SARs, i.e., SARs not included in the SmPCs for pharmaceutical interventions). Assessments of causality for potential SUSARs will be made by the investigators.

Risk proportionate approach for registration and reporting of safety outcomes
Participants in *INCEPT* will be hospitalised, critically ill patients in the ICU, for whom adverse events and reactions are routinely monitored and documented in the EPRs. The EPRs will be used to continuously evaluate the occurrence of safety outcomes. A risk proportionate approach for recording and using safety outcomes will be used in *INCEPT* according to EU regulations (Regulation EU No 536/2014) [123] and the *Danish Medicine Agency*'s guidance [125] based on the EU legislation, which is also in adherence with recommendations by the *WHO* [1]. A separate risk assessment will be performed in each domain and included in the domain-specific appendices. Each domain will be classified and handled in one of the following three risk categories based on the *Danish Medicine Agency*'s guidance [125] with definitions based on this guidance and the EU recommendations [123]:

Risk level 1, low-risk (corresponding to 'low intervention' clinical trials in the EU regulation [123]*)*
Classification: *all* the following requirements apply:

- the investigational medicinal product(s) (excluding eventual placebo(s) or 'no additional treatment' arms) has marketing authorisation(s)
- the intervention(s) are comparable with standard care
- the evidence base and safety profile(s) for the intervention and the investigational medicinal product is robust, including with regards to rare adverse effects
- the probability of discovering new safety signals is expected to be minimal

Required handling: a risk proportionate approach to registering and reporting safety data is justifiable. Registration and reporting of AEs, SAEs, and SARs can be omitted, and only SUSARs are required to be registered and reported to the sponsor within 24 hours and will be included in the annual safety reports. Investigators will always be able to report any SAEs immediately at their own discretion [126].

Specific handling in INCEPT: although registration of SARs is not required, specific, clinically relevant SARs (defined in the domain-specific appendices) will be registered and included in the annual safety reports and final domain reports in *INCEPT* as part of the secondary outcome *'one or more domain-specific safety outcomes'* (section 8.9).

Risk level 2, intermediate risk
Classification: *all* the following requirements apply:

- the investigational medicinal product(s) (excluding eventual placebo(s) or 'no additional treatment' arms) has marketing authorisation(s) but are used for an unapproved indication (off-label use)
- the intervention(s) does not substantially deviate from standard care and the safety profile is expected to be comparable to that of standard care
- the safety profile(s) of the investigational medicinal product(s) is robust

Required handling: a risk proportionate approach to registering and reporting safety data can be justified if motivated by the domain's risk assessment, which should address the factors outlined in the *Danish Medicine Agency*'s guidance [125]: marketing authorisation, total exposure, existing safety data; type of investigational medicinal product/intervention (e.g., mechanistic characteristics, form of pharmaceutical, route of administration); indication, including whether this differs from standard clinical practice; population, including age, sex, or other patient characteristics; dose and treatment regimen compared to approved dose and treatment regimen as listed in SmPC(s), including new combinations or simultaneous use with other pharmaceuticals and an assessment about whether this can lead to more serious/frequent adverse effects or interactions; and complexity of the trial design.
Registration of AEs can be omitted; registration of specific SAEs (e.g., SAEs related to either the intervention(s) or the underlying disease) and specific SARs (e.g., known SARs according to the SmPCs) according to a predefined list can be omitted if adequately justified (all registered SAEs do not need to be reported within 24 hours but must be included in the annual safety reports; investigators will be able to report any SAEs immediately at their own discretion [126]). All registered SARs must be reported to the domain sponsor within 24 hours unless part of the domains' primary/secondary outcomes with an independent data monitoring and safety committee (IDMSC) established or otherwise continuously monitored.

Specific handling in INCEPT: SAEs related to the underlying disease (i.e., SAEs common in critically ill patients [127–129]) as specified in **Table S1** (appendix 2, section 21.2) will not be registered. Pre-defined SARs will be registered and included in the annual safety reports and final domain reports in *INCEPT* as part of the secondary outcome *'one or more domain-specific safety outcomes'* (section 8.9), but not reported to the domain sponsor within 24 hours due to the inclusion in this secondary outcome and the IDMSC monitoring of each domain. SUSARs will always be registered and reported to the domain sponsor within 24 hours.

Risk level 3, high risk
Classification: *one or more* of the following requirements reply:

- investigational medicinal product(s) (excluding eventual placebo(s) or 'no additional treatment' arms) or indication not approved
- intervention(s) not previously investigated or substantially deviating from standard care
- the safety profiles of the intervention(s) and investigational medicinal product(s) are not sufficiently investigated and evidence regarding efficacy and safety are lacking
- the investigational medicinal product(s) has (have) marketing authorisations but with *stricter reporting requirements* [130]

Required handling: thorough handling of adverse effects is required to ensure patient safety and data about the safety profile(s) of the investigational medicinal product(s). Complete recording and reporting of safety outcomes is required *unless* a risk proportionate approach can be justified with a robust justification based on the risk assessment for the domain.

Specific handling in INCEPT: all AE and SAEs will be registered, and all SAEs/SARs will be reported to the domain sponsor within 24 hours and included in the annual safety reports and final domain reports as part of the secondary outcome *'one or more domain-specific safety outcomes'* (section 8.9), except in special cases where a robust justification based on a thorough risk assessment is made in the domain-specific appendices and approved by the competent authorities.

Monitoring of participants
All participants will be monitored closely due to the severity of their illness according to the clinical standards at the participating ICUs, regardless of the risk level(s) of the domain(s) each participant is active in. This will typically include continuous or frequent measurement of vital parameters (e.g., oxygen saturation, heart rate, blood pressure, respiratory rates, and temperature), daily or frequent measures of biochemistry (e.g., C-reactive protein [CRP], leukocyte counts, haemoglobin, creatinine, electrolytes, pH, arterial blood gases, lactate, and blood glucose), and additional measurements as clinically indicated (e.g., microbiological cultures, electrocardiograms [ECGs], and other diagnostic tests). These data will not be registered in *INCEPT* if not included in the general variable list (section 14.6) or the domain-specific variable lists but will be available in the EPRs for the investigators and/or competent authorities if needed.
In case of safety events, participants will be monitored and followed according to usual clinical practice decided by the treating clinician, e.g., until resolution of the safety event or similar. This will be done using the EPRs and additional contact to the participant by, e.g., phone if deemed relevant. The platform and domain sponsors or their delegates may be consulted regarding safety events and subsequent follow-up as relevant.

Timing
In all participants, the occurrence of safety outcomes will be assessed for a relevant time duration with a follow-up period at least as long as the intervention period in each domain.

Classification and reporting of events
Safety outcomes will be collected in accordance with the risk assessment as outlined above. Specified SARs will be registered for all interventions in a domain due to *a priori* being expected to being causally related to the intervention, except if specified otherwise in a domain-specific appendix. This is done to ensure complete and unbiased reporting, especially for open-label domains, and resembles the procedure used in previously approved critical care trials by our group [81,83,89–92,126,131]. Reporting of all safety outcomes will be done by the investigators to the coordinating centre, which will report them to the domain sponsor(s) or their delegate(s) within the timeframes specified above. Events deemed to be SUSARs will always be reported to the domain sponsor(s) or their delegate(s) within 24 hours. If a SUSAR is adjudicated as fatal or life-threatening, the domain sponsor will report it to all sites participating in the domain as well as to the competent authorities in the participating countries within 7 days (for countries in the EU via the *Hospital Pharmacy in the Capital Region of Denmark*; for countries outside EU in collaboration with the national investigator). No later than 8 days after the reporting, the domain sponsor will inform the competent authorities about relevant follow-up actions by the domain sponsor and the investigator. Any other SUSARs (i.e., those that are not life-threatening or fatal) will be reported via the *Hospital Pharmacy in the Capital Region of Denmark* to the competent authorities no later than 15 days from the time when the domain sponsor is informed (or as required in countries outside the EU).

The domain sponsor will submit an annual safety report, describing the rules of registration and reporting of safety events as described in the core protocol and domain-specific appendix, and including a list of all safety outcomes collected in each interventional arm (in total, and separated by category and event type) at all sites during the trial period to the relevant entities through *CTIS*. The annual safety report will include all relevant items from the newest version of the Danish GCP units' example template [132]. The annual safety report will also be submitted to the domain IDMSC (section 17) and the domain and platform management committees.

All collected safety outcomes will be included in the final domain report as part of the secondary outcome *'one or more domain-specific safety outcomes'* (section 8.9) and secondarily separately by category and event type. Of note, as the specific types of safety outcomes collected between domains and the follow-up periods for safety outcomes between domains will differ, these may not be directly comparable between domains.

In case of urgent changes due to important safety signals, this will be reported to the competent authorities in *CTIS* (or as required in countries outside the EU) along with a description of any intended follow-up activities and communicated as described in section 9.4.

Benefit-risk assessment
A summarised benefit-risk assessment for each domain will be provided in the domain-specific appendices.

8.11 | End of trial and domains

For each domain, the domain sponsor will notify the relevant competent authorities no later than 90 days after a domain is closed (last participant's last visit) with the final domain decision (e.g., stopped for superiority, practical equivalence, futility, or at a maximum sample size, as described in section 9.4). Whenever a domain has been closed, its results will be reported through *CTIS* within 12 months of the last participant's last visit (i.e., end of follow-up for all outcomes) in that domain.

INCEPT has no planned overall stopping date and may potentially run perpetually. If, however, *INCEPT* is stopped, the platform sponsor will notify the competent authorities no later than 90 days after the last domain has been closed (last participant's last visit in the last domain).

The publication policy for *INCEPT*, including all domains, is described in section 18.1.

8.12 | Other design considerations

Feasibility and separation, including integrated pilot/feasibility phases
Where relevant, feasibility and separation between arms may be assessed. This will be specified in the domain-specific appendices.
Domains may use be designed with multiple phases including one or more integrated pilot/feasibility phase(s), which seamlessly continue into an adaptive phase with assessment of patient-important outcomes including the *INCEPT* core outcomes. If so, one or more feasibility phase(s) may be conducted with feasibility determined according to pre-specified criteria unrelated to the general *INCEPT* adaptation rules. If all feasibly criteria are fulfilled, domains will continue enrolment in an adaptive phase, which may use clinical outcome data collected during the feasibility phase to guide initial adaptations already when the second phase starts (e.g., initial allocation profiles in the adaptive phase). If feasibility criteria are not fulfilled, domains may be modified or stopped. Pauses in enrolment to allow assessment of feasibility before continued enrolment to a domain may be used or enrolment may continue while feasibility is assessed, as outlined in the relevant domain-specific appendices, although enrolment will generally not be

paused while feasibility is assessed. Multiple feasibility phases may be used, possibly depending on the results of earlier feasibility phases; this will be specified in the domain-specific appendices. Feasibility will generally be assessed across all arms (i.e., not stratified by allocation), except for feasibility outcomes related to separation between arms. Examples of possible feasibility outcomes and criteria, based on recommendations and previous outcomes and criteria [29,126], are provided in **Table 3**.

Table 3. Examples of feasibility outcomes and criteria

Feasibility outcome example	Definition/operationalisation	Feasibility criteria example
Time to completion of the feasibility phase	Time to enrolment of the number of participants required for feasibility assessment. Decimal number.	<## months.
Recruitment proportion	Proportion of potentially eligible patients included in the domain. Percentage (0-100%)	≥## %.
Proportion of participants without consent to the use of data	The proportion of participants for whom the participant themselves or their proxies do not consent to the use of data. Percentage (0-100%).	<# %.
Protocol adherence	Proportion of participants without (major) protocol deviations. Percentage (0-100%).	≥## %.
Retention proportion	Proportion of participants with data on the primary/guiding outcome within the outcome-data lag period. Percentage (0-100%).	≥## %.
Separation	Separation between arms according to specific measures affected by the intervention(s). Operationalisation and type depends on the intervention(s).	Criteria depends on the intervention(s).

Examples of possible feasibility outcomes and criteria that may be used in *INCEPT* domains with one or more integrated feasibility phase(s), partially adapted from the feasibility outcomes in the *Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis (EMPRESS)* adaptive randomised clinical trial [126]. Exact feasibility outcomes and criteria, including variable definitions, will be specified in the domain-specific appendices where used.

Sample sizes for integrated feasibility phases will generally be determined based on the expected precision of the feasibility outcome estimates, practical considerations, and considering sample sizes in other stand-alone pilot or feasibility trials [133–135]. Details on integrated pilot/feasibility phases will be described in the applicable domain-specific appendices.
Data on feasibility or separation may be presented to the domain IDMSC regularly (e.g., at the yearly meeting, section 17) regardless of whether formal feasibility phases are used. The domain IDMSC may then make recommendations based on these data without any fixed criteria for continued feasibility, although the domain IDMSC may use any criteria specified for formal feasibility analyses as a point of reference.

Stand-alone feasibility/pilot trials using the INCEPT platform

The *INCEPT* platform may be partially used to conduct stand-alone feasibility or pilot trials [135] where relevant, e.g., when the *a priori* expectations that a trial will be feasible are not large

enough to conduct it as a domain on *INCEPT* with an integrated feasibility phase. In these cases, the infrastructural and data collection frameworks of *INCEPT* will mainly be used, while other methodological choices may differ from the *INCEPT* core protocol, including the outcomes assessed. If the *INCEPT* core outcomes are assessed in a stand-alone feasibility/pilot trial and a similar domain is later added to the platform, these outcome data may be used as priors in primary or secondary analyses of the domain; this will be specified in the domain-specific appendices. Stand-alone feasibility/pilot trials using the *INCEPT* platform will be handled and approved as separate trials but may reference the *INCEPT* core protocol with regards to relevant methodologic choices.

Seamless designs

Seamless designs covering multiple clinical trial phases, e.g., seamless *phase II/III* trials, [32,136] may be conducted on the *INCEPT* platform where relevant. In that case, the first phase may use a primary outcome and analysis methods differing from those specified in the core protocol, while the last phase must adhere to the *INCEPT* core protocol, including with regards to the choice of guiding (and primary) outcome according to the list of *INCEPT* core outcomes (section 8.9). It is required that all *core outcomes* are registered and reported for all participants in all phases and that all phases are compatible with analysis and reporting according to the core protocol. The success criteria for the first included phase must be specified in the domain-specific appendix, along with analysis methods and sample size considerations for this phase. If the domain is terminated before reaching the final planned phase in the seamless design, all *INCEPT* core outcomes must be analysed and reported according to the core protocol and domain-specific appendix in addition to any specific outcomes for the earlier phase(s) on the domain. The final phase will generally include data from all participants across phases in the adaptive and final analyses, except if specified otherwise in the domain-specific appendices with clear rationales.

Cluster-randomised trials using the INCEPT platform

The *INCEPT* platform may be partially used to conduct cluster-randomised trials [137] where relevant; in these cases, the infrastructural and data collection frameworks of *INCEPT* will mainly be used (including core outcomes, the data collection framework, etc.), while appropriate methodology (related to randomisation, analysis, and overall conduct including potential adaptivity and sample size determinations) specific to cluster-randomised trials will be defined specifically for each cluster-randomised trial using the *INCEPT* platform [137,138]. Such trials will be handled and approved as separate trials but may reference the *INCEPT* core protocol or any appendices for some methodological choices.

9 | Statistics and simulation

9.1 | Overall principles

INCEPT will be conducted as an adaptive platform trial with interventions nested in domains and employing adaptive arm-dropping, adaptive stopping, and response-adaptive randomisation (section 8) [2,35,38]. Not all adaptive elements will be used in all domains, and additional adaptive elements (e.g., separate adaptive decisions in different strata and adaptive enrichment [2,35]) are expected to be added in later versions of the protocol. Adaptation rules are described in detail in section 9.4 and section 9.5 below.

Statistical framework
INCEPT will primarily use Bayesian statistical methods for both adaptive and final analyses unless explicitly defined otherwise in a domain-specific appendix. Conventional, frequentist statistical methods may be employed as supplementary analyses, sensitivity analyses, in substudies (section 18.2), or as the primary methods for specific domains if explicitly specified *a priori* in the appropriate domain-specific appendices.

Challenges in conventional trials analysed using frequentist statistical methods
Conventional, frequentist statistical inference is based on a definition of probability according to the long-run frequencies over repeated (theoretical) experiments and is typically heavily focused on null hypothesis significance testing [139]. In this framework, a null hypothesis - most commonly that there is truly no difference between interventions - is assessed using P-values. P-values are defined as the long-run probabilities of obtaining results *at least as extreme* as those observed assuming that the null hypothesis is true with results dichotomised as *statistically significant* if the P-value is below a pre-specified threshold (typically 5%) [2]. Sample sizes in frequentist trials are generally derived using specific closed-form formulae including assumptions about the intervention effect size and the risk of type 1 errors (i.e., the risk of erroneously asserting that an ineffective intervention is effective, typically 5%) and type 2 errors (i.e., the risk of erroneously asserting that an effective intervention is ineffective, typically 10-20%). Unfortunately, P-values are difficult to understand and frequently misinterpreted [139–141] as they are *indirect* probabilities for the hypothesis of interest (i.e., that there is an intervention effect) and calculated under an assumption that is often unrealistic (i.e., that there is *exactly* no intervention effect) [2]. The issues with dichotomizing results according to P-value thresholds are aggravated by the use of effect sizes of interest in conventional sample size calculations that are often implausibly large and generally larger than the clinically minimally relevant differences [21–24]. This increases the risk that trials assessing potentially effective interventions end up as *not statistically significant* [2], which is frequently misinterpreted as if there is no intervention effect [26,140,141]. Ultimately, this leads to research waste and premature abandoning of effective interventions, which may

cause patient harm or prevent improvements of care. As such, trials that are only powered for implausibly large effect sizes may be considered unethical if interpreted dichotomously [2,142]. While this issue is not specific to frequentist statistical methods *per se*, it is closely tied to how this approach is typically used in most conventional trials.

Bayesian statistical methods and their application in adaptive trials
Bayesian statistical inference uses probability distributions to express uncertainty, and analyses start with *prior* probability distributions expressing beliefs in intervention effects before conducting the trial [2,143]. These are updated to *posterior* probability distributions using the trial data, which may be used to calculate *direct* probabilities of effect sizes of interest, including any benefit or harm, clinically important benefit or harm, or effect sizes smaller than those considered clinically important [2,143]. Different priors may be used corresponding to different prior beliefs. Often, priors used in Bayesian analyses in critical care trials carry minimal or no information; results from such analyses are generally numerically similar to results from corresponding frequentist analyses, although the interpretations differ [2,143]. Bayesian analyses are well suited for adaptive trials and are often used in adaptive platform trials [2,35,144]. *INCEPT* will primarily use Bayesian statistical methods with neutral priors (i.e., priors not favouring one intervention over the other(s)) in the primary analyses as has been recommended [143,145]. The exact priors will be specified in each domain-specific appendix, and somewhat sceptical (i.e., regularising), neutral priors may be used to limit the influence of random fluctuations early [146,147].

Analysis conduct
Statistical analyses will be conducted according to the principles outlined in the core protocol with additional details not covered by the core protocol specified in the statistical analysis plan for each domain in the domain-specific appendix. Any deviations from the general principles outlined in the core protocol will be described with rationales in the applicable domain-specific appendix. All analyses will be planned and conducted in adherence with the *ICH-GCP* guidelines [148]. Adaptive features will be planned and used in each domain in accordance with guidance from the *ACT EU* Steering Group [72] and the *FDA* [55]. Domain designs, including adaptation rules, will be evaluated using statistical simulation prior to domain initiation (section 9.9) [38].

Members of the statistical analysis team will be unblinded, but will not participate in patient screening, inclusion, treatment, or outcome assessment to avoid that knowledge of results from adaptive analyses may influence decisions to enrol patients, treatment decisions, or outcome adjudication [55]. We will use a high level of detail when specifying statistical analysis plans and will prepare analysis scripts and run them with simulated data prior to initiating domains to limit researcher degrees of freedom [149].

9.2 | Analysis sets, comparisons, and estimands

Analysis sets
All primary analyses (including all adaptive analyses) in *INCEPT* will be conducted in a full analysis set based on the ITT principle, unless explicitly pre-specified otherwise in the domain-specific appendices. Each domain's full analysis set will consist of all participants randomised to that domain (the ITT population) except participants for whom we do not have consent to the use of *any* data. Patients randomised in error to blinded domains may be excluded from the full analysis set if they never received the allocated intervention and the exclusion takes place before unblinding and analysis, according to methodological recommendations on valid post-randomisation exclusions from analysis sets adhering to the ITT principle [150,151]. Additional analysis sets (e.g., per-protocol [PP] populations excluding participants with major protocol violations) may be specified for specific domains but will generally not be the primary analysis population.

Simultaneous comparison of all arms versus pairwise comparisons with a common control arm
For multi-arm domains (>2 arms), one arm may be specified as the control arm, typically corresponding to an active usual care or placebo/no treatment arm when assessing add-on therapies. If a control arm is defined, the domain-specific appendix will define one of two possible methods for comparing arms, and statistical simulation may be used to inform this choice. Either all arms may be compared simultaneously against each other, i.e., the control will be handled similarly to all other arms in the analyses, but the implications of inconclusive trials when calculating performance metrics (section 9.9) may then consider the control as most likely to be used in clinical practice if the domain ends up inconclusive or with an equivalence decision [38]. Alternatively, the control arm will be used as a *common* control arm that all non-control interventions will be compared pairwise against; if a non-control arm is superior to the common control, the control arm will be dropped and the superior non-control arm will be promoted as the new common control arm [38] as described in detail in section 9.4. For domains with only 2 arms, comparisons will always be pairwise, and thus the two methods are identical.

Concurrent controls
Participants will only be compared to participants randomised within the same domain; as arm-adding and *staggered entry* of interventional arms in specific domains is not supported in *INCEPT*, participants will only be compared to *concurrent* controls, thus avoiding the need to handle the potential biases that may otherwise be introduced by the comparison due to non-concurrent controls [40,152,153].

Estimands

Estimands precisely describe the exact intervention effect being assessed (and thus the question answered by a trial or analysis) according to five key attributes: the population, the interventions being compared, the outcome(s) assessed, the summary measure(s) used, and the handling of intercurrent events (including, e.g., protocol deviations and events that make registration of the endpoint impossible) [154,155]. These attributes are covered in separate sections of the core protocol and will be covered in separate sections of the domain-specific appendices but will be summarised in wording as well as in tabular format for the primary estimand (and optionally additional, secondary estimands) in each domain-specific appendix in a format as exemplified in **Table 4** below.

Table 4. Example of summary of key attributes of the primary estimand

Attribute	Description
Population	Acutely admitted adult ICU patients, with additional domain-specific restrictions of the population described.
Interventions (*treatment conditions*)	Summarised for each intervention arm.
Outcome (*endpoint*)	The primary outcome for the domain.
Summary measure	Sample-average absolute difference (risk difference or mean difference, as described in section 9.6).
Handling of intercurrent events	Participants analysed as randomised (i.e., according to the ITT principle) regardless of protocol adherence. Description of any special handling of non-survival (penalization of death for the days alive without life support/days alive out of hospital/days free of delirium outcomes; use of the 0 or the worst possible value for HRQoL/cognitive function outcomes).

Examples of how the attributes of the primary estimand in each domain will be summarised; a table with this structure should be included in each domain-specific appendix but edited as relevant.

9.3 | Timing of adaptive analyses

For all domains, the minimum number of participants randomised and with follow-up data available at each adaptive (interim) analysis will be pre-specified in the domain-specific appendices and may either be a constant increase or varying numbers. It will also be specified whether a *burn-in* period is used, i.e., an initial minimum number of randomised participants required to have reached follow-up before any adaptive analyses are conducted, based on performance metrics assessed through simulation [38,156]. In addition, it may be specified in the domain-specific appendices that adaptive analyses will first be conducted after the conclusion of specific integrated feasibility phase(s) (section 8.12), if used.

Adaptive analyses will – except where specified otherwise in a domain-specific appendix – be conducted at specific time intervals (e.g., the first workday of the month) after the required number of participants for an adaptive analysis have completed their outcome-data lag period (consisting of the follow-up duration plus a 15-day data collection/verification period) to

streamline data collection, validation, and analysis across domains in *INCEPT*. Where relevant, adaptive analyses will be conducted at intervals according to this definition, even if the maximum sample size has been enrolled in a domain, but all participants have not yet completed their outcome-data lag period. If multiple adaptive analyses are triggered to be conducted at the same time-point (e.g., due to fast recruitment and multiple thresholds for adaptive analyses being triggered in the same month), only the latest triggered analysis (i.e., the analysis including the largest number of participants) will be conducted. Adaptive analyses will include all participants who have completed outcome-data lag period at the time of analysis conduct. We will thus allow overrunning [157], i.e., continuing inclusion in domains while awaiting the results of the adaptive analyses. Consequently, the number of participants included in each adaptive analysis will generally be slightly higher than the pre-specified minimum number.
Only participants who have completed the outcome-data lag period for the guiding outcome will be included in the adaptive analyses to avoid early events from upwards biasing adaptive analyses compared to final analyses (for binary outcomes) or to avoid incomplete continuous outcome data affecting the results [47]. In addition to the pre-planned adaptive analyses, the IDMSC for each domain may request additional analyses at other times or of other outcomes if deemed relevant due to results or safety concerns caused by external evidence (section 17). Adaptive analyses will – unless otherwise specified – only be of the guiding outcome. If the guiding outcome is not the primary outcome, it may be specified in a domain-specific appendix that the primary outcome will also be analysed at regular intervals and presented to the IDMSCs or that the correlation between the guiding and the primary outcome may be analysed during the adaptive analyses, with adaptation rules using results from the guiding outcome. Following adaptive analyses, the domain IDMSC will be informed of the results, with adaptations implemented 48 hours after informing the domain IDMSC (or as soon as possible after) except in cases where the domain IDMSC objects to their immediate implementation (section 17).

9.4 | Adaptation rules

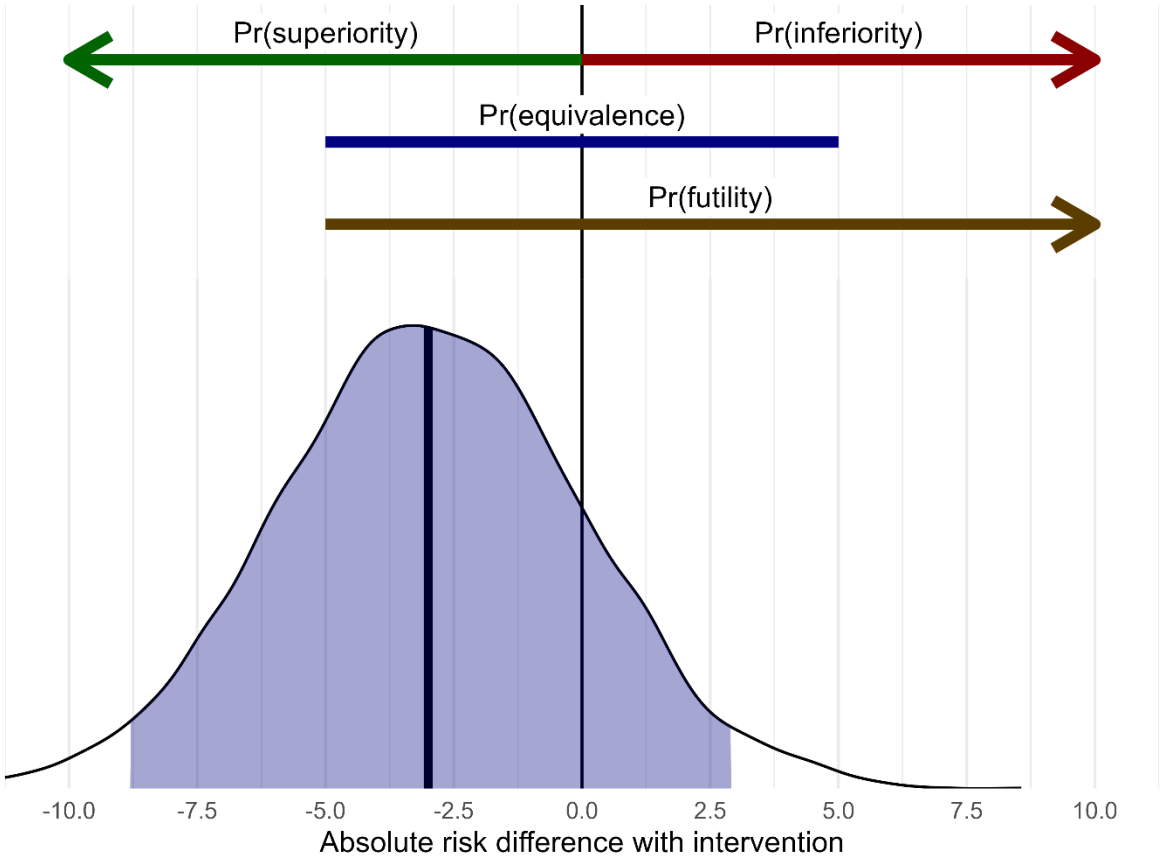
General considerations
Domains in *INCEPT* may use adaptation rules for adaptive stopping, adaptive arm-dropping (in domains with >2 arms), and response-adaptive randomisation [35,38,158] (section 9.5). The exact rules will be specified for each domain in the domain-specific appendices, but the general principles and considerations are outlined here.
In addition to the Bayesian stopping rules generally employed in *INCEPT*, specific domains may be conducted without adaptations (e.g., some domains may use designs with fixed sample sizes and fixed randomisation weights without allowing early arm-dropping). Likewise, specific domains may use additional adaptation rules (e.g., a pilot/feasibility phase with specific stopping or adaptation rules related to pre-specified analyses of feasibility, followed by adaptation rules as generally used in *INCEPT*), or use more conventional analyses or designs (including frequentist analyses and group

sequential designs [32] with conventional stopping rules) as long as these rules are clearly described in the domain-specific appendices.
For all domains using Bayesian adaptation rules, the performance metrics of the domain design will be evaluated using simulations with results presented for the final design and relevant sensitivity analyses of its performance (e.g., assuming different event proportions or inclusion rates) in the domain-specific appendix [38,156] (section 9.9).

Stopping rule hierarchy

INCEPT allows arm-dropping and stopping for inferiority, superiority, practical equivalence (optional for each domain), and futility (optional, but only applicable for domains with a common control arm and all non-control arms compared pairwise to that). The stopping rules are evaluated hierarchically based on the clinical utility of each stopping decision (**Figure 9**). All stopping rules are based on the guiding outcome only and will be binding [55]. In domains with >2 arms, comparisons of remaining arms will continue after arm-dropping, whereas in domains with 2 arms, dropping a single arm will by definition lead to overall stopping of the domain.
First, inferior arm(s) (overall or compared against a common control arm, depending on the design) will be dropped. Second, superiority (overall or compared against the common control arm, depending on the design) will be assessed; if only one arm remains after dropping inferior arms, the superiority stopping rule will, by definition, be triggered. For domains with a common control arm that all non-control arms are pairwise compared to, a superior non-control arm will become the new common control with the old common control dropped for inferiority, immediately followed by a new analysis of the same dataset after exclusion of participants allocated to the dropped arm. Third, practical equivalence is assessed for domains where used. In domains where all domains are compared against each other, the entire domain will be stopped if all remaining arms are practically equivalent; in domains where non-control arms are compared against a common control arm, arms that are practically equivalent compared to the common control will be dropped. As practical equivalence is less clinically useful than inferiority/superiority, this has lower priority in the stopping rule hierarchy. Fourth, futility is assessed in domains where this is used (only relevant for domains with a common control arm to which all non-control arms are pairwise compared). Arms that are futile compared to the common control will be dropped. As futility is less clinically useful than inferiority/superiority and practical equivalence, it has the lowest priority.

Figure 9. Stopping rules in INCEPT



Stopping rules in *INCEPT*, based on a similar figure in [38] (Creative Commons CC BY licence [159]). The figure illustrates stopping rules for a pairwise comparison between two arms, e.g., in a 2-arm domain or a domain with a common control and a single non-control arm for an undesirable outcome, e.g., mortality. The full posterior probability distribution on the absolute risk difference (%-points) scale is presented, with the 95% percentile-based credible interval highlighted in blue and the median with a vertical line. The probabilities (Pr) of each stopping rule are illustrated and further described in the text.

Inferiority

Arms will be dropped for inferiority if the probability that the arm is the best in its domain (in domains *without* a common control arm) or if the probability that the arm is better compared to the common control arm (in domains *with* a common control and non-control arms being pairwise compared to it) is less than a pre-specified probability threshold [38,156]. In domains without a common control arm, analyses will be immediately re-run once an arm is dropped for inferiority (using the same dataset, but excluding participants allocated to the dropped arm), as this may alter the relative comparisons and final probabilities for the other comparisons. Stopping rules for inferiority will (unless otherwise specified) relate to differences of *any* size, and will thus perform similarly on both the absolute and relative scales [38,156].

Superiority

In domains where all arms are compared simultaneously against each other, the domain will be stopped for superiority if the probability that one arm is superior, i.e., the best in its domain is above a pre-specified probability threshold, with all other remaining arms dropped for inferiority [38,156]. In domains with a common control arm, an arm will be declared superior if the probability that it is better than the common control arm on the guiding outcome is above a pre-specified probability threshold. When this occurs, the common control arm will be dropped and the superior arm will become the new control, followed by an immediate updated analysis (using the same dataset, but excluding participants allocated to the dropped arm), where the remaining non-control arms are compared against the new control [38,156]. In cases where multiple arms are superior compared to the common control in a single adaptive analysis, the arm with the highest overall probability of being the best will become the new control, followed by an immediate updated analysis (using the same dataset, but excluding participants allocated to the dropped arm). Similar to stopping rules for inferiority, stopping rules for superiority relate to differences of any size (unless otherwise specified) and will thus perform similarly on both the absolute and relative scales [38,156].

Practical equivalence

Stopping rules for practical equivalence may be defined in the domain-specific appendices. For domains without a common control (where all arms are simultaneously compared), all active arms may be declared practically equivalent if the absolute difference between all arms (i.e., the absolute difference between the best and worst remaining arms) is less than a pre-specified amount with a probability exceeding a pre-specified threshold [38,156]. Pairwise assessments of practical equivalence between all arms may be presented in such domains if specified in the domain-specific appendices but will not be used to guide adaptations in domains with >2 arms and no common control. For domains with a common control arm, non-control arms may be declared as practically equivalent compared to the control and dropped from the domain if the absolute difference between the two arms is smaller than a pre-specified amount (in either direction) with a probability exceeding a pre-specified threshold. Whether equivalence will be assessed only against the original control or also against new control(s) will also be pre-specified.

Futility

Futility stopping rules may be defined for domains with a common control arm to which all non-control arms are compared. If a futility stopping rule is used, non-control arms will be dropped for futility if the probability that a non-control arm is *not* better than the common control by a certain pre-specified amount on the absolute effect scale exceeds a pre-specified threshold [38,156]. Futility will only be assessed against the original common control arm in each domain.

Format of stopping rules

INCEPT will use constant stopping thresholds, i.e., stopping rules similarly shaped as conventional

Pocock monitoring boundaries in conventional (frequentist) group sequential trials [44], except where otherwise specified in the domain-specific appendices. Compared to stopping rules that are strict to begin with and increasingly lenient with more participants (i.e., stopping rules resembling *O'Brien-Fleming* monitoring boundaries in conventional group sequential trials [44]), constant stopping rules generally leads to smaller expected sample sizes but larger required maximum sample sizes to detect the same effect with the same certainty [160]. Constant stopping rules also limit potential overestimation of effect sizes [44] due to adaptive stopping, although the potential overestimation is generally small and unimportant, especially in large trials [45,46], regardless of the format of stopping rules used. Stopping rules for inferiority and superiority will generally be symmetrical, i.e., the stopping threshold for inferiority will by default be one (100%) minus the stopping threshold for superiority.

Maximum sample size

A maximum sample size of each domain will be specified for each domain for logistical/economic reasons and as this is necessary for simulation-based design evaluation (section 9.9). If reached, randomisation of patients in the domain will be stopped, even if none of the other stopping rules have been fulfilled. Adaptive analyses will then continue as specified until all already-randomised participants complete their outcome-data lag period with all relevant stopping rules assessed in each adaptive analysis.

Final analysis

A final analysis will be conducted once data for the guiding outcome are available for all participants. This final analysis will include all participants, i.e., including those randomised to arms previously dropped. For domains with a common control arm, the common control arm in the final analysis will be the final, superior arm if stopped for superiority, and otherwise the last common control arm used. Of note, the final analysis (including all arms) may coincide with the last adaptive analysis or be identical if no arms have previously been dropped. Stopping rules will be assessed in all adaptive analyses, including the last adaptive analysis, but not in the final analysis. Consequently, the final domain conclusion will be based on the last adaptive analysis, while the final analysis will be used to calculate all final effect estimates and probabilities.

Stopping, conclusion, and communication of results

The final domain conclusion will be based on whether a stopping rule is triggered in the last adaptive analysis as described above, with the domain considered inconclusive for the guiding outcome if no stopping rule is triggered in this last adaptive analysis. The stopping decision will be considered final, even if the stopping rule criteria are no longer fulfilled in the final analysis with all randomised participants.

The final analysis and the results of all adaptive analyses will be reported. If stopped for superiority, all participants still active in the domain may be switched to the superior intervention

at the discretion of the treating clinician/local investigators. While this may affect protocol adherence, this is preferred for ethical reasons.

INCEPT is primarily focused on identifying a *single* superior intervention within each domain to aid clinical decision-making to the highest extent possible and not on superiority of multiple interventions compared to a common control. For each domain, it will be specified *a priori* whether decisions to drop arms (before the domain is finally stopped) will be communicated to the investigators and/or the public. In some cases, this may be appropriate, e.g., to allow currently active participants randomised to inferior arms to be switched to other interventions at the treating clinician's discretion. In other cases, arm-dropping may not be disclosed, if it is believed that it can threaten trial integrity [55] (e.g., if two doses of a drug are assessed in a multi-arm domain against other interventions and one dose is dropped, this information may affect the inclination to randomise further patients). For any *a priori* specification that arm-dropping decisions prior to domain closure will not be communicated to investigators/site staff/the public, the domain IDMSC may suggest that this decision be overridden, if it is deemed that differences are sufficiently important to warrant such disclosure regardless of the specified plan. The final decision on whether to follow such a recommendation will be made by the domain and platform management committees. In case of important safety signals or other results that are asserted to require immediate communication, this will be done in an appropriate format without unnecessary delay as decided by the domain and platform management committees. Communication of changes due to important safety signals, e.g., arm dropping as an urgent measure, will always be communicated (including to the competent authorities in *CTIS* or as required in countries outside the EU) along with a description of any intended follow-up activities.

9.5 | Randomisation profiles and rules

Initial allocation

For each domain, initial allocation profiles will be specified in the domain-specific appendix. Generally, domains with 2 arms or >2 arms that are all simultaneously compared to each other will use equal initial allocation unless otherwise specified to optimise power for all comparisons [38]. For domains with a common control arm (to which all non-control arms are pairwise compared) and >2 arms, a higher allocation proportion to the control arm will generally be used to increase power in the pairwise comparisons [38]; unless otherwise specified, a *square-root(number of non-control arms):1* ratio for the control arm and all non-control arms normalised to sum to 100% will be used [38,59,161].

For domains only employing fixed randomisation, this will be stratified for site and possibly other anticipated prognostic baseline characteristics, as specified in each domain-specific appendix. Stratified randomisation will be conducted using stratified block randomisation with blocks of randomly varying sizes [78], with blocks computer-generated with only involvement by members

of the *INCEPT* data or methodological-statistical teams, who will not be involved in patient inclusion, treatment, or outcome collection. For domains employing response-adaptive randomisation, randomisation will generally be stratified for at least site and, depending on the *burn-in* used, possibly also other anticipated prognostic baseline characteristics in the initial period similarly to domains with fixed randomisation. After the first adaptation of the allocation ratios, *simple* randomisation (i.e., not using stratification or blocks) [78] will be used instead, because combining stratified block randomisation with response-adaptive randomisation is impractical [162]. For domains with a common control arm, the square-root-based allocation ratios may be rounded to obtain numbers that facilitate reasonably sized varying block sizes as needed; this will be specified in the domain-specific appendices.

Fixed- or response-adaptive randomisation

The use of fixed- or response-adaptive randomisation or combinations will be pre-specified in the domain-specific appendices with choices evaluated using statistical simulation [38,156]. For 2-arm domains and multi-arm domains where all arms are compared with each other simultaneously, we will generally use either fixed allocation or response-adaptive randomisation with equal initial allocation. For domains with >2 arms and a common control group that all non-control arms are pairwise compared against, we will generally use a relatively higher, fixed allocation proportion to the control group than the other groups (e.g., a square-root-based allocation ratio as outlined above or a control group allocation probability, which always matches the highest non-control arm [38,48,59]) and response-adaptive randomisation in the other groups.

Allocation profiles when using response-adaptive randomisation will be calculated based on the probability of each arm being the overall best among all active arms, regardless of whether a common control arm is used [38,156,158]. Of note, response-adaptive randomisation rules based on the probability of each arm being the overall best performs better in multi-arm trials than adaptations based on the probabilities (or P-values) of each arm being superior to a control arm [163,164]. Following calculation of the raw probabilities of each arm being the best, any minimum/maximum restrictions in use will be applied, as will fixed allocation probabilities and *matched* probabilities (i.e., it may be specified that a common control arms' allocation probability is *matched* to the highest non-control arm) [38,156]. Finally, the allocation probabilities will be normalised to sum to one (100%), by re-allocating the remaining probability to the arms not affected by minimum/maximum restrictions and fixed/matched probabilities [38,156]. Response-adaptive randomisation will generally employ restrictions (e.g., minimum/maximum allocation probabilities and/or *softening* of[38] the allocation profiles) to limit extreme allocation profiles due to random fluctuations early [38,164–166]. Restricting allocation ratios avoids over-aggressive adaptations to random fluctuations and makes it harder to guess the allocation profile in non-blinded domains, which may otherwise prematurely influence treatment decisions or enrolment [55]. Further, restricting response-adaptive randomisation mitigates the potential for undesirable effects on overall sample sizes and power in some designs and scenario combinations (e.g., domains with 2 arms and no or small between-arm differences) [38,147,167]. The exact

restrictions and settings will be evaluated using simulations as discussed elsewhere [38,156] (section 9.9).

9.6 | Statistical analyses, models, and presentation of results

The following approach will generally be used for conducting statistical analyses of the core outcomes included in *INCEPT* (including both final analyses and adaptive analyses); deviations may be specified in domain-specific appendices. Analyses will be conducted separately for each domain using concurrent controls only [168]. Mock tables exemplifying how baseline data, outcome data, and results from adaptive analyses will be presented are included as **Table S2**, **Table S3**, and **Table S4** in appendix 4, section 21.4. Versions of these mock tables adapted for specific domains will be included in the domain-specific appendices, where relevant supplemented with additional mock tables.

Descriptive data
Baseline, process, and outcome data will be presented descriptively in each arm in each domain; numerical variables will be summarised using medians with 25% and 75% percentiles (interquartile ranges [IQRs]; which may be supplemented with categorisations), and categorical variables will be presented as counts with percentages. In addition, baseline and outcome data will be presented separately for each time period (with a new time period defined each time arms are dropped, or allocation ratios are changed after an adaptive analysis) for all participants and each intervention group separately in supplementary tables [34,169].

Models and presentation of results
All models will include the interventions (with the control group, if any, as the reference; otherwise, the reference will be specified in each domain-specific appendix), adjustment for all stratification variables used in the domain and additional anticipated prognostic baseline variables (described below). Sample-average estimates in each intervention group and sample-average intervention effects from the adjusted models will primarily be presented. Adjustment for carefully selected baseline covariates expected to be prognostic of the outcomes is recommended [170] as it increases precision and power with limited risk of minimal negative effects [171–173]. This approach is robust even in the presence of potential model misspecification [170,174,175], and does not change how the estimands [176] are interpreted when average intervention effects are presented [177].

All binary core outcomes will be analysed using adjusted Bayesian binary logistic regression models with results presented as estimated probabilities of the outcome with each intervention and adjusted absolute differences (risk differences [RDs]) and relative differences (relative risks [RRs]). Estimated probabilities and adjusted RDs and RRs will be all calculated as sample-averages

using a G-computation-like approach [170,178,179]. First, a logistic regression model will be fitted. Second, outcome probabilities for all participants will be predicted under the assumption that each participant was allocated to each intervention (i.e., factual predictions and counterfactual predictions with all adjustment variables unchanged). Third, the mean estimated probabilities of the outcome with each intervention will be calculated, reported for each group, and subsequently used to calculate sample-average RDs and RRs. This will be done for each set of draws from the joint posteriors. Adjusted odds ratios (ORs) either directly from the models (i.e., conditional ORs) or calculated using the G-computation approach (i.e., marginal/sample-average ORs) may be presented secondarily.

All continuous/count core outcomes will be analysed using adjusted Bayesian linear regression models with results presented as estimated mean values with each intervention and adjusted absolute differences (mean differences [MDs]) and relative differences (ratios of means [RoMs]) calculated using the same G-computation approach outlined above with prediction of the sample-average expected (mean) values for each participant. While the continuous/count outcomes assessed have certain minimum/maximum values and are expected to have complex, non-normal distributions [99], we consider the Bayesian linear regressions with subsequent use of the complete, joint posterior distributions to calculate the expected values in each group to be appropriate. The rationale for this is that these models will not be substantially affected by the non-normal distributions, they appropriately consider uncertainty, and specification of sensible, interpretable priors and final interpretation is easier for these models than for more complex models (e.g., ordinal or multi-part models) [99].

The primary results, which will be used with the adaptation rules [38,156], will be the sample-average estimates with each intervention and the corresponding absolute differences (RDs/MDs). For inferiority/superiority, similar probabilities would be obtained on the absolute and relative scales, whereas adaptation rules for practical equivalence and futility depend on the scale used. Posterior distributions of estimates in each group and intervention effect estimates will be summarised using median posterior values as point estimates, supplemented with 95% percentile-based credible intervals (CrIs) and graphical presentation of full posteriors for the relative and absolute differences and expected probabilities of the outcome or expected mean values with each intervention.

Results will be presented for the final analysis in each domain and for each adaptive analysis as exemplified in **Table S3** and **Table S4** in appendix 4, section 21. Estimated probabilities of the outcome or mean values with each intervention will be presented, along with probabilities of each intervention being overall superior and superior to the other arms (including a common control arm, where used), probabilities of practical equivalence of all arms and all active arms at the time of the final analysis (where relevant in domains without a common control, which may be supplemented with pairwise probabilities of practical equivalence), and probabilities of practical

equivalence and/or futility (where relevant in domains with a common control; supplemented with probabilities of effects larger than the threshold(s) used, in both directions). Finally, absolute and relative intervention effect estimates for all relevant comparisons will be presented and visualised (**Table S3** and **Table S4** in appendix 4, section 21).

Adjustment variables

Models will be adjusted for the following baseline variables unless specified otherwise in the domain-specific appendices (including a rationale):

- Site of enrolment
- Age
- Sex
- Active haematologic malignancy or metastatic cancer
- Acute surgery within 7 days prior to randomisation
- Use of invasive mechanical ventilation
- Use of circulatory support (continuous infusion of vasopressors or inotropes)
- Use of RRT within 72 hours prior to randomisation
- Time period (where relevant; categorical, with a new period defined each time arms are dropped, or allocation ratios are changed, with the most recent period as reference)
- All domain-specific stratification variables

All binary/categorical variables will be modelled as linear additive effects on the scale of the model (i.e., on the log odds scale for logistic regression models). For categorical variables, we will use absence of the characteristic or the most common value as the reference, except where otherwise specified. Thus, for site, the largest site will be the reference, and for sex, male sex will be the reference as most patients admitted to the ICU are male [180,181]. Continuous variables (age and additional continuous variables if specified in a domain-specific appendix) will be modelled using a linear term and a quadratic term without centring or standardisation, except if explicitly specified for analyses in the domain-specific appendices. Any domain-specific stratification variables used will be analysed on the continuous scale (using the same approach as for other continuous variables) if the underlying data are continuous, even if stratification is done according to one or more cut-offs (i.e., despite categorisation for the purpose of stratification, the variable will be analysed on the continuous scale) [182]. The G-computation-like approach described above is robust to potential model misspecifications [170], and even if the perfect form of the continuous predictors are not captured by the strategy above, it is still preferable to not adjusting for or categorizing relevant continuous variables [183] due to the robustness of the approach and the expected increased precision.

Some model terms may be pooled (e.g., sites with few inclusions, especially early in early analyses) or omitted (e.g., binary or categorical adjustment variables with most or all responses being

identical) if necessary for model convergence or due to few included participants. Adjustment for time period is used to control for potential *time drift* [2,35,40,41,47] due to, e.g., seasonal variations in case mix [41,184], inclusions of new centres to the trial with different case mix at different domain stages [41], or changes in the use of other interventions or usual care during the domain conduct. Adjustment for time period will be omitted where not relevant (e.g., in 2-arm domains where allocation ratios are fixed and constant or in domains with >2 arms not using response-adaptive randomisation and not allowing early arm dropping), but it will always be used when response-adaptive randomisation is used or where early dropping of arms in domains with >2 arms is possible.

Priors

Generally, we will use weakly informative priors for the intervention effects and for all adjustment variables included in the primary analyses. These will be neutral (i.e., centred on no difference between interventions) and may also be slightly-to-moderately sceptical to limit the influence of random fluctuations early [147]. The exact priors will be specified in the domain-specific appendices. Sensitivity analyses using other priors (e.g., more informative/sceptical priors, evidence-based priors, or priors elicited from experts [143,185]) will generally be conducted, as recommended [186]. Analyses using other priors will be pre-specified in the domain-specific appendices. If deemed relevant due to external evidence or suggested by the IDMSC for each domain, additional *post hoc* sensitivity analyses using other priors (e.g., priors incorporating external evidence) may be used.

Model fitting and assessment of convergence

Bayesian models will be fit using *R* software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and *Stan* [187] (directly or through another package, e.g., *brms* [188]) using *Stan*'s default dynamic Hamiltonian Monte Carlo sampler with at least 4 chains, at least 30,000 post-warm-up samples in total, and bulk/tail Markov chain Monte Carlo effective sample sizes of at least 5,000 for all model terms. Settings will be tuned as necessary to avoid divergent transitions, and chain convergence will be assessed as previously described [179,189]. Thus, convergence will be ascertained by visual inspection of overlain density and trace plots [190,191], and by the updated *Rhat* statistic [192], which must be ≤1.01 for all parameters [192]. To supplement this, we will use graphical posterior predictive checks [191,193] (focused primarily on expected values for the continuous/count data models) and Pareto-smoothed importance sampling leave-one-out cross validation (focused on the effective number of parameters compared to the actual number of parameters in each model) [194,195].

Sensitivity analyses

Sensitivity analyses may be pre-specified for each domain or conducted *post hoc*. If *post hoc* analyses are conducted, these will be explicitly labelled as such. Sensitivity analyses may use other

models, alternative adjustments, different approaches to the handling of missing data (section 9.8), or other priors, as discussed above [2,146,147,196].

9.7 | Heterogeneous intervention effects and interactions

Heterogenous intervention effects

Initially, *INCEPT* will solely focus on average intervention effects in the primary analyses and for all adaptations. Thus, separate adaptive arm-dropping/domain stopping decisions or separate randomisation profiles according to different participant characteristics will not be used in the initial version of *INCEPT*. However heterogenous intervention effects according to different baseline characteristics may be present, as ICU patients constitute a heterogeneous group with different admission diagnoses (often according to broadly defined syndromes), comorbidities, and past medical histories [2,197–202]. Thus, plans for assessing heterogeneity in intervention effects after domain stopping may be pre-specified in the domain-specific appendices. Heterogeneity in intervention effects may be assessed either using conventional subgroup analyses or more advanced approaches [2,198,202–205], such as hierarchical models, according to baseline characteristics on the continuous scale (transformed and/or centred/standardised, if relevant, which will be specified where applicable), according to baseline risks of adverse outcomes according to internally or externally developed prediction models, or by the use of complex data-driven methods. These more advanced approaches may be preferable to conventional subgroup analyses, as they may consider the potentially additive effects of multiple baseline characteristics simultaneously (hence more resembling clinical practice), they may avoid categorisation (or at least dichotomisation) of continuous variables, or they may partially pool data from multiple subgroups limiting the risk of chance findings in smaller groups [2,198,203,205–207].

Interactions between domains

General considerations regarding co-enrolment between different domains are discussed in section 12. In situations where interventions across domains may *a priori* be suspected to interact, it may be pre-specified that potential between-domain interactions will be formally assessed. Where domains are not added/planned simultaneously, this will be specified in the later-added domains' domain-specific appendices. Interactions may then be assessed for participants in both relevant domains but will not be used to guide adaptive decisions in the initial version of *INCEPT*. In specific cases where interactions are deemed highly likely *a priori*, it may be specified that potential interactions may be assessed at specific adaptive analyses with results presented to the IDMSCs of the relevant domains, who may then include these results in their recommendations. Interactions will, except where otherwise specified, be assessed using Bayesian methods and evaluated probabilistically without dichotomisation of results. Potential between-domain interactions may similarly be assessed in certain cases, even if such interactions are *a priori* considered unlikely. Somewhat informative, *sceptical,* neutral priors [146,196] may be pre-

specified and used for the assessment of potential interactions, especially when considered unlikely *a priori*.

9.8 | Handling of missing data

We will minimise missing data by continuous monitoring of missingness in the eCRF and by contacting sites where missing data is prevalent to ensure high data completeness, and by implementing (increasingly over time) automated data collection (section 14). We expect limited missing data for most core outcomes (except the HRQoL and cognitive function outcomes, where moderate [e.g., between 5% and 20%] amounts of missing data are expected [94]), and very limited missing data for all adjustment variables listed above (section 9.6). The proportions of missing data (total and in each intervention group) will be presented separately for each variable in each report. If any data are missing for an analysis, regardless of the proportions, we will assume that data are *missing at random* and use multiple imputation (MI) [208–211]. While this assumption cannot be verified, it is the most reasonable assumption in large trials with reasonable amounts of variables collected, compared to the alternative assumptions of data being *missing completely at random* (which is unlikely for substantial proportions of missing data in large trials or platform domains) or *missing not at random* [211,212]. Even if the *missing at random* assumption does not hold, MI will still generally retain precision and power (regardless of the missingness mechanism) and reduce bias compared to alternative approaches when data are *missing not at random* [211,212].

We will create 25 imputed datasets separately in each intervention arm in a domain using the multiple imputation with chained equations procedure with the predictive mean matching method for numerical variables and the binary/ordinal/polytomous logistic regression methods for binary/ordinal/nominal categorical variables, respectively [208]. All adjustment variables included in a domain (section 9.6), all available outcomes (generally, outcomes with similar or shorter follow-up durations than the outcome of interest), relevant baseline variables (specified in domain-specific appendices, but always including baseline variables used in the analyses, including analyses of heterogeneous intervention effects, and baseline variables used for calculating the outcome variables, e.g., treatment with antipsychotics at hospital admission) and any additional variables specified for inclusion in the domain-specific appendices will be included in the imputation models for the final analyses in each domain. For the adaptive analyses, we will generally only include the guiding outcome, mortality after the same follow-up duration as the guiding outcome (if the guiding outcome is not mortality), and all adjustment variables included in the adaptive analyses in the imputation models, as data for all other variables will not be collected and validated at the same frequency as data for the variables included in the adaptive analyses. For the yearly analyses of safety data presented to the IDMSC (section 17) a similarly simplified imputation model will be used, but also with the inclusion of the *one or more domain-specific*

safety outcomes data. For both adaptive analyses and yearly analyses of safety data presented to the IDMSC of domains with *days free of delirium at day 30* as the guiding outcome, participants with missing data for treatment with antipsychotics at hospital admission will be assumed to not have been treated with antipsychotics at hospital admission (logical imputation) to facilitate calculation of the outcome according to daily registrations regarding the use of in-hospital antipsychotics.

For partially missing data (e.g., days alive without life support, where data may only be missing for some days), we will calculate each participants' possible range of values and truncate imputed values to this range immediately after imputation, within the MI procedure. For variables calculated based on multiple separate variables (e.g., EQ-5D-5L index values calculated using vital status and responses in the five separate domains), we will multiply impute the separate variables and calculate the derived variables following the MI procedure. For outcomes where non-survivors are assigned a special value (e.g., the HRQoL outcomes, cognitive function, and the variants of the days alive without life support, days alive out of hospital, and days free of delirium outcomes with penalisation of death), this will be done after the MI procedure. The variants without penalisation for days alive without life support, days alive and out of hospital, days free of delirium, HRQoL variables, and cognitive function will be entered as missing for non-survivors in the imputation procedure and thus multiply imputed followed by setting these variables to the final values, i.e., assigning the specific values for non-survivors or penalisation. This is done to avoid overly large influence of the 'special' values assigned to non-survivors on the imputation of values for survivors.

We will generally not present complete case analyses when data are missing, as these are at higher risk of bias compared with the analyses using multiply imputed data and may therefore be misleading or confusing [212]. Supplementary best-worst/worst-best case scenario imputations may be used as sensitivity analyses if pre-specified in domain-specific appendices (for domains with only 2 arms, or in some cases for domains with >2 arms, assuming in turn a best case scenario for participants with missing outcome data in one arm and worst case scenarios in the remaining arms) [210]. For binary outcomes, best/worst cases are defined according to absence/presence of the outcome; for continuous outcomes with minimum/maximum values (including the continuous core outcomes), these will be used (for EQ-5D-5L index values, the lowest value appearing in the dataset will be used for the worst case scenario); for domain-specific continuous outcomes without minimum/maximum values, the mean value in each group plus/minus two standard deviations will be used [210]. Partial missingness in the best-worst/worst-best case scenarios will be handled using truncation to each participants' possible range of values, as described above.

Where MI is used, the Bayesian models will be fit separately to each imputed dataset with convergence assessed before the posteriors from each imputed dataset are pooled and

summarised. In these cases, the required Markov chain Monte Carlo effective sample sizes (section 9.6) will apply to the pooled posteriors.

9.9 | Statistical simulation and performance metrics (including sample sizes)

The complexity of adaptive platform trials renders conventional closed-form sample size/power calculations infeasible. Instead, statistical simulation is necessary [2,35,38,59,156] and will be used to evaluate performance metrics of multiple relevant combinations of design features (including decision rules, timing/frequency of adaptive analyses, randomisation strategies, etc.) when preparing each specific domain [38,156]. If a specific domain solely uses a conventional design with conventional adaptations (e.g., a group-sequential design [32,160]) conventional closed-form sample size calculations may be used for that domain, possibly supplemented with simulation to evaluate other performance metrics; this will be specified in the domain-specific appendix. A rationale for the maximum sample size used in each domain will be provided in the domain-specific appendices.

Simulations and scenarios
Simulations will generally be conducted using the *adaptr* R package developed by members of the *INCEPT* group [156]. We will generally conduct at least 10,000 simulations of each possible trial design, although fewer simulations may be used as part of preliminary screenings aimed at excluding designs that are substantially inferior compared with alternative options. For the final design chosen for each domain, 100,000 simulations will always be conducted [55].

Designs considered will be assessed under at least three different scenarios, assuming different outcomes (e.g., event rates) in each intervention arm:

1. A null scenario with identical outcomes in all arms. This scenario will generally be implausible, but is used to evaluate the type 1 error rate [156] and calibrate the stopping rules to achieve the desired type 1 error rate (as previously done [126,147,167])
2. A scenario with relatively small differences between intervention arms; these differences will generally correspond to the thresholds for practical equivalence where used, if such a difference is defined for the guiding outcome in a specific domain.
3. A scenario with large differences between intervention arms (with at least 1 intervention arm being substantially different than the others, while other arms may be less different); these differences will generally correspond to effects larger than the thresholds used for assessing practical equivalence (where used).

For domains with >2 arms, multiple combinations of no/small/large differences (in either direction) may be assessed as specified in the domain-specific appendices. Further assumptions underlying the simulations will be specified in detail during the simulation phase for each domain;

this includes the expected inclusion rates as required for simulations (as faster inclusion rates will lead to higher numbers and proportions of randomised participants without available outcome data at the time of each, which negatively affects trial performance [167,213]). In addition to the primary simulations, sensitivity analyses of the simulations will be conducted using scenarios with different baseline outcome distributions (e.g., different control group event rates), with differences in both directions, but the same relative or absolute differences as in the primary scenarios, to assess how this affects the performance metrics (including the type 1 error rate), as recommended [55]. The exact scenarios assessed will be presented in each domain-specific appendix, and the performance metrics will be presented for the same design(s) in all scenarios considered.

Performance metrics

Multiple performance metrics (operating characteristics) [38,48,164] will be considered. These include metrics that may be prioritised for practical/economical/logistical reasons (e.g., total sample sizes), to maximise benefit to patients *internal* to the trial (e.g., total event rates or probabilities of being allocated to better arms), to maximise benefit to *external* including future patients (probability of conclusiveness/power/type 1 and 2 error rates, and the ideal design percentage (IDP) [38,164]), and the accuracy (root mean squared error [RMSE] or median absolute errors [MAEs] of the effect in the selected arm and RMSEs/MAEs of the differences between the selected arm and the common control arm, if any [38]). Several of these metrics (e.g., RMSEs, MAEs, and IDPs) can be calculated under different assumptions about which arm would be used in clinical practice if a domain does not end with a superiority decision; consequently, those metrics will generally be calculated in the following ways [38,156]:

1) in all domains: for simulations ending in superiority only.
2) in domains without a common control arm: assuming that the best remaining arm (the remaining intervention with highest probability of being the best arm in the final analysis) is selected in simulations not ending with superiority; alternatively, the standard of care/usual care arm (if any) may be selected if available and the best remaining arm selecting otherwise, or the selection may be based on cost/feasibility of the arms, as defined in the domain-specific appendices.
3) in domains with a common control arm: assuming that the common control arm is selected in inconclusive domains, unless the original common control arm is dropped early, in which case the best remaining arm (highest probability of being the best in the final analysis) will be selected in simulations not ending with superiority.

Calculations under different arm selection strategies may be chosen for different domains and will be planned in the domain-specific appendices. The final design will be decided considering both simulation results (with possible different focus on different metrics for each specific domain [38]), feasibility/practical considerations (e.g., if a design using response-adaptive randomisation is only slightly superior to a design with fixed randomisation for a single domain, the design with fixed

randomisation may be chosen due to lower complexity), and considerations according to presumed or assessed preferences among patients, family members, and other stakeholders (section 11).

For each domain, the selection strategies, assumptions, scenarios, and performance metrics for at least the final design will be presented in the domain-specific appendix. Domain-wise type 1 and type 2 error rates and probabilities of different conclusions (including inconclusiveness) for the guiding outcome in each domain will be assessed according to the different scenarios described above and presented [38,72,214]. Unless otherwise specified, type 1 error rates for the guiding outcome in each domain will be approximately kept at or below the conventional 5% threshold, by using simulation-based calibration of stopping rules [126,147,167]. Domains will generally be required to have at least 90% probability of conclusiveness (probability of triggering a stopping rule at an adaptive analysis, i.e., superiority, practical equivalence, or futility) for the final design according to the primary assumptions assessed; any deviations from this must be motivated in the domain-specific appendices. As each domain in *INCEPT* will consist of distinct groups of interventions, domains are considered independent of each other. Hence while error rates for the guiding (and typically primary) outcome will be controlled, controlling or assessing domain-wise error rates for all outcomes or platform wise-error rates will generally not be considered necessary or relevant [41,215]. Of note, the approach used in *INCEPT* is technically hybrid frequentist-Bayesian, as the evaluation of the Bayesian analogues of typical frequentist performance metrics is generally recommended by the competent authorities [55,72,143,214]. While the final analyses and conclusions in a strictly Bayesian context relies only on *what actually happened* (the data obtained) and the prior probability distributions, frequentist performance metrics consider what *may happen* or *could have happened*, which is relevant with regards to evaluating uncertainties and random variations that may occur once a domain starts at the domain planning stage [216].

10 | Trial integrity

This section summarises the methodological decisions and safeguards used in *INCEPT* to ensure that the integrity of the trial is not threatened by the complex adaptive platform trial design and to minimise operational biases in the conduct of the platform trial [34,55,72].

First, stopping rules in *INCEPT* will be binding and thus cannot be affected by operational biases. In addition, each domain's IDMSC may suggest stopping due to other factors, e.g., external evidence or due to safety signals. Second, stopping rules will be calibrated to ensure adequate control of type 1 error rates using extensive statistical simulation including sensitivity analyses to assess performance metrics under other assumptions, e.g., assuming different baseline (e.g., control group) outcome distributions [38,55,72] or different inclusion rates [167]. Third, access to domain data before a domain is stopped will be restricted to trial staff performing data validation, cleaning, and analysis, and these persons will not be involved in the inclusion of participants or outcome data collection. Further, only trial staff involved in the conduct of the statistical analyses and implementation of trial changes (e.g., updated allocation profiles when response-adaptive randomisation is used) will have access to the adaptive (interim) analysis results. A clear strategy for when and how results of adaptive analyses will be presented will be specified in the domain-specific appendices, including the option to communicate safety signals without undue delay. Fourth, several measures to mitigate potential disadvantages of response-adaptive randomisation are used. Updated adaptive allocation profiles will not be revealed to anyone besides the statistical team and those implementing the updated profiles in the randomisation system. Further, response-adaptive randomisation will be restricted to avoid overly aggressive adaptation to random fluctuations and to minimise potential premature effects on equipoise, the inclination to enrol patients and to participate, and protocol adherence. Fifth, while it will not be feasible to blind all domains, *INCEPT* uses primarily objective outcomes. Sixth, only concurrent controls will be used in the analyses [40,152], and analyses will be adjusted for time period whenever an adaptation is made. These methodological features mitigate potential effects of time drift (e.g., seasonal variations in case mix or outcomes) in *INCEPT*. Seventh, the primary analyses will generally use neutral priors that are either weakly informative or somewhat sceptical, which stabilises performance metrics and, for sceptical priors, protect against early chance findings, while having acceptable effects on expected sample sizes [147].

11 | Stakeholder involvement including advisory board and research panels

Stakeholder involvement, including patient and public involvement and involvement of other key stakeholders, is a central part of the *INCEPT* programme. Stakeholder involvement in multiple research stages is prioritised as recommended [1,29], with the aim of ensuring relevancy of *INCEPT* to those who will use or be affected by its results, and the additional benefit of likely improvements to design and delivery of the platform and individual domains [217]. We aim to involve stakeholders in several of the six research stages outlined by Pii and colleagues to the extent relevant [218] (of note, these stages largely overlap with the stage classifications from the *National Institute for Health and Care Research (NIHR)* in the United Kingdom [219]):

1. Development of research focus (research definition and prioritisation)
2. Development of research design (method development and study design development)
3. Recruitment (recruitment strategy and recruitment)
4. Data generation
5. Data processing (analysis)
6. Dissemination (dissemination strategy and dissemination)

This section describes current and future planned involvement in various parts of the *INCEPT* programme with reference to the six stages.

Advisory board and research panels

The platform and domain management committees are advised on central aspects related to the conduct of *INCEPT* and specific domains by a central advisory board and multiple research panels consisting of key stakeholders including ICU survivors, their family members, clinicians, trialists, methodologists/biostatisticians, and other relevant stakeholders (e.g., representatives of hospital management, legal units, and health economists).

Research panels consist of ICU survivors, family members, clinicians, and researchers [3] and have currently been established in 4 out of 5 Danish regions with regular meetings taking place. Similar research panels have been established in other countries (see below) and informed *INCEPT*. The research panels provide stakeholder involvement in *INCEPT* and individual domains in an advisory role, through separate meetings (primarily on topics that require more detailed involvement) or as part of the advisory board.

The central advisory board includes additional stakeholder categories than those included in the research panels, and, in addition, include research panel members in a loosely structure manner as relevant. No formal charter for the advisory board exists, as this board will only serve in an advisory role to the platform and domain management committees. The platform and domain

management committees will consult the full advisory board or parts of it in specific situations (described below) and as required on a case-by-case basis, i.e., the entire advisory board will not hold regular, mandatory meetings and the entire advisory board does not have to be consulted on every occasion. The advisory board will continuously be informed about the progress and key milestones of *INCEPT* (e.g., starting or stopping of domains), through electronic newsletters whenever relevant (at least once yearly) and through a voluntary online meeting held once yearly. A list of participants of the advisory board (not including research panel members) will be made available on the *INCEPT* website (www.incept.dk) and continuously updated. The advisory board will be dynamic, with replacements expected and accepted for all categories of included stakeholders.

All participation in the *INCEPT* advisory board and research panels is voluntary and unpaid.

Stakeholder involvement in the design of INCEPT

Members of the research panels have participated in discussions regarding the recruitment and informed consent process and written information materials in *INCEPT* (stage #3). We have held meetings with representatives from the competent authorities (*the Danish National Research Ethics Committee* and the *Danish Medicines Agency*) and monitors (4 out of 5 Danish GCP units, with the last unit subsequently informed) about the conduct of platform trials in general and *INCEPT* specifically, including the consent process, data collection, and cross-domain monitoring (stage #2, stage #3, and stage #4). Meetings with representatives from hospital management in *the Capital Region of Denmark*, *Region Zealand*, and *the Region of Southern Denmark* regarding the optimal implementation of *INCEPT* and the use of platform trial designs in other settings and specialties are ongoing. Finally, the *Organization of Danish Medical Societies* promotes the use of platform trials at multiple levels nationally [220], and the concept is one of the recommendations from the working group on improved clinical research by the *Danish Ministry of Industry, Business and Financial Affairs* [221]. Platform trials are now part of *Copenhagen University Hospital – Rigshospitalet's* research strategy, including the collaboration within the *Nordic University Hospital Alliance*. As a key part of the strategy, *Rigshospitale*t establishes a central platform trial unit to escalate the concept across specialties locally, nationally, and internationally.

Core outcome set and core outcome measurement set

A core outcome set applicable for trials conducted in a broad population of adult ICU patients has been developed with extensive stakeholder involvement [3,4,222] (stage #2). Based on a literature search covering existing core outcome sets, semi-structured interviews with 82 stakeholders (27 ICU survivors, 25 family members, 26 clinicians, and 4 researchers), a modified Delphi process involving 264 stakeholders (65 ICU survivors, 49 family members, 136 clinicians, and 14 researchers), and discussions and consensus meetings with a total of 22 research panels encompassing 225 stakeholders (56 ICU survivors, 32 family members, 80 multi-professional clinicians, and 57 multi-professional researchers) in 14 countries (Australia, Czech Republic,

Denmark, Finland, Iceland, India, Italy, Lithuania, Norway, the Netherlands, Poland, Sweden, Switzerland, and the United Kingdom) [4]. An initial core outcome set was initially developed in Denmark, and subsequently externally validated internationally [4,222]. A *core outcome measurement set* (defining how outcomes will be defined and measured, including the tools used) will be developed later based on a modified Delphi consensus process involving relevant stakeholders [3,4]. When the core outcome set and the core outcome measurement set has been finalised, we will update the list of core outcomes in *INCEPT* and their definitions (section 8.9).

Future stakeholder involvement in INCEPT and specific domains

Relevant stakeholders from the advisory board and research panels will be consulted whenever deemed relevant by the platform or domain management committees regarding methodological, practical, ethical, communication/dissemination-related aspects, and other matters. For each task, information about the purpose (i.e., motivation), expected time required, and any time-frames or deadlines for responses will be provided.

Specifically, we plan to at least include stakeholders from the advisory board and/or research panels in the aspects mentioned below (stages and categories of stakeholders involved in parentheses; involvement will generally be through either panel discussions or individual communication in person or by email/telephone):

- Development of and feedback on written information and any eventual additional information materials (e.g., videos) used in the informed consent process when materials for *INCEPT* and specific domains are developed (stage #3; involvement of ICU survivors, family members, clinicians, and researchers not involved in daily *INCEPT*/domain management, and representatives from the competent authorities).
- Lay summaries in the core protocol and domain-specific appendices when written (stage #3; involvement of ICU survivors and family members).
- Lay summaries of domain results used for dissemination (stage #6; involvement of ICU survivors and family members). These will generally be written to cover the four points described elsewhere (question, findings, implications, additional information [223]).
- Development of dissemination strategies (stage #6; broad written invitation to the advisory board/research panels with request to suggest relevant dissemination strategies and channels; where relevant, e.g., for specific domains, representatives from patient organisations may be involved as well).
- Discussion of outcome selection in domains, including inputs to the guiding/primary outcome(s) and suggestions or discussion of additional outcomes supplementing the core outcomes (stage #2; involvement of ICU survivors, family members, clinicians, and researchers not involved in daily *INCEPT*/domain management; involvement based on a suggested prioritisation made by the domain management committee).
- Prioritisation of domains to be added to the platform (whenever the number of planned/suggested domains surpasses the capacity of the platform/involved sites) or in

cases where domain co-enrolment is not permitted (stage #1; involvement of ICU survivors, family members, clinicians, and researchers not involved in daily *INCEPT*/domain management).
- Suggestions of new domains (stage #1; request in writing to the advisory board/research panel members at least yearly with request to suggest additional domains that may be assessed on the platform, depending on available resources; additional physical or online brainstorming meetings with participation of relevant stakeholders may also be conducted).
- Inputs to the design and methodology (including intervention-specific protocol details, analytical strategies, analysis methods, and code) of the platform when new design features are added and to specific domains, including on secondary analyses not covered in detail by the core protocol, when considered relevant (stage #2 and stage #5; involvement of specific relevant stakeholders from the advisory board).
- Commercial product development on *INCEPT*, e.g., phase 2, 3, or 4 drug trials or testing of devices (various research stages and variable involvement; the framework for such collaboration will be discussed with relevant stakeholders including the legal department of the *Capital Region of Denmark*, the relevant companies, the *Danish Association of the Pharmaceutical Industry* [*Lægemiddelindustriforeningen*], and the industry association for companies in Denmark involved in medical devices [*Medicoindustrien*]).
- Funding issues (primarily stages #2 and #3; will be discussed with the relevant parties, e.g., major public and private foundations and with hospital managers and owners).

Future projects and research studies on stakeholder involvement in INCEPT

As part of the *INCEPT* programme, we plan to undertake additional projects, including quantitative and qualitative studies, covering stakeholder involvement in general and in *INCEPT*. These studies will be protocolised later, but studies on the following topics are considered:

- An exploratory study using a qualitative or survey design of the *INCEPT* research panel members to assess the experiences or perceptions of being involved in the research process.
- A thorough description of the roadmap of current and future stakeholder involvement in *INCEPT* along with plans for implementation, to aid and inspire other research groups wanting to increase stakeholder involvement.
- A qualitative study exploring the perception on how stakeholder involvement affected trials conducted by other research teams and how they perceived to benefit (or not) from stakeholder involvement by interviewing researchers that have conducted trials with stakeholder involvement [9].
- Exploratory studies using qualitative or survey designs of the experiences of participants (and possibly family members) and clinical staff regarding participation in *INCEPT*, including the inclusion and informed consent procedures.

- Development of a tool that can be used to assess the impact of stakeholder involvement on trials.
- Evaluation of the impact of stakeholder involvement in *INCEPT* in general and specific *INCEPT* domains [219].

Summary of stakeholder involvement in the INCEPT

At the time of writing, the following categories and numbers of stakeholders have been involved in aspects directly related to the *INCEPT* core protocol:

- Core outcome set (stage #2; as described above).
- Consent procedure (stage #3; 4 Danish research panels including 6 patients, 5 family members, and 3 clinicians not otherwise involved in *INCEPT*).
- Lay description of the platform trial (stage #3; 1 patient, 1 family member, and 1 clinical doctor not otherwise involved in *INCEPT*).
- Feedback on the informed consent material (stage #3; 3 patients, 1 family member, and 8 clinicians not otherwise involved in *INCEPT*).

Stakeholder involvement in specific domains will be described in the domain-specific appendices and domain reports.

12 | Enrolment in multiple domains, co-enrolment, and collaboration

Multiple considerations are important regarding co-enrolment in separate, conventional clinical trials [76]. Most of these considerations apply equally to platform trials with interventions nested in multiple domains.

General considerations

Patient autonomy and consent
Co-enrolment in multiple separate trials or multiple platform domains needs to respect patients' autonomy. Where there is equipoise about which intervention is best for the individual patient (regardless of participation in other trials or platform domains), preventing patients from participating in trials or platform domains conflicts with central principles of research ethics [76]. Previous research indicates that patients and family members are generally positive towards co-enrolment [224]. Co-enrolment or inclusion in multiple domains in a platform trial may ease informed consent procedures compared to multiple separate, stand-alone trials [225].

Research output and costs
Interventional research is necessary to improve patient care, and co-enrolment maximises research output and may decrease costs as multiple interventions may be assessed simultaneously in multiple trials or platform domains and share research resources [76]. Further, allowing co-enrolment limits competition between trials or platform domains, which may decrease the time until trial or platform domain completion, in turn decreasing costs and increasing feasibility [224].

Sampling bias
Allowing co-enrolment decreases the risk of sampling bias that may occur if some eligible patients with specific characteristics are not included in a trial or platform domain if they are included in another trial or platform domain [76,225,226]; thus, co-enrolment increases generalisability and external validity.

Impact
The existing empirical evidence, although limited, indicates that sensible co-enrolment has limited influence on trial results in practice [227].

Current practice
While co-enrolment is often prohibited in industry trials of new drug interventions, it is commonly allowed in academic and pragmatic clinical trials assessing well-known interventions already in use in critically ill patients [225,226,228]. This reflects clinical practice in the ICU, where patients receive multiple interventions simultaneously, and hence the risk and influence of interactions

with sensible co-enrolment in trials or platform domains assessing interventions already in common use are comparable to the risks in clinical practice.

Statistical considerations

Co-enrolment may affect the statistical power to detect intervention effects, which is also affected by whether trial participation substantially changes the proportions of patients receiving each intervention in a domain/trial compared to usual practice [76]. If interventions interact, synergistic effects may increase power and precision while antagonistic effects may decrease power and precision; even if there are no interactions, an effective intervention in one trial or platform domain may reduce power in another [76] due to, e.g., lowering of the event rates in both groups in the other trial or platform domain [76,225]. While the practical effect of this may be limited, especially for interventions already in common clinical use [76,225], it may lead to larger required samples in each trial or platform domain. The implications of this will generally be lower in adaptive trials (including adaptive platform trials) with maximum sample sizes larger than the expected sample sizes, as the potential power decrease and inflations of the required sample sizes can be accommodated in such designs without substantially increasing the risks of inconclusive results compared to conventional, fixed sample size trials [2].

Issues considered before allowing co-enrolment to domains in INCEPT

Before allowing co-enrolment or simultaneous enrolment to multiple domains in *INCEPT*, the following will be considered [76,225]:

Interaction

When substantial biological interaction between interventions/domains is considered highly probable *a priori* (i.e., based on existing clinical knowledge) *and* this is likely to be different from what would be expected during regular clinical practice, co-enrolment may not be appropriate [225] or will require careful planning and handling. Co-enrolment to multiple interventions targeting, e.g., the same organ system requires special consideration as interactions are more likely, which may hamper interpretability, increase the risk of adverse events, and bias effect estimates of the interventions in isolation. Thus, co-enrolment may be restricted to domains containing interventions with different biological targets [76,224,225]. However, when patients routinely receive both interventions outside the trial, *even* if interactions are considered likely (as may sometimes be the case due to the large number of interventions most ICU patients receive) [76], co-enrolment may be sensible from a scientific and ethical point and permitted. *INCEPT* will primarily assess interventions already in common use, which may generally be considered low risk [72,123,125], and where clinical practice varies; as patients are thus often likely to receive combinations of the studied interventions *outside* the platform trial, inclusion to multiple domains in *INCEPT* will generally not pose a meaningfully different risk of interaction than usual clinical practice for most interventions.

Co-enrolment allows formal assessment of potential interactions [76], which may be desirable. Co-enrolment to domains on the same platform trial will, similarly to factorial trials, typically be better suited at assessing these interactions than similar co-enrolment in separate trials, due to standardisation between domains and an expected higher number of patients simultaneously randomised to the different combinations of interventions. The latter is likely to increase power compared to assessing interactions between multiple separate co-enrolling trials, where power is often limited [229], hampering interpretations.

Protocol adherence
If there is substantial probability that co-enrolment to one trial or platform domain affects adherence to the allocated intervention in another, co-enrolment is not optimal [225]. This is relatively unlikely for pragmatic, blinded trials and platform domains conducted in the critically ill but must be carefully considered in unblinded platform domains.

Other interventions and outcome registration
Co-enrolment can be problematic if knowledge of interventions received or early knowledge of outcomes in one trial or platform domain is likely to affect non-randomised interventions received, actual outcomes, or outcome assessment in another [225].

Adverse event handling
If adverse events due to participation in one trial or platform domain is deemed likely to affect interventions, outcomes, or outcome registration in another, co-enrolment is likely inappropriate [76]. Theoretically, more adverse events may be expected with co-enrolment or simultaneous enrolment in multiple domains in a platform trial [227]. However, this has negligible influence in practice if all interventions are routinely used in clinical practice outside the trial context.

Summary
Based on the arguments outlined above, co-enrolment is sensible unless there are case-specific arguments against it. Thus, co-enrolment in multiple domains in *INCEPT* and with other trials will generally be allowed and encouraged. Co-enrolment will be evaluated on a case-by-case basis with co-enrolment with other trials permitted after approval by the platform management committee. Formal co-enrolment agreements will be made with trials that are expected frequently to co-enrol with INCEPT; for other trials, this will be decided on a trial basis by the platform management committee. Where co-enrolment between *INCEPT* domains is not permitted, strategies for prioritising screening and enrolment to different domains will be outlined in the relevant appendices.

In addition, we will generally be supportive of coordination, collaboration, and integration with other trials (including other platform trials) as necessary, including use of *INCEPT* data in prospective meta-analyses [2,230,231] and multi-platform trials [2]. Such collaboration will be

supported and encouraged but will similarly require formal approval by the platform and domain management committees based on the considerations outlined above, in addition to any required approvals by the competent authorities.

13 | Timeline, changes, and stopping

We expect the *INCEPT* trial to initiate inclusion in the first quarter of 2025. Additional domains will continuously be added after development and approval of the domain-specific appendices by the competent authorities. For each domain, an expected timeline will be specified in the domain-specific appendix. The first domain(s) will be monitored extensively with necessary amendments being implemented as soon as possible and before initiation of new domains.

We expect to continuously update and revise the *INCEPT* core protocol and relevant appendices as needed. All substantial changes will be approved by the competent authorities before implementation, and a summary of changes will be provided (section 19).

INCEPT has no planned overall stopping date and may potentially run perpetually. The platform may be temporarily paused or stopped for financial, logistic, or other reasons after approval by the management committee if required. If overall stopping of the *INCEPT* platform trial is planned, we will strive to do this stepwise by first stopping the inclusion of new domains followed by full platform trial closure after all active domains have concluded.

14 | Data collection, data management, and embedding

14.1 Electronic case report form and user interfaces

After inclusion in one or more domains in *INCEPT*, baseline-, process- (i.e., data on intervention delivery and adherence), and outcome data will be collected during the follow-up period. *INCEPT* uses an eCRF specifically being developed for *INCEPT* with planned input from *GCP* units and the *Danish Medicines Agency* before the eCRF is finalised. The eCRF will be hosted in Denmark by *the Capital Region of Denmark* in a set-up based on an existing hardware set-up also used for other sensitive healthcare data. The eCRF uses secure connections between users/systems and the database.
Upon completion of a domain, the final dataset for that domain will be processed and saved in a format appropriate for persistent storage, archived in an appropriate location (e.g., a secure, logged network drive in the *Capital Region of Denmark*). The platform sponsor, the domain sponsor and their delegates will have access to the final domain dataset, whereas investigators will have access to data for participants enrolled at their respective sites. All final domain-specific datasets will be stored for 25 years following completion of the last domain on the platform, if not running perpetually.

User interfaces
The eCRF will consist of several user interfaces each serving specific functions and used for collecting specific data.

Screening interface

- Assessment of eligibility criteria and registration of central variables (e.g., stratification variables and adjustment variables included in all analyses) for staff enrolling patients.
- Pertinent data entry validation (section 14.5) and data standardisation upfront (e.g., conversion between different units).
- Supports duplicate entry of most variables (with exclusion of some variables related to the randomisation/consent process, where this is irrelevant) to bolster the confidence in the resulting findings by 1) facilitating quality control and ascertaining accuracy of manually entered data, and 2) validating automatic data capture once implementation of automatic data capture starts.

Data entry interface

- All data registered in baseline forms (baseline data not registered in the screening interface), day forms, and follow-up forms, and logging of the consent process.
- This interface includes overview functions to keep data entry as easy and as close to real-time as possible.

- Pertinent data entry validation (section 14.5) and data standardisation upfront (e.g., conversion between different units).
- Supports duplicate entry of variables to bolster the confidence in the resulting findings as described above (under *Screening interface*).

Administration interface

- Continuous quality control (i.e., missingness and summary statistics of key variables, overall, and site-specific for each domain).
- Extraction of aggregate (meta)data, i.e., site-specific screening and exclusion data.

Participant (and participant representative) interface

- An interface to facilitate electronic registration of informed consent (from all those consenting) and patient-reported outcome measures (e.g., HRQoL and cognitive function) will eventually be developed. This system will also support registration of data for patient-reported outcome measures by family members (proxies) if participants are unable or through direct contact by trial staff to participants who are unable or unwilling to electronically register these outcomes.

Monitoring interface

- Read-only interface for external trial monitors (e.g., the *GCP* units) with the ability to write/respond to queries by both *GCP* monitors and trial staff.

14.2 Integration and embedding

The eCRF application programming interface (API) will support hybrid data-entry, including both manual data entry by research staff through the graphical user interface and automated data capture from EPRs for sites with EPR systems with the appropriate APIs and data-transfer protocols (e.g., based on the *Fast Healthcare Interoperability Resources [FHIR]* standard) and relevant clinical registers (e.g., the *Danish Intensive Care Database* [10], the *Danish National Patient Register* [88], and the *Danish Civil Registration System* [232]). Automated data capture will gradually be implemented during the running of *INCEPT*, and has potential to substantially lowering the costs and workload associated with data collection to automatic capture and re-use of data already collected instead of manual transfer from, e.g., EPRs to a trial-specific eCRF [233]. We aim to build embeddings within the EPR(s) to allow automatic notifications to clinicians/research staff about potentially eligible patients, transfers, and potential outcome events, including adverse events, even if these need secondary, manual verification.

14.3 Operational datasets

For each adaptive (interim) analysis and domain, operational datasets may be extracted when required. These will be logged and saved using a versioning system also including details on the eCRF version and state of the randomisation module. These operational datasets will undergo standardised processing yielding transformed, derived, and summarised data as appropriate for the analysis in question.

14.4 Randomisation module

The randomisation module is part of the eCRF and implements the necessary schemes for stratification (none or participant-level [also supporting cluster-level; section 8.12]) and randomisation. Adaptive analyses will be carried out by the *INCEPT* statistical team. Based on the results of the adaptive analyses, allocation rules will be manually updated in the randomisation eCRF module.

14.5 Quality control and external monitoring

The eCRF will contain options to edit automatically and manually entered data as applicable. Appropriate checks (range check, valid values, etc.) will be put in place; some as “soft limits” (e.g., very high/low values that are unusual but not impossible) that may be bypassed and “hard limits” (e.g., impossible values or combinations of values in multiple fields) that cannot be bypassed. Automatically captured data will be monitored for unusual values corresponding to the “soft limits”, with such values flagged for review. As described above, the eCRF will also implement features to monitor data completeness and summary measures overall and across site in each domain, to facilitate continuous monitoring of data collection.
The platform and domain sponsors and management committees are responsible for organising trial sites and sufficient capacity building in local investigators, trial site staff, and clinical staff at participating trials before initiation of *INCEPT* and any new domains on each site.

INCEPT and all domains will be externally monitored according to the *GCP* directive and the monitoring and data verification plan including documentation of informed consent. The monitoring and data verification plan(s) will be developed in collaboration with the *GCP* unit of *Copenhagen University Hospital* (specific monitoring plans for domains, including domain-specific data, may be developed with the *GCP* units at the sites of the domain sponsors). After inclusion, site investigators and their delegates will have access to participant files (including EPRs) at each hospital for quality control and monitoring. *GCP* units and the competent authorities will be allowed direct access to source data for monitoring purposes and control, as required.

We will ensure that participating sites have procedures in place for the collection of all variables listed in section 14.6, including data sources used. Central monitoring of data quality, including proportions of missingness, will be implemented to detect outlying sites where data quality may be improved. We will primarily use simple descriptive statistics and visualisations for this, although this may be supplemented with more complex methods later. Sites will be contacted regarding missing data and potential systematic deviations to clarify possible reasons and, if relevant, implement initiatives to increase data completeness and quality at such sites.

For participants transferred from one trial site to another, the receiving trial site will continue data collection as applicable (including for domains where the receiving site does not actively participate); for participants transferred to non-trial sites, the transferring site will be responsible for continued collection of relevant data through EPRs and contact to the receiving site, the participant, and/or the participant's legal representatives as necessary.

Finally, the *Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis (EMPRESS)* trial [126], which precedes *INCEPT*, will use the eCRF system developed for *INCEPT* and thus serve as a test of this system with the possibility to revise and adapt the system as deemed necessary.

Drug traceability
Drug traceability measures will be implemented for specific domains where relevant and described in the relevant domain-specific appendices prior to domain initiation.

14.6 Variables

The variables listed in this section will be collected for all participants in *INCEPT*. Additional variables will be collected for participants in specific domains and specified in the domain-specific appendices. Detailed variable definitions are listed in appendix 5, section 21.5.
We have intentionally limited the variable list to the most central clinical variables that generally have limited missing data proportions when used in clinical trials, based on the combined experience of the group.

Screening and baseline variables
Baseline data are defined as data from the time of inclusion and prior, including previous medical history and data from the ICU or hospital stay prior to inclusion. Baseline variables that change between inclusion in different domains in *INCEPT* will be collected multiple times (corresponding to the baseline for each domain) as relevant. Baseline variables that are included as covariates in the primary models (section 9.6) will be collected in the screening form of each domain, while

additional baseline variables will be collected in a separate baseline form that may be completed later. Screening and baseline variables included in all domains are:

- Unique participant identifiers
- Site of randomisation
- Time and date of randomisation
- Date of index hospital admission
- Date of index ICU admission
- Age
- Sex
- Weight
- Height
- Use of invasive mechanical ventilation
- Use of vasopressors/inotropes
- Use of RRT
- Limitations of care
- Co-existing conditions:
    - Active haematological malignancy or metastatic cancer
    - History of ischaemic heart disease or heart failure
    - Diabetes mellitus
    - Chronic pulmonary disease
    - Chronic liver disease
    - Known use of immunosuppressive therapy within the last 3 months
    - Previous organ transplantation
    - Chronic use of RRT
    - Treatment with antipsychotics at hospital admission
- Acute surgery within 7 days prior to randomisation
- Lowest systolic blood pressure in the 24 hours prior to randomisation (mmHg)
- *Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)* [234]
- *Clinical Frailty Scale*, version 2.0 (9 levels) [235,236]
- Highest plasma creatinine in the 24 hours prior to randomisation
- Highest plasma lactate in the 24 hours prior to randomisation

Variables collected daily until 90 days after inclusion to the last domain

- Use of invasive mechanical ventilation
- Use of circulatory support
- Use of any form of RRT
- Vital status
- Admitted to the hospital

- Any registered positive delirium score with a validated screening tool (section 8.9) (only 30 days)
- Treatment with antipsychotics (section 8.9) (only 30 days)
- Any registered coma (section 8.9) (only 30 days)

Clinical outcomes
As defined above in section 8.9, including follow-up time-points according to inclusion in different domains. Safety outcomes will be collected as specified in the domain-specific appendices.

Feasibility outcomes
Data required for the assessment of feasibility outcomes in each domain (section 8.12) will be collected as defined in the domain-specific appendices.

Consent data
Data on consent (from all relevant parties) will be electronically collected, including details on the process of obtaining consent, potential withdrawals from one or multiple domains, and whether withdrawal is only from the intervention(s) or also from continued data collection or use of already collected data.

Process data and protocol adherence
Relevant data on process-variables (i.e., the delivery of interventions of data required to assess whether there is separation between groups) and adherence to the protocol will be defined in the domain-specific appendices and collected accordingly.

15 | Threats, challenges, and limitations

This section summarises the key threats, challenges, and limitations of *INCEPT* and its domains due to the adaptive platform trial design. Measures implemented to mitigate those limitations are briefly discussed. Specific limitations are also discussed elsewhere in the protocol.

Planning and funding domains
First, when using adaptive stopping and arm-dropping, the expected sample sizes will be lower than the maximum allowed sample sizes. Depending on the exact design choices in specific domains and the magnitudes of between-arm differences, the difference in expected and maximum sample sizes may be substantial [38,126,147,167]. This poses a challenge when planning domains, as participating sites may have limited capacity with regards to the number of domains they can participate in, and with obtaining funding for domains. However, given that the adaptive design was chosen as it is more likely to obtain conclusive results and likely more efficient than comparable non-adaptive designs [32], this potential limitation is mitigated by the increased efficiency. Thus, even though domain planning must ensure that the domain can run to the planned maximum sample size, this corresponds to what would have to be planned for in a stand-alone trial. However, more flexible funding models may be necessary, as may substantial coordination and collaboration between domains by key persons to use research resources as efficiently as possible.

Conclusiveness and sample sizes
INCEPT aims for high probabilities of conclusiveness when initiating new domains to limit the risk of uncertain results that may be of limited clinical importance. We expect that this will often require larger sample sizes compared with those commonly used in many trials conducted in the ICU setting [2,237]. As most domains in *INCEPT* are expected to be relatively large, time to completion of domains may – at least initially, when the number of sites participating in *INCEPT* is limited – take longer time than what is common for typical ICU trials. This challenge is unavoidable in order to maximise the probabilities of conclusive trials, and this is not specific to the use of an adaptive platform trial design, which will mitigate this challenge somewhat due to increased efficiency [32,35]. Appropriately handling this challenge will ideally require many sites in *INCEPT*. However, we expect this to be feasible, as participating in multiple domains in *INCEPT* should be less burdensome for participating sites compared with that of multiple stand-alone trials.

Standardisation
To benefit fully from the platform design, a greater degree of standardisation between domains compared with conventional stand-alone trials is required to ensure that as much as possible of the data requirements are similar between domains, as this will substantially lessen data collection burden and make automating data collection easier. Similarly, the guiding outcome in

each domain on *INCEPT* must be one of the *core outcomes* outlined in section 8.9. This standardisation means that some restrictions will be imposed on single domains, limiting the flexibility compared with separately designed stand-alone trials. Generally, we expect the benefits of standardisation to outweigh the necessary compromise in most cases, but this balance must be carefully considered before domain initiation, and some research questions may be better answered in stand-alone trials than in domains in *INCEPT*.

Adaptation

While adaptation comes with benefits (e.g., potential efficiency gains and probabilities of receiving superior interventions with response-adaptive randomisation) [32,38], it also comes with potential challenges.

Overly aggressive adaptation may increase the risk of chance findings early and negatively affect performance metrics. To mitigate this, adequate *burn-in periods* (i.e., initial enrolment periods without adaptive analyses) and/or somewhat sceptical priors will be used [38,147], with the domain designs extensively evaluated using statistical simulation [38]. As both follow-up durations and inclusion rates affect adaptive trial performance [167,213], this will also be evaluated using simulation. In some situations, when the follow-up/data collection period is relatively long compared to the expected inclusion period, the disadvantages of adaptive features may outweigh the advantages; i.e., a follow-up duration to inclusion period ratio of <0.25 has previously been suggested as the threshold for when adaptive trials are worthwhile [238]. Thus, for some domains, adaptation may be limited or omitted.

Further, in unblinded domains, response-adaptive randomisation may prematurely affect clinical equipoise or willingness to participate or enrol patients, if substantially different allocation probabilities are allowed and if these are used by clinicians or trial staff to make premature inferences about any potential intervention effects. Likewise, substantially different allocation probabilities may occur due to random fluctuations (primarily early in domains), which may affect performance metrics negatively as it takes time for the allocation probabilities to 'recover'. Consequently, we will impose restrictions on response-adaptive randomisation whenever used [38], and generally use stronger restrictions in unblinded domains.

While adaptive stopping may lead to overestimated intervention effects [44], the potential overestimation is generally small and of limited importance in practice, especially when trials or platform domains are relatively large [45,46]. We expect most domains in *INCEPT* to be relatively large, and this combined with sufficient burn-in periods and/or somewhat sceptical priors will reduce the risk of overestimated intervention effects in *INCEPT* [38,147].

Finally, adaptations based on only the guiding (and typically primary) outcome require careful consideration regarding other outcomes. First, it is important that the minimum sample size in each domain (corresponding to the number of participants randomised at the time of the first adaptive analysis) is large enough to provide reasonably precise estimates for other important outcomes, e.g., safety outcomes and long-term outcomes. Second, guiding outcomes in each domain should either be the outcome considered the most important outcome realistically

affected by the intervention or have very high expected correlations with other more important outcomes, as a domain may otherwise stop for benefit (or adapt allocation ratios) on the primary outcome but show harmful or neutral effects on other outcomes. While these considerations are especially important in complex adaptive trials, they are fundamentally like considerations in conventional trials.

Controls

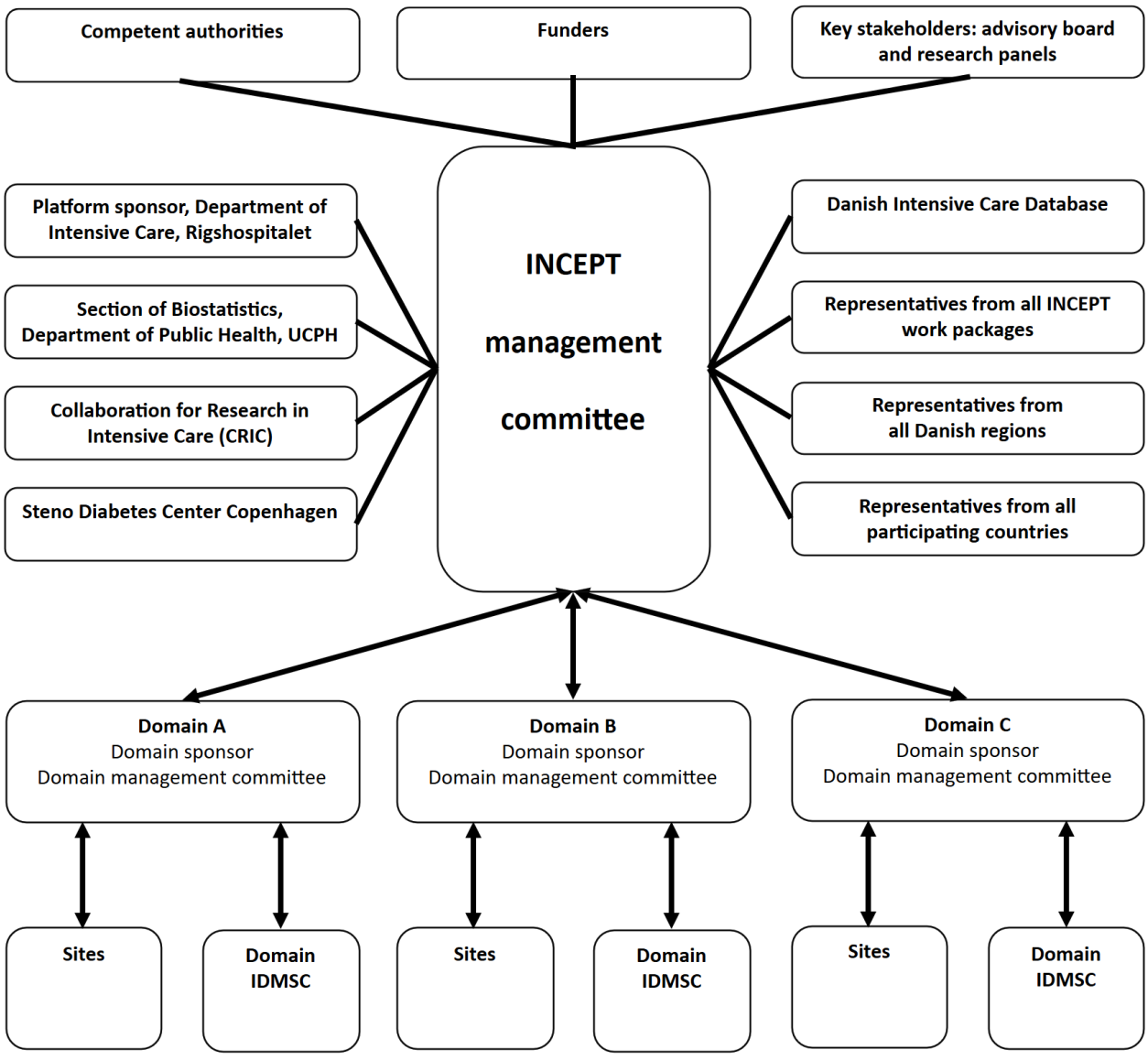
The use of non-concurrent controls (i.e., participants randomised in the trial before a new intervention to which they are compared becomes active) in platform trials poses a challenge and may introduce bias if not handled using complex statistical methods [40,239]. As all interventions in *INCEPT* are nested within domains and as arm adding to already initiated domains is not permitted at the time of initiation, *INCEPT* will only make comparisons against concurrent controls, and thus this is not a limitation for *INCEPT*.

16 | Organisational and financial aspects

16.1 | Organisational framework

The organisational structure is outlined in **Figure 10**.

Figure 10. INCEPT organisational diagram



Abbreviations: IDMSC: independent data monitoring and safety committee; UCPH: *University of Copenhagen*.

The *INCEPT* platform trial is ultimately organised and led by the platform management committee, chaired by the platform sponsor, taking overall responsibility for the platform trial. In addition, each platform domain will have domain-specific management committees, chaired by domain

sponsors, and responsible for day-to-day conduct of each domain. The platform sponsor is thus the primary sponsor of *INCEPT*, and each domain sponsor fulfils the role of a secondary sponsor with allocated responsibility of sponsorship for the specific domain, as defined by the *WHO* [240]. Each sponsor of an active domain (or a delegate) will be included in the platform management committee. If domain sponsors have conflicts of interest [241] with regards to other domains or the general management (e.g., in case of partnerships with industry or commercial actors), they will only hold an advisory role. Finally, the platform and domain management committees will consult the competent authorities, funders, and key stakeholders (advisory board and research panels; section 11) where relevant.

16.2 | Funders and roles

At the time of writing this protocol, *INCEPT* is primarily funded by grants from the *Novo Nordisk Foundation* and *Sygeforsikringen "danmark"*, and has received additional support from *Savværksejer Jeppe Juhl og hustru Ovita Juhls Mindelegat*, *Grosserer Jakob Ehrenreich og Hustru Grete Ehrenreichs Fond*, and *Dagmar Marshalls Fond*. None of the funders have had any influence on the planning of the platform trial, and none will have any influence on the design, conduct, analysis, or reporting of any domains assessed on the platform. Moreover, none of the funders will have ownership of any trial data. All funding sources will be acknowledged in all relevant trial reports.

Additional funding will be sought for *INCEPT* in general and for specific domains. Additional funders of both *INCEPT* in general and for specific domains that contribute later will similarly have no influence on the planning/design, conduct, analysis, reporting or decision to publish on *INCEPT* or any specific domains, except if explicitly specified otherwise. Partnerships with industry or other commercial actors in specific domains within *INCEPT* are permitted; if this occurs, these commercial partners may have influence on the design of specific domains, but not on the conduct, analysis, or reporting/decision to publish, and these partners will not have any ownership of trial data.

16.3 | Conflicts of interest

Conflicts of interest (including both financial and non-financial conflicts of interest) [241] for all members of the platform management committee (section 2.1), all key persons at the coordinating and methodological sites (section 2.2), and all protocol contributors (section 2.4) at the time of writing are listed here. Members of the platform management committee (section 2.1) have no financial conflicts of interest to any of the funders outside the trial, i.e., they have not received any personal honoraria or payments and do not own any stocks in any company owned by the funders.

All potential conflicts of interest relevant to the general conduct of *INCEPT* are listed, with potential conflicts of interest relevant to specific domains or additional contributors listed elsewhere as relevant (e.g., in the domain-specific appendices or domain reports). This list will be updated when the protocol is updated, and an updated list of conflicts of interest will always be included with all reports of results from *INCEPT*. If conflicts of interest for members of the platform management committee or for key persons at coordinating and methodological sites emerge during the conduct of *INCEPT*, the platform management committee and ultimately the platform sponsor will decide on the appropriate handling [241,242], e.g., replacing those persons or placing restrictions on the discussions and decisions they may take part in.

Reported conflicts of interest
Anders Perner: *research grants from the Novo Nordisk Foundation.*
Theis Lange: *has served on data safety monitoring boards in studies run by Novo Nordisk and Leo Pharma. None related to interventions considered at the time of writing in INCEPT.*
Bodil Steen Rasmussen: *unrestricted grant from the Novo Nordisk Foundation for long-term follow-up in the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial (ended June 2024).*
Marie Oxenbøll Collet: the *Novo Nordisk Foundation, Grant NNF21OC0072048 Postdoc followships in Nursing Research 2021.*
Ole Mathiesen: *funding to research group from the Novo Nordisk Foundation and Sygeforsikringen 'danmark' for other projects.*
Mathias Maagard: *holds shares in Novo Nordisk.*
Peter Rossing: *grants for investigator-initiated studies to Steno Diabetes Center Copenhagen, from Novo Nordisk, Bayer, AstraZeneca, and Lexicon. Honoraria to Steno Diabetes Center Copenhagen for steering group membership, consultancy and education from AstraZeneca, Abbott, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Gilead, Sanofi. No personal honoraria and no shares/patents.*
Tine Sylvest Meyhoff: *coordinating investigator of the CLASSIC trial (NCT03668236) which was supported by a grant (NNF17OC0028608) from the Novo Nordisk Foundation and by the Sofus Friis' Foundation, Rigshospitalet's Research Council, and supported by the Danish Society of Anesthesiology and Intensive Care Medicine.*
Asger Granfeldt: *paid member of data safety monitoring board for Noorik Pharmaceuticals (ended November 2022), work for hire for NMD Pharma, and task force member International Liaison Committee on Resuscitation (ILCOR) advanced life support task force.*
Theis Skovsgaard Itenov: *the Department of Anaesthesiology and Intensive Care, Copenhagen University Hospital – Bispebjerg and Frederiksberg Hospital has a collaboration with Radiometer Medical Denmark on test and evaluation of equipment. The department receives reimbursements from the company. No individual receives any personal benefits or payments from the collaboration.*
Johanna Hästbacka: *advisory board honorary fee from Paion (2022)*.

Carmen Andrea Pfortmueller: *no personal conflict of interests (personal financial interest). The department of Intensive Care at Inselspital, University Hospital of Bern report grants from Orion Pharma, Abbott Nutrition International, B. Braun Medical AG, CSEM AG, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, Nestle, Pierre Fabre Pharma AG, Pfizer, Bard Medica S.A., Abbott AG, Anandic Medical Systems, Pan Gas AG Healthcare, Bracco, Hamilton Medical AG, Fresenius Kabi, Getinge Group Maquet AG, Dräger AG, Teleflex Medical GmbH, Glaxo Smith Kline, Merck Sharp and Dohme AG, Eli Lilly and Company, Baxter, Astellas, Astra Zeneca, CSL Behring, Novartis, Covidien, and Nycomed outside the submitted work. The money was paid into departmental funds; no personal financial gain applied.*
Davide Placido: *holds stocks in Novo Nordisk A/S.*
All others: *no relevant conflicts of interest.*

16.4 | Other financial and legal considerations

Compensation
Dependent on the workload and funding for each domain, trial sites will either receive case money according to the number of participants enrolled and followed or a fixed monthly compensation to be used to support the salaries of dedicated trial staff. Compensation models will be pre-specified for each domain and may consider enrolment of the same participants in multiple domains (e.g., the inclusion of a participant in the first domain may lead to more case money than the inclusion in subsequent domains, as the workload per domain for sites and investigators will generally decrease for those included in multiple domains due to shared infrastructure and data collection), and may subsequently be changed according to the amount of manual data entry required at each site (i.e., due to data collection being automated in some EPRs before others) and over time (i.e., as data collection is increasingly automated, case money will be adjusted accordingly). Compensation models including any adjustments for each domain will be approved by the *INCEPT* management committee and be made available and continuously updated at the trial website

Insurance
Trial participants in Denmark are covered by the Danish law *"Lov om klage- og erstatningsadgang indenfor sundhedsvæsenet"* [243]; insurance details for other countries participating in *INCEPT* will be specified prior to the start of enrolment in those countries in the relevant national/local appendices.

17 | Independent data monitoring and safety committees

To oversee platform trial conduct and to support trial integrity and participant's safety, the *INCEPT* platform trial will be overseen by multiple IDMSCs, with each domain having a separate IDMSC. Each IDMSC will be multidisciplinary and consist of members that, collectively, have experience with conducting, monitoring, and analysing RCTs. Each domain IDMSC will include a clinical trialist (chairing the IDMSC), a clinician with relevant knowledge on the interventions assessed in the domain, and a biostatistician with adequate knowledge on the trial design and the relevant statistical analyses, as recommended [55]. Additional members may be added in specific domains if deemed relevant. The same individuals may serve as members of multiple domain IDMSCs. To ensure continuity and due to the required specialised knowledge on adaptive trial methods and the analyses used, we will aim for the IDMSC biostatistician(s) to cover multiple domains. Domain IDMSC membership is to be for the duration of each domain. If any member(s) leave the IDMSC before the domain is completed, the domain management committee will appoint the replacement(s).

Conflicts of interest

Members of the IDMSCs will be required to have no relevant conflicts of interest (including both financial and non-financial conflicts [241]) and will be required to complete a conflicts of interest form prior to being appointed; whether any potential conflicts of interest disqualify from IDMSC membership will ultimately be determined by the domain and platform management committees. For these reasons, trial investigators or individuals employed by the platform sponsor or the domain-specific sponsors, or individuals who have regulatory responsibilities for interventions assessed may not be members of the IDMSCs. Furthermore, domain IDMSC members will not own stocks in companies producing products evaluated or products that are competitive with those being evaluated in the domain, and members will disclose any consulting agreements or other financial interests with relevant companies. If conflicts of interest that were not present at the time of appointment emerge during conduct of the specific domain or if relevant in other domains on the platform, the domain management committees will assess the conflicts of interest and the status of applicable domain(s) and handle those as appropriate [241,242], with the concerned IDMSC members replaced if necessary.

Responsibilities

The domain IDMSCs' primary responsibility is safeguarding the interests of participants in each domain, assessing safety of the interventions, and monitoring the overall conduct of each domain. Each domain IDMSC will constitute its own plan of monitoring and meetings. The minimum requirements are specified in this section of the core protocol and additional domain-specific requirements may be specified in each domain-specific appendix as needed. As all stopping rules are binding, the IDMSCs serves as advisory to the domain and platform management committees.

The IDMSC may provide recommendations regarding the conduct of each domain (e.g., to stop a domain or make amendments); the selection, recruitment, and retention of participants; procedures for data management and quality control; or other aspects. Each domain management committee will be responsible for promptly reviewing the IDMSC recommendations to decide whether to continue, pause, or terminate the domain, and to decide whether amendments to the domain-specific appendix or changes to the domain conduct are required.
Recommendations to amend domain-specific appendices (or the core protocol) or to change the conduct of any domain on the platform made by the domain IDMSCs will be considered and accepted or rejected by the domain or platform management committees. The domain management committees will be responsible for deciding whether to continue, alter, pause, or stop the domain or specific arms based on the domain IDMSC recommendations.
Each domain IDMSC will be notified of all changes to the core protocol and the applicable domain-specific appendices (including analyses plans, if relevant) or conduct. The concurrence of domain IDMSCs will be sought on all substantive recommendations or changes to the domain-specific appendices (or core protocol) or to domain conduct prior to their implementation.

Adaptive analyses and statistical methods
Prior to enrolment of the first participant in a domain, the domain IDMSC will receive detailed information about *INCEPT* and the domain. This will include thorough information about the core protocol, methodology, statistical approach, and all relevant adaptation rules in writing and by a meeting (physical, online, or telephone) with at least two members of the domain or platform management committees (including at least one member with sufficient clinical experience and one with sufficient statistical/methodological expertise). The domain IDMSC will be provided with a simulated dataset of similar structure to the dataset used during the adaptive analyses and complete analysis code (in *R*) similar to what will be used during the adaptive analyses. The domain IDMSC biostatistician will be responsible for verifying the analysis code with any questions or potential amendments resolved by contact with the *INCEPT* methodological-statistical team, until the domain IDMSC biostatistician can vouch for the code. The domain IDMSC will not be responsible for running the adaptive (interim) analyses due to their large number and the standardised procedure used for these analyses. Instead, the domain IDMSC will be provided with the results in a format outlined in **Table S4** (appendix 4, section 21.4) and information about whether a stopping rule has been reached as soon as possible after an adaptive analysis has been conducted.

In addition, the domain IDMSC biostatistician will receive the dataset and code used to conduct each adaptive analysis, to make it possible for the domain IDMSC biostatistician to replicate the analysis if desired. As the adaptation rules are binding, the domain IDMSC will not have to decide upon whether the domain will continue based on the regular adaptive analyses and IDMSC meetings are not required following each adaptive analysis. However, the domain IDMSC will have 48 hours after receiving the results of an adaptive analysis to object to the immediate

implementation of the results (i.e., stopping domains, dropping arms, or changing the allocation probabilities) in case of any concerns regarding the analysis results. In that case, the domain IDMSC and domain sponsor (or a delegate) will, as soon as possible, decide on a plan for the replication/verification of the analysis by the domain IDMSC (or other required steps) that will be implemented within the shortest possible time to avoid unnecessary delays in adaptations.

Safety and yearly formal meetings

Each domain's IDMSC will receive unblinded data on the guiding outcome, mortality after the same follow-up duration as the guiding outcome (if this is not mortality), and safety data once yearly, i.e., data on domain-specific safety outcomes according to the risk assessment [section 8.10], stratified by intervention group. All data will be presented descriptively and analysed as described in section 9, with further details provided below. Of note, if the analysis of the guiding outcome does not coincide with one of the pre-specified adaptive analyses for the yearly IDMSC safety meeting, an additional analysis of the guiding outcome will be conducted to present the results to the IDMSC, but this will not trigger any adaptations rules and will not lead to updating of allocation profiles.

The IDMSC will be required to meet at least once yearly (physically, online, or by telephone) after receiving safety data. At the yearly meetings, each domain IDMSC will be responsible of making a recommendation to the domain management committee about whether to continue, alter, pause, or stop the domain based on their review of safety data. Domain IDMSCs will provide recommendations in written reports submitted to both the platform and domain management committees. It is the responsibility of the domain IDMSC to communicate their recommendation to the domain management committee without delay. Following a recommendation by the domain IDMSC, the domain management committee will inform all trial sites and investigators participating in the domain within maximum 48 hours about the recommendation of the IDMSC and the domain management committee's decision following this.

Final analysis meeting

Following stopping of a domain, the domain's IDMSC will have a meeting once all data for the guiding and primary outcomes have been obtained, verified, and analysed, regardless of whether stopping was due to a stopping rule being triggered or the maximum sample size being reached. At this meeting, the IDMSC can make a recommendation to the domain management committee about whether to submit a primary report on the available outcomes of participants having completed follow-up prior to awaiting the completion of follow-up, data collection, verification, and analysis of all additional outcomes for all participants randomised.

Additional data and meetings

Each domain IDMSC can, at any time during the conduct of the domain, request additional information, data, or analyses relevant for their domain and may also request or conduct additional analyses, e.g., incorporating external data from other trials that become available

during domain conduct. Each domain IDMSC may at any time hold additional meetings at their own discretion if deemed relevant.
In addition (except where otherwise specified, with rationale, in a domain-specific appendix), for each domain employing adaptive analyses, an IDMSC meeting will be held after the first such analysis, and similarly, for domains with integrated feasibility phases, an IDMSC meeting will be held after each formal feasibility phase has concluded. If these meetings are triggered to be close to the time of the required annual safety meeting (decided by the domain management committee), the meetings may be combined. Finally, the domain management committee may request additional IDMSC meetings and recommendations regarding continued domain conduct if external evidence arises that makes this relevant.

Sessions
IDMSC meetings will generally start with open sessions with participation of relevant members of the domain's daily management (e.g., the domain sponsor and domain coordinating investigator), one or more members of the methodological-statistical team, and the IDMSC. In these parts of the meetings, the domain status in general may be discussed, including the contents of the *open reports* described below. This will be followed by a closed session with participation of an unblinded member of the methodological-statistical team and the IDMSC only. Here, the contents of the *closed reports* described below will be discussed, followed by the IDMSC making their recommendation(s). The IDMSC may request that all non-IDMSC members leave the closed sessions while they discuss and make their recommendations.

Data and reports
Preceding the mandated, yearly safety meetings, an unblinded member of the methodological-statistical team will prepare open and closed reports.

Open reports will include information about whether a stopping rule has been triggered (and in that case, which stopping rule, without further details); aggregated data on the primary/guiding outcome and safety outcomes (always including mortality after the same follow-up duration as the primary/guiding outcome) ***across all participants*** (i.e., not separately in each arm); ***aggregated*** data on total recruitment; data on consent (separate percentages in each arm, but not raw counts to avoid potentially revealing changed allocation probabilities); data on protocol adherence (separate percentages in each arm, but not raw counts to avoid potentially revealing changed allocation probabilities); data on feasibility and separation (where relevant; separately in each arm, as percentages only). These reports will be shared with the domain IDMSC and the platform and domain sponsors and management committees at least three days prior to the IDMSC meeting.

Closed reports will in addition include results of the most recent adaptive analysis (if any; **Table S4**, appendix 4, section 21.4); descriptive data on the primary/guiding and safety outcomes (including

mortality) ***separately in each arm***; and updated analyses of the primary/guiding and safety outcomes (including mortality). These reports may only be shared with the domain IDMSC (until the domain is stopped and the final analysis meeting has been conducted) and will similarly be shared at least three days prior to the IDMSC meeting.

The IDMSC will prepare minutes following their meetings, including their recommendations, but without any of the confidential data included in the closed reports. The recommendations with the IDMSC minutes will be forward to the platform and domain sponsor and management committees and will be shared with the competent authorities as described in section 7.2.

Recommendations
All adaptive stopping rules are binding. The domain IDMSCs will recommend pausing or stopping a domain or one or more arms within a domain if group-differences in domain-specific safety outcomes are concerning with no pre-defined rules. If the recommendation is to stop the domain or specific arms, the domain IDMSC will recommend: *a)* whether the final decision to stop the domain or specific arms is to be made after an analysis including outcome data for all participants included at the time (including participants randomised after the analysis leading to the decision), and if so, *b)* whether a moratorium shall take place (pausing the domain) on the further inclusion of participants during these extra analyses. If further analyses of the participants included after the analysis leading to the recommendation is advised, the rules for finally recommending stopping should be specified with the recommendation. Furthermore, a domain IDMSC can recommend pausing or stopping the domain or specific arms if continuing clearly compromises participant safety. Similarly, if convincingly strong external evidence arises, the domain IDMSC may discuss this (upon request from the domain management committee or at their own initiative) and make recommendations for domain/arm pausing, stopping, or alterations, to safeguard the safety of participants. All recommendations from the domain IDMSCs will be non-binding and advisory only to the platform and domain sponsors and management committees.

Communication and trial integrity
Each domain's IDMSC will have access to adaptive analysis results (and the IDMSC biostatistician the corresponding data) based on unblinded information from each domain during conduct; these results are confidential and may not be shared with any external parties or members of the platform or domain management committees, investigators, clinicians, research staff, participants, or family members until the domain has closed without explicit written permission by the domain management committee. Besides the domain IDMSCs, only the members of the *INCEPT* methodological-statistical team directly involved in data cleaning, verification and analyses will have access to data prior to the stopping of a domain, and these persons will not be permitted to include patients in *INCEPT*. The platform and domain management committees and other members of the trial organisation will only be informed when an adaptive analysis has been conducted about whether the domain is stopped (and if so, the reason, without any further details

until follow-up for the guiding/primary outcome in that domain concludes); for unblinded domains, they will similarly be informed about arm-dropping only (and the reason, without further details). Whether information on arm-dropping will be provided in blinded domains will be specified in each domain-specific appendix.

Procedures will be implemented to ensure proper communication between the domain IDMSCs and the platform and domain management committees. Communication between the domain IDMSCs and the domain and platform management committees about recommendations and decisions will be in writing.

18 | Publication, authorship, substudies, and data sharing

18.1 | Publication and authorship considerations

A protocol article summarising the central contents of the *INCEPT* core protocol will be published in a peer-reviewed medical journal. Whenever a platform domain concludes and results have been analysed, they will be published, no matter the results, in peer-reviewed medical journals. In addition, results will be published on the *INCEPT* website (www.incept.dk). Reporting will adhere to the *CONSORT-ACE* [34] statement, which covers items related to general reporting of trial results and items specifically related to adaptive trials. There is currently not an *EQUATOR* (*Enhancing the QUAlity and Transparency of health Research*; www.equator-network.org) *Network* guideline or other reporting guideline specifically aimed at adaptive platform trials, but if a relevant reporting guideline is developed during the running of *INCEPT*, it may replace or supplement *CONSORT-ACE*. If unplanned changes to *INCEPT* as a whole or specific domains are required due to unforeseen circumstances, these will be reported in adherence with the *CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances (CONSERVE) 2021 Statement* [244]. Regardless, central design characteristics [38,40,59] will be reported with reference to the *INCEPT* core protocol and the protocol article. Results of the Bayesian analyses will be reported in accordance with the *Reporting of Bayes Used in clinical STudies (ROBUST)* guideline [186].

Reports on results from each domain will be written by each domain's management committee, with input and approval by the platform management committee prior to submission for publication or results being shared outside the *INCEPT* organisation.
Authorship will be granted according to the *International Committee for Medical Journal Editors (ICMJE)* guidelines [245] by the platform and domain management committees according to the individual authors' input. Detailed authorship criteria and the listing of authors may be pre-defined to the extent possible for each domain in the domain-specific appendices. The domain IDMSC, and all investigators and contributors not qualifying for authorship will be acknowledged with their names under an appropriate heading in supplements to the primary reports.

Generally, we aim to present domain-specific results in separate reports once domains conclude and make results public on pre-print servers simultaneously with submission for publication, although we may deviate from this in some instances, e.g., if required by a journal.
Findings that are important and potentially practice-changing may be communicated in alternative shorter formats (e.g., on the *INCEPT* website) before publication or pre-print availability after approval by the platform and domain management committees and, where relevant, after discussion with members of the advisory board or research panels (section 11).

18.2 | Substudies

Substudies, ancillary studies, and contribution of data or results from *INCEPT* or specific domains to collaborative research efforts (e.g., prospective or individual participant data meta-analyses [231]) will be encouraged and supported as long as they do not hamper the completion or integrity of specific domains or the platform. All such studies must be approved by the platform and domain management committees, and, if necessary, by the competent authorities, regardless of whether they are planned *a priori* or after one or more domains conclude. Such studies and data usage must generally be proposed to the platform management committee and the relevant domain management committees with a brief protocol synopsis, which should outline the research question, rationale, methodology, expected contributions and authorship considerations. A full protocol will generally be required following approval of a synopsis and will also require approval by the platform and relevant domain management committees.
An updated overview of planned and completed substudies and ancillary studies will be available and continuously updated at the *INCEPT* website.

18.3 | Data ownership and sharing

The platform management committee owns the rights to all intellectual property and the combined data collected as part of *INCEPT*; individual sites retain ownership of data collected at their specific sites.
An anonymised version of the final dataset (without personal, identifiable information, with timestamps replaced by relative time differences with respect to the time of randomisation, and other measures as deemed relevant) in each domain may be shared with other researchers following a reasonable request (i.e., a research proposal outlining the objectives, methodologies, and plans for data usage) and subsequent approval by the platform and domain management committees. Any sharing of data that is not considered anonymised will be after the necessary approvals; alternatively, aggregation, scrambling, or synthetic datasets [246] (i.e., datasets with similar structure and attempts to preserve the overall relationships between variables as the original dataset) may be shared. For each domain, data will generally only be shared after a grace period of at least 9 months following initial publication of results based on the data. Approved researchers will sign appropriate agreements to ensure compliance with the approved purpose and ethical and eventual legal requirements. Participants will be informed about the possibility of data sharing during the informed consent process.
Analysis code may be shared with other researchers after reasonable request and approval by the platform management committee.

19 | Summary of changes

This section summarises all changes to the core protocol after initial submission for approval.

Version 1.3, 2025-02-13:

- Added section on approval and oversight by the competent authorities (section 7.2). This section now describes approvals (previously in section 7.1), annual reports to the competent authorities regarding each domain, and an explicit statement that domains will be paused or stopped if required by the competent authorities. The previous sections 7.2 and 7.3 have been renumbered accordingly.
- The IDMSC section (section 17) has been slightly modified to refer to the annual reports sent to the competent authorities described in the new section 7.2.

Version 1.2, 2025-02-07:

- Added explicit statement that first-in-human investigational medicinal products or combinations with very limited clinical experience and advanced therapy medicinal products without EU marketing authorisations will not be assessed on *INCEPT* (section 8.3).
- Added explicit statements in multiple protocol sections emphasising that all domains will constitute medical emergencies and follow the applicable regulation for clinical trials in such situations (section 8.3 and section 8.5).
- Multiple clarifications and edits regarding the inclusion, randomisation, and informed consent procedures, including updated figures (section 8.5).
- Minor corrections, updates, and semantic edits in multiple places not leading to any changes in meaning.

Version 1.1, 2025-01-10:

- Names of members of the management committee and key persons and coordinating and methodological sites have been removed from the core protocol and replaced with statements that they will instead be made available and continuously updated at the *INCEPT* website (section 2.1 and section 2.2).
- Added section about serious breaches and notification of the competent authorities (section 7.3).
- Added statement that the platform sponsor and management committee will continuously evaluate the complexity of *INCEPT* with regards to the number of active domains permitted on the platform (section 8.3).
- Added statement that an overview of countries and trial sites participating in *INCEPT* and each domain will be made available and continuously updated at the trial website (section 8.4).

- Added description about the informed consent procedure using a modular approach (i.e., only including information about domains relevant for a particular participant) (section 8.5).
- Added explicit statements that all domains must be required according to the regulation for clinical trials conducted in emergency situations (section 8.5).
- Added a schedule of activities table (section 8.8).
- Clarifications with regards to the registration and use of day 180 outcome data for cases where domain inclusion occurs on different days (section 8.9).
- Added additional details regarding reporting to the authorities and communication of urgent safety measures due to important safety signals (section 8.10 and section 9.4).
- Added details on monitoring and following of participants after safety events (section 8.10).
- Added statement that the annual safety report will include all relevant items from the Danish GCP units' example template (section 8.10).
- Added section regarding end of trial and domains (section 8.11) and moved relevant details from section 8.10 to this section. The previous section 8.11 has been renumbered accordingly.
- Added mention of future possible studies on the experiences of participating in *INCEPT* (section 11).
- Clarification that variables related to delirium are only registered until 30 days after inclusion to the last domain (section 14.6).
- Added statement that additional funding will be sought for *INCEPT* and specific domains (section 16.2).
- Added statement that compensation models will be made available and continuously updated at the trial website (section 16.4).
- Minor corrections, updates (including in references), and semantic edits in multiple places not leading to any changes in meaning.

Version 1.0, 2024-11-04: first version submitted for approval.

20 | References

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21 | Appendices

21.1 | Appendix 1: completed reporting checklists

Completed *SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)* [69] and *CONSORT-ACE (Consolidated Standards Of Reporting Trials [CONSORT], Adaptive designs CONSORT extension)* [34] checklists are included in this appendix. Similar checklists will be completed in each domain-specific appendix and in the domain reports with reference to the core protocol where relevant; some items will primarily be covered in the domain-specific appendices. Some items on the checklists are not relevant at the protocol stage.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents* (www.spirit-statement.org)

Section/item	Item No	Description	Page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	7, 98
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	8-11
	5b	Name and contact information for the trial sponsor	8
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	98
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8-9

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	18-25
	6b	Explanation for choice of comparators	29-30
Objectives	7	Specific objectives or hypotheses	16
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	28-55

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	30
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	28
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	29-30
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Domain-specific appendices
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Domain-specific appendices
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	30
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	42-52
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	39-52
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	60-64

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Domain-specific appendices
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	37-38, 65-66
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	37-38
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	65-66
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	38-39
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	38-39
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	88-93, 145-148
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	39-42
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	88-93
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	56-70

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	70-71
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	58-59, 72-73
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 101-106
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	59-65
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	47-52
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	90
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	26
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	26-27
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	31-37
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	88-90, 108
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	98-100
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	88, 108

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	100
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	107
	31b	Authorship eligibility guidelines and any intended use of professional writers	107
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15, 108
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Separate documents
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable, 16

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Consolidated Standards of Reporting Trials (CONSORT) - Adaptive designs CONSORT Extension (ACE) Checklist

Section/Topic	Item no	Checklist item	Page no
Title and abstract	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see ACE checklist for abstracts)	5-7
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	18-25
	2b	Specific objectives or hypotheses	16
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	28-55
	3b« ǂ	Type of adaptive design used, with details of the pre-planned trial adaptations and the statistical information informing the adaptations	28, 37-38, 56-70
	3c«3b ‡	Important changes to the design or methods after trial commencement (such as eligibility criteria) outside the scope of the pre-planned adaptive design features, with reasons	107
Participants	4a	Eligibility criteria for participants	28
	4b	Settings and locations where the data were collected	30
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	29-30
Outcomes	6a ‡	Completely define pre-specified primary and secondary outcome measures, including how and when they were assessed. Any other outcome measures used to inform pre-planned adaptations should be described with the rationale	42-52
	6b ‡	Any unplanned changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size and operating characteristics	7a ‡	How sample size and operating characteristics were determined	74-76
	7b ‡‡	Pre-planned interim decision-making criteria to guide the trial adaptation process; whether decision-making criteria were binding or non-binding; pre-planned and actual timing and frequency of interim data looks to inform trial adaptations	59-66
Randomisation			
Sequence generation	8a	Method used to generate the random allocation sequence	37-38
	8b ‡	Type of randomisation; details of any restriction (such as blocking and block size); any changes to the allocation rule after trial adaptation decisions; any pre-planned allocation rule or algorithm to update randomisation with timing and frequency of updates	37-38, 65-66
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	37-38
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	37-38
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	38-39
	11b	If relevant, description of the similarity of interventions	Domain-specific appendices
	11c ǂ	Measures to safeguard the confidentiality of interim information and minimise	57, 77

		potential operational bias during the trial	
Statistical methods	12a ‡	Statistical methods used to compare groups for primary and secondary outcomes, and any other outcomes used to make pre-planned adaptations	56-73
	12b« ǂ	For the implemented adaptive design features, statistical methods used to estimate treatment effects for key endpoints and to make inferences	56-70
	12c«2b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	56, 70, 71, 73
Results			
Participant flow (a diagram is strongly recommended)	13a ‡	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome and any other outcomes used to inform pre-planned adaptations, if applicable	138-139
	13b	For each group, losses and exclusions after randomisation, together with reasons	138-139
Recruitment and adaptations	14a ‡	Dates defining the periods of recruitment and follow-up, for each group	Not applicable
	14b †	Why the trial ended or was stopped	64-65
	14c ǂ	Specify what trial adaptation decisions were made in light of the pre-planned decision-making criteria and observed accrued data	144
Baseline data	15a«15 †	A table showing baseline demographic and clinical characteristics for each group	67, 140-141
	15b ǂ	Summary of data to enable the assessment of similarity in the trial population between interim stages	67
Numbers analysed	16 †	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	138-139
Outcomes and estimation	17a †	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	142-143
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	1412-143
	17c ǂ	Report interim results used to inform interim decision-making	144
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) [1]	142-143
Discussion			
Limitations	20 †	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	94-96
Generalisability	21 †	Generalisability (external validity, applicability) of the trial findings	Not applicable
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Not applicable
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24a«24	Where the full trial protocol can be accessed	15
SAP and other relevant trial documents	24b ǂ	Where the full statistical analysis plan and other relevant trial documents can be accessed	15
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7, 98

SAP, statistical analysis plan; ACE, Adaptive designs
CONSORT Extension; "X« Y" means original
CONSORT 2010 item Y has been renumbered to X;
"X«" means item reordering resulted in new item X replacing the number of the original CONSORT 2010 item X
ǂ New items that should only be applied in reference to the ACE;
‡ Modified items that require reference to both CONSORT 2010 and ACE;
‡‡ Replacement (modified) item that only requires reference to the ACE;
† Item wording remains unchanged in reference to CONSORT 2010 but we expanded the ACE explanatory text to clarify additional considerations for certain adaptive designs. These unchanged items require reference to CONSORT 2010 except item 14b.

21.2 | Appendix 2: frequent serious adverse events in intensive care unit patients

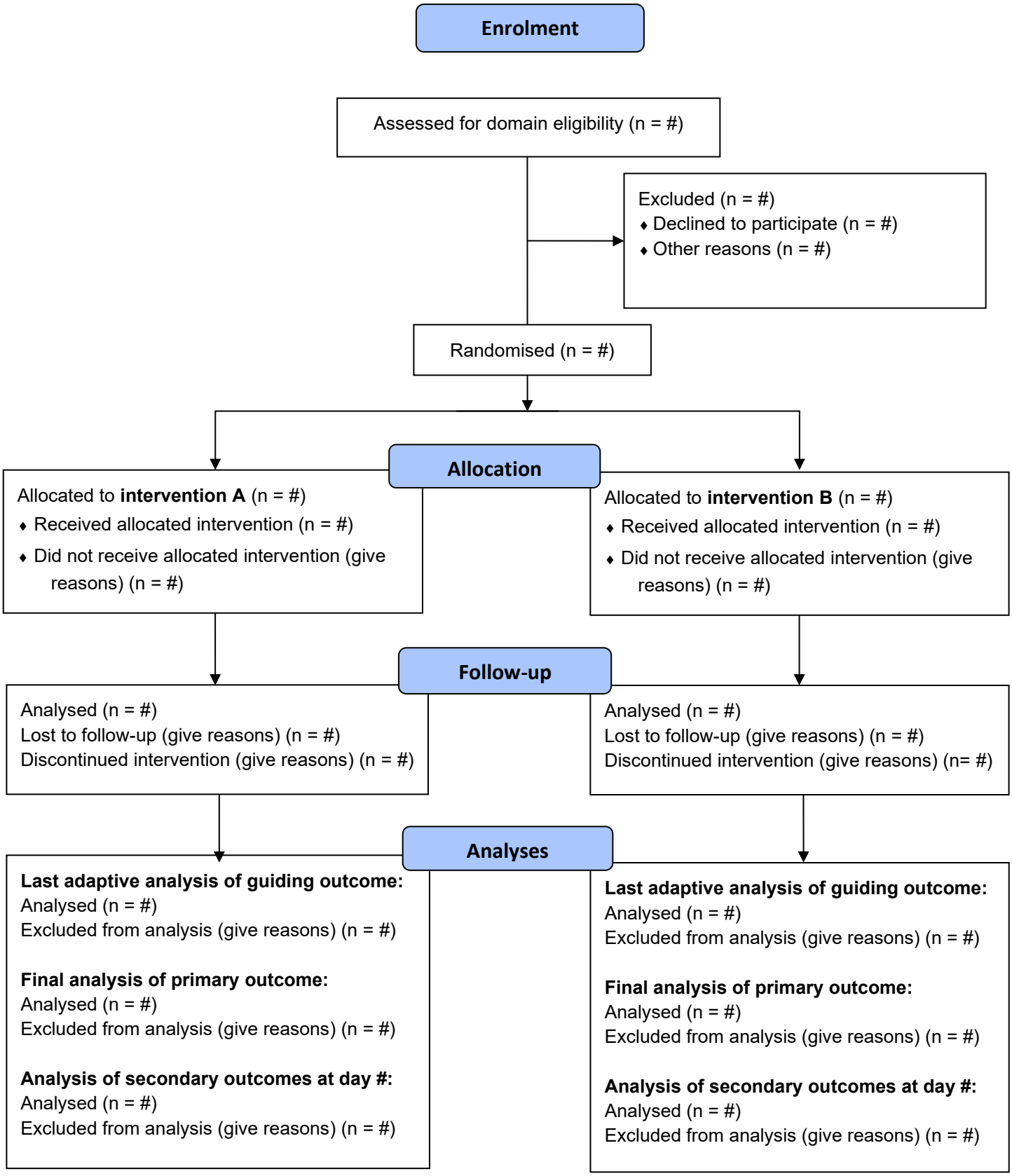
Table S1. Frequent serious adverse events in intensive care unit patients

Organ system	Serious adverse events (SAEs)
Nervous system	Stroke [247] Delirium [92,248] Seizures [248] Coma [248]
Respiratory system	Pneumothorax [249] Pneumonia [250] Acute respiratory failure [251]
Circulatory system	Severe heart failure (including cardiogenic shock) [252] Cardiac arrest [252] Acute coronary syndrome [252] Pulmonary embolus [253]
Digestive system	Pancreatitis [254] Acute liver injury [255] Ileus [256] Bowel ischemia [256] Gastrointestinal bleeding [257]
Urinary system	Acute kidney injury [17] Urinary tract infection [250]
Skeletal and muscular system, skin, and soft tissue	Soft tissue infection [250] Osteomyelitis [250] Decubitus [258]
Endocrine system	Diabetic ketoacidosis and/or coma [259] Adrenal insufficiency [260,261]
Blood and lymphatic system	Clinically important thrombosis [253] Clinically important bleeding (e.g., transfusion of ≥400 ml, approximately corresponding to 2 units, of red blood cells) [262]

Serious adverse events (SAEs) frequently seen in acutely critically ill adults admitted to the intensive care unit (ICU) are listed in the table. Considerations regarding collection and reporting of SAEs are described in section 8.10.

21.3 | Appendix 3: example domain inclusion flowchart

Figure S1. Example domain inclusion flowchart



Example of a domain inclusion flowchart, as will be used for each domain, adapted from the *Consolidated Standards Of Reporting Trials (CONSORT) 2010* flowchart [263]. A separate flowchart will be provided for each domain. For domains with >2 interventions, the flowchart will be expanded accordingly. For domains with interventions dropped prior to the stopping of the entire domain, the flowcharts will reflect that.

21.4 | Appendix 4: example baseline and outcome data tables

This section contains example tables (*mock tables*) of how baseline and outcome data, including results from adaptive analyses, will be presented for each domain in *INCEPT*. The tables are based on similar tables in the *Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis trial (EMPRESS)* [126]. For each domain, these tables will be adapted as necessary, i.e., additional variables will be included, outcomes will be listed according to the domain prioritisation, and the tables will be expanded to report data for all arms in >2-arm-domains. Domain-specific mock tables will be included in each domain-specific appendix.

Table S2. Example domain baseline data table

Characteristic	**Intervention A (N = #)**	**Intervention B (N = #)**
Country of enrolment		
- *[Each participating country listed separately in the domain report(s)]*	n (#.#%)	n (#.#%)
Age, median (IQR), years	## (## to ##)	## (## to ##)
Sex		
- Female	n (#.#%)	n (#.#%)
- Male	n (#.#%)	n (#.#%)
Weight, median (IQR), kg	## (## to ##)	## (## to ##)
Height, median (IQR), m	## (## to ##)	## (## to ##)
Use of invasive mechanical ventilation	n (#.#%)	n (#.#%)
Use of vasopressors/inotropes	n (#.#%)	n (#.#%)
Use of RRT	n (#.#%)	n (#.#%)
Limitations of care	n (#.#%)	n (#.#%)
Co-existing conditions		
- Active haematological malignancy or metastatic cancer	n (#.#%)	n (#.#%)
- History of ischaemic heart disease or heart failure	n (#.#%)	n (#.#%)
- Diabetes mellitus	n (#.#%)	n (#.#%)
- Chronic pulmonary disease	n (#.#%)	n (#.#%)
- Chronic liver disease	n (#.#%)	n (#.#%)
- Known use of immunosuppressive therapy within the last 3 months	n (#.#%)	n (#.#%)
- Previous organ transplantation	n (#.#%)	n (#.#%)
- Chronic use of RRT	n (#.#%)	n (#.#%)
- Treatment with antipsychotics at hospital admission	n (#.#%)	n (#.#%)
Acute surgery within 7 days prior to randomisation	n (#.#%)	n (#.#%)
SMS-ICU, median (IQR)	## (## to ##)	## (## to ##)
Clinical Frailty Scale, median (IQR)	## (## to ##)	## (## to ##)
Lowest systolic blood pressure in the 24 hours preceding randomisation, median (IQR), mmHg	## (## to ##)	## (## to ##)
Highest plasma lactate in the 24 hours prior to randomisation, median (IQR), mmol/L	## (## to ##)	## (## to ##)
Highest plasma creatinine in the 24 hours prior to randomisation, median (IQR), µmol/L	## (## to ##)	## (## to ##)

Abbreviations: IQR: interquartile range, mmHg: millimetres of mercury, mmol/L: millimoles per litre, N or n: total counts or counts, RRT: renal replacement therapy; SMS-ICU: *Simplified Mortality Score for the Intensive Care Unit* [234], µmol/L: micromoles per litre.

Binary or categorical variables are presented as counts with percentages; numerical variables are presented as medians with interquartile ranges. Definitions of all baseline variables are provided in appendix 5, section 21.5. The counts and proportions of participants with missing data for all baseline variables will be reported with the final table in each domain, with only complete data presented in this table (i.e., baseline data will be presented without multiple imputation).

Table S3. Example domain outcome data table

	Outcome data by intervention[1] descriptive data [n/N (%) or median (IQR)] *model estimate [probability or mean with (95% CrI)]*		**Intervention effect estimates[2]**		**Probabilities of each intervention being best/better[3]**	
Outcome	**Intervention A (N = #)**	**Intervention B (N = #)**	**Relative difference (RR/RoM, 95% CrI)**	**Absolute difference (RD/MD, 95% CrI)**	**Interven-tion A**	**Interven-tion B**
All-cause 30-day mortality	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#) *#.#% (#.# to #.#)*	#.## (#.## to #.##)	#.#%-points (#.# to #.#)	#.##%	#.##%
Days alive without life support at day 30	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.## (#.## to #.##)	#.## (#.## to #.##)	#.##%	#.##%
Days alive out of hospital at day 30	#.# (#.# to #.##) *#.# (#.# to #.#)*	#.# (#.## to #.#) *#.# (#.# to #.#)*	#.## (#.## to #.##)	#.## (#.## to #.##)	#.##%	#.##%
Days free of delirium at day 30	#.# (#.# to #.##) *#.# (#.# to #.#)*	#.# (#.## to #.#) *#.# (#.# to #.#)*	#.## (#.## to #.##)	#.## (#.## to #.##)	#.##%	#.##%
All-cause 90-day mortality	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	#.## (#.## to #.##)	#.#%-points (#.# to #.#)	#.##%	#.##%
Days alive without life support at day 90	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.## (#.## to #.##)	#.## (#.## to #.##)	#.##%	#.##%
Days alive out of hospital at day 90	#.# (#.# to #.##) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.## (#.## to #.##)	#.## (#.## to #.##)	#.##%	#.##%
All-cause 180-day mortality	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	#.## (#.## to #.##)	#.#%-points (#.# to #.#)	#.##%	#.##%
EQ-5D-5L index values at day 180	#.## (#.## to #.##) *#.## (#.## to #.##)*	#.## (#.## to #.##) *#.## (#.## to #.##)*	#.## (#.## to #.##)	#.## (#.## to #.##)	#.##%	#.##%
EQ VAS at day 180	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.## (#.## to #.##)	#.## (#.## to #.##)	#.##%	#.##%
Cognitive function at day 180	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.## (#.## to #.##)	#.## (#.## to #.##)	#.##%	#.##%
One or more domain-specific safety outcomes (follow-up time varying)	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	#.## (#.## to #.##)	#.#%-points (#.# to #.#)	#.##%	#.##%

Example of the primary table with data from the final, primary analyses of all clinical outcomes in each domain. Outcomes in each domain will be listed by domain prioritisation and follow-up times as relevant, along with eventual additional clinical outcomes as per the domain-specific appendices. Several variations of the precise intervention effect estimates and probabilities to be presented are outlined below; all model-based estimates, intervention effects, and probabilities are based on the sample-average posterior distributions for the parameter of interest, as described in section 9.6.

[1] For each intervention, descriptive outcome data (counts with percentages for binary outcomes, medians with interquartile ranges for continuous/count outcomes) and estimated sample-average probabilities (binary outcomes) or mean values (continuous/count outcomes) from the primary models will be presented with 95% CrIs. The counts and proportions of participants with missing data for all outcome variables will be reported in each domain, with descriptive data and model estimates based on multiply imputed data unless complete.

[2] For 2-arm domains, sample-average intervention effect estimates will be presented as between-arm comparisons with one arm considered the reference (the standard of care or usual care/control arm where relevant). For domains with >2 arms simultaneously compared all versus all (i.e., no common control group), between-arm comparisons will be presented in separate tables, each with one arm as the reference and comparisons with all other arms separately. When stopped for superiority, the superior arm will be the reference in the primary table; otherwise, the standard of care or usual care arm (if any) or the arm with the highest probability of being overall best will be the reference in the primary table, as per the domain-specific appendices. For domains with >2 arms and a common control arm, separate sets of between-arm comparisons for all arms, with the final superior arm (if any) or original common control arm as the reference in the primary table.

[3] For 2-arm domains, the probabilities of one intervention being superior and the other being inferior will be presented, with the reference arm chosen as outlined in footnote #2. For domains with >2 arms compared all versus all (i.e., no common control group), the probabilities of each arm being the best will be presented; secondarily, the probabilities of each arm being superior compared to the other arms will be presented. For domains with >2 arms and a common control group, the probabilities of each arm being better than the superior arm (if any) or otherwise the original control group (as per footnote #2) will primarily be presented, and secondarily, probabilities of each arm being better than the other arms in turn based on pairwise-comparisons and otherwise the probabilities of each arm being overall superior will be presented. Where relevant, probabilities of effect sizes smaller than the threshold(s) for practical equivalence or futility will also be presented along with the probabilities of intervention effects larger than the practical equivalence/futility threshold(s) in both directions. For all outcomes, the complete posterior distributions of the primary set of sample-average intervention effects and the corresponding probabilities of *all* effect sizes will be visualised as previously done [179].

Abbreviations (in alphabetical order): CrI: credible interval; MD: mean difference; n and N: n denotes number of participants with the outcome, N denotes to the total number of participants in each arm; RD: (absolute) risk difference; RoM: ratio of means; RR: relative risk.

Table S4. Example results from successive adaptive analyses table

Adaptive analysis	**Analysed/ randomised**		**Outcome data per intervention[1]** descriptive data [n/N (%) or median (IQR)] *model estimate [probability or mean with (95% CrI)]*		**Probabilities of each intervention[2]** superiority *(equivalence)* *[futility]*		**Subsequent allocation profile[3]**	
Number, last inclusion date, analysis date, implementation date	**Intervention A**	**Intervention B**	**Intervention A**	**Intervention B**	**Intervention A**	**Intervention B**	**Intervention A**	**Intervention B**
#1, YYYY-MM-DD, YYYY-MM-DD, YYYY-MM-DD	n/N (#.#%) [complete: n/N (#.#%)]	n/N (#.#%) [complete: n/N (#.#%)]	Binary outcome: n/N (#.#%) *#.#% (#.# to #.#)* Continuous/count outcome: #.# (#.# to #.#) *#.# (#.# to #.#)*	Binary outcome: n/N (#.#%) *#.#% (#.# to #.#)* Continuous/count outcome: #.# (#.# to #.#) *#.# (#.# to #.#)*	#.##% *(#.##%)* *[#.##%]*	#.##% *(#.##%)* *[#.##%]*	#.##%	#.##%
#2, …								

Example of the table that will be used to present the results of all adaptive analyses in a domain, with each analysis presented in a separate row. All analyses will be conducted as described in section 9. Generally, comparative intervention effect estimates (absolute and/or relative differences) will not be included in these tables but may be calculated during the adaptive analyses where relevant or if specified in the domain-specific appendices.

[1] For each intervention, descriptive outcome data (counts with percentages for binary outcomes, medians with interquartile ranges for continuous/count outcomes) and sample-average estimates from the primary models (probabilities for binary outcomes or mean values for continuous/count outcomes) with 95% CrIs. All descriptive data and model estimates in this table will be based on multiply imputed data unless complete.

[2] For domains with 2 arms or >2 arms compared all versus all (i.e., no common control group), the probabilities of superiority of each active arm will be presented. The probability of practical equivalence of all active arms will be included where relevant (this will be the same probability for all active arms), and futility will not be assessed in domains without a common control arm and thus probabilities of futility will not be presented here. For domains with >2 arms and a common control arm, all probabilities (superiority, practical equivalence where relevant, futility where relevant) will be presented for comparisons between each non-control arm and the current common control arm, with the cells left blank for the current common control arm. Where relevant (e.g., where arm(s) are dropped and analyses are repeated without inclusion of more participants), results from all analyses conducted during each adaptive analysis round will be included.

[3] Subsequent allocation profile for all arms following the adaptive analyses may be omitted for domains with fixed allocation ratios.

Abbreviations (in alphabetical order): CrI: credible interval; YYYY-MM-DD: year, month, day, date of the time of the follow-up dates and the dates when analyses were conducted and results implemented (e.g., stopping/arm-dropping or allocation ratios changed); n and N: n denotes number of participants with the outcome, N denotes to the total number of participants in each arm.

21.5 | Appendix 5: variable definitions

Variables will be collected multiple times for each participant where relevant, e.g., if randomisation to multiple domains does not take place simultaneously, variables that can change between randomisation times will be collected separately for each domain. Definitions of clinical outcomes, including times of assessment, are listed in section 8.9.

Screening and baseline variables

- Adult acutely admitted ICU patient: yes/no, patient (≥18 years bold) acutely admitted to the ICU, including ICU admissions after emergency surgery and unplanned ICU admissions after elective surgery (i.e., admissions occurring due to an unexpected, worsened condition, but excluding planned ICU admissions after elective surgery without clinical deterioration).
- Coercive measures: yes/no, any coercive measures, e.g., ongoing involuntary hospital stay or patient under the jurisdiction of correctional authorities.
- Unique participant identifiers: unique identifier outside *INCEPT*, e.g., national identification number (only accessible to local investigators and monitors), and an *INCEPT*-specific unique identifier.
- Site of randomisation: all participating ICUs will be assigned a number identifying the site. If the same local investigators and trial personnel randomises and follows patients across multiple ICUs, this will be considered a single site, but separately randomising ICUs in the same hospital will be considered as separate sites.
- Age: age in whole years, calculated using the date of screening/randomisation in each domain and the date of birth.
- Time and date of randomisation: time (hours and minutes, local time) and date of domain randomisation.
- Date of index hospital admission: the date of admission to the first hospital the participant was admitted to during the current hospital admission.
- Date of index ICU admission: the date of the first ICU admission for the participant during the current ICU admissions, with ICU admissions considered separate when the participant has been discharged to a non-ICU location (e.g., for connected ICU admissions for participants transferred from one ICU to another, regardless of participation in *INCEPT*, the date of admission to the first ICU will be used as long as the participant has not been discharged to a non-ICU location in between).
- Sex: female/male, the sex of the participant assigned at birth.
- Weight: kg, measured or estimated actual body weight.
- Height: m, measured or estimated.
- Use of invasive mechanical ventilation: yes/no, use of mechanical ventilation via a cuffed endotracheal tube or tracheostomy at the time of randomisation.

- Use of vasopressors/inotropes: yes/no, continuous infusion (i.e., ≥1 hour) of any vasopressor/inotrope agent (i.e., norepinephrine, epinephrine, phenylephrine, vasopressin analogues, angiotensin, dopamine, dobutamine, milrinone, or levosimendan) at the time of randomisation (excluding strictly procedure-related infusions).
- Use of renal replacement therapy (RRT): yes/no, use of any form of in-hospital RRT (e.g., haemodialysis, haemofiltration, or haemodiafiltration) at any rate within the last 72 hours prior to randomisation.
- Limitations of care: yes/no, participant with limitation(s) in use of life support (i.e., invasive mechanical ventilation, circulatory support, RRT) and/or cardiopulmonary resuscitation at the time of randomisation.
- Co-existing conditions: any of the following co-existing conditions present in the past medical history prior to randomisation:
    - Active haematological malignancy or metastatic cancer: yes/no, any of the following:
        - Leukaemia: acute lymphoblastic leukaemia, acute myelogenous leukaemia, chronic myelogenous leukaemia, chronic lymphocytic leukaemia.
        - Lymphoma: Hodgkin's disease and non-Hodgkin lymphoma (e.g., small lymphocytic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma).
        - Hairy cell leukaemia, marginal zone lymphoma, Burkitt's lymphoma, posttransplant lymphoproliferative disorder, T-cell prolymphocytic leukaemia, B-cell prolymphocytic leukaemia, Waldenström's macroglobulinemia and other NK- or T-cell lymphomas.
        - Multiple myeloma/plasma cell myeloma.
        - Metastatic cancer: proven metastasis by surgery, computed tomography (CT) scan, or any other method.
    - History of ischaemic heart disease or heart failure: yes/no, history of ischaemic heart disease or heart failure: previous myocardial infarction, invasive intervention for coronary artery disease, stable or unstable angina, New York Heart Association functional class 3 or 4 or any measured left ventricular ejection fraction <40%.
    - Diabetes mellitus: yes/no, treatment at time of index hospital admission with any anti-diabetic medications.
    - Chronic pulmonary disease: yes/no, treatment at time of index hospital admission with any relevant drug indicating chronic pulmonary disease.
    - Chronic liver disease: yes/no, portal hypertension; cirrhosis proven by biopsy, CT scan or ultrasound; history of variceal bleeding; or hepatic encephalopathy in the past medical history.
    - Known use of immunosuppressive therapy within the last 3 months: yes/no, chronic use of systemic corticosteroids (excluding short-term use for e.g., exacerbations of

pulmonary disease) or other systemic immunosuppressive drugs (e.g., tumour necrosis factor inhibitors, calcineurin inhibitors, mTOR inhibitors, anti-thymocyte globulins, interleukin (IL) 2 inhibitors, IL-6 inhibitors, mycophenolate, azathioprine, belimumab) or chemotherapy (e.g., alkylating agents, anti-metabolites, mitotic inhibitors, topoisomerase inhibitors, others) within the last 3 months before randomisation.
    - Previous organ transplantation: yes/no, history of any solid organ transplantation except for cornea transplants.
    - Chronic use of RRT: yes/no, chronic use of any form of RRT (e.g., haemodialysis or peritoneal dialysis) at least once a week prior to index hospital admission.
    - Treatment with antipsychotics at hospital admission: yes/no, treatment with *any* antipsychotic at index hospital admission according to Anatomical Therapeutic Chemical (ATC) code N05A. This includes typical antipsychotics (e.g., chlorprothixene, flupentixol, haloperidol, levomepromazine, loxapine, melperone, perphenazine, periciazine, pimozide, prochlorperazine, zuclopenthixol, pipamperone, and sulpiride) and atypical antipsychotics (e.g., amisulpride, aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, cariprazine, and brexiprazole).
- Acute surgery within 7 days prior to randomisation: yes/no, participants who have undergone any acute surgical procedure (i.e., surgery added to the operating room schedule 24 hours or less before surgery) during the current hospital stay within 7 days prior to randomisation.
- *Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)* [234]: severity score ranging from 0 to 42 points, with higher scores indicating higher severity of illness and higher risk of death. In *INCEPT*, *SMS-ICU* will use the following baseline variables defined above with some variations from the original model definitions [234]: age, lowest systolic blood pressure in the 24 hours prior to randomisation, active haematological malignancy or metastatic cancer, acute surgery within 7 days prior to randomisation, use of vasopressors/inotropes, use of invasive mechanical ventilation, and use of RRT.
- *Clinical Frailty Scale*, version 2.0 (9 levels) [235,236]: investigator-assessed clinical frailty scale, version 2.0. The investigator will assign the participant one value from 1 (very fit) to 9 (terminally ill) representing the measure of fitness and frailty [235,236] based on information from the participants, the relatives, and the electronic patient records.
- Lowest systolic blood pressure in the 24 hours prior to randomisation: mmHg, lowest registered systolic blood pressure in the 24 hours preceding randomisation, measured either invasively or non-invasively in mmHg. In case of cardiac arrest in the 24 hours preceding randomisation, 0 mmHg will be registered.

- Highest plasma lactate in the 24 hours prior to randomisation: mmol/L, the highest level of lactate from any blood sample (i.e., venous, or arterial) in the 24 hours preceding randomisation.
- Highest plasma creatinine in the 24 hours prior to randomisation: µmol/L, the highest level of creatinine from any blood sample (i.e., venous, or arterial) in the 24 hours preceding randomisation.

Variables collected daily until 90 days after inclusion to the last domain

- Use of invasive mechanical ventilation: yes/no, as defined above, excluding mechanical ventilation solely used during procedures/surgery and any mechanical ventilation used outside the hospital.
- Use of vasopressors/inotropes: yes/no, as defined above, excluding vasopressors/inotropes solely used during procedures/surgery.
- Use of RRT: yes/no, as above, including days in between intermittent RRT, with pauses of up to three days between RRT sessions considered as days receiving intermittent RRT, and only including in-hospital RRT.
- Use of antipsychotics: yes/no, any in-hospital use of haloperidol, olanzapine, or quetiapine.
- Positive delirium score: yes/no, any registered positive delirium score (as defined in section 8.9).
- Coma: yes/no, any registered coma on this day using any accepted scale (as defined in section 8.9).
- Vital status: vital status (dead/alive), if deceased also date of death.
- Admitted to the hospital: yes/no, admitted to any hospital on this day.