The Intensive Care Platform Trial (INCEPT)

INCEPT-Albumin

Domain-specific appendix

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Websites
www.incept.dk

www.incept.dk/albumin

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1 | Abstract

Background

Use of intravenous albumin is suggested for certain types of shock if patients have received large volumes of crystalloids. This recommendation is primarily based on moderate certainty of evidence for positive effects of albumin on short-term circulatory endpoints. Albumin is also used for substitution, as hypoalbuminemia is frequent in critical illness and associated with poor outcomes. Yet, the clinical use of albumin varies markedly. At present it is uncertain if the potential desirable circulatory effects of albumin translate into patient benefits in adult intensive care unit (ICU) patients with shock.

Objectives

We aim to assess the effects of albumin for resuscitation and substitution therapy versus no use of albumin on the number of days alive without life support at 30 days and other patient-important outcomes in adult ICU patients with shock. We hypothesise that the use of albumin may result in more days alive without life support at 30 days.

Design

The albumin versus no albumin in shock (*INCEPT-Albumin*) domain will be an investigator-initiated, open-label domain with an integrated feasibility phase on the pragmatic, embedded, multifactorial, international, adaptive *Intensive Care Platform Trial* (*INCEPT*). The domain will employ adaptive stopping for superiority/inferiority and practical equivalence and restricted response-adaptive randomisation.

Inclusion and exclusion criteria

Adult acutely admitted ICU patients will be screened for the *INCEPT-Albumin* domain if both interventions are considered clinically appropriate and they have shock irrespective of cause. We will exclude patients for whom legal consent is expected to be unobtainable, patients under coercive measures, patients who have received albumin during the current ICU stay, patients with traumatic brain injury, pregnant patients, patients with known religious objection to albumin, patients with known albumin allergy and patients who are included in another interventional trial

or *INCEPT* domain where co-enrolment with *INCEPT-Albumin* is not permitted.

Interventions and comparisons

The intervention period is from time of randomisation to a maximum of 90 days in the ICU. If participants are transferred or readmitted to a participating ICU during this period, the assigned intervention will continue.

Albumin use in the ICU (intervention)

Albumin should be used for the following indications:

- During circulatory failure in addition to crystalloids (resuscitation)
- For substitution in case of:
    - Suspected or overt albumin loss
    - Plasma albumin levels ≤25 g/L

No albumin use in the ICU (control)

Albumin should not be used.

In case of the following special circumstances, albumin may be considered:

- Large ascites drainage (i.e., >1L tapped)
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome

Outcomes

The primary outcome guiding all adaptations is days alive without life support at day 30 (non-survivors will be assigned 0 days). Additional outcomes will be the remaining core outcomes in *INCEPT:* all-cause 30-, 90-, and 180- day mortality, days alive without life support at day 90; days alive out of hospital at day 30 and 90; days free of delirium at day 30; health-related quality of life (HRQoL; evaluated using EQ-5D-5L index values and EQ VAS) and cognitive function (evaluated using the Montreal Cognitive Assessment test 5-minute version [Mini MoCA]) at 180 days); and one or more domain-specific safety outcomes including serious adverse reactions (severe anaphylactic reactions and major bleeding) and suspected unexpected serious adverse reactions at day 90.

Statistics and adaptation rules

This domain will use Bayesian statistical methods with neutral, weakly informative priors conducted in the intention-to-treat population (primary analyses). Adaptive analyses will start after follow-up and data collection for the first 1,000 participants and every subsequent 250 participants up to a maximum of 10,000 participants.

The domain will use constant, symmetrical stopping rules for superiority/inferiority calibrated to keep the type 1 error rate at 5%. The domain will be stopped for practical equivalence if there is >90% probability that the absolute mean difference between arms is less than 1 day.

Equal initial allocation will be used followed by response-adaptive randomisation with minimum allocation probabilities of 40% to each arm.

Domain design performance metrics

Performance metrics have been evaluated assuming a mean of 14.5 days alive without life support in the control arm (*no albumin use*) and scenarios with no, small, and large differences between arms corresponding to 0 days, 1 day and 5 days in either direction in different combinations. The expected (mean) sample sizes under these scenarios range from 1,137 to 3,547 participants. The probabilities of conclusiveness (i.e., superiority/inferiority or equivalence) are ~100% in all scenarios, and the probabilities of superiority (power) range from 59% to ~100% in the scenarios with differences between arms.

Estimated timeline

- First quarter, 2025: domain approved, and first participant randomised
- First quarter, 2026: feasibility phase analysis concluded
- Third quarter, 2028: expected inclusion of the last participant if the domain continues to the expected sample size in the small-difference scenario (i.e., the largest expected sample size under the different scenarios assessed)
- First quarter, 2034: expected inclusion of the last participant if the domain continues to the maximum sample size (n = 10,000); the probability for this is very low
- Approximately 5 months after inclusion of the last participant: primary report on 30- and 90-day outcomes submitted

- Approximately 9 months after inclusion of the last participant: report on 180-day outcomes submitted

Funding

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2 | Administrative information

2.1 | Protocol and domain-specific appendix structure

This is a domain-specific appendix to the *Intensive Care Platform Trial (INCEPT)* core protocol. Everything described in the version of the core protocol listed on the front page applies except where explicitly stated otherwise. This domain-specific appendix only covers details that are specific to this domain and not otherwise covered by the *INCEPT* core protocol. The domain-specific appendix should be read along with the core protocol.

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3 | Abbreviations

CI: *confidence interval*
CLASSIC: *Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care trial*
CONSORT-ACE: *Adaptive designs CONSORT Extension*
CONSORT: *Consolidated Standards of Reporting Trials statement*
CrI: *credible interval*
CTIS: *Clinical Trials Information System*
DeIC: *Danish e-infrastructure Consortium*
CRIC: *Collaboration for Research in Intensive Care*
eCRF: *electronic case report form*
EMPRESS: *Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis trial*
EPR: *electronic patient record*
ESICM: *European Society of Intensive Care Medicine*
EUCT number: *European Union Clinical Trials Information System (CTIS) number*
GODIF: *Goal Directed Fluid Removal in Intensive Care Patients With Fluid Overload trial*
hCG: *human chorionic gonadotropin*
HPC: *high-performance computing*
HRQoL: *health-related quality of life*
ICU: *intensive care unit*
ICMJE: *International Committee for Medical Journal Editors*
IDMSC: *independent data monitoring and safety committee*
IDP: *ideal design percentage*
INCEPT: *the Intensive Care Platform Trial*
IQR: *interquartile range*
ITT: *intention-to-treat*
IV*: intravenous*
kg: *kilogram*
L: *litre*
LCA: *life cycle analysis*
MAE: *median absolute error*
MD: *mean difference*
mmHg: *millimetres of mercury*
mmol: *millimoles*
P25: *25th percentile*
P75: *75th percentile*
PP: *per-protocol*
Pr: *probability*

RCT: *randomised clinical trial*
RD: *risk difference*
RMSE: *root mean squared error*
RoM: *ratio of means*
RR: *relative risk*
SAE: *serious adverse event*
SAR: *serious adverse reaction*
SD: *standard deviation*
SMS-ICU: *Simplified Mortality Score for the Intensive Care Unit*
SPIRIT: *Standard Protocol Items: Recommendations for Interventional Trials statement*
SSC: *Surviving Sepsis Campaign*
SUSAR: *suspected unexpected serious adverse reaction*
YYYY-MM-DD*: year, month, date*
µmol: *micromoles*

4 | Objectives and lay description

4.1 | Objectives

The mainstay initial management of shock includes intravenous (IV) fluids. Albumin is suggested for certain types of shock if patients have received large volumes of crystalloids [1]. This recommendation is primarily based on moderate certainty evidence for positive effects of albumin on short-term circulatory endpoints [2,3]. Being a colloid fluid, albumin may offer volume-sparing effects through maintained or augmented plasma oncotic pressure [4,5]. Albumin is also used for substitution, as hypoalbuminemia is frequent in critical illness and associated with poor outcomes [6]. Yet, the clinical use of albumin varies markedly [7,8], and harmful effects have been observed in some ICU patients [9,10]. At present it is uncertain if the potential desirable circulatory effects of albumin translate into patient benefits in adult ICU patients with shock.

We aim to assess the effects of albumin for resuscitation and substitution versus no use of albumin on the number of days alive without life support at 30 days and other patient- and society-important outcomes in adult ICU patients with shock. We hypothesise that the use of albumin may result in more days alive without life support at 30 days without harmful adverse effects.

4.2 | Lay description

Shock is a critical medical disorder characterised by circulatory failure, resulting in impaired oxygen and nutrient delivery to vital organs [11]. It can result from various conditions, including severe infection, significant blood loss or heart failure [11]. Irrespective of the origin, symptoms of shock include low blood pressure and signs of inadequate blood flow [11]. Therefore, the main goal in the treatment is to counteract circulatory failure by ensuring sufficient blood flow to perfuse vital organs. This is attempted by the administration of intravenous (IV) fluids, and crystalloids, which are mixtures of water and electrolytes, are recommended as first-in-line treatment [1]. It has been suggested that albumin solutions, which are derived from human blood, might be a beneficial additive for patients who have received large volumes of crystalloids [1]. Albumin is a protein produced primarily in the liver. It is the most abundant blood protein, and it plays an important part in many physiological processes. The use of albumin in patients with shock may improve the circulation and fluid balance [12,13], and it may have direct patient-important benefits [3,14], but concerns of harm from albumin have been observed in some ICU patients

[9,10]. Additionally, the use of albumin varies among clinicians and hospitals [7,8]. Therefore, the overall effect of albumin on patient-important outcomes, i.e., time without organ support, survival, time outside the hospital, and health-related quality of life, is uncertain [2,3,14].

We aim to assess the effects of albumin for resuscitation and substitution therapy versus no use of albumin on patient-important outcomes in adult ICU patients with shock. We assume that the use of albumin in these patients will have a beneficial effect on patient-important outcomes.

5 | Background

5.1 | Shock

Shock is a life-threatening condition with circulatory failure resulting in inadequately perfused tissues, hypoxia, and a risk of multiorgan failure [11]. Aetiologies of shock include sepsis, severe bleeding and heart failure, and less prevalent types such as obstructive shock [11]. Irrespective of the cause, common clinical manifestations are hypotension and signs of tissue hypoperfusion such as skin mottling and elevated plasma lactate [11].

Shock is common in ICUs, affecting one in three patients [15], many of whom will not survive to hospital discharge [16,17]. Therefore, interventions that have the potential to improve survival from shock are important for patients, clinicians, and society, in particular if they also translate into more days alive without life support and out of hospital, and better quality of life.

5.2 | Albumin in shock

Management strategies for shock vary according to aetiology, but often involve fluid resuscitation, vasoactive/inotropic agents, and treatment of the underlying cause [11]. Albumin is a hyperoncotic fluid derived from human plasma, which is often used during circulatory management of shock [8]. For septic shock, it is recommended for patients who have received large amounts of crystalloids solutions during fluid resuscitation [1,18]. In addition, albumin may be used to correct hypoalbuminemia, which has been associated with poor outcomes [6,8]. However, the general use of albumin in shock has not been confirmed by current evidence.

A recent Cochrane systematic review with meta-analysis of 20 randomised clinical trials (RCTs) including 13,047 critically ill patients found little to no differences in 30-day or 90-day mortality with the use of albumin or fresh-frozen plasma versus crystalloids (moderate certainty evidence) [14]. Similar results were found in another systematic review of crystalloid versus colloid solutions in ICU patients, yet results, despite uncertainty, were mostly compatible with a small survival benefit with the use of albumin [3]. In addition, it concluded that albumin may positively affect fluid balance and hemodynamic endpoints as compared with crystalloids [3]. Notably, the results from both reviews are mainly driven by two large RCTs [2,19]. These two trials suggested heterogenous treatment effects with use of albumin in subpopulations of critically ill patients. In

the *Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit* (*SAFE)* trial, results of prespecified subgroup analyses showed heterogeneous treatment effects in patient sub-populations [9,19]. The subgroup of patients with traumatic brain injury allocated to albumin had higher mortality as compared with saline (28-day mortality: relative risk [RR], 1.62; 95% confidence interval [CI], 1.12 to 2.34) [9,19]. The subgroup of patients with sepsis suggested reduced mortality with albumin as compared with saline (28-day mortality RR, 0.87, 95% CI: 0.74–1.02) [19,20]. The other trial, the *Albumin Replacement in Patients with Severe Sepsis or Septic Shock (ALBIOS)* trial [2], randomised ICU patients to use of 20% albumin (for resuscitation and to maintain daily plasma albumin levels at 30g/L or above) in addition to crystalloids versus crystalloids alone [2]. The main result of *ALBIOS* was little or no overall differences in outcomes [2]. A *post hoc* subgroup analysis of a secondary outcome, 90-day mortality, indicated potential benefit of albumin in patients with septic shock as compared with sepsis without shock (RR for septic shock, 0.87; 95% CI, 0.77 to 0.99; RR for sepsis without shock, 1.13; 95% CI, 0.92 to 1.39; P=0.03 for heterogeneity) [2].

Taken together, evidence from systematic reviews with meta-analyses have not identified differences in patient-important outcomes with certainty, but the overall point estimate for mortality in ICU patients suggests, if anything, a small survival benefit with the use of albumin. Any such effect is supported by subgroup results from two large trials using albumin in shock [2,19,20].

5.3 | Current recommendations in clinical guidelines

The uncertainty around the use of albumin solutions for critically ill patients with shock is reflected in recent guidelines [1,18,21]. The 2021 *Surviving Sepsis Campaign (SSC) guideline* suggests using albumin in patients with sepsis or septic shock who have received large volumes of crystalloids [1]. This is a conditional recommendation based on moderate certainty evidence, largely informed by evidence of positive effects on hemodynamic endpoints [1–3]. Further, the guideline includes no recommendation for what should be considered as large volumes of crystalloids. The *International Collaboration for Transfusion Medicine Guideline* suggests not using IV albumin for first-line resuscitation or to increase serum albumin levels in critically ill adult patients based on moderate certainty of evidence [21]. However, these guidelines do not address its potential as second-line treatment as is done in the SSC guideline [1,21]. Similarly, the 2024 *European Society of Intensive*

Care Medicine (ESICM) guideline, recommends using crystalloids rather than albumin for volume expansion in critically ill patients in general (moderate certainty evidence) [18].
Hence, guideline recommendations are currently divergent, and little to no recommendations can currently be provided for the use of albumin as second-line resuscitation fluid or substitution fluid in patients with shock.

5.4 | Use of albumin in clinical practice

The non-uniform recommendations in recent guidelines are likely reflected in the use of albumin in clinical practice, which is subject to variation [8]. In the largest and recent European fluid trial of patients with septic shock, the *Conservative vs liberal fluid therapy in septic shock (CLASSIC)* trial [16], 45% of participants received albumin [7,16]. A *post hoc* analysis of this trial highlighted that the use of albumin varied markedly between trial sites beyond what could be explained by patient characteristics [7]. This variability was confirmed in recent survey findings among 1,248 ICU doctors across 21 countries, where 26% almost always or frequently preferred using albumin in patients with shock, while 40% rarely or never used it [8]. For patients with septic shock, around 30% of respondents almost always or frequently preferred using albumin, while around 40% rarely or never used it. Further, more than 90% of respondents would enrol their ICU patients with shock in an RCT comparing albumin for circulatory management and substitution versus no use of albumin.

5.5 | Use of albumin in the INCEPT-Albumin domain

In the albumin versus no albumin in shock domain (*INCEPT-Albumin*), participants in the albumin arm will receive any albumin solution (concentration, dose, and timing at the clinicians' discretion) for fluid resuscitation in addition to crystalloids and/or as substitution in case of hypoalbuminaemia. The albumin arm largely aligns with the reported albumin use in clinical practice[8] and approximates the before-mentioned *SAFE* and *ALBIOS* trials in which albumin was administered for resuscitation and particularly in the *ALBIOS* trial also as a daily substitution to maintain serum albumin at 30 g/L or more [2,19]. Participants in the no use of albumin arm should not receive albumin unless special predefined circumstances occur, including spontaneous

bacterial peritonitis, large volume ascites drainage or hepatorenal syndrome as these specific patient groups may benefit from infusion of albumin [22–24].

5.6 | Domain rationale and ethical justification

In summary of the above (section 5.1-5.4), it seems that albumin may have positive effects on the circulation and fluid balance in ICU patients with shock [3], but it is uncertain if these effects translate into improved patient-important outcomes. As a result, recent guidelines are not consistent in their recommendations [1,18,21], which may contribute to the current practice variation observed across European ICUs [7,8]. Hence, clinical equipoise exists regarding the use of albumin in ICU patients with shock, and it is a priority to assess the effects of these solutions on patient-important outcomes. Any such improvements have the potential to reduce the burden for patients, family members, and society. Based on our documentation of current clinical practice, [7, 8] participation in *INCEPT-Albumin* will increase the probability that participants receive albumin and hence benefit because the hypothesis of *INCEPT-Albumin* is benefit with the use of albumin in patients with shock.

The *INCEPT-Albumin* domain will be conducted according to high methodological standards assessing the effects of albumin use versus no albumin use on patient-important outcomes in adult ICU patients with shock. The adaptive design will additionally increase the probability that participants receive the better intervention, if any, and that the domain results will be conclusive and thus directly inform clinical guidelines and practice [25,26].

Additional rationale and ethical justification for the overall *INCEPT* design is provided in the core protocol.

6 | Domain design and interventions

6.1 | Overall domain design and sample size

INCEPT-Albumin will be an investigator-initiated, open-label domain with an integrated feasibility phase on the pragmatic, embedded, multifactorial, international, adaptive *Intensive Care Platform Trial* (*INCEPT*). The *INCEPT-Albumin* domain compares the effects of albumin for resuscitation and substitution therapy versus no use of albumin on the number of days alive without life support at 30 days and other patient-important outcomes in adult ICU patients with shock. The domain will employ adaptive stopping for superiority/inferiority and practical equivalence and restricted response-adaptive randomisation.

The maximum sample size will be 10,000 participants, which is required to ensure ~100% probabilities of the domain being conclusive, i.e., ultimately fulfilling the criterion for either superiority or practical equivalence across a range of plausible clinical scenarios evaluated (detailed in section 7.10 and appendix 5, section 14.5). The maximum sample size is larger than any of the trials conducted to date [14]. The expected sample sizes across the clinical scenarios evaluated range from 1,137 to 3,547 participants (section 7.10). With an assumed inclusion rate of 3 participants per day in the domain after site initiation, we expect a faster inclusion rate compared to the *CLASSIC* trial, which had an inclusion rate of 1.5 participants per day (enrolling during the COVID-19 pandemic) [16]. We expect a higher inclusion rate because this domain includes a broader shock population and because *INCEPT* is likely to increase the overall number of recruitments in participating ICUs. The domain is expected to conclude enrollment within a realistic and feasible time range from 1.1 to 3.5 years, if the final sample size is within the range of expected sample sizes across the clinical scenarios evaluated. The domain will enrol for 9.3 years, if it continues until the maximum sample size, however, this scenario is very unlikely.

This domain-specific appendix describes all required items included in the *Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement* [27] and the relevant items from the *Consolidated Standards of Reporting Trials (CONSORT) Adaptive designs CONSORT Extension (ACE)* checklist [28], except those already covered by the core protocol and where no domain-specific adaptations are made; for these points, both checklists refer back to the core protocol appendix 1, section 21.1).

6.2 | Domain-specific eligibility criteria

In addition to the general *INCEPT* eligibility criteria, the following domain-specific criteria apply.

Domain-specific inclusion criteria:

All the following criteria must be fulfilled:

- Both interventions in this domain are considered clinically appropriate.
- Shock defined as both of the following fulfilled:
    - Ongoing infusion of a vasopressor or inotropic agent (e.g., noradrenaline, adrenaline, vasopressin, phenylephrine, dopamine, dobutamine, milrinone, or levosimendan).
    - Plasma lactate ≥2 mmol/L in any blood sample performed within the last 3 hours.

Domain-specific exclusion criteria:

We will exclude patients who fulfil any of the exclusion criteria:

- Traumatic brain injury.
- Use of albumin during current ICU stay.
- Known pregnancy.
- Religious objection to the administration of albumin
- Known albumin allergy.
- Inclusion in another interventional trial or *INCEPT* domain where co-enrolment with the *INCEPT-Albumin* domain is not permitted.

Participants that have previously been randomised to *INCEPT-Albumin* may not be included and randomised in the domain again. A flowchart as illustrated in **Figure S1** (appendix 2, section 14.2) will summarise screening, randomisation, and data availability in the analyses.

6.3 | Interventions

Intervention period

The intervention period is up to 90 days from randomisation, until discharge from a participating

ICU or death, whichever comes first. When participants are transferred or readmitted to a participating ICU, the intervention will be resumed.

Albumin use in the ICU (intervention)

Albumin should be used for the following indications:

- During circulatory failure in addition to crystalloids (resuscitation)
- For substitution in case of:
    - Suspected or overt albumin loss
    - Plasma albumin levels ≤25 g/L

Decisions around timing, volume, and concentration of albumin, and its use for other indications, are at the clinician's discretion. Plasma albumin should be measured according to local practice.

Preparation and administration

Albumin as shelf medication from the participating site's pharmacies will be used.

Dose adjustments

Albumin in all concentrations (usually 4%, 5%, or 20%) is allowed.

Intervention accountability

Albumin is often used for treatment of ICU patients with shock and has been so for decades. Albumin will be handled by clinical staff, who are trained and certified in the caring of ICU patients. As shelf medication will be used from pharmacies of the participating sites, batch numbers for the albumin used can be accounted for if needed.

No albumin use in the ICU (control)

Albumin should not be used.

In case of the following special circumstances, albumin may be considered [22,24,29,30]:

- Large volume ascites drainage (i.e., >1L tapped)
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome

Co-interventions

Co-interventions such as other types of fluids, vasopressors or renal replacement therapy will be used at the discretion of treating clinicians.

Drug traceability measures

Batch numbers for the albumin used will not be registered in the electronic case report form (eCRF) but registered according to usual clinical practice and applicable local regulations.

6.4 | Randomisation and stratification

Randomisation will initially be stratified for site and shock type (septic shock versus other types of shock) [31]. Simple (unstratified), restricted response-adaptive randomisation will be used after the first adaptive analysis [26].

6.5 | Justification for using an open-label design

Albumin will be used open-label as albumin solutions are easily recognisable compared with other types of IV fluids, making blinding logistically challenging, extremely costly and time-consuming especially as part of the albumin use will be guided by plasma albumin results obtained in clinical practice. By opting for an open-label design, we can enrol more patients at the same cost, which will provide conclusive results with higher certainty.

The life support component of the primary and guiding outcome (days alive without life support, which combines survival and time off life support) is not completely free of risk of bias with an open-label design, as knowledge of treatment allocation might influence clinical decision-making [32]. However, we consider the risk low as clinical decisions regarding the initiation or discontinuation of life support are typically done by several ICU clinicians based on multiple objective measures, not limited to circulatory and fluid balance parameters.

6.6 | Outcomes

Primary and guiding outcome

The primary and guiding outcome will be days alive without life support at 30 days with non-survivors assigned 0 days alive [33].

Secondary outcomes

The secondary outcomes will be the remaining core outcomes in *INCEPT*: all-cause 30-, 90-, and 180- day mortality, days alive without life support at day 90; days alive out of hospital at day 30 and 90; days free of delirium at day 30; health-related quality of life (HRQoL; evaluated using EQ-5D-5L index values and EQ VAS [34]) and cognitive function (evaluated using the Montreal Cognitive Assessment test 5-minute version [Mini MoCA]) at 180 days[35,36]); and one or more domain-specific safety outcomes as specified below. No other domain-specific secondary outcomes will be collected in this domain.

Variants of *INCEPT* core outcomes

For the days alive without life support, days alive out of hospital, and days free of delirium outcomes at any timepoint, we will use the penalised values (non-survivors assigned 0 days [33]) as the primary definitions. The remaining *INCEPT* core outcomes will be registered according to the definitions and operationalisations specified in the core protocol.

6.7 | Benefit-risk assessment and safety outcomes

Risk classification

The *INCEPT-Albumin* domain is considered to be at risk level 1 (low risk), for the following reasons:

1. Albumin solutions have been used worldwide to treat critically ill patients and patients losing albumin for four decades [37].
2. Albumin is currently used as part of standard of care in many intensive care unit (ICU) patients for resuscitation and substitution, however, *not* using albumin in the situations relevant to the interventions in this domain is equally part of standard of care; thus, clinical practice varies [8].

3. Albumin is not subject to stricter reporting requirements in Denmark [38], the safety profile is well-known, and the risk of new safety issues arising is considered minimal.

Domain-specific safety outcomes

The serious adverse reactions (SAR) listed in **Table 1** will be collected with the possibility for local adaptations in single countries if required.

In addition to these SARs, any suspected unexpected serious adverse reactions (SUSARs) will be collected and included in the '*One or more domain-specific safety outcomes'* outcome.

Investigators always will be able to report any serious adverse events (SAEs) immediately at their own discretion. Follow-up for safety outcomes will be 30 days (matching the primary and guiding outcome) and 90 days (matching the maximum intervention period).

In case of safety events, participants will be monitored and followed as described in the core protocol, i.e., according to usual clinical practice decided by the treating clinician, e.g., until resolution of the safety event. This will be done using the electronic patient records (EPRs) as the domain-specific safety outcomes are expected to occur during hospital admission.

Table 1. Domain-specific serious adverse reactions

Name	Definition/operationalisation	Remarks
Severe anaphylactic reaction	Severe anaphylactic reactions defined as urticarial skin reaction **AND** at least one of the following observed after randomisation: • Worsened circulation (>20% decrease in blood pressure or initiation of new vasopressor infusion or >20% increase in vasopressor dose). • Increased airway resistance (>20% increase in the peak pressure on the ventilation). • Clinical stridor or bronchospasm. • Subsequent treatment with bronchodilators.	
Major bleeding	Major bleeding defined as: • Fatal bleeding. **OR** • Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome. **OR** • Bleeding that requires any of the following interventions: transfusion of ≥400ml whole blood or red cells, endoscopy, endovascular management, or surgery (open, laparoscopic, arthroscopic, endovascular).	The components of this outcome are based on guidance by the International Society on Thrombosis and Haemostasis, with adaptations to the ICU environment [39,40].

Benefit-risk assessment

Albumin has been marketed for four decades and is used daily in clinical practice. The safety profile of albumin is well-known [41–43] , which is why the expectation of new safety issues is minimal. We therefore anticipate that the risks for participants are minimal and similar to that of standard clinical practice, why we assess the domain as being low-risk. Based on the available evidence from recent systematic reviews and guidelines, the use of albumin may have a positive effect on survival in ICU patients with shock [3,14]. Furthermore, the use of response-adaptive randomisation ensures that more participants will be allocated to the intervention with the highest probability of being superior following the first adaptive analysis, which constitutes a direct benefit to participants. Taken together, we anticipate that domain participants overall will benefit from participation and that their risk is minimal.

The exclusion criterion for known pregnancy will be for women with known pregnancy based on clinical examination, the history or human chorionic gonadotropin (hCG). We will not demand negative hCG-status in all eligible fertile women, because (i) pregnancy is very rare in ICU patients

with shock and (ii) waiting for the hCG result will delay screening and result in fewer fertile women included. The same procedure was approved in the *CLASSIC* trial [16], which has many similarities to this domain. Taken together, such an approach is also supported by the 2024-update of the Declaration of Helsinki [44].

6.8 | End of domain

When the domain is closed, the competent authorities will be notified, and results will be reported as described in the core protocol.

6.9 | Other domain design considerations

Protocol delivery and adherence and criteria for modification of interventions for participants
We will record the occurrence of protocol violations on each day during the 90-day intervention period defined as:

Table 2. Protocol violations

Intervention arm	Protocol violation definition
Albumin use	No albumin given during resuscitation or as substitution in case of suspected or overt albumin loss or plasma albumin levels ≤25 g/L
No albumin use	Albumin given without one of the extenuating circumstances occurring i.e., large volume ascites drainage, spontaneous bacterial peritonitis, or hepatorenal syndrome

Protocol adherence at each *INCEPT-Albumin* site will be monitored centrally at the coordinating centre through the eCRF with alerts being send to trial sites in the case of concerns for violations. If the treating clinicians assess that continued protocol adherence will lead to suboptimal treatment for any participant, the clinical team can at any time deviate from the protocol to ensure participant safety. Deviations will be classified and registered according to the definitions outlined above. A 24-hour trial hotline will enable discussion at any time between the clinical team and the *INCEPT* and the *INCEPT-Albumin* domain teams regarding protocol-related issues.

Feasibility and separation

We will include the first 200 participants in the integrated feasibility phase. We have based the size of the feasibility phase on practical considerations and the design of similar trials [45–47]. The following outcomes will be assessed after the feasibility phase (Table 2):

- Separation in albumin volumes (all concentrations combined)
- Time to completion of the feasibility phase
- Protocol violations
- Recruitment proportion
- Proportion of participants without consent to the use of data
- Retention proportion

For the primary feasibility evaluation, most outcomes will be assessed for all participants together (except separation and protocol violations) and secondarily for each arm. The domain will continue without alterations if all criteria for feasibility are fulfilled and if there is adequate separation; if not, the domain management committee will decide if modifications of the domain protocol are required. We will not pause the domain during the feasibility outcome analyses, as we find it unlikely that major changes to the protocol will result. Pausing would slow down recruitment and postpone conclusive domain results.

Table 3. Domain-specific feasibility outcomes

Name	Definition/operationalisation	Feasibility criteria	Expected precision
Separation of mean volumes	Difference in mean albumin[1] volumes between arms	≥500 ml[2]	-
Separation of median volumes	Difference in median albumin[1] volumes between arms	≥500 ml[2]	-
Protocol adherence in albumin arm	Proportion of participants receiving ≥100 ml albumin[1] in the albumin arm	>90%	85% to 94%
Protocol adherence in the no albumin arm	Proportion of participants receiving ≥100 ml albumin[1] in the no albumin arm	<10%	6% to 15%
Feasibility phase completion	Time to completion of enrolment for the feasibility phase	<9 months	-
Recruitment proportion	Percentage of screened patients included in this domain	>50%	43% to 57%
Participants without consent	Percentage of participants who did not consent to data use	<5%	3% to 9%
Protocol violations	Combined percentage of patients who did not receive albumin in the albumin arm, and those who did in the no albumin arm	<17%[3]	12% to 23%
Retention proportion	Percentage of participants with primary outcome data within maximum 15 days of follow-up	≥95%	91% to 97%

[1] Total volumes, all concentrations combined.

[2] Half of the difference observed in the ALBIOS trial [2].

[3] Proportion participants with protocol violations in the *CLASSIC* trial on IV fluids in septic shock [16].

For all binary feasibility outcomes, the expected precision of the proportions presented are the 95% confidence intervals (CI; rounded) that would be obtained with 200 participants analysed and a proportion matching the threshold used to define the feasibility criteria (calculated using the Clopper-Pearson method as done for a previous trial [46].

7 | Statistics and simulation

7.1 | Overall principles

The *INCEPT-Albumin* domain will employ Bayesian statistical methods, adaptive stopping, and response-adaptive randomisation.

7.2 | Analysis sets and estimands

Analysis sets

All primary analyses of the *INCEPT-Albumin* domain will be conducted in the intention-to-treat (ITT) population, as defined in the core protocol.

Additional analyses will be conducted in the per-protocol (PP) population (i.e., the ITT population, except those with one or more protocol violations).

Estimands

The primary estimand in the *INCEPT-Albumin* domain is the sample-average mean difference in the days alive without life support at day 30 between the albumin versus no albumin arms according to treatment allocation regardless of protocol adherence with non-survivors assigned 0 in acutely admitted adult ICU patients with shock [48,49].

Table 4. Key attributes of the primary estimand

Attribute	Description
Population	Acutely admitted adult ICU patients, with shock.
Interventions (*treatment conditions*)	Albumin used for resuscitation and substitution in the ICU (intervention). No albumin use in the ICU unless special circumstances occur (control).
Outcome (*endpoint*)	Days alive without life support at day 30.
Summary measure	Sample-average mean difference.
Handling of intercurrent events	Participants analysed as randomised (i.e., according to the ITT principle) regardless of protocol adherence. Non-survivors will be assigned 0 days alive without life support.

Key attributes of the primary estimand in the *INCEPT-Albumin* domain summarised according to recommendations [48,49]

7.3 | Adaptive analyses and adaptation rules

Timing

The first adaptive (interim) analysis will be conducted after an initial *burn-in* period of 1,000 participants. Subsequent adaptive analyses will occur after every additional 250 participants, until a maximum sample size of 10,000 participants.

When the prespecified number of participants have been randomised and completed their *outcome-data lag* period (consisting of the 30-day follow-up duration for the guiding outcome and a data collection and validation period of 15 days), an adaptive analysis will be conducted on the first workday of the next month or as soon as possible thereafter. Adaptive analyses will include data from all participants who have completed their *outcome-data lag* period. No adaptive analyses will be conducted prior to the conclusion of the initial feasibility phase.

Stopping rules

The following adaptive stopping rules will be used in the *INCEPT-Albumin* domain:

Superiority/inferiority:

Constant, symmetrical stopping rules for superiority/inferiority of 99.54% and 0.46%, respectively, will be used. The stopping rules for superiority/inferiority have been calibrated to ensure a type 1 error rate for the primary outcome of approximately 5.0%.

Practical equivalence:

The domain will be stopped for practical equivalence if there is >90% probability that the mean difference in the primary outcome between the two arms is <1 day in any adaptive analysis.

Futility:

No stopping rules for futility will be used in this domain.

Stopping and communication of results

If the domain is stopped, the reason, whether due to superiority or practical equivalence, will be openly communicated to all participating sites. It may also be communicated externally. Additional

analysis details including exact probabilities, estimates and uncertainty measures will not be communicated before all participants have completed follow-up for the primary and guiding outcome. This detailed information will only be communicated alongside the primary, final analysis results. If the domain is stopped for superiority, active participants may be switched to the superior intervention at the discretion of the treating clinicians. While this will lead to protocol violations in these participants, such action is accepted for ethical reasons. If the domain is stopped for practical equivalence, all active participants should continue with the intervention they were initially allocated.

Primary and guiding outcome

The primary and guiding outcome will be days alive without life support at 30 days with non-survivors assigned 0 days alive [33]

7.4 | Randomisation profiles and rules

Initial stratified randomisation will use a 1:1 allocation ratio and varying block sizes.[31] Simple, (unstratified), restricted response-adaptive randomisation will be used after the first adaptive analysis with minimum allocation probabilities of 40% [26]

7.5 | Statistical analyses, models, and presentation of results

Descriptive and inferential analyses will be conducted as outlined in the *INCEPT* core protocol. Baseline data, primary outcome analyses, results from the adaptive analyses, and separation data will be reported as illustrated in **Tables S1-S4** (appendix 3, section 14.3). Analyses will be adjusted for the baseline variables outlined in the core protocol and the additional stratification variable shock type (septic shock versus other types of shock). The *no albumin* arm will be the reference for the intervention term in all analyses.

Analyses will primarily use neutral, weakly informative priors, supplemented with sensitivity analyses using sceptical and evidence-based priors for the outcomes where relevant external evidence is available.

Results will be presented as sample-average estimates in each intervention arm. The sample-average intervention effects (i.e., risk differences [RDs], mean differences [MDs], relative risks

[RRs], and ratios of means [RoMs]) will be summarised numerically and visualised as outlined in the core protocol.

In addition, probabilities for superiority/inferiority with each arm for all outcomes will be presented. We will also report probabilities for practical equivalence and effects larger than what is considered practically equivalent in either direction for the primary and guiding outcome.

7.6 | Heterogeneous intervention effects and interactions

Heterogeneous intervention effects

After the domain is stopped, we will assess whether heterogeneous intervention effects for the primary outcome are present according to the pre-defined baseline characteristics outlined in **Table 5**.

Table 5. Heterogeneity of intervention effects on the primary outcome will be analysed according to the following baseline characteristics

Baseline characteristics	Definition	Expected direction of interaction
Severity of illness	Baseline severity of illness according to the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU; assessed on the continuous scale) [50]	Larger beneficial effect of albumin in patients with more severe illness.
Primary cause of shock	Septic, cardiogenic, haemorrhagic or traumatic versus other types of shock (e.g., neurogenic, anaphylactic, burn and obstructive shock).	Larger beneficial effect of albumin in patients with septic shock compared with other types of shock.
Albumin levels	Plasma albumin at baseline (assessed on the continuous scale).	Larger beneficial effect of albumin in patients with lower baseline plasma albumin.
Renal function	Highest plasma creatinine value in the 24 hours before randomisation (assessed on the continuous scale).	Larger beneficial effect of albumin in patients with worse baseline renal function (higher plasma creatinine).
Liver failure	Patients with chronic liver failure versus patients with normal liver function.	Larger beneficial effect of albumin in patients with chronic liver failure.
Baseline IV fluids	IV crystalloid volumes administered in the 24 hours before randomisation (assessed on the continuous scale).	Larger beneficial effect of albumin in patients who received more IV fluid before randomisation.

Analyses of heterogeneity in intervention effects for continuous baseline variables:

Analyses of heterogeneity in intervention effects according to continuous baseline variables will be conducted using linear regression models. These models will be similar to the primary analysis model but will also include the baseline variable of interest using a linear and a squared term along with interaction terms between these and the intervention indicator. Before being entered into the model, plasma creatinine and baseline IV fluids will be log2-transformed due to expected substantial right skew [46]. In addition, all continuous variables will be mean-centred prior to modelling (after log2-transformation of baseline plasma creatinine and baseline IV fluids). All presentation of results will be on the original scale.

Using the models, we will make predictions of the expected mean number of days alive without life support at 30 days for each intervention arm across the full range of values of the baseline variable of interest. Average predictions will be made across a grid that covers the entire range, as previously described [46]. This involves using the entire dataset and in turn setting the baseline variable of interest to each value on the grid, while keeping all other adjustment variables at their original values. Prediction will then be made in turn with the intervention indicator for all participants set to first the *no albumin* arm and then the *albumin* arm. The posterior distribution of mean values at each point in the grid will be presented visually. This will be done using the median posterior values as point estimates with 95% percentile-based credible intervals. Additionally, similar plots displaying the absolute and relative differences across the range of values of the baseline variable will be included. When relevant, the axis corresponding to the baseline variable of interest may be transformed (e.g., for baseline plasma creatinine and baseline IV fluids) to aid visualisation. The results will be interpreted probabilistically across the range of values.

Analyses of heterogeneity in intervention effects for categorical baseline variables:
Analyses of categorical baseline variables (i.e., cause of shock and liver failure) will use hierarchical linear regression models. These models will be similar to the primary models but will additionally include uncorrelated random effects for the intercept and intervention indicator variable within each category as previously done [46,51–53]. The models will predict the mean number of days in each category in turn. Each prediction will use a dataset where the baseline variable of interest is set to each category one at a time. All adjustment variables will remain at their original values, and the intervention effect indicator is first set to the *no albumin* arm and then the *albumin* arm. Posterior distributions for the estimates in each arm along with relative and absolute differences will be presented visually, with posteriors summarised and interpreted as described above.

Interactions with other domains
No assessment of interaction with other domains is planned, as this will be the first domain on *INCEPT*.

7.7 | Priors

The adaptive and final, primary analyses will be conducted using neutral, weakly informative priors for the intervention effects and all adjustment variables and additional model terms. Sensitivity analyses will be conducted using two types of priors for the intervention effect across all outcomes: sceptical priors reflecting cautious assumptions and evidence-based priors based on external evidence from an updated systematic review and meta-analysis at the time of conducting the final analyses.

The exact priors are presented in appendix 4, section 14.4, including evidence-based priors based on the external evidence at the time of writing; these will be updated before conduct of the final analyses.

7.8 | Handling of missing data

The proportions of missing data for all variables will be presented. Missingness will be handled in the analyses using multiple imputation as outlined in the core protocol [54]. These imputation models will include all outcomes which are available at time of analysis, all adjustment variables, and all baseline variables listed in **Table S1** (appendix 3, section 14.3), excluding SMS-ICU and predicted mortality as the variables used for these will be included separately and subsequently calculated. In addition, best-worst/worst-best case sensitivity analyses are planned as outlined in the core protocol.

7.9 | Overview of analyses including secondary and sensitivity analyses

This section provides an overview of all planned analyses supplementing the primary analyses described above. All secondary analyses, sensitivity analyses, and analyses of heterogeneous intervention effects will be conducted for the primary outcome only in the ITT population, unless stated otherwise. All analysis choices will reflect the corresponding choices from the primary analysis except stated otherwise.

- Primary analyses: all clinical outcomes, ITT population, neutral, weakly informative priors
- Adaptive analyses: primary/guiding outcome only, no sensitivity analyses
- Analyses of heterogeneous intervention effects: primary outcome only, neutral, weakly informative priors only

- Secondary analyses:
    - Primary outcome: *per-protocol* analysis
- Sensitivity analyses:
    - All clinical outcomes: neutral, sceptical priors and evidence-based priors where relevant evidence is available
    - Days alive without life support and days alive out of hospital at 30 and 90 days and days free of delirium at 30 days: using the actual values without penalisation of death
    - Health-related quality of life (EQ-5D-5L index values and EQ VAS at 180 days): analysis conducted in survivors only and analysis conducted in all participants using the national value set applicable to most participants [55]
    - Cognitive function (Mini MoCA at 180 days): analysis conducted in survivors only
    - All clinical outcomes: best-worst/worst-best case sensitivity analyses

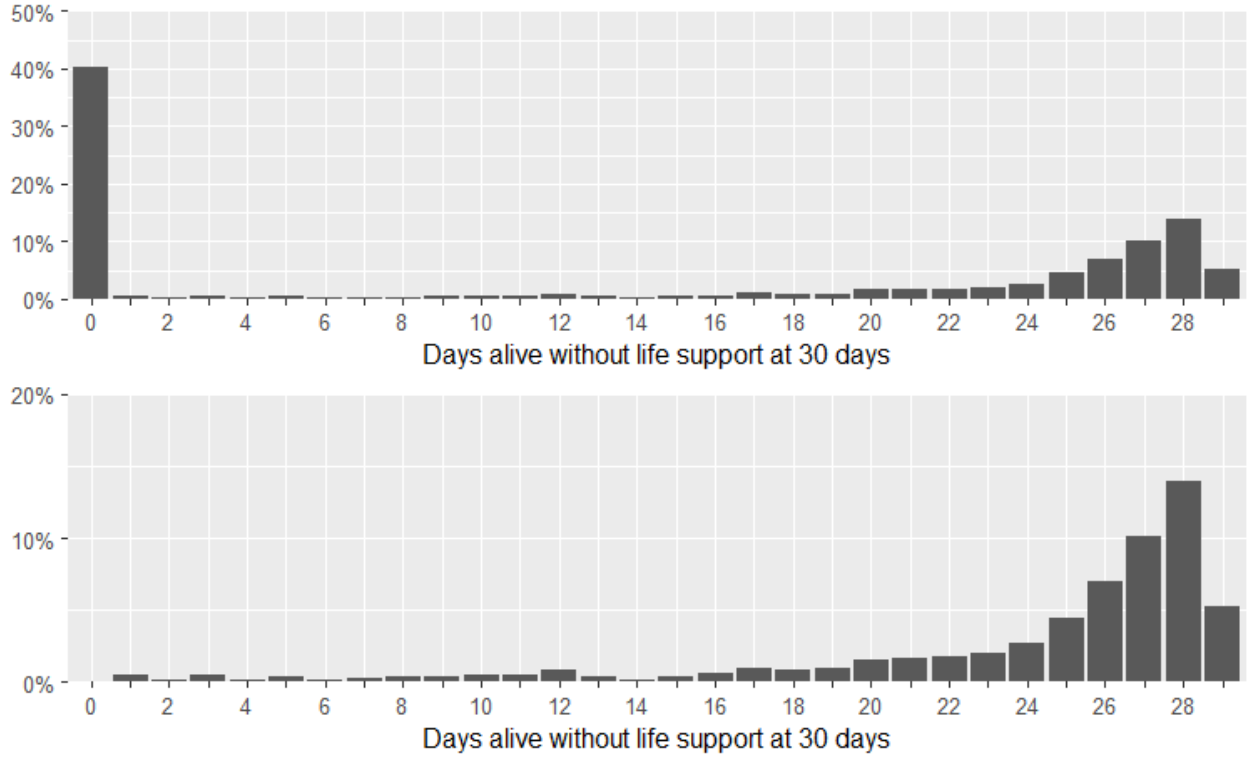
7.10 | Simulations and performance metrics (including sample sizes)

Performance metric evaluation, assumptions, and clinical scenarios

The final domain design has been developed and evaluated using statistical simulation as recommended [26]. The evaluation used 100,000 simulations under various clinical scenarios to assess multiple performance metrics. These metrics included Bayesian analogues of the type 1 error rate (the probability of stopping for superiority if there is truly no difference between arms) and power (the probability of stopping for superiority with specific differences between arms) for the primary and guiding outcome [26].

For performance evaluation, we used data from the *CLASSIC* trial to specify the distribution of days alive without life support in the *no albumin* arm [16]. The outcome distribution ranged from 0 days (minimum) to 29 days (maximum), with non-survivors assigned 0 days [33]. This range reflects the eligibility criterion that required participants to be on life support with vasopressors at baseline. Although three participants who were not on life support at baseline were mistakenly included, they were assigned 29 days instead of 30 for the purpose of this reference distribution. As illustrated in **Figure 1**, the distribution was substantially zero-inflated.

Figure 1. Distribution of days alive without life support in the *CLASSIC* trial



Distribution of days alive without life support at 30 days in the *CLASSIC* trial [16]. Upper subplot contains the entire distribution, while the lower subplot presents all values >0 to better visualize this part of the distribution.

The *CLASSIC* distribution was modelled using two combined distributions: a binomial distribution handling the probability of having 0 or >0 days, and the rest of the distribution summarised by a beta-distribution (after dividing by the maximum value, 29 days, plus a small offset of 0.01 days to avoid having to use a third distribution to model 29 days or 100% of the maximum possible value). In summary, 40.2% of participants had 0 days (36.7% due to death). The overall estimated mean according to the combined distributions was 14.05 (rounded to 14 below; raw mean 14.37 days), with an estimated mean of 23.5 days from the beta distribution and a variance of 0.04133 (calculated from the proportion out of the maximum number of days scale, so on the proportion^2 scale).

These binomial and beta distributions were used jointly to simulate data under the different clinical scenarios, with the randomly generated data on the 'proportion of the maximum number of days'-scale converted back to days and rounded up to the nearest whole number of days. This

ensured that zeroes were only generated by the binomial distribution and that all generated outcome data are whole numbers, matching how it will be registered in *INCEPT* and this domain. In the different clinical scenarios assessed, differences in the *albumin* arm were simulated by changing the overall mean value according to a desired mean value, without changing the variance of the beta distribution. This was done primarily by assuming that the change occurred equally to both sub-distributions, e.g., 50% of the effect mediated by a change in the proportion of zeroes and 50% in the number of mean days in those with >0 days. Secondarily, the change was assumed to only affect each separate part of the distribution to the extent possible. However, in some simulations, achieving the desired overall difference was not possible by solely changing the mean number of days in those with >0 days; in those cases, the remaining differences was mediated by a change in the probability of zero days as well. Due to rounding, the overall means of data simulated from the specified distributions differ slightly from the overall mean of the reference distribution due to rounding (appendix 5, section 14.5).

Performance metrics were assessed under the following clinical scenarios:

- No difference/null scenario: identical distributions in both arms (MD ~0 days)
- Small benefit with albumin: an increased overall mean in the albumin arm of approximately 1 day compared to the no albumin arm (MD ~1 day)
- Small harm with albumin: a decreased overall mean in the albumin arm of approximately 1 day compared to the no albumin arm (MD ~-1 day)
- Large benefit with albumin: an increased overall mean in the albumin arm of approximately 5 days compared to the no albumin arm (MD ~5 days)
- Large harm with albumin: a decreased overall mean in the albumin arm of approximately 5 days compared to the no albumin arm (MD ~-5 days)

All scenarios with differences presented were assessed in three variants: obtaining the same overall difference by effect either both parts of the distribution, or only one of the sub-distributions, as described above. As for the reference distributions, between-arm differences are approximately as specified (with slight deviations due to rounding; appendix 5, section 14.5).

For the primary simulations, we assumed constant inclusion rates of 3 participants/day throughout the domain, with combined follow-up, data collection, and data verification lags of 15 days. Candidate designs were calibrated to ensure type 1 error rates for the guiding and primary outcome of approximately 5% (i.e., 4.9-5.0%) based on 100,000 simulations.

During simulations, posteriors in each arm were generated from a normal distribution. The mean value corresponded to the current estimated mean and a standard deviation (SD) corresponding to the standard error of the mean, calculated as the *SD/square root (number of participants in arm – 1)*, corresponding to the use of linear regression models in the final analyses. Of note, improper, completely uninformative priors were used during the simulations for simplicity. The influence of this is expected to be minimal and negligible when compared to the very weakly informative priors used in the actual analyses, which are based on the accrued sample size at the time of the first adaptive analysis.

The following performance metrics were assessed [26]: sample sizes; mean and total number of days alive without life support at 30 days; probabilities of superiority, practical equivalence, conclusiveness (superiority or practical equivalence), and inconclusiveness (enrolling 10,000 participants without triggering a stopping rule); arm selection probabilities; root mean squared errors (RMSEs) and median absolute errors (MAEs) for the estimated mean number of days in the selected arm; and ideal design percentages [26,56,57]. The expected sample sizes and the probabilities of conclusiveness performance metrics were prioritised when deciding on the final domain design including ethical, practical, and economical considerations. We believe that the chosen design will maximise the probability of a conclusive result within a reasonable timeframe so that care may be improved for future patients.

Performance metrics RMSEs, MAEs, and ideal design percentages were in multiple ways:

1) For simulations ending in superiority only

   AND

2) Assuming that the best arm (the intervention with highest probability of being the best arm in the final analysis) is selected in simulations not ending with superiority

   AND

3) Assuming that the *no albumin* arm was selected in simulations not ending with superiority, as albumin is a scarce and expensive resource; avoiding albumin use is therefore rational if there is not firm evidence to support its use.

Several design variants were also assessed, along with sensitivity analyses with varying key assumptions. These included different underlying outcome distributions, effects mediated differently on the overall outcome distribution, different randomisation strategies (fixed and less restricted randomisation), different inclusion rates, different analysis frequencies, and a stricter threshold for practical equivalence, with differences in both directions assessed, all reported in appendix 5, section 14.5. Key performance metrics are presented in **Table 6**; all performance metrics for the final design and additional design variants assessed are presented in **Tables S5-S17** (appendix 5, section 14.5).

Table 6: Key performance metrics of the final domain design under the primary assumptions

Metric	No difference	Small benefit with albumin	Small harm with albumin	Large benefit with albumin	Large harm with albumin
Sample size – mean [25; 50; 75%-percentiles]	2,971 [2,136; 2,637; 3,387]	3,437 [2,136; 3,135; 4,635]	3,247 [2,136; 2,886; 4,386]	1,137 [1,137; 1,137; 1,137]	1,137 [1,137; 1,137; 1,137]
Mean number of days alive without life support at 30 days – mean [25; 50; 75%-percentiles]	14.5 days [14.3; 14.5; 14.6]	15.0 days [14.9; 15.0; 15.2]	14 days [13.9; 14.0; 14.2]	16.9 days [16.6; 16.9; 17.2]	12.0 days [11.7; 12.0; 12.2]
Probability of conclusiveness	~100.0%	~100.0%	~100.0%	~100.0%	~100.0%
Probability of superiority	5.0%	71.8%	75.5%	~100.0%	~100.0%
Probability of equivalence	95.0%	28.2%	24.5%	~0.0%	~0.0%
Probability of inconclusiveness	~0.0%	~0.0%	~0.0%	~0.0%	~0.0%
Root mean squared error (for estimated mean number of days in the superior arm, for simulations stopped for superiority only)	0.8 days	0.4 days	0.4 days	0.6 days	0.5 days
Probability of stopping for superiority for the *no albumin* arm	2.7%	~0.0%	75.4%	~0.0%	~100.0%
Probability of stopping for superiority for the *albumin* arm	2.3%	71.8%	~0.0%	~100.0%	~0.0%

Key performance metrics of the final domain design under the primary assumptions used based on 100,000 simulations for each scenario. The probability of conclusiveness corresponds to the combined probabilities of superiority and practical equivalence; the probability of superiority may be interpreted as the type 1 error rate in the scenario with no difference and as the power in the scenario with differences present [26]. The probability of inconclusiveness refers to the proportion of simulated trials stopped at the maximum sample size without triggering any stopping rule.

8 | Data registration and sharing

8.1 | Data registration

In addition to the *INCEPT* core outcomes and variables described in the core protocol or elsewhere in this domain-specific appendix, the following variables will be collected (for detailed variable definitions, see appendix 6, section 14.6):

Screening and baseline variables:

- Lowest plasma albumin within the last 24 hours
- IV crystalloid volumes within the last 24 hours
- Primary cause of shock:
    - Septic shock
    - Cardiogenic shock
    - Haemorrhagic or traumatic shock
    - Other type of shock:
        - Neurogenic shock
        - Anaphylactic shock
        - Burn shock
        - Obstructive (e.g., tension pneumothorax, massive pulmonary embolism, pericardial tamponade)
- Traumatic brain injury
- Use of albumin during the current ICU stay
- Known pregnancy
- Religious objection to the administration of albumin
- Known allergy to albumin

Variables collected daily until 90 days after inclusion in the domain:

- Albumin volumes and concentrations (4% and 5% combined, and 20% or higher concentration)
- Total fluid input
- Total fluid balance
- Total volume of packed red blood cells
- Protocol violations

Process data and protocol adherence:

Data collection for these variables is described in section 6.8.

The data collected will be presented as outlined in the core protocol and illustrated in **Tables S1-S4** (appendix 3, section 14.3).

8.2 | Data sharing

Data may be shared according to the procedure outlined in the core protocol (including after additional approvals, where required) after a grace period of at least 9 months following initial publication of results based on the data.

9 | Other considerations

9.1 | Co-enrolment and collaboration

An overview of permitted co-enrolment between domains and with other interventional trials will be continuously updated and available at the *INCEPT* website, including any formal co-enrolment agreements. At the time of writing, there are no other *INCEPT* domains active or expected to start prior to *INCEPT-Albumin*. Co-enrolment agreements with both the *EMPRESS* (*Empirical Meropenem Versus Piperacillin/Tazobactam for Adult Patients With Sepsis*) trial [46] and the *GODIF* (*Goal Directed Fluid Removal in Intensive Care Patients With Fluid Overload*) trial [58] and the *INCEPT-Albumin* domain have been made. No collaboration between the *INCEPT-Albumin* domain and other trials or research projects is currently planned.

9.2 | Stakeholder involvement

This section describes involvement of key stakeholders (including ICU survivors, family members, clinicians, and researchers) in the *INCEPT-Albumin* domain at the time of writing and planned future stakeholder involvement in the domain according to the research stages described by Pii and colleagues [59]. Only domain-specific stakeholder involvement is described; stakeholder involvement relevant to the entire platform trial is described in the core protocol.

Development of research design (method development and study design development)

All stakeholder involvement was initiated through an existing research panel to which all stakeholders were affiliated. Stakeholders consisted of 2 ICU survivors, 1 family member, and 3 clinicians not involved in the planning or daily management of *INCEPT-Albumin*. Stakeholders were involved in discussions of *INCEPT-Albumin* domain outcomes including inputs to the primary/guiding outcome. Moreover, stakeholders could suggest potential additional domain-specific secondary outcomes. Stakeholders were involved through group discussions using the nominal group technique [60], which invited all perspectives and aimed to reach a shared conclusion (consensus).

Recruitment (recruitment strategy and recruitment)

Stakeholders from existing research panels participated in group discussions using the nominal group technique [60]. We explored participants' perspective on the lay summary within the domain specific appendix and all written information materials for *INCEPT-Albumin* to be used in the informed consent process. A total of 3 ICU survivors, 1 family member, and 10 clinicians not involved in the planning or daily management of *INCEPT-Albumin* provided input which was incorporated into subsequent revisions.

Dissemination (dissemination strategy and dissemination)

Future lay summaries of domain results used for dissemination are planned to be discussed among the advisory board including key stakeholders (i.e., ICU survivors, family members, clinicians, and researchers). We will discuss dissemination strategies and explore potentially relevant channels and patient organisation.

9.3 | Modifications of the domain-specific appendix

All modifications to the domain-specific appendix will be approved by the competent authorities before implementation. If necessary, the information to participants will be changed and approved accordingly to reflect any changes in the domain. Upon approval, notifications about relevant modifications to the domain-specific appendix and thus the conduct of the domain will be sent to all primary investigators and monitors. The most recent and all previous approved versions of the domain-specific appendix will be available at the *INCEPT* website.

9.4 | Substudies

At the time of writing, we aim to conduct secondary studies on life cycle analyses (LCAs) and health-economic analyses of human albumin within the two interventions. These will be conducted alongside *INCEPT-Albumin* and are not part of the present domain specific appendix but will have specific protocols written and made publicly available prior to their initiation.
An overview of planned and completed substudies will be continuously updated and available at the *INCEPT* website.

10 | Domain independent data monitoring and safety committee

10.1 | Members

IDMSC trialist (chair)
Fernando Godinho Zampieri
Department of Critical Care Medicine, University of Alberta,
Alberta, Canada

IDMSC clinician
Yaseen Arabi
King Abdulaziz Medical City, Ministry of National Guard Health Affairs
Riyadh, Kingdom of Saudi Arabia

IDMSC biostatistician
Erin Evelyn Gabriel
Section of Biostatistics, Department of Public Health
University of Copenhagen
Denmark

All members of the domain IDMSC have no relevant conflicts of interest and have completed a conflicts of interest form prior to being appointed as outlined in the core protocol.

10.2 | Monitoring plan

The domain IDMSC will monitor the domain and conduct annual safety meetings with review of the domain safety data according to the requirements outlined in the core protocol. Additionally, for these meetings, the IDMSC will receive summarised data regarding the separation, presented visually for each arm with the same effect measures for evaluation.
Meetings will also be held after the feasibility phase concludes and after the first adaptive analysis in the domain has been conducted. If any concerns arise, they should be communicated to the domain management committee, which will then decide what action to be taken.

11 | Organisational and financial aspects

11.1 | Conflicts of interest

The Department of Intensive Care at Rigshospitalet has received grants from the Novo Nordisk Foundation for other projects.

Reported conflicts of interest:

Anders Perner: *research grants from Novo Nordisk Foundation, Sygeforsikringen 'danmark' and Savværksejer Jeppe Juhl. Research grants from the Novo Nordisk Foundation and honorarium for advisory board work from Novartis.*
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 the Danish Society of Anesthesiology and Intensive Care Medicine.*
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All other members of the domain management committee and all other domain contributors have no relevant conflicts of interest.

11.2 | Funders, supporters, and roles

At the time of writing this domain-specific appendix, *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.
The *INCEPT-Albumin* domain is partly funded by a grant from *Danmarks Frie Forskningsfond*.
Additional funding will be sought for *INCEPT* in general and for the *INCEPT-Albumin* domain.
Simulations were performed on the UCloud [61] interactive high-performance computing system managed by the eScience Center at the University of Southern Denmark, and thus partially supported by the Danish e-infrastructure Consortium (DeiC) National HPC (DeiC-KU-S1-000114).
The funding organisations and supporters have and will not be involved in the planning/design, conduct, analysis, reporting or decision to publish of the domain nor will it have ownership of the data.

11.3 | Compensation

In *INCEPT-Albumin*, trial sites will receive case money according to the number of participants enrolled and followed to support the salaries of dedicated trial staff. The compensation model will follow specifications from the *INCEPT* management committee, which will be made available prior to the first inclusion in the domain and continuously updated at the trial website.

11.4 | Publication and authorship considerations

We plan to publish the results in two stages: short-term at 30 days and later longer-term outcomes. Additionally, we intend to make results of both stages available as pre-prints prior to publication.
Authorship will be granted according to the International Committee for Medical Journal Editors (ICMJE) guidelines [62] by the platform and domain management committees according to single investigators input. All sites enrolling patients will be offered that at least one investigator be invited as author on the main paper. With many enrolled participants at a site, more authorships invitations will be offered those sites as it has been done in previous *Collaboration for Research in Intensive Care (CRIC)* trials [16,63–65].

11.5 | Estimated timeline

- First quarter, 2025: domain approved, and first participant randomised
- First quarter, 2026: feasibility phase analysis concluded
- Third quarter, 2028: expected inclusion of the last participant if the domain continues to the expected sample size in the small-difference scenario (i.e., the largest expected sample size under the different scenarios assessed)
- First quarter, 2034: expected inclusion of the last participant if the domain continues to the maximum sample size (n = 10,000); the probability for this is very low
- Approximately 5 months after inclusion of the last participant: primary report on 30- and 90-day outcomes submitted
- Approximately 9 months after inclusion of the last participant: report on 180-day outcomes submitted

12 | Summary of changes

This section summarises all changes to the domain-specific appendix after initial submission for approval.

Version 1.3, 2025-02-13:

- Updated to change core protocol version.

Version 1.2, 2025-02-07:

- Deleted roles of domain-specific appendix contributors to avoid future updates. They will be available and continuously updated at the *INCEPT* website (section 2.2).
- More nuanced specification of surveyed preferences for the use or not of albumin in shock and septic shock (section 5.4).
- Specified that participation in *INCEPT-Albumin* will increase the probability that participants receive albumin and hence benefit compared with current standard care (section 5.6).
- Added explicit exclusion criterion: “Inclusion in another interventional trial or *INCEPT* domain where co-enrolment with the *INCEPT-Albumin* domain is not permitted.” (section 6.2).
- Added definition of exclusion criterion in variable definitions (section 14.6).

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 domain specific appendix and replaced with statements that they will instead be made available and continuously updated at the *INCEPT* website (section 2.2).
- Added specification of secondary outcomes and removed the section “domain-specific secondary outcomes” (section 6.6).
- Added statement that *INCEPT* core outcomes other than those already specified in section 6.6 will be registered as specified in the core protocol (6.6).
- Added details on monitoring and following of participants after safety events (6.7).

- Added reference to the core protocol regarding end of domain (section 6.8). The previous section 6.8 has been renumbered accordingly.
- Added current funders of *INCEPT* and a statement that additional funding will be sought for *INCEPT* and *INCEPT-Albumin* (section 11.2).
- Specified that compensation for *INCEPT-Albumin* follows specifications from the INCEPT management committee which will be made available and continuously updated at the trial website (section 11.3).
- Minor corrections, updates (including in references), and semantic edits in multiple places not leading to any changes in meaning.

Version 1.0, 2024-11-07: first version submitted for approval.

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14 | Appendices

14.1 | Appendix 1: completed reporting checklists

Completed SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [27] and CONSORT-ACE (Consolidated Standards Of Reporting Trials [CONSORT], Adaptive designs CONSORT extension) [28] checklists for the *INCEPT-Albumin* domain are included in this appendix. Items not relevant at the protocol stage are denoted as such, while items not covered by this domain-specific appendix but covered by the core protocol refer to that.

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, 48
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	8, 9
	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	48
	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
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	15-18

	6b	Explanation for choice of comparators	16-18
Objectives	7	Specific objectives or hypotheses	4,13
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)	19
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	Core protocol
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)	20
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	20-22
	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)	23-26
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	26-27
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	22
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	23-24
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)	20, core protocol
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	36-40, 81-133
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Core protocol
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	22, core protocol
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	Core protocol
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Core protocol
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	22, core protocol
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
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	Core protocol
	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	26-28, core protocol
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	Core protocol
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	29-36, core protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	32-34
	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)	29, 36

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	46
	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	30-31, 46
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	23-25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	46

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Core protocol
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)	Core protocol
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Core protocol
	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	Core protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	47-48
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	Core protocol
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	Core protocol
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	48-49, core protocol

	31b	Authorship eligibility guidelines and any intended use of professional writers	48
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	43, core protocol
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

*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)	4-7
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	15-18
	2b	Specific objectives or hypotheses	4, 13
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	19
	3b« ǂ	Type of adaptive design used, with details of the pre-planned trial adaptations and the statistical information informing the adaptations	
	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	29-32
Participants	4a	Eligibility criteria for participants	20
	4b	Settings and locations where the data were collected	Core protocol
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	20-22
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	23-24
	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	36-41, 81-133
	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	30-32
Randomisation			
Sequence generation	8a	Method used to generate the random allocation sequence	Core protocol
	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	22, core protocol
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	Core protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Core protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	22, core protocol
	11b	If relevant, description of the similarity of interventions	Not relevant

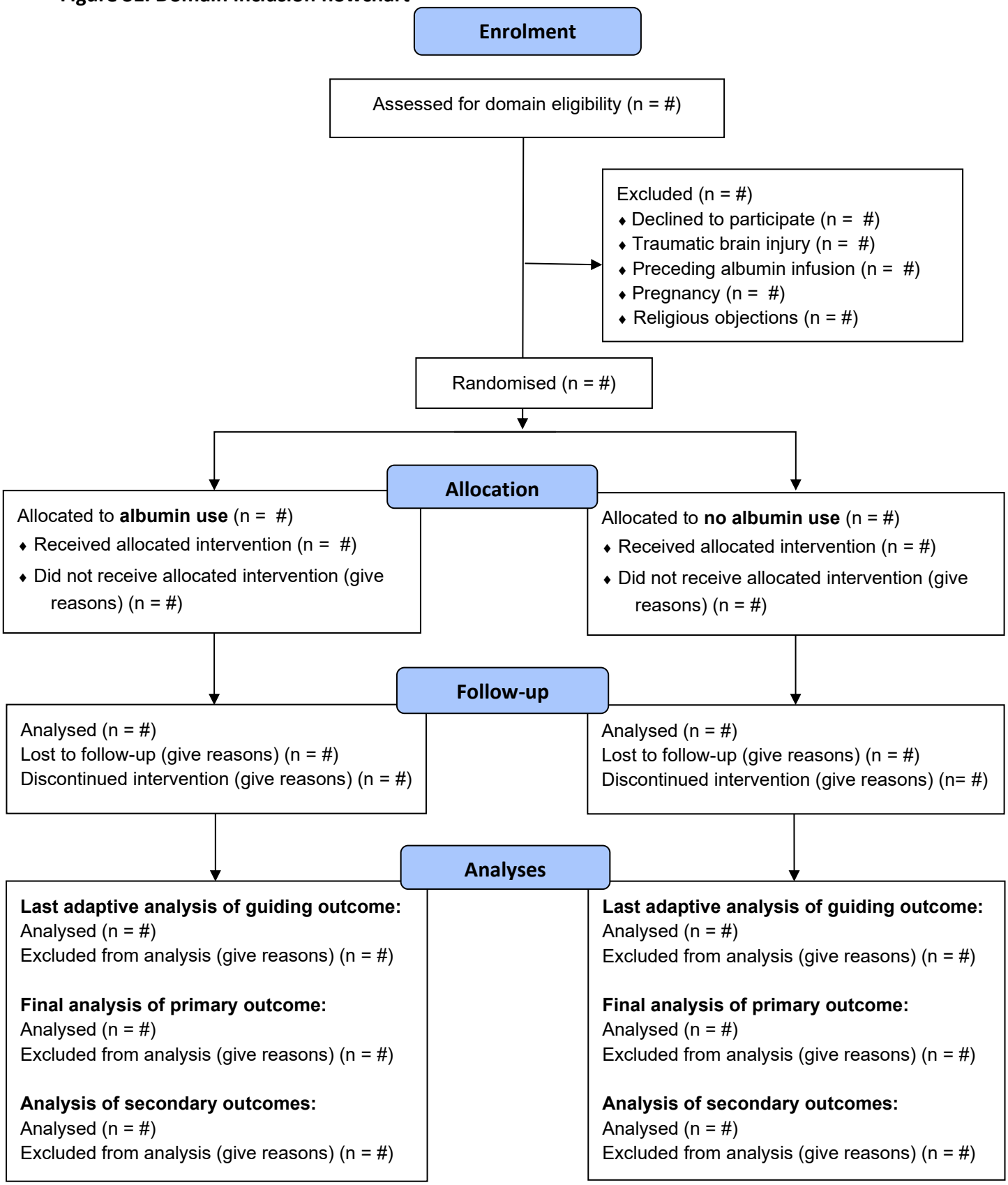
	11c ǂ	Measures to safeguard the confidentiality of interim information and minimise potential operational bias during the trial	Core protocol
Statistical methods	12a ‡	Statistical methods used to compare groups for primary and secondary outcomes, and any other outcomes used to make pre-planned adaptations	29-32
	12b« ǂ	For the implemented adaptive design features, statistical methods used to estimate treatment effects for key endpoints and to make inferences	29-32
	12c«2b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	32-34
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	67-68
	13b	For each group, losses and exclusions after randomisation, together with reasons	67-68
Recruitment and adaptations	14a ‡	Dates defining the periods of recruitment and follow-up, for each group	Not relevant
	14b †	Why the trial ended or was stopped	Not relevant
	14c ǂ	Specify what trial adaptation decisions were made in light of the pre-planned decision-making criteria and observed accrued data	Not relevant
Baseline data	15a«15 †	A table showing baseline demographic and clinical characteristics for each group	69-70
	15b ǂ	Summary of data to enable the assessment of similarity in the trial population between interim stages	Core protocol
Numbers analysed	16 †	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	67-68, 71-72
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)	71-72
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	71-72
	17c ǂ	Report interim results used to inform interim decision-making	73
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	74
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) [1]	71-72
Discussion			
Limitations	20 †	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Core protocol
Generalisability	21 †	Generalisability (external validity, applicability) of the trial findings	Not relevant
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Not relevant
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24a«24	Where the full trial protocol can be accessed	1
SAP and other relevant trial documents	24b ǂ	Where the full statistical analysis plan and other relevant trial documents can be accessed	1, core protocol
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7, 48

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.

14.2 | Appendix 2: domain inclusion flowchart

Figure S1. Domain inclusion flowchart



Mock domain inclusion flowchart, adapted from the CONSORT 2010 flowchart [66]. The total number of participants included in the platform trial while the domain has been active will be presented in the figure legend.

14.3 | Appendix 3: mock baseline and outcome tables

Table S1. Domain baseline data

Characteristic	Albumin use (N = #)	No albumin use (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 renal replacement therapy	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 dialysis	n (#.#%)	n (#.#%)
- Treatment with antipsychotics at hospital admission	n (#.#%)	n (#.#%)
Primary cause of shock		
- Septic	n (#.#%)	n (#.#%)
- Cardiogenic	n (#.#%)	n (#.#%)
- Haemorrhagic or traumatic	n (#.#%)	n (#.#%)
- Other (e.g.,neurogenic, anaphylactic, burn and obstructive shock)	n (#.#%)	n (#.#%)
Acute surgery within 7 days prior to randomisation		
SMS-ICU, median (IQR)	## (## to ##)	## (## to ##)
Predicted 90-day mortality[1], 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 ##)
Lowest plasma albumin within the last 24 hours, median (IQR), g/L		
IV fluid volumes administered in the 24 hours before randomisation, median (IQR), mL	## (## to ##)	## (## to ##)

Abbreviations: IQR: interquartile range, mmHg: millimetres of mercury, mmol/L: millimoles per litre, N or n: total counts or counts, SMS-ICU: *Simplified Mortality Score for the Intensive Care Unit* [50], µmol/L: micromoles per litre. Binary or categorical variables are presented as numbers with percentages; numerical variables are presented as medians with interquartile ranges. Definitions of all baseline variables are provided in the core protocol and appendix

6, section 14.6 Counts and proportions of participants with missing data for each separate baseline variable will be reported, with only complete data presented in this table (i.e., baseline data will be presented without imputation).
[1] The predicted 90-day mortality will be calculated using the Simplified Mortality Score (SMS)-ICU [50], with the scores ranging from 0-42 points with corresponding predicted 90-day mortality of 3.3 to 91.0%.

Table S2. Domain outcome data

	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	**Albumin use (N = #)**	**No albumin use (N = #)**	**Relative difference (RR/RoM, 95% CrI)**	**Absolute difference (RD/MD, 95% CrI)**	**Albumin use**	**No albumin use**
Days alive without life support at day 30 (primary and guiding outcome)	#.# (#.# 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 30-day mortality	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#) *#.#% (#.# to #.#)*	#.## (#.## to #.##)	#.#%-points (#.# 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 at day 30	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	#.## (#.## to #.##)	#.#%-points (#.# to #.#)	#.##%	#.##%
One or more domain-specific safety outcomes at day 90	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	#.## (#.## to #.##)	#.#%-points (#.# to #.#)	#.##%	#.##%

Table with data from the final, primary analyses of all clinical outcomes in the *INCEPT-Albumin* domain. All model-based estimates, intervention effects, and probabilities are based on the sample-average posterior distributions for the parameter of interest.

[1] For both interventions, 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 each separate outcome variable will be reported, with descriptive data and model estimates based on multiply imputed data unless complete.

[2] Sample-average intervention effect estimates will be presented as between-arm comparisons with the no albumin use (control) arm considered the reference.

[3] 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. Probabilities of effect sizes smaller than the threshold(s) for practical equivalence will also be presented along with the probabilities of intervention effects larger than the practical equivalence 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.

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 S3. Results from successive adaptive analyses

Adaptive analysis	**Analysed/ randomised**		**Outcome data per intervention** descriptive data [median (IQR)] *model estimate [mean with (95% CrI)]*		**Probabilities of superiority and practical equivalence**			**Subsequent allocation profile**	
Number, last inclusion date, analysis date, implementation date	**Albumin use (N = #)**	**No albumin use (N = #)**	**Albumin use (N = #)**	**No albumin use (N = #)**	**Albumin use superior (N = #)**	**No albumin use superior (N = #)**	**Practical equivalence**	**Albumin use (N = #)**	**No albumin use (N = #)**
#1, YYYY-MM-DD, YYYY-MM-DD, YYYY-MM-DD	n/N (#.#%) [complete: n/N (#.#%)]	n/N (#.#%) [complete: n/N (#.#%)]	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.##%	#.##%	#.##%	#.##%	#.##%
#2, …									

Results of all adaptive analyses in the *INCEPT-Albumin* domain.

Abbreviations (in alphabetical order): CrI: credible interval; YYYY-MM-DD: year, month, date, date of the time of the follow-up dates and the dates where 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.

Table S4. Domain-specific separation and protocol adherence

Separation and protocol adherence	Albumin use (N = #)	No albumin use (N = #)	Absolute difference
Albumin volumes, mL[1]	Mean (SD) #.# (#.#)	Mean (SD) #.# (#.#)	Difference in means #.#
	Median (IQR) #.# (#.# to #.#)	Median (IQR) #.# (#.# to #.#)	Difference in medians #.#
Proportion of patients receiving ≥100 ml albumin[1]	#.#%	#.#%	-
Protocol violations[2]	n/N (#.#%)	n/N (#.#%)	-

[1] Total volumes, all concentrations combined.

[2] For the albumin use arm, protocol violations are defined as no albumin given during resuscitation or as substitution in case of suspected or overt albumin loss or plasma albumin levels below 25 g/L. For the no albumin use arm, protocol violations are defined as albumin given without one of the extenuating circumstances occurring i.e., large volume ascites drainage, spontaneous bacterial peritonitis, or hepatorenal syndrome.

Abbreviations: IQR: interquartile range.

14.4 | Appendix 4: priors

Prior probability distributions used for all analyses of the clinical outcomes in the *INCEPT-Albumin* domain are described in this section, which is based on a corresponding section in the *EMPRESS* trial protocol [46]. Models will generally have the following form and include adjustments for stratification variables and anticipated prognostic baseline variables, as described in additional details in the core protocol and section 7.5:

outcome ~ intercept + intervention + site of enrolment + septic shock [versus other types of shock] age + age squared + active haematologic malignancy or metastatic cancer + acute surgery within 7 days prior to randomisation + use of invasive mechanical ventilation + use of circulatory support + use of renal replacement therapy within 72 hours prior to randomisation + time period

The linear models used for analysing continuous/count outcomes will also include an auxiliary nuisance parameter, *sigma*, for the estimated standard deviation (SD) of the residuals, and models used for analyses of heterogenous intervention effects will include additional terms as appropriate (described below).
The *no albumin* arm will be the reference category for the intervention effect in all analyses.

Primary priors for the linear regression models

- Intercept: *N(x, y)* priors with *x* corresponding to the midpoint of the range of possible values for each outcome, and *y* corresponding to the distance from the midpoint to either end of the range of possible values. This prior corresponds to the prior mean value for a participant allocated to the reference intervention arm and with all covariates set to 0/no/the reference site; as such a participant will not exist in the trial (due to age being set to 0), this prior is not directly interpretable, but extremely vague. The prior is centred at *x* (the midpoint for each scale) and the 68% central probability mass covers the range of each scale. The prior thus also includes implausible values, but as it corresponds to minimal information, it will quickly be overwhelmed by the data.
  For EQ-5D-5L index values, the vast majority of participants have values between 0 and 1, although values below 0 are typically present in a small minority of participants [17,67–69]. For this outcome, we will define both *x* and *y* as 0.5 (i.e., using the 0-1 range of the scale and the strategy outlined above).

- Intervention effect: *N(0, z)* priors with *z* corresponding to the 15% of the range of the scale of each outcome (using 15% of 0 to 1 for EQ-5D-5L index values) corresponding to prior probability distributions for mean differences centred at 0 and with 95% probability mass between -29.4% and 29.4% of the full outcome range, e.g., for days alive without life support at day 30 (maximum value 29), 95% prior probability mass will be centred between -8.5 and 8.5 days.
- Age (years) and age squared: a *N(0, z)* for each 1 unit increase as for the intervention effect, with *z* corresponding to 2.5% of the range of the scale of each outcome (as outlined above, using 2.5% of 0 to 1 for EQ-5D-5L index values), corresponding to prior probability distributions for mean differences centred at 0 and with 95% probability mass between -4.41% and 4.41% of the full outcome range for each 1 unit increase; these priors are very vague considering to the expected substantial range of age and age squared.
- All binary and categorical adjustment variables: *N(0, z)* priors, with *z* defined as twice as large as the primary priors for the intervention effects, i.e., 30% of the range of scale of each outcome (using 30% of 0 to 1 for EQ-5D-5L index values) corresponding to prior probability distributions for mean differences centred at 0 and with 95% probability mass between -58.8% and 58.8% of the full outcome range, e.g., for days alive without life support at day 30 (maximum value 29), 95% prior probability mass will be centred between -17.0 and 17.0 days.
- Sigma: *half-N(y)* [a half-normal distribution, i.e., a folded normal distribution with mean 0/a normal distribution truncated to only contain non-negative values, with SD = y], with *y* defined as for the intercept. This prior conveys very minimal information and will have minimal influence on the results.

Primary priors for the logistic regression models

All binary outcomes will be analysed using logistic regression models with the following priors, specified on the log odds scale.

- Intercept: *N(0, 2.5)* [denoting a normally distributed prior with mean 0 and standard deviation (SD) 2.5], corresponding to an event probability for a participant allocated to the reference intervention (as described above) and with all covariates set to 0/no/the

reference site; as such a participant will not exist in the trial (due to age being set to 0), this prior is not directly interpretable, but extremely vague. The prior is centred at a probability of 50% with 95% probability mass between 0.7% and 99.3% and corresponds to essentially no information.

- Intervention effect: *N(0, 0.5)*, corresponding to a distribution on the odds ratio scale centred at 1.00 (no difference) and with 95% probability mass between 0.38 and 2.66. This prior corresponds to approximately 69 participants in a 2-arm trial with fixed equal allocation and identical event probabilities of 36.7% in both arms (based on the 30-day mortality from the *CLASSIC* trial [16] used as reference population for the simulations, as described in section 7.10) analysed using a conventional, frequentist logistic regression model [70,71] (event probability 30%: 76 participants; 50%: 64 participants).
- Age (years) and age squared: a *N(0, 0.15)* for each 1-unit increase; these priors are very vague considering the expected substantial range of age and age squared and corresponds to odds ratio for each 1-unit change centred at 1.00 (no difference) and with 95% probability mass between 0.75 and 1.34.
- All binary and categorical adjustment variables: *N(0, 1)* priors, corresponding to distributions on the odds ratio scale centred at 1.00 and with 95% probability mass between 0.14 and 7.10.

Sensitivity analyses

Several sensitivity analyses will be conducted using different priors for the primary, final analyses of each outcome, using different priors for the intervention effects but identical priors for all other model terms.

More informative, neutral, sceptical priors

A set of sensitivity analyses using more informative, neutral, sceptical priors for the intervention effects will be conducted. For all continuous outcomes, *N(0, z)* priors will be used, with *z* defined as 2.5% of the range of each outcome (as outlined above, using 2.5% of 0 to 1 for EQ-5D-5L index values). This corresponds to priors with mean differences centred at 0 and 95% probability mass between -4.9% and 4.9% of the outcome range. For days alive without life support at day 30 (max value 29), this corresponds to 95% prior probability mass between -1.4 and 1.4 days. For the

binary outcomes, *N(0, 0.15)* priors will be used. This corresponds to priors on the odds ratio scale centred at 1.00 (no difference) with 95% probability mass between 0.75 to 1.34, corresponding to the same information as 765 participants in a two-arm trial with event rates of 36.7% in both arms (as described above).

Less informative, neutral priors

A set of sensitivity analyses using less informative, neutral priors for the intervention effects will be conducted. For all continuous outcomes, *N(0, z)* priors will be used, with *z* defined as 50% of the range of each outcome (as outlined above, using 50% of 0 to 1 for EQ-5D-5L index values). This corresponds to priors with mean differences centred at 0 and 95% probability mass between -98% to 98% of the outcome range. For days alive without life support at day 30 (max value 29), this corresponds to 95% prior probability mass between -28.4 and 28.4 days. For the binary outcomes, *N(0, 2.55)* priors will be used. This corresponds to priors on the odds ratio scale centred at 1.00 (no difference) with 95% probability mass between <0.01 to 134, corresponding to the same information as 3 participants in a two-arm trial with event rates of 36.7% in both arms (as described above).

Evidence-based priors

A set of sensitivity analyses using informative, *evidence-based priors* for the intervention effects will be conducted for the outcomes where relevant external evidence is available at the time of conduct. Evidence-based priors will be defined based on the summarised evidence base from, e.g., an updated systematic review with meta-analysis. Evidence-based priors based on the evidence available at the time of writing of the domain-specific appendix is only for the mortality outcomes, which is outlined below. This will be updated, including for the remaining clinical outcomes, if relevant, before the final analyses using evidence-based priors are conducted to reflect the best summary of the relevant external evidence at the time of analysis.

Mortality priors

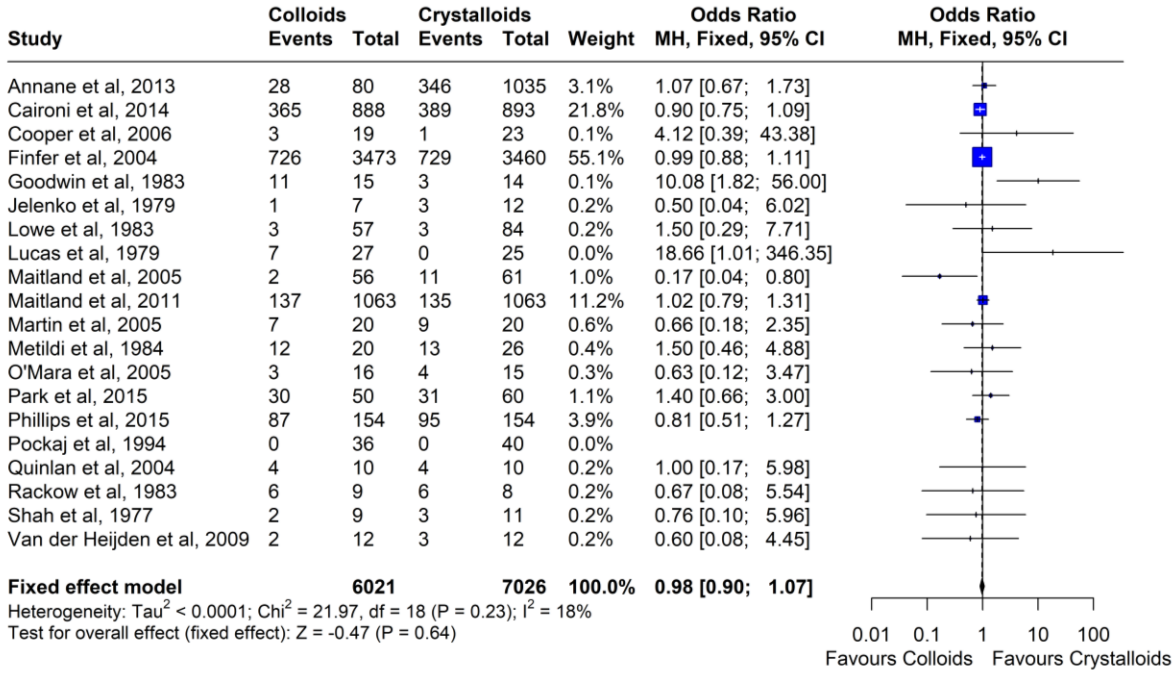
All priors for the covariates following the definitions provided above. Priors for intercepts and the intervention effects below are based on estimates from the most recent Cochrane systematic review and meta-analyses [14]. Mortality was reported at several timepoints, but we chose to

focus om end of follow-up as it included data from all available trials. The estimates at earlier timepoints were similar and would therefore yield consistent priors [14].

Mortality at end of follow-up

- Intervention effect: *N(-0.02, 0.04)* corresponding to a prior probability distribution on the OR scale centred on 1.00 with 95% probability mass between 0.90 and 1.06 with mean 0.98. The meta-analyses, which included 20 randomised clinical trials (RCTs) and 13,047 patients, provides the following forest plot for mortality at end of follow-up (**Figure S2**), adapted from the risk ratio to the odds ratio scale, based on the meta-analysis in [14]:

Figure S2. Meta-analysis of previous evidence



Meta-analysis of previous evidence, adapted from a previous meta-analysis [14]. The meta-analysis used a fixed effect model and the Mantel-Haenszel method with results presented on the odds ratio scale. Abbreviations: CI: confidence interval; MH: Mantel-Haenszel.

Priors for analyses of heterogeneous intervention effects

Analyses of heterogeneous intervention effects will use the same sets of priors as the primary analyses for all model terms, including the intervention effects, that were also part of the primary analysis models.

For the analyses of heterogeneous intervention effects based on continuous baseline variables, *N(0, z)* priors will be used for the additional model terms (on the linear scale and after quadratic transformation) for each 1-unit increase (after log2-transformation of baseline plasma creatinine and baseline IV fluids). The value of *z* will be defined as for *age* and will therefore be very weakly informative.

For the analyses of heterogeneous intervention effects according to categorical baseline variables, *N(0, omega)* priors will be used. Here, *omega* is the shrinkage factor estimated which will have a *half-N(z)* hyper-prior, with *z* defined as for the intervention effects for the primary outcome, i.e., 15% of the range of the scale, which for days alive without life support at day 30 (maximum value 29) corresponds to 4.35 days. This hyper-prior is thus also weakly informative as it corresponds to a standard deviation (omega) that with 95% probability is between 0.14 days and 9.75 days with mean 3.47 days and median 2.93 days.

Sensitivity analyses using informative, evidence-based priors for the intervention effects will be conducted for outcomes where relevant external evidence is available, as specified above.

14.5 | Appendix 5: simulation-based assessment of performance metrics

This appendix includes details on the simulation-based assessment of the domain design, including simulation details, and performance metrics for the final domain design and several additional design variants. This section is based on a corresponding section in the *EMPRESS* trial protocol [46]. Simulations were conducted in R v4.4.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the *adaptr* package v1.4.0 [72,73]. We conducted 100,000 simulations for each design considered as recommended [74] and described in the core protocol.

Model and priors

Data generation model

As described in section 7.10, the expected reference distribution (i.e., the distribution in the *no albumin* arm) for the primary and guiding outcome (days alive without life support at 30 days [DAWOLS30]) was based on the distribution of the same outcome in the full *CLASSIC* trial population (1,487 participants with available data) [16]. The distribution ranged from 0 (minimum) to 29 (maximum) days, as participants were required to be on life support at baseline (of note, three participants randomised in error in *CLASSIC* had 30 days as they were not on life support at baseline, but this was truncated to 29 days for the purpose of using this as a reference population). Of note, DAWOLS30 was not an outcome in the *CLASSIC* trial, but calculated based on the data collected for the same outcome at 90 days [16]. Non-survivors were assigned 0 days [33]. As illustrated in **Figure 1** in the main text, the distribution was substantially zero-inflated, with 40.2% 0'es, of which 36.7% were due to mortality at day 30 [33]. The overall mean was 14.4 days, with a mean of 24.0 days in those with >0 days.

We used a two-part outcome generation model consisting of a *binomial* distribution for the proportion of 0'es (40.2% probability of 0 days) and a *beta* distribution for the number of days in those with >0 days according to the *binomial* part of the model (i.e., a *'hurdle-beta*' model). The *beta* distribution parameters were estimated on the proportion scale (between 0 and 1) using the *mean-and-variance* parameterization [75]. We fitted a *beta* distribution to the subset of the *CLASSIC* trial population with >0 days using the *fitdistrplus* R package v1.1-11 [76] after dividing the DAWOLS30 values with 29.01 (the maximum value plus a slight offset of 0.01, to avoid proportions of 1, which cannot be included in the *beta* distribution; as there were no maximum-inflation, a three-part model [76] was avoided). The estimated mean proportion was 0.81

(corresponding to 23.5 days in those with >0 days, and 14.05 [shortened to 14 below] days in the full distribution including those with 0 days) and the estimated variance on the proportion scale was 0.041331 (standard deviation [SD] 0.2033).

During simulations, outcome data were simulated from the described model. Proportions drawn from the *beta* model were multiplied by the maximum number of days 29 (without an offset) and rounded upwards to the nearest whole number, ensuring that the proportion of zeroes were only modelled by the binomial sub-part of the model. Consequently, due to rounding, the *actual* overall means from the combined distributions used to generate simulated outcome data differ slightly from the mean values used to specify the distributions.

The distributional parameters were generally unchanged in the *no albumin* arm, but the proportion of zeroes and the mean number of days in those with >0 days were changed according to different scenarios in the *albumin* arm, with the *beta* model variance unchanged in all clinical scenarios simulated. As for the overall means in the *reference* distribution, the *actual* means in these distributions (and thus also the actual simulated differences) differ slightly from the values used to derive the distributions due to rounding. All the *actual* overall mean values (derived by drawing 1,000,000 random samples from the resulting distributions) are reported with the simulation results in **Tables S5-S17** below.

Analysis model and priors

During simulations, a simple model using a *normal* distribution for the posterior mean number of DAWOLS30 and the associated uncertainty was used to estimate the posteriors to correspond to the overall analysis method (adjusted Bayesian linear regression; no covariates were simulated here); while both the simulation model and the final model are unable to generatively replicate the distribution analysed, they adequately estimate the mean value and the associated uncertainty [33], which is what all subsequent adaptations and decisions are based upon. A separate *normal* distribution was used in each intervention arm, using the raw group mean as the distribution mean and the standard error of the mean (calculated as the group SD divided by the square root to the number of group participants minus one) was used as the distribution SD. While this is a simplified approximation, it is adequate despite the non-*normal* underlying distribution due to the moderately large sample size at the time of the first adaptive analysis (500 participants in each arm) [33,77].

As the raw means and standard errors of the means were used directly as the *posterior* distribution, this technically means that exactly no prior information, i.e., improper priors, were used. This deviates slightly from the planned actual analyses of the primary and guiding outcome, where a weakly informative prior for the intervention effect (section 7.9, 7.10 and appendix 14.4, section 4) will be used to stabilise and the speed up the Markov chain Monte Carlo sampling. However, this prior is so weak that it will cause minimal discrepancy between the simulations and the actual analyses, and it is not easily 'translatable' to the distributions used for simulations, which were necessary to conduct a vast number of simulations within a realistic timeframe.
In each analysis in each arm, 20,000 independent posterior samples were drawn from the posterior distributions and used in all adaptations.

Timing of analyses

The first adaptive analyses were conducted once primary and guiding outcome data were available for 1,000 simulated participants, with subsequent analyses after each additional 250 participants until a maximum of 10,000 participants. The number of participants *randomised* at the time of each adaptive analyses was calculated based on a total outcome-data lag of 45 days (follow-up duration of 30 days plus a 15-day data collection/verification period) and an assumed constant inclusion rate of 3 participants per day, based on previous trials by our group in which overall inclusion rates have been approximately constant after initiation of most sites [63–65,78]. Of note, the longer the combined outcome-data lag and the higher the inclusion rate, the larger the proportion of participants randomised (using the allocation profile active at the time of their randomisation) but without outcome data available at the time of an adaptive analysis will be. Larger proportions of participants without outcome data available at the time of analysis increases the potential for subsequent important changes in the estimates once all randomised participants are later included in a final analysis [79].

Scenarios

The performance of the *INCEPT-Albumin* domain design was evaluated under the clinical scenarios described in section 7.10:

- No difference/null scenario: identical distributions in both arms (MD ~0 days)

- Small benefit with albumin: an increased overall mean in the albumin arm of approximately 1 day compared to the no albumin arm (MD ~1 day)
- Small harm with albumin: a decreased overall mean in the albumin arm of approximately 1 day compared to the no albumin arm (MD ~-1 day)
- Large benefit with albumin: an increased overall mean in the albumin arm of approximately 5 days compared to the no albumin arm (MD ~5 days)
- Large harm with albumin: a decreased overall mean in the albumin arm of approximately 5 days compared to the no albumin arm (MD ~-5 days)

Three versions of each scenario with differences were assessed. In the primary scenario, differences in the overall mean were mediated 50% by changes in the proportion of zeroes and 50% in the mean number of days in those with >0 days. Additionally, each scenario was assessed assuming that differences were *a)* solely mediated by changes in the proportion of zeroes and *b)* solely mediated by changes in the mean number of days in those with >0 days (for some combinations of effects and sensitivity analyses of changes to the reference distribution, mediating the effect solely through changes in the mean in those with >0 days was not possible due to the upper limit; in these instances, the effect was mediated to the extent possible on the means in those with >0 days and the rest mediated on the proportion of 0 days to obtain the overall difference of interest). Below, the scenarios are denoted as "B" (effect mediated on both parts of the distribution)/"Z" (effect mediated on the proportion of zeroes only)/"M" (effect mediated on the means in those with >0 days only) and the MD in the *albumin* arm, e.g., "B +1" means the scenario with a small benefit (increased MD of 1 day) with albumin mediated through both parts of the distribution, while "Z -5" means the scenario with large harm (decreased MD of 5 days) with albumin mediated through the proportion of zeroes only. The scenario without a difference is denoted "ND" (no difference) throughout.

Adaptation rules

Constant, symmetrical stopping thresholds for superiority and inferiority were used, with the probability thresholds *calibrated* to obtain a probability of stopping for superiority of approximately 5% in the scenario without differences, corresponding to the domain-wise type 1 error rate [26]. Calibration was performed using a Gaussian process-based Bayesian optimisation

algorithm,[80] 100,000 simulations for each evaluation step, and a tolerance range of 4.9-5.0% for the probability of superiority in the primary scenario without differences. The calibrated stopping thresholds for superiority are included with the performance metrics below (rounded to 6 decimals), with the calibrated stopping thresholds for inferiority being symmetrical, i.e., defined as 1 minus the threshold for superiority.

Simulations were stopped for practical equivalence according to the stopping rule described in section 7.3. The initial and subsequent allocation rules were as outlined in section 7.4.

Performance metrics

Multiple performance metrics [26,72] were calculated for the assessed designs:

1) Sample size (mean [expected], SD, median, 25th percentile [P25], 75th percentile [P75], minimum, maximum)
2) Total number of days alive without life support (total number of days in both arms in the simulations; same summary measures as for #1)
3) Mean number of days alive without life support (mean number of days across both arms in the simulations, i.e., total number of days alive without life support; same summary measures as for #1).
4) Pr(conclusive): the probability of conclusiveness, i.e., the proportion of simulations triggering the superiority or practical equivalence stopping rule at any adaptive analysis.
5) Pr(superiority): the probability of superiority, i.e., the proportion of simulations triggering the superiority stopping rule at any adaptive analysis. This corresponds to the type 1 error rate in scenarios with no difference present and the power in scenarios with a difference present [26].
6) Pr(equivalence): the probability of practical equivalence, i.e., the proportion of simulations triggering the stopping rule for practical equivalence at any adaptive analysis.
7) Pr(max): the proportion of simulations reaching the maximum allowed sample size without triggering a stopping rule, i.e., the probability of the domain being inconclusive.
8) Pr(no albumin superior): the probability of declaring *no albumin* superior, i.e., the proportion of simulations with the *no albumin* arm triggering the stopping rule for superiority.

9) Pr(albumin superior): the probability of declaring *albumin* superior, i.e., the proportion of simulations with the *albumin* arm triggering the stopping rule for superiority.
10) Pr(none superior): the probability of not declaring any arm superior, i.e., the proportion of simulations stopped due to triggering the equivalence stopping rule or reaching the maximum sample size without triggering any stopping rule.
11) RMSE (superiority only): the root mean squared error (RMSE) of the estimated versus the true simulated mean number of days alive without life support in the superior arm (only calculated for trials stopped for superiority; days).
12) MAE (superiority only): the median absolute error (MAE) of the estimated versus the true simulated mean number of days alive without life support in the superior arm (only calculated for trials stopped for superiority; days).
13) IDP (superiority only): the ideal design percentage (IDP, %) [26,56,57], for simulations ending in superiority only. The IDP is 100% for a design that always ends selecting the best arm and lower otherwise.
14) RMSE (select best arm in inconclusive simulations): the RMSE of the estimated versus the true simulated mean number of days alive without life support in the selected arm, with the arm with the highest probability of being superior in the final analysis selected if not stopped for superiority (days).
15) MAE (select best arm in inconclusive simulations): the MAE of the estimated versus the true simulated mean number of days alive without life support in the selected arm, with the arm with the highest probability of being superior in the final analysis selected if not stopped for superiority (days).
16) IDP (select best arm in inconclusive simulations): the IDP calculated for all simulations, considering the arm with the highest probability of being superior in the final analysis selected in simulations not stopped for superiority.
17) RMSE (select no albumin arm in inconclusive simulations): the RMSE of the estimated versus the true simulated mean number of days alive without life support in the selected arm, with the *no albumin* arm selected if not stopped for superiority (days).

18) MAE (select no albumin arm in inconclusive simulations): the MAE of the estimated versus the true simulated mean number of days alive without life support in the selected arm, with the *no albumin* arm selected if not stopped for superiority (days).
19) IDP (select no albumin arm in inconclusive simulations): the IDP calculated for all simulations, considering the *no albumin* arm selected in simulations not stopped for superiority.

Final design and variants

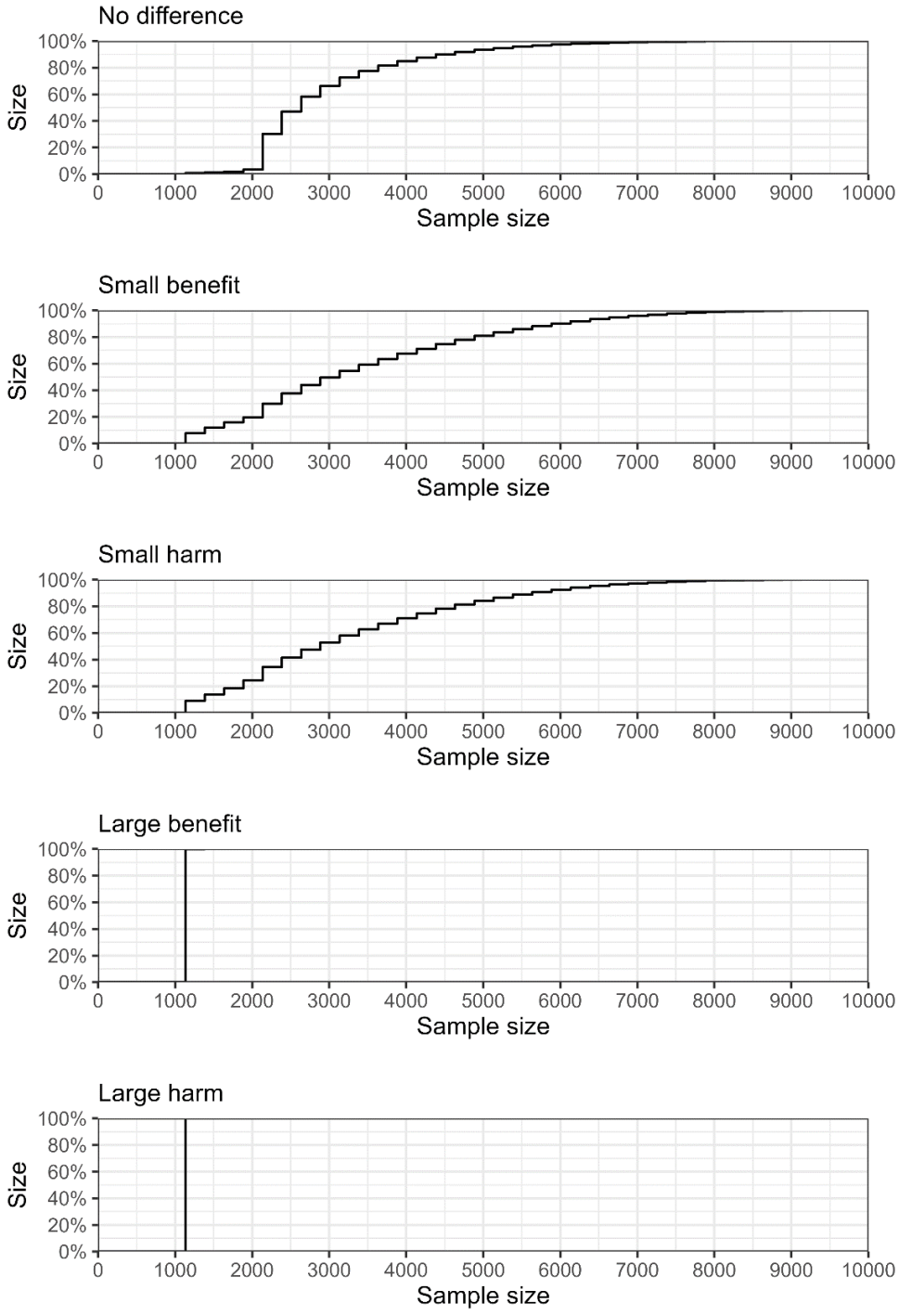
The evaluation of final *INCEPT-Albumin* domain design (**Table S5**) and several variants (**Tables S6-S17**) are summarised here; details are in the tables (including the range of metrics across all scenarios evaluated and the *actual* overall means in each arm in each scenario). Variants included sensitivity analyses of both design choices (which are fixed and thus require re-calibration of stopping rules) and assumptions (which cannot be controlled and thus are conducted without re-calibration of stopping rules, with the stopping rules calibrated under the primary assumptions used; as such the type 1 error rate in the scenario with no difference may deviate from the tolerated range in these simulations, and assessing this is a central reason for these variants of the simulations). Except where noted otherwise, all design choices and assumptions reflect those from the primary trial design.

First, the final primary domain design was evaluated (**Table S5**). Across all scenarios, the mean (expected) sample sizes ranged from 1,137 to 3,555 participants, while maximum observed sample sizes ranged from 1,386 to 10,000. The probability of conclusiveness was approximately 100% in all scenarios.

Second, the final primary trial design was re-evaluated with the calibrated stopping thresholds for superiority/inferiority rounded to 4 decimal places for practical purposes, as the calibration process itself does not limit the number of decimals (**Table S6**). Results were essentially unchanged, with mean sample sizes ranging from 1,137 to 3,547, maximum observed sample sizes ranging from 1,386 to 10,000, and probabilities of conclusiveness of approximately 100% across all scenarios. The empirical cumulative distribution functions for the sample sizes with this design under all the clinical scenarios are presented in **Figures S3-S5** below.

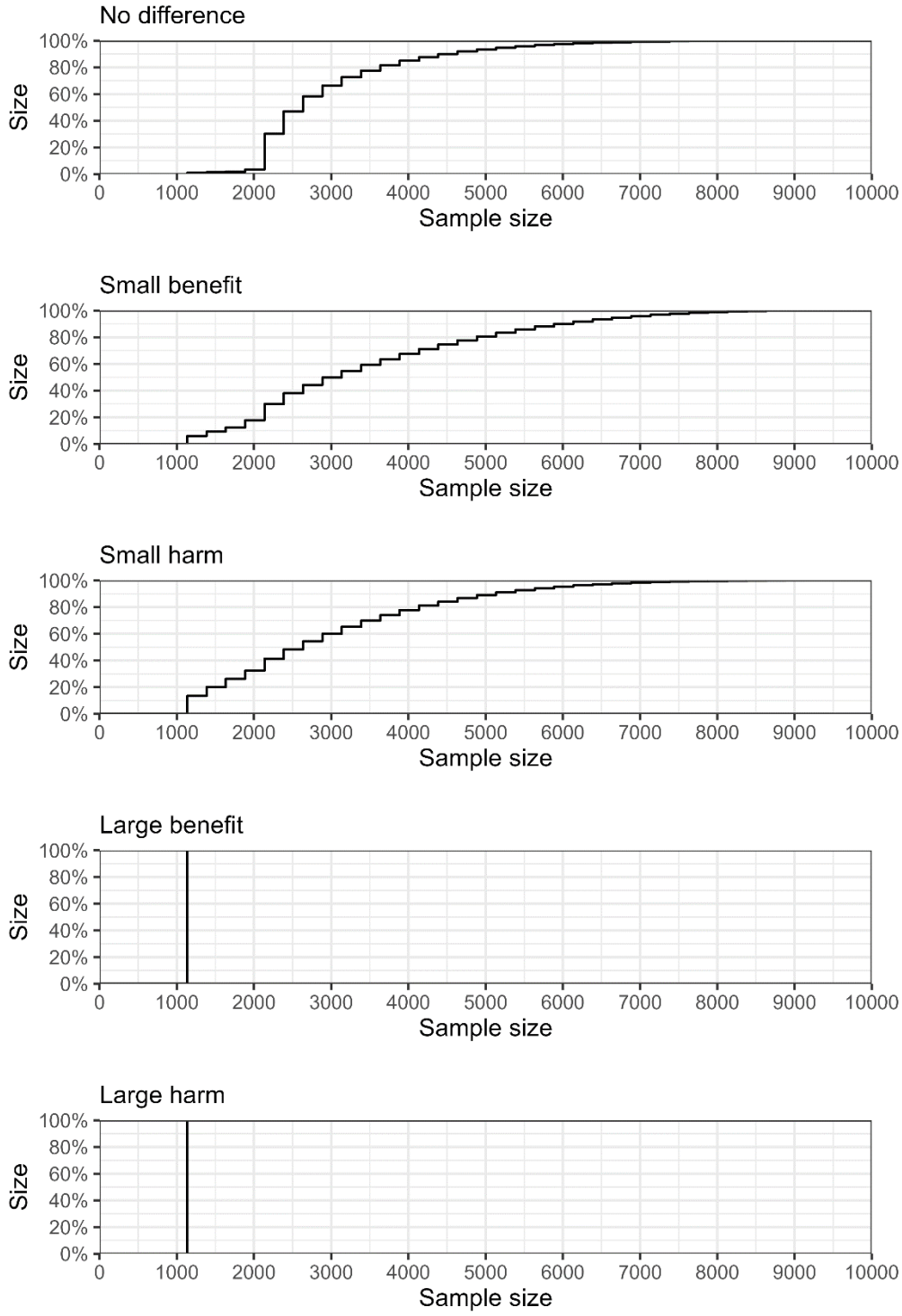
The probability of superiority in the scenario with no differences (i.e., the type 1 error rate) was 0.050. Importantly, the rounded stopping rules will be used during the actual conduct of the *INCEPT-Albumin* domain, so these results should be considered the primary.

Figure S3. Empirical cumulative distribution functions for sample sizes (difference mediated on both parts of the distribution)



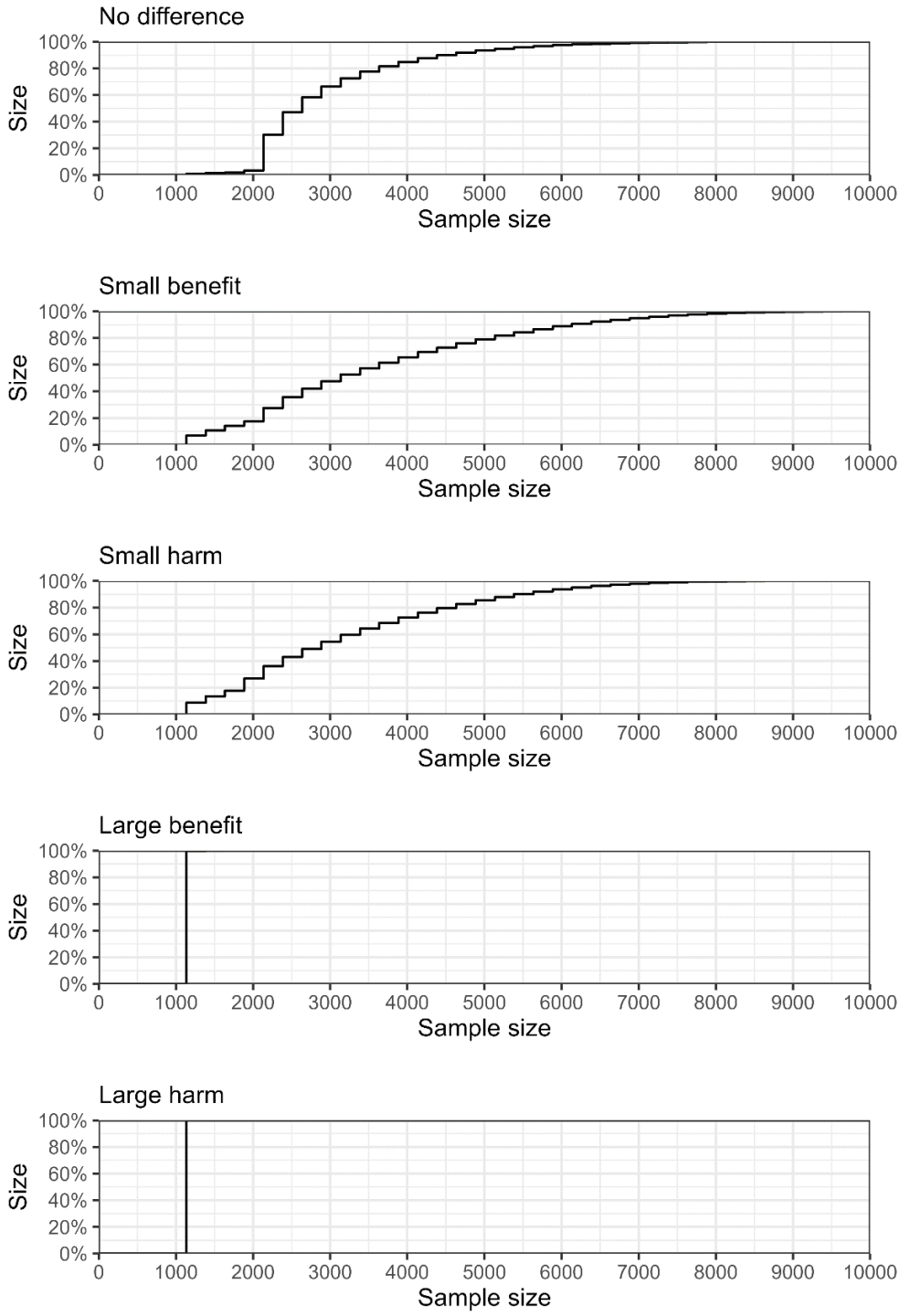
Empirical cumulative distribution functions for sample sizes in the primary trial design with rounded stopping rules under the clinical scenarios with differences mediated on both parts of the distribution. The values on the vertical axes correspond to the percentage of simulated trials ending with a sample size equal to or lower than the value on the horizontal axes.

Figure S4. Empirical cumulative distribution functions for sample sizes (difference mediated on the proportion of zeroes)



Empirical cumulative distribution functions for sample sizes in the primary trial design with rounded stopping rules under the clinical scenarios with differences mediated on the proportion of zeroes in the distribution. The values on the vertical axes correspond to the percentage of simulated trials ending with a sample size equal to or lower than the value on the horizontal axes.

Figure S5. Empirical cumulative distribution functions for sample sizes (difference mediated on the mean number of days in those with >0 days)



Empirical cumulative distribution functions for sample sizes in the primary trial design with rounded stopping rules under the clinical scenarios with differences mediated on the mean number of days in those with >0 days. The values on the vertical axes correspond to the percentage of simulated trials ending with a sample size equal to or lower than the value on the horizontal axes.

Third, a sensitivity analysis using fixed, equal (50%:50%) allocation probabilities was evaluated (**Table S7**). Results were largely similar to the primary results although sample sizes were slightly smaller in some scenarios. Mean sample sizes ranged from 1,137 to 3,507, maximum sample sizes ranged from 1,137 to 10,000, and probabilities of conclusiveness were approximately 100% across all scenarios.

Fourth, a sensitivity analysis using less restricted response-adaptive randomisation (minimum allocation probabilities of 35% instead of 40%) was evaluated (**Table S7**). Results were largely similar to the primary results although mean sample sizes were slightly larger in some scenarios and maximum sample sizes slightly smaller in some scenarios. Mean sample sizes ranged from 1,137 to 3,628, maximum sample sizes ranged from 1,137 to 10,000, and probabilities of conclusiveness were approximately 100% across all scenarios.

Fifth, a sensitivity analysis using less frequent adaptive analyses (first analysis after 1,000 participants, subsequent analyses after each additional 500 participants) was evaluated (**Table S9**). Results resembled those of the primary design, with some small differences in mean and maximum sample sizes in both directions across scenarios. Mean sample sizes ranged from 1,137 to 3,735, max sample sizes ranged from 1,137 to 10,000, and probabilities of conclusiveness were approximately 100% across all scenarios.

Sixth, a sensitivity analysis using more frequent adaptive analyses (first analysis after 1,000 participants, subsequent analyses after each additional 125 participants) was evaluated (**Table S10**). Results resembled those of the primary design, with some small differences in mean and maximum sample sizes in both directions across scenarios. Mean sample sizes ranged from 1,137 to 3,448, max sample sizes ranged from 1,260 to 10,000, and probabilities of conclusiveness were approximately 100% across all scenarios.

Seventh, a sensitivity analysis using a higher probability threshold for stopping for practical equivalence (>95% probability of the between-arm difference being <1 day in any analysis) was evaluated (**Table S11**). Sample sizes were either somewhat smaller or larger across scenarios, and the probabilities of conclusiveness were slightly lower in some scenarios due to less stopping for practical equivalence. Mean sample sizes ranged from 1,137 to 4,408, maximum sample sizes ranged from 1,137 to 10,000, and probabilities of conclusiveness ranged from 98.8% to approximately 100% across scenarios.

Eight, a sensitivity analysis of the primary domain design but assuming a slower inclusion rate (1 participant/day) was evaluated (**Table S12**). Sample sizes were somewhat smaller due to less lag in outcome data collection. Mean sample sizes ranged from 1,045 to 3,463, maximum sample sizes ranged from 1,295 to 10,000, and probabilities of conclusiveness were approximately 100% across all scenarios. The probability of superiority in the scenario with no differences (i.e., the type 1 error rate) was 0.050.

Ninth, a sensitivity analysis of the primary domain design but assuming a faster inclusion rate (5 participants/day) was evaluated (**Table S13**). Sample sizes were somewhat larger due to more lag in outcome data collection. Mean sample sizes ranged from 1,225 to 3,640, maximum sample sizes ranged from 1,225 to 10,000, and probabilities of conclusiveness were approximately 100% across

all scenarios. The probability of superiority in the scenario with no differences (i.e., the type 1 error rate) was 0.049.

Tenth, a sensitivity analysis of the primary domain design but assuming a higher proportion of zeroes in the reference distribution (45%, with the mean value in those with >0 days unchanged, leading to an overall mean of 12.92 days used to specify the reference distribution; actual overall means differ slightly due to rounding) was evaluated (**Table S14**). Compared to the primary results, there were no important differences, although maximum sample sizes were smaller in some scenarios. Mean sample sizes ranged from 1,137 to 3,616, maximum sample sizes ranged from 1,137 to 10,000, and probabilities of conclusiveness were approximately 100% across all scenarios. The probability of superiority in the scenario with no differences (i.e., the type 1 error rate) was 0.05.

Eleventh, a sensitivity analysis of the primary domain design but assuming a lower proportion of zeroes in the reference distribution (35%, with the mean value in those with >0 days unchanged, leading to an overall mean of 15.27 days used to specify the reference distribution; actual overall means differ slightly due to rounding) was evaluated (**Table S15**). Compared to the primary results, there were no important differences, although maximum sample sizes were smaller in some scenarios. Mean sample sizes ranged from 1,137 to 3,442, maximum sample sizes ranged from 1,386 to 9,885, and probabilities of conclusiveness were approximately 100% across all scenarios. The probability of superiority in the scenario with no differences (i.e., the type 1 error rate) was 0.050.

Twelfth, a sensitivity analysis of the primary domain design but assuming a lower mean number of days in those with >0 days in the reference distribution (21.5 days, with the proportion of zeroes unchanged, leading to an overall mean of 12.86 days used to specify the reference distribution; actual overall means differ slightly due to rounding) was evaluated (**Table S16**). Compared to the primary results, there were no important differences, although maximum sample sizes were smaller in some scenarios. Mean sample sizes ranged from 1,137 to 3,119, maximum sample sizes ranged from 1,137 to 9,387, and probabilities of conclusiveness were approximately 100% across all scenarios. The probability of superiority in the scenario with no differences (i.e., the type 1 error rate) was 0.047.

Finally, a sensitivity analysis of the primary domain design but assuming a higher mean number of days in those with >0 days in the reference distribution (25.5 days, with the proportion of zeroes unchanged, leading to an overall mean of 15.25 days used to specify the reference distribution; actual overall means differ slightly due to rounding) was evaluated (**Table S17**). Compared to the primary results, there were no important differences, although maximum sample sizes were slightly larger in some scenarios. Mean sample sizes ranged from 1,137 to 4,001, maximum sample sizes ranged from 1,386 to 10,000, and probabilities of conclusiveness ranged from 98.8% to approximately 100% across all scenarios. The probability of superiority in the scenario with no differences (i.e., the type 1 error rate) was 0.052, which was considered within the estimation uncertainty and acceptable.

To summarise, rounding stopping rules to 4 decimal places led to similar results. Fixed, equal allocation probabilities and less restricted response-adaptive randomisation did not majorly affect performance metrics, and we considered primary design choice to strike an adequate balance between the ethical arguments in favour of using response-adaptive randomisation and the practical arguments for fixed, equal allocation. Different adaptive analysis frequencies did not lead to major changes; the expected inclusion rate (3 participants/day) combined with analyses every 250 participants will lead to an analysis being conducted approximately every third month, which is considered suitable from a logistical point of view. Using a stricter threshold for practical equivalence led to slight negative effects on some performance metrics, and the 90% threshold was considered adequate. Of note, this threshold resembles thresholds used in other trials.[46,81] Different inclusion rates and variations of the reference distribution did not substantially affect performance, and type 1 error rates were very close to 5% in all cases.
In conclusion, we consider the final, primary *INCEPT-Albumin* domain design to have adequate performance metrics and to be either comparable or superior to the most obvious different design choices and robust across all sensitivity analyses of the assumptions used.

Table S5. Performance metrics of the final *INCEPT-Albumin* domain design without rounding of stopping thresholds

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19	9.5
Sample size – mean	1137 to 3555.2	2972.6	3444.3	3253.8	1137.3	1137	3468	2931.9	1137	1137	3555.2	3175.9	1137.8	1137
Sample size –SD	1.1 to 1788.4	1110.8	1737.9	1642.2	8.6	1.1	1710.5	1531.5	2.6	1.4	1788.4	1574.1	15.5	1.1
Sample size – median	1137 to 3135	2637	3135	2886	1137	1137	3135	2637	1137	1137	3135	2886	1137	1137
Sample size – P25	1137 to 2136	2136	2136	2136	1137	1137	2136	1635	1137	1137	2136	1887	1137	1137
Sample size – P75	1137 to 4635	3387	4635	4386	1137	1137	4635	3885	1137	1137	4635	4137	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1386 to 10000	10000	10000	9636	1635	1386	9885	9885	1635	1386	10000	9135	1887	1386
Total DAWOLS - mean	13467.7 to 53323.1	43021.4	51738	45675.1	19201.2	13596.5	51839.8	40896.9	19254.3	13467.7	53323.1	44628.5	19077.2	13647.9
Total DAWOLS – SD	382.9 to 26888.8	16086.1	26171.6	23123.4	474.7	403.2	25638.4	21452.8	410.8	431.8	26888.8	22177.9	521.6	382.9
Total DAWOLS – median	13465 to 47042	37739	46238	40469	19197	13595	45810.5	36399.5	19256	13465	47042	39999	19066	13647
Total DAWOLS – P25	13175 to 32357.8	31429	32032	29045.8	18893	13326	32008	23201.8	18979	13175	32357.8	26918	18760	13389
Total DAWOLS – P75	13759 to 70090.5	49020	68694.2	60566.5	19504	13867	68554.2	53830.2	19530	13759	70090.5	58581.2	19373	13906
Total DAWOLS – minimum	11734 to 17521	15117	15123	14103	17059	11819	15153	14096	17521	11734	15330	14359	17028	12055
Total DAWOLS – maximum	16936 to 150937	146168	150212	135478	28670	17288	148851	140619	28369	16936	150937	129367	32206	17613

Mean DAWOLS – mean	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12
Mean DAWOLS – SD	0.244 to 0.399	0.246	0.254	0.254	0.397	0.354	0.244	0.272	0.359	0.379	0.252	0.25	0.399	0.336
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.9	13.9	16.6	11.7	14.8	13.8	16.7	11.6	14.8	13.9	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.2	14.2	17.2	12.2	15.1	14.1	17.2	12.1	15.1	14.2	17	12.2
Mean DAWOLS – minimum	10.3 to 15.4	13.3	13.3	12.4	15	10.4	13.3	12.4	15.4	10.3	13.5	12.6	15	10.6
Mean DAWOLS – maximum	13.4 to 18.6	15.7	16.5	15.3	18.6	13.4	16.3	15.4	18.5	13.5	16.6	15.3	18.4	13.4
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0498 to 1	0.0498	0.718	0.754	1	1	0.593	0.883	1	1	0.68	0.723	1	1
Pr(equivalence)	0 to 0.95	0.95	0.282	0.246	0	0	0.407	0.117	0	0	0.32	0.277	0	0
Pr(max)	0 to 0.00004	0	0	0	0	0	0	0	0	0	0.00004	0	0	0
Pr(no albumin superior)	0 to 1	0.027	0.00023	0.754	0	1	0.0002	0.883	0	1	0.00029	0.723	0	1
Pr(albumin superior)	0 to 1	0.0229	0.718	0.00012	1	0	0.592	0.00001	1	0	0.68	0.00009	1	0
Pr(none superior)	0 to 0.95	0.95	0.282	0.246	0	0	0.407	0.117	0	0	0.32	0.277	0	0
RMSE (superiority only)	0.398 to 0.769	0.769	0.421	0.404	0.572	0.534	0.415	0.398	0.463	0.533	0.423	0.419	0.575	0.535
MAE (superiority only)	0.209 to 0.61	0.61	0.214	0.209	0.386	0.361	0.218	0.215	0.312	0.361	0.212	0.219	0.388	0.36
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.32 to 0.575	0.32	0.418	0.411	0.572	0.534	0.397	0.411	0.463	0.533	0.419	0.416	0.575	0.535
MAE (select best)	0.201 to 0.388	0.201	0.238	0.235	0.386	0.361	0.231	0.234	0.312	0.361	0.24	0.24	0.388	0.36
IDP (select best)	92.8 to 100	-	95.4	96	100	100	92.8	98.3	100	100	94.5	95.2	100	100

RMSE (select no albumin)	0.326 to 0.575	0.326	0.425	0.413	0.572	0.534	0.411	0.413	0.463	0.533	0.422	0.421	0.575	0.535
MAE (select no albumin)	0.208 to 0.388	0.208	0.249	0.235	0.386	0.361	0.252	0.234	0.312	0.361	0.248	0.242	0.388	0.36
IDP (select no albumin)	59.2 to 100	-	71.8	100	100	100	59.2	100	100	100	68	100	100	100

Calibrated stopping threshold for superiority: 0.995420.

Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S6. Performance metrics of the final *INCEPT-Albumin* domain design with stopping rules rounded to 4 decimals

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19	9.5
Sample size – mean	1137 to 3546.8	2971.1	3436.8	3246.7	1137.3	1137	3460.8	2925.5	1137	1137	3546.8	3168.8	1137.7	1137
Sample size –SD	1.1 to 1784	1109	1733.6	1638.1	8.6	1.1	1705.9	1528.1	2.6	1.4	1784	1570.3	15.3	1.1
Sample size – median	1137 to 3135	2637	3135	2886	1137	1137	3135	2637	1137	1137	3135	2886	1137	1137
Sample size – P25	1137 to 2136	2136	2136	2136	1137	1137	2136	1635	1137	1137	2136	1887	1137	1137
Sample size – P75	1137 to 4635	3387	4635	4386	1137	1137	4635	3885	1137	1137	4635	4137	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1386 to 10000	10000	10000	9636	1635	1386	9885	9885	1635	1386	10000	9135	1887	1386
Total DAWOLS - mean	13467.7 to 53196.9	42999.3	51624.7	45575.1	19201.2	13596.5	51731.8	40806.6	19254.3	13467.7	53196.9	44529.1	19076.9	13647.9
Total DAWOLS – SD	382.9 to 26822	16061.4	26106.2	23065.3	474.5	403.2	25569.4	21405	410.8	431.8	26822	22125.1	520.1	382.9
Total DAWOLS – median	13465 to 46991	37734.5	46134	40429	19197	13595	45651	36357	19256	13465	46991	39930	19066	13647
Total DAWOLS – P25	13175 to 32336.8	31426	32016	28990.8	18893	13326	31997	23160.8	18979	13175	32336.8	26888.8	18760	13389
Total DAWOLS – P75	13759 to 69961	49008	68463	60320.5	19504	13867	68425	53735.2	19530	13759	69961	58494.2	19373	13906
Total DAWOLS – minimum	11734 to 17521	15117	15123	14103	17059	11819	15153	14096	17521	11734	15330	14359	17028	12055

Total DAWOLS – maximum	16936 to 150937	146168	150212	135478	28670	17288	148851	140619	28369	16936	150937	129367	32206	17613
Mean DAWOLS – mean	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12
Mean DAWOLS – SD	0.244 to 0.399	0.247	0.254	0.254	0.397	0.354	0.244	0.272	0.359	0.379	0.252	0.25	0.399	0.336
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.9	13.9	16.6	11.7	14.8	13.8	16.7	11.6	14.8	13.9	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.2	14.2	17.2	12.2	15.1	14.1	17.2	12.1	15.1	14.2	17	12.2
Mean DAWOLS – minimum	10.3 to 15.4	13.3	13.3	12.4	15	10.4	13.3	12.4	15.4	10.3	13.5	12.6	15	10.6
Mean DAWOLS – maximum	13.4 to 18.6	15.7	16.5	15.3	18.6	13.4	16.3	15.4	18.5	13.5	16.6	15.3	18.4	13.4
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0503 to 1	0.0503	0.718	0.755	1	1	0.593	0.883	1	1	0.681	0.723	1	1
Pr(equivalence)	0 to 0.95	0.95	0.282	0.245	0	0	0.407	0.117	0	0	0.319	0.277	0	0
Pr(max)	0 to 0.00003	0	0	0	0	0	0	0	0	0	0.00003	0	0	0
Pr(no albumin superior)	0 to 1	0.0272	0.00023	0.754	0	1	0.0002	0.883	0	1	0.0003	0.723	0	1
Pr(albumin superior)	0 to 1	0.0231	0.718	0.00012	1	0	0.593	0.00001	1	0	0.681	0.00009	1	0
Pr(none superior)	0 to 0.95	0.95	0.282	0.245	0	0	0.407	0.117	0	0	0.319	0.277	0	0
RMSE (superiority only)	0.399 to 0.769	0.769	0.421	0.405	0.572	0.534	0.416	0.399	0.463	0.533	0.423	0.419	0.575	0.535
MAE (superiority only)	0.209 to 0.609	0.609	0.214	0.209	0.386	0.361	0.218	0.215	0.312	0.361	0.212	0.219	0.388	0.36
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.32 to 0.575	0.32	0.419	0.411	0.572	0.534	0.398	0.411	0.463	0.533	0.42	0.416	0.575	0.535
MAE (select best)	0.201 to 0.388	0.201	0.239	0.235	0.386	0.361	0.231	0.234	0.312	0.361	0.24	0.24	0.388	0.36

IDP (select best)	92.8 to 100	-	95.4	96	100	100	92.8	98.3	100	100	94.5	95.2	100	100
RMSE (select no albumin)	0.326 to 0.575	0.326	0.425	0.413	0.572	0.534	0.411	0.413	0.463	0.533	0.422	0.421	0.575	0.535
MAE (select no albumin)	0.208 to 0.388	0.208	0.25	0.236	0.386	0.361	0.252	0.234	0.312	0.361	0.248	0.242	0.388	0.36
IDP (select no albumin)	59.3 to 100	-	71.8	100	100	100	59.3	100	100	100	68.1	100	100	100

Stopping threshold for superiority: 0.9954 (primary calibrated stopping rule rounded to 4 decimals).

Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S7. Performance metrics of the *INCEPT-Albumin* domain design if using fixed, equal allocation

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19.1	9.5
Sample size – mean	1137 to 3507.3	2939.3	3403	3196.3	1137.2	1137	3421	2889.3	1137	1137	3507.3	3152.7	1137.7	1137
Sample size –SD	0 to 1743.5	1068.5	1694.5	1591.6	8	1.1	1657.9	1484.5	2.2	1.4	1743.5	1546.5	14.8	0
Sample size – median	1137 to 3135	2637	3135	2886	1137	1137	2886	2637	1137	1137	3135	2886	1137	1137
Sample size – P25	1137 to 2136	2136	2136	2136	1137	1137	2136	1635	1137	1137	2136	1887	1137	1137
Sample size – P75	1137 to 4635	3387	4386	4137	1137	1137	4386	3885	1137	1137	4635	4137	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1137 to 10000	9387	9885	9387	2136	1386	9885	9387	1386	1386	10000	9135	2136	1137
Total DAWOLS - mean	13465.9 to 52399.9	42542.2	50916.2	44674.3	19199.9	13594.6	50962.1	40106.3	19253.3	13465.9	52399.9	44124.1	19076.6	13644.4
Total DAWOLS – SD	382.2 to 26051.9	15473.8	25351.8	22255.2	470.5	402.7	24707.1	20622.2	411.2	429.3	26051.9	21634.7	516	382.2
Total DAWOLS – median	13465 to 46623	37646	45664	40001.5	19199	13592	44446.5	35954.5	19254	13465	46623	39679.5	19065	13645
Total DAWOLS – P25	13176 to 32273.8	31401	31963	28661	18891	13324	31925.8	23105	18978	13176	32273.8	26850	18759	13386
Total DAWOLS – P75	13756 to 69179	48680	66475	58270	19503	13864	66354	52728	19529	13756	69179	57947.2	19375	13903
Total DAWOLS – minimum	11557 to 17463	15143	15476	14104	17182	12001	15441	14274	17463	11557	15414	14307	17165	11996
Total DAWOLS – maximum	15261 to 153013	135458	148170	132946	35782	16934	146015	130274	24098	16665	153013	130882	35112	15261

Mean DAWOLS – mean	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	14.9	14	16.8	12
Mean DAWOLS – SD	0.245 to 0.4	0.249	0.253	0.253	0.398	0.354	0.245	0.269	0.36	0.377	0.251	0.25	0.4	0.336
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	14.9	14	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.8	13.8	16.6	11.7	14.7	13.7	16.7	11.6	14.8	13.8	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.1	14.1	17.2	12.2	15.1	14	17.2	12.1	15.1	14.2	17	12.2
Mean DAWOLS – minimum	10.2 to 15.4	13.3	13.6	12.4	15.1	10.6	13.6	12.6	15.4	10.2	13.6	12.6	15.1	10.6
Mean DAWOLS – maximum	13.4 to 18.6	15.7	16.5	15.4	18.6	13.5	16.3	15.3	18.5	13.5	16.5	15.6	18.4	13.4
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0499 to 1	0.0499	0.721	0.758	1	1	0.593	0.883	1	1	0.681	0.726	1	1
Pr(equivalence)	0 to 0.95	0.95	0.279	0.242	0	0	0.407	0.117	0	0	0.319	0.274	0	0
Pr(max)	0 to 0.00002	0	0	0	0	0	0	0	0	0	0.00002	0	0	0
Pr(no albumin superior)	0 to 1	0.0269	0.00017	0.757	0	1	0.00023	0.883	0	1	0.00024	0.726	0	1
Pr(albumin superior)	0 to 1	0.023	0.721	0.0001	1	0	0.593	0.00005	1	0	0.681	0.00012	1	0
Pr(none superior)	0 to 0.95	0.95	0.279	0.242	0	0	0.407	0.117	0	0	0.319	0.274	0	0
RMSE (superiority only)	0.409 to 0.827	0.827	0.429	0.414	0.57	0.532	0.425	0.409	0.462	0.531	0.43	0.424	0.576	0.535
MAE (superiority only)	0.219 to 0.678	0.678	0.224	0.219	0.384	0.36	0.23	0.223	0.312	0.359	0.221	0.225	0.39	0.361
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.337 to 0.576	0.337	0.431	0.423	0.57	0.532	0.41	0.425	0.462	0.531	0.432	0.427	0.576	0.535
MAE (select best)	0.214 to 0.39	0.214	0.254	0.249	0.384	0.36	0.246	0.245	0.312	0.359	0.256	0.255	0.39	0.361
IDP (select best)	92.8 to 100	-	95.4	96	100	100	92.8	98.2	100	100	94.5	95.3	100	100

RMSE (select no albumin)	0.569 to 0.746	0.569	0.746	0.651	0.616	0.684	0.683	0.667	0.571	0.682	0.727	0.651	0.576	0.686
MAE (select no albumin)	0.39 to 0.626	0.449	0.626	0.483	0.42	0.488	0.572	0.497	0.404	0.486	0.608	0.48	0.39	0.488
IDP (select no albumin)	59.3 to 100	-	72.1	100	100	100	59.3	100	100	100	68.1	100	100	100

Calibrated stopping threshold for superiority: 0.995371 (re-calibrated due to changed design choice).

Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S8. Performance metrics of the *INCEPT-Albumin* domain design if using less restricted response-adaptive randomisation

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19	9.5
Sample size – mean	1137 to 3628.5	3014.8	3515.3	3320.3	1137.2	1137	3563.1	3004.9	1137	1137	3628.5	3241.7	1137.7	1137
Sample size –SD	0 to 1854.6	1163	1809.3	1707.8	8.1	0.787	1796.4	1598.6	1.6	1.6	1854.6	1642.3	14.7	0
Sample size – median	1137 to 3135	2637	3135	2886	1137	1137	3135	2637	1137	1137	3135	2886	1137	1137
Sample size – P25	1137 to 2136	2136	2136	2136	1137	1137	2136	1635	1137	1137	2136	1887	1137	1137
Sample size – P75	1137 to 4887	3387	4635	4386	1137	1137	4635	3885	1137	1137	4887	4386	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1137 to 10000	10000	10000	10000	1887	1386	10000	10000	1386	1386	10000	9885	1887	1137
Total DAWOLS - mean	13467.2 to 54530.8	43633.9	52904.3	46713.1	19200.7	13595.4	53355.9	42030.7	19252.4	13467.2	54530.8	45652.6	19073.6	13645.9
Total DAWOLS – SD	380.8 to 27975	16846.2	27333.2	24135.3	471.1	404.1	27007.8	22493.1	408.9	431.8	27975	23224.3	518	380.8
Total DAWOLS – median	13466 to 47490	37940	46718	40841	19199	13595	46656	36812	19254	13466	47490	40348	19064	13648
Total DAWOLS – P25	13178 to 32552	31467	32127	29233	18893	13322	32095	23457	18977	13178	32552	27054	18758	13390
Total DAWOLS – P75	13759 to 72581.2	49437	69907	61791	19502	13868	70234.5	54904.2	19527	13759	72581.2	60611.2	19373	13904
Total DAWOLS – minimum	11585 to 17473	15145	15396	14424	17186	11932	15552	14144	17473	11585	15542	14513	17090	12079
Total DAWOLS – maximum	15576 to 152513	145371	152513	141807	32892	17046	151649	144071	24250	16836	152415	138672	32323	15576

Mean DAWOLS – mean	11.8 to 16.9	14.5	15	14.1	16.9	12	15	14	16.9	11.8	15	14.1	16.8	12
Mean DAWOLS – SD	0.245 to 0.399	0.247	0.255	0.255	0.396	0.355	0.245	0.273	0.359	0.379	0.254	0.253	0.399	0.335
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14.1	16.9	12	15	14	16.9	11.8	15	14.1	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.9	13.9	16.6	11.7	14.8	13.8	16.7	11.6	14.9	13.9	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.2	14.2	17.2	12.2	15.1	14.1	17.2	12.1	15.2	14.2	17	12.2
Mean DAWOLS – minimum	10.2 to 15.4	13.3	13.5	12.7	15.1	10.5	13.7	12.4	15.4	10.2	13.7	12.8	15	10.6
Mean DAWOLS – maximum	13.4 to 18.7	15.7	16.2	15.7	18.7	13.5	16.5	15.3	18.4	13.4	16.6	15.4	18.4	13.7
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0497 to 1	0.0497	0.716	0.754	1	1	0.593	0.882	1	1	0.679	0.721	1	1
Pr(equivalence)	0 to 0.95	0.95	0.284	0.246	0	0	0.407	0.118	0	0	0.321	0.279	0	0
Pr(max)	0 to 0.00016	0	0.00012	0.00003	0	0	0.00002	0.00004	0	0	0.00016	0	0	0
Pr(no albumin superior)	0 to 1	0.0273	0.00011	0.754	0	1	0.00026	0.882	0	1	0.00025	0.721	0	1
Pr(albumin superior)	0 to 1	0.0224	0.716	0.00018	1	0	0.592	0.00003	1	0	0.679	0.00012	1	0
Pr(none superior)	0 to 0.95	0.95	0.284	0.246	0	0	0.407	0.118	0	0	0.321	0.279	0	0
RMSE (superiority only)	0.386 to 0.764	0.764	0.411	0.386	0.571	0.534	0.404	0.403	0.46	0.534	0.422	0.393	0.576	0.532
MAE (superiority only)	0.197 to 0.598	0.598	0.208	0.197	0.387	0.361	0.205	0.212	0.309	0.361	0.211	0.199	0.389	0.359
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.319 to 0.576	0.319	0.41	0.397	0.571	0.534	0.39	0.412	0.46	0.534	0.414	0.403	0.576	0.532
MAE (select best)	0.199 to 0.389	0.199	0.231	0.224	0.387	0.361	0.221	0.228	0.309	0.361	0.233	0.232	0.389	0.359
IDP (select best)	92.7 to 100	-	95.3	96	100	100	92.7	98.2	100	100	94.5	95.3	100	100

RMSE (select no albumin)	0.325 to 0.576	0.325	0.421	0.404	0.571	0.534	0.407	0.413	0.46	0.534	0.425	0.412	0.576	0.532
MAE (select no albumin)	0.207 to 0.389	0.207	0.249	0.226	0.387	0.361	0.247	0.228	0.309	0.361	0.251	0.234	0.389	0.359
IDP (select no albumin)	59.2 to 100	-	71.6	100	100	100	59.2	100	100	100	67.9	100	100	100

Calibrated stopping threshold for superiority: 0.995536 (re-calibrated due to changed design choice).

Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S9. Performance metrics of the *INCEPT-Albumin* domain design with less frequent adaptive analyses

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19	9.5
Sample size – mean	1137 to 3734.9	3148.6	3621.1	3425.9	1137.4	1137	3668.7	3083.4	1137	1137	3734.9	3379.9	1138	1137
Sample size –SD	0 to 1864.2	1194.4	1807.6	1708.5	14.5	1.6	1786.8	1593.7	4.2	2.7	1864.2	1655.6	22.7	0
Sample size – median	1137 to 3135	2637	3135	3135	1137	1137	3135	2637	1137	1137	3135	3135	1137	1137
Sample size – P25	1137 to 2136	2136	2136	2136	1137	1137	2136	1635	1137	1137	2136	2136	1137	1137
Sample size – P75	1137 to 5136	3636	4635	4635	1137	1137	4635	4137	1137	1137	5136	4635	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1137 to 10000	10000	10000	10000	2136	1635	10000	10000	1635	1635	10000	9636	1635	1137
Total DAWOLS - mean	13466.7 to 56024.2	45570.8	54396.2	48098	19200.2	13595.1	54844.4	43017.6	19252.8	13466.7	56024.2	47504	19083	13643.5
Total DAWOLS – SD	383.2 to 28025.8	17295.8	27224.1	24060.5	514.6	403.6	26787.5	22324.8	416.8	432.1	28025.8	23328	592.9	383.2
Total DAWOLS – median	13466 to 47963.5	38717	47532.5	43815	19196	13596	47336	37193.5	19253	13466	47963.5	43690.5	19069	13643
Total DAWOLS – P25	13174 to 32530	31501	32280	29840.8	18888	13322	32290.8	23441	18977	13174	32530	29864	18761	13385
Total DAWOLS – P75	13755 to 75903	52679	70359	64599	19499	13868	70505.2	57415.2	19530	13755	75903	64169.2	19374	13903
Total DAWOLS – minimum	11189 to 17431	15021	15106	14280	17147	11883	15316	13958	17431	11189	15297	14507	17037	11529
Total DAWOLS – maximum	15460 to 152839	145648	152839	141201	36561	20127	149311	140326	28622	20458	152600	137883	28908	15460

Mean DAWOLS – mean	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12
Mean DAWOLS – SD	0.239 to 0.398	0.241	0.249	0.249	0.398	0.355	0.239	0.265	0.361	0.379	0.248	0.244	0.398	0.337
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14.1	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.9	13.9	16.6	11.7	14.8	13.8	16.7	11.6	14.8	13.9	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.2	14.2	17.1	12.2	15.1	14.1	17.2	12.1	15.1	14.2	17	12.2
Mean DAWOLS – minimum	9.8 to 15.3	13.2	13.3	12.6	15.1	10.5	13.5	12.3	15.3	9.8	13.5	12.7	15	10.1
Mean DAWOLS – maximum	13.5 to 18.6	15.7	16.5	15.3	18.6	13.5	16.4	15.3	18.6	13.6	16.2	15.5	18.5	13.6
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0497 to 1	0.0497	0.732	0.774	1	1	0.612	0.894	1	1	0.695	0.744	1	1
Pr(equivalence)	0 to 0.95	0.95	0.268	0.226	0	0	0.388	0.106	0	0	0.305	0.256	0	0
Pr(max)	0 to 0.00003	0	0	0	0	0	0	0	0	0	0.00003	0	0	0
Pr(no albumin superior)	0 to 1	0.0272	0.00011	0.774	0	1	0.00034	0.894	0	1	0.0002	0.744	0	1
Pr(albumin superior)	0 to 1	0.0226	0.732	0.00007	1	0	0.611	0.00007	1	0	0.695	0.00015	1	0
Pr(none superior)	0 to 0.95	0.95	0.268	0.226	0	0	0.388	0.106	0	0	0.305	0.256	0	0
RMSE (superiority only)	0.392 to 0.753	0.753	0.403	0.398	0.57	0.532	0.4	0.392	0.463	0.534	0.421	0.392	0.576	0.535
MAE (superiority only)	0.2 to 0.592	0.592	0.203	0.205	0.385	0.36	0.205	0.209	0.312	0.361	0.212	0.2	0.39	0.362
IDP (superiority only)	99.9 to 100	-	100	100	100	100	99.9	100	100	100	100	100	100	100
RMSE (select best)	0.314 to 0.576	0.314	0.405	0.402	0.57	0.532	0.388	0.403	0.463	0.534	0.412	0.4	0.576	0.535
MAE (select best)	0.197 to 0.39	0.197	0.229	0.226	0.385	0.36	0.223	0.225	0.312	0.361	0.232	0.229	0.39	0.362
IDP (select best)	93.5 to 100	-	95.6	96.7	100	100	93.5	98.4	100	100	95	96.3	100	100
RMSE (select no albumin)	0.318 to 0.576	0.318	0.406	0.404	0.57	0.532	0.402	0.404	0.463	0.534	0.413	0.406	0.576	0.535

MAE (select no albumin)	0.202 to 0.39	0.202	0.232	0.227	0.385	0.36	0.243	0.225	0.312	0.361	0.236	0.231	0.39	0.362
IDP (select no albumin)	61.1 to 100	-	73.2	100	100	100	61.1	100	100	100	69.5	100	100	100

Calibrated stopping threshold for superiority: 0.994614 (re-calibrated due to changed design choice).

Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S10. Performance metrics of the *INCEPT-Albumin* domain design with more frequent adaptive analyses

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19.1	9.5
Sample size – mean	1137 to 3447.5	2843.8	3326.3	3148.5	1137.2	1137	3352.8	2854.9	1137	1137	3447.5	3083.2	1137.5	1137
Sample size –SD	0.389 to 1748.9	1077.1	1697.1	1598.3	5.9	0.55	1677.1	1496.4	1	0.55	1748.9	1541.3	10.9	0.389
Sample size – median	1137 to 3012	2385	2886	2760	1137	1137	2886	2511	1137	1137	3012	2637	1137	1137
Sample size – P25	1137 to 2136	2136	2010	2010	1137	1137	2010	1635	1137	1137	2136	1887	1137	1137
Sample size – P75	1137 to 4512	3261	4386	4137	1137	1137	4386	3762	1137	1137	4512	4011	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1260 to 10000	9636	10000	9762	1512	1260	9762	9636	1260	1260	10000	9135	1635	1260
Total DAWOLS - mean	13467.4 to 51702.4	41158.9	49960.5	44193.9	19199.6	13593.8	50112.1	39823.7	19254.7	13467.4	51702.4	43331.4	19069.7	13645.9
Total DAWOLS – SD	380.6 to 26292.8	15601.1	25559.1	22511.5	460.1	402.3	25143.9	20966.5	408.8	429.6	26292.8	21721.1	488.4	380.6
Total DAWOLS – median	13467 to 45165	35413.5	43558.5	38737.5	19198	13593	43165.5	34826	19256	13467	45165	37855	19066	13646
Total DAWOLS – P25	13177 to 31966	30622	30829.8	27451	18895	13322	30675.8	22969	18977	13177	31966	26774	18757	13390
Total DAWOLS – P75	13757 to 68143.2	46637.2	65820.2	58123	19502	13865	65887.2	52112	19532	13757	68143.2	56891.5	19371	13902
Total DAWOLS – minimum	11353 to 17518	15051	15227	14362	17252	11930	15233	14050	17518	11353	15149	14364	16855	12090
Total DAWOLS – maximum	15201 to 152717	138582	152575	137385	25912	15304	146215	133710	22300	15268	152717	128019	28563	15201

Mean DAWOLS – mean	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12
Mean DAWOLS – SD	0.249 to 0.4	0.254	0.258	0.257	0.396	0.354	0.249	0.275	0.359	0.378	0.256	0.254	0.4	0.335
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14.1	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.9	13.9	16.6	11.7	14.8	13.8	16.7	11.6	14.8	13.9	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.2	14.2	17.2	12.2	15.1	14.1	17.2	12.1	15.2	14.2	17	12.2
Mean DAWOLS – minimum	10 to 15.4	13.2	13.4	12.6	15.2	10.5	13.4	12.4	15.4	10	13.3	12.6	14.8	10.6
Mean DAWOLS – maximum	13.4 to 18.7	15.7	16.4	15.5	18.5	13.5	16.3	15.3	18.7	13.4	16.4	15.7	18.4	13.4
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0499 to 1	0.0499	0.705	0.743	1	1	0.582	0.873	1	1	0.667	0.709	1	1
Pr(equivalence)	0 to 0.95	0.95	0.295	0.257	0	0	0.418	0.127	0	0	0.333	0.291	0	0
Pr(max)	0 to 0.00002	0	0.00002	0	0	0	0	0	0	0	0	0	0	0
Pr(no albumin superior)	0 to 1	0.027	0.00011	0.743	0	1	0.0003	0.873	0	1	0.00021	0.709	0	1
Pr(albumin superior)	0 to 1	0.0229	0.704	0.00005	1	0	0.582	0.00004	1	0	0.667	0.00007	1	0
Pr(none superior)	0 to 0.95	0.95	0.295	0.257	0	0	0.418	0.127	0	0	0.333	0.291	0	0
RMSE (superiority only)	0.405 to 0.772	0.772	0.426	0.405	0.572	0.533	0.41	0.413	0.46	0.535	0.445	0.41	0.576	0.531
MAE (superiority only)	0.21 to 0.618	0.618	0.221	0.21	0.386	0.361	0.212	0.222	0.311	0.36	0.229	0.214	0.389	0.359
IDP (superiority only)	99.9 to 100	-	100	100	100	100	99.9	100	100	100	100	100	100	100
RMSE (select best)	0.322 to 0.576	0.322	0.424	0.413	0.572	0.533	0.4	0.423	0.46	0.535	0.429	0.417	0.576	0.531
MAE (select best)	0.202 to 0.389	0.202	0.246	0.237	0.386	0.361	0.234	0.241	0.311	0.36	0.245	0.245	0.389	0.359

IDP (select best)	92.2 to 100	-	94.8	95.7	100	100	92.2	97.9	100	100	94.1	95	100	100
RMSE (select no albumin)	0.332 to 0.576	0.332	0.432	0.416	0.572	0.533	0.408	0.424	0.46	0.535	0.433	0.424	0.576	0.531
MAE (select no albumin)	0.213 to 0.389	0.213	0.26	0.238	0.386	0.361	0.248	0.241	0.311	0.36	0.254	0.247	0.389	0.359
IDP (select no albumin)	58.2 to 100	-	70.4	100	100	100	58.2	100	100	100	66.7	100	100	100

Calibrated stopping threshold for superiority: 0.996034 (re-calibrated due to changed design choice).

Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S11. Performance metrics of the *INCEPT-Albumin* domain design with higher equivalence stopping probability threshold

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19.1	9.5
Sample size – mean	1137 to 4408.1	3966.7	4188.6	3897.5	1137.3	1137	4408.1	3332.8	1137	1137	4385.1	3863.4	1137.8	1137
Sample size –SD	0 to 2274.4	1410.5	2207.7	2080.6	9.9	0	2216.7	1865.8	2.4	2.2	2274.4	2011.2	15.6	1.8
Sample size – median	1137 to 3885	3387	3885	3387	1137	1137	3885	2886	1137	1137	3885	3387	1137	1137
Sample size – P25	1137 to 2886	2886	2385	2136	1137	1137	2886	1887	1137	1137	2637	2385	1137	1137
Sample size – P75	1137 to 5886	4635	5637	5136	1137	1137	5886	4386	1137	1137	5886	5136	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1137 to 10000	10000	10000	10000	1887	1137	10000	10000	1386	1386	10000	10000	1887	1635
Total DAWOLS - mean	13468.2 to 65915.8	57407.7	62942.6	54734.1	19200.1	13593.3	65915.8	46505.6	19254.9	13468.2	65791.3	54314	19076.9	13646.1
Total DAWOLS – SD	382.6 to 34178	20427.1	33233.5	29286.9	480.9	401.3	33222.5	26122.4	414.1	432	34178	28325.5	521.8	382.6
Total DAWOLS – median	13467 to 59090	49910	57142	48777.5	19195	13594	59090	40751.5	19255	13467	59046	48513.5	19065	13645
Total DAWOLS – P25	13178 to 42826	42826	37055.8	31342.8	18890	13324	42215	25706	18975	13178	40253.8	33220	18760	13389
Total DAWOLS – P75	13758 to 88645	65822.2	84638	73153.8	19499	13863.2	88323	61740.2	19534	13758	88645	72417.2	19373	13903
Total DAWOLS – minimum	11543 to 17638	14903	15397	14310	17341	11716	15244	13980	17638	11543	15185	14554	16883	11931
Total DAWOLS – maximum	15447 to 155019	148500	154871	143999	31423	15447	153598	143236	24139	17187	155019	144664	31717	19775

Mean DAWOLS – mean	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14.1	16.8	12
Mean DAWOLS – SD	0.214 to 0.398	0.214	0.237	0.239	0.396	0.353	0.224	0.262	0.362	0.379	0.234	0.234	0.398	0.336
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14.1	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.9	13.9	16.6	11.7	14.8	13.8	16.7	11.6	14.9	13.9	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.2	14.2	17.1	12.2	15.1	14.1	17.2	12.1	15.1	14.2	17	12.2
Mean DAWOLS – minimum	10.2 to 15.5	13.1	13.5	12.6	15.3	10.3	13.4	12.3	15.5	10.2	13.4	12.8	14.8	10.5
Mean DAWOLS – maximum	13.6 to 18.5	15.6	16.2	15.5	18.5	13.6	16.2	15.4	18.5	13.7	16.3	15.4	18.4	13.6
Pr(conclusive)	0.988 to 1	0.999	0.993	0.997	1	1	0.992	0.999	1	1	0.988	0.999	1	1
Pr(superiority)	0.0498 to 1	0.0498	0.822	0.855	1	1	0.703	0.948	1	1	0.786	0.83	1	1
Pr(equivalence)	0 to 0.949	0.949	0.171	0.142	0	0	0.29	0.0506	0	0	0.202	0.169	0	0
Pr(max)	0 to 0.0121	0.00138	0.0072	0.00338	0	0	0.00752	0.00133	0	0	0.0121	0.00119	0	0
Pr(no albumin superior)	0 to 1	0.0272	0.00005	0.855	0	1	0.00013	0.948	0	1	0.00018	0.83	0	1
Pr(albumin superior)	0 to 1	0.0227	0.822	0.0001	1	0	0.702	0	1	0	0.786	0.00009	1	0
Pr(none superior)	0 to 0.95	0.95	0.178	0.145	0	0	0.297	0.0519	0	0	0.214	0.17	0	0
RMSE (superiority only)	0.375 to 0.752	0.752	0.39	0.383	0.571	0.531	0.375	0.39	0.462	0.535	0.405	0.394	0.577	0.534
MAE (superiority only)	0.183 to 0.582	0.582	0.19	0.19	0.385	0.359	0.183	0.204	0.312	0.361	0.194	0.195	0.391	0.359
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.287 to 0.577	0.287	0.39	0.386	0.571	0.531	0.368	0.395	0.462	0.535	0.397	0.392	0.577	0.534
MAE (select best)	0.174 to 0.391	0.174	0.209	0.207	0.385	0.359	0.201	0.213	0.312	0.361	0.211	0.212	0.391	0.359
IDP (select best)	95.6 to 100	-	97.6	98	100	100	95.6	99.3	100	100	96.9	97.6	100	100

RMSE (select no albumin)	0.292 to 0.577	0.292	0.396	0.387	0.571	0.531	0.382	0.395	0.462	0.535	0.401	0.395	0.577	0.534
MAE (select no albumin)	0.181 to 0.391	0.181	0.218	0.207	0.385	0.359	0.221	0.213	0.312	0.361	0.22	0.213	0.391	0.359
IDP (select no albumin)	70.2 to 100	-	82.2	100	100	100	70.2	100	100	100	78.6	100	100	100

Calibrated stopping threshold for superiority: 0.996138 (re-calibrated due to changed design choice).

Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S12. Performance metrics of the primary *INCEPT-Albumin* domain design with slower assumed inclusion

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19.1	9.5
Sample size – mean	1045 to 3462.6	2889.1	3359.6	3165.9	1045.2	1045	3390.4	2849.1	1045	1045	3462.6	3094.1	1045.7	1045
Sample size –SD	0.791 to 1781.5	1113.2	1741	1642.9	8.4	1.8	1705.8	1532.3	1.1	1.6	1781.5	1578.9	13.7	0.791
Sample size – median	1045 to 3045	2545	3045	2795	1045	1045	3045	2545	1045	1045	3045	2795	1045	1045
Sample size – P25	1045 to 2045	2045	2045	2045	1045	1045	2045	1545	1045	1045	2045	1795	1045	1045
Sample size – P75	1045 to 4545	3295	4545	4295	1045	1045	4545	3795	1045	1045	4545	4045	1045	1045
Sample size – minimum	1045 to 1045	1045	1045	1045	1045	1045	1045	1045	1045	1045	1045	1045	1045	1045
Sample size – maximum	1295 to 10000	10000	10000	9795	1545	1295	9795	10000	1295	1295	10000	9295	1545	1295
Total DAWOLS - mean	12377.8 to 51937	41811.9	50470.3	44450.3	17647.5	12492.5	50682.3	39750.3	17695	12377.8	51937	43485.1	17532.1	12542.5
Total DAWOLS – SD	365.5 to 26785.5	16122	26220.9	23133.8	455.2	385.4	25574	21462.8	394.6	413.8	26785.5	22247.2	488.5	365.5
Total DAWOLS – median	12377 to 45599	36538	44921.5	39244	17642	12490	44876.5	35203	17696	12377	45599	38800.5	17523	12542
Total DAWOLS – P25	12099 to 31025	30114.8	30687	27890	17353	12232	30681	22037.8	17430	12099	31025	25668.8	17226	12295
Total DAWOLS – P75	12655 to 68751.2	47728	67597.2	59154	17938	12753	67473.2	52652	17963	12655	68751.2	57279.2	17818	12789
Total DAWOLS – minimum	10561 to 15915	13889	14057	13087	15788	10837	14042	12797	15915	10561	14017	13091	15675	11115
Total DAWOLS – maximum	15387 to 151543	144912	151455	137433	26770	15497	147716	138388	22384	15387	151543	130509	26917	15492

Mean DAWOLS – mean	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12
Mean DAWOLS – SD	0.249 to 0.415	0.251	0.259	0.259	0.414	0.368	0.249	0.278	0.377	0.396	0.257	0.257	0.415	0.35
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14.1	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.9	13.9	16.6	11.7	14.8	13.8	16.7	11.6	14.8	13.9	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.2	14.2	17.2	12.2	15.1	14.1	17.2	12.1	15.2	14.2	17	12.2
Mean DAWOLS – minimum	10.1 to 15.2	13.3	13.5	12.5	15.1	10.4	13.4	12.2	15.2	10.1	13.4	12.5	15	10.6
Mean DAWOLS – maximum	13.6 to 18.7	15.8	16.6	15.4	18.7	13.6	16.3	15.6	18.5	13.8	16.7	15.8	18.5	13.7
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0503 to 1	0.0503	0.717	0.756	1	1	0.593	0.881	1	1	0.678	0.725	1	1
Pr(equivalence)	0 to 0.95	0.95	0.283	0.244	0	0	0.407	0.119	0	0	0.322	0.275	0	0
Pr(max)	0 to 0.00001	0.00001	0	0	0	0	0	0	0	0	0.00001	0	0	0
Pr(no albumin superior)	0 to 1	0.027	0.00014	0.756	0	1	0.00027	0.881	0	1	0.00027	0.725	0	1
Pr(albumin superior)	0 to 1	0.0233	0.717	0.00011	1	0	0.593	0.00001	1	0	0.678	0.00016	1	0
Pr(none superior)	0 to 0.95	0.95	0.283	0.244	0	0	0.407	0.119	0	0	0.322	0.275	0	0
RMSE (superiority only)	0.42 to 0.805	0.805	0.432	0.424	0.595	0.556	0.422	0.42	0.483	0.557	0.454	0.439	0.602	0.556
MAE (superiority only)	0.215 to 0.633	0.633	0.217	0.215	0.404	0.375	0.218	0.22	0.327	0.377	0.226	0.227	0.407	0.375
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.327 to 0.602	0.327	0.43	0.427	0.595	0.556	0.407	0.431	0.483	0.557	0.438	0.433	0.602	0.556
MAE (select best)	0.203 to 0.407	0.203	0.243	0.24	0.404	0.375	0.236	0.24	0.327	0.377	0.247	0.248	0.407	0.375
IDP (select best)	92.8 to 100	-	95.3	96	100	100	92.8	98.1	100	100	94.4	95.3	100	100

RMSE (select no albumin)	0.332 to 0.602	0.332	0.436	0.428	0.595	0.556	0.421	0.432	0.483	0.557	0.442	0.439	0.602	0.556
MAE (select no albumin)	0.21 to 0.407	0.21	0.255	0.24	0.404	0.375	0.258	0.24	0.327	0.377	0.256	0.25	0.407	0.375
IDP (select no albumin)	59.3 to 100	-	71.7	100	100	100	59.3	100	100	100	67.8	100	100	100

Calibrated stopping threshold for superiority: 0.995420 (re-used from the simulations of the primary design with the primary assumptions without re-calibration).
Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S13. Performance metrics of the primary *INCEPT-Albumin* domain design with faster assumed inclusion

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	14.5 to 14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
Mean number of days (albumin arm)	9.2 to 19.4	14.5	15.4	13.5	19.3	9.4	15.3	13.3	19.4	9.2	15.4	13.5	19.1	9.5
Sample size – mean	1225 to 3640	3062.2	3518.4	3334	1225.3	1225	3556.4	3025.2	1225	1225	3640	3261.1	1225.7	1225
Sample size –SD	0 to 1783.9	1111.5	1735.8	1639.5	9	0.791	1708.8	1538.1	1.6	1.4	1783.9	1575.1	13.9	0
Sample size – median	1225 to 3225	2725	3225	2975	1225	1225	3225	2725	1225	1225	3225	2975	1225	1225
Sample size – P25	1225 to 2225	2225	2225	2225	1225	1225	2225	1725	1225	1225	2225	1975	1225	1225
Sample size – P75	1225 to 4725	3475	4725	4475	1225	1225	4725	3975	1225	1225	4725	4225	1225	1225
Sample size – minimum	1225 to 1225	1225	1225	1225	1225	1225	1225	1225	1225	1225	1225	1225	1225	1225
Sample size – maximum	1225 to 10000	9975	10000	9975	1725	1475	10000	9975	1475	1475	10000	9225	1975	1225
Total DAWOLS - mean	14510 to 54591.4	44315.6	52842.1	46796.9	20685.6	14646	53155.2	42194.7	20745	14510	54591.4	45823.3	20549.5	14702.7
Total DAWOLS – SD	396.1 to 26820.6	16100.6	26136.3	23095.4	493.1	417.6	25614.2	21549.1	427.2	447.5	26820.6	22197.2	524.4	396.1
Total DAWOLS – median	14510 to 48323.5	39045	47277.5	41623	20681	14646	47189	37616	20745	14510	48323.5	41179	20540	14703
Total DAWOLS – P25	14209 to 33704	32722	33306	30187	20365	14364	33327.8	24446.8	20459	14209	33704	28154	20222	14436
Total DAWOLS – P75	14812 to 71382.2	50296	69130.5	61613.5	20997	14928	69839	55199.2	21033	14812	71382.2	59665	20857	14971
Total DAWOLS – minimum	12626 to 18834	16355	16673	15554	18313	12628	16694	15078	18834	12626	16551	15621	18468	12982
Total DAWOLS – maximum	16448 to 152997	145092	152230	137940	29907	17172	150292	138997	25532	18295	152997	131379	32485	16448
Mean DAWOLS	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12

– mean														
Mean DAWOLS – SD	0.239 to 0.384	0.243	0.249	0.248	0.382	0.341	0.239	0.265	0.348	0.365	0.248	0.245	0.384	0.323
Mean DAWOLS – median	11.8 to 16.9	14.5	15	14	16.9	12	14.9	13.9	16.9	11.8	15	14	16.8	12
Mean DAWOLS – P25	11.6 to 16.7	14.3	14.9	13.9	16.6	11.7	14.8	13.8	16.7	11.6	14.8	13.9	16.5	11.8
Mean DAWOLS – P75	12.1 to 17.2	14.6	15.2	14.2	17.1	12.2	15.1	14.1	17.2	12.1	15.1	14.2	17	12.2
Mean DAWOLS – minimum	10.3 to 15.4	13.4	13.6	12.7	14.9	10.3	13.6	12.3	15.4	10.3	13.5	12.8	15.1	10.6
Mean DAWOLS – maximum	13.3 to 18.7	15.5	16.4	15.4	18.7	13.3	16.1	15.3	18.4	13.4	16.3	15.2	18.6	13.4
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0493 to 1	0.0493	0.718	0.755	1	1	0.591	0.882	1	1	0.679	0.72	1	1
Pr(equivalence)	0 to 0.951	0.951	0.282	0.245	0	0	0.409	0.118	0	0	0.321	0.28	0	0
Pr(max)	0 to 0.00001	0	0.00001	0	0	0	0.00001	0	0	0	0.00001	0	0	0
Pr(no albumin superior)	0 to 1	0.0262	0.00015	0.755	0	1	0.00013	0.882	0	1	0.00017	0.72	0	1
Pr(albumin superior)	0 to 1	0.0231	0.718	0.00006	1	0	0.591	0.00004	1	0	0.678	0.00005	1	0
Pr(none superior)	0 to 0.951	0.951	0.282	0.245	0	0	0.409	0.118	0	0	0.321	0.28	0	0
RMSE (superiority only)	0.389 to 0.744	0.744	0.403	0.393	0.551	0.512	0.394	0.389	0.444	0.514	0.42	0.408	0.557	0.512
MAE (superiority only)	0.207 to 0.603	0.603	0.21	0.207	0.372	0.345	0.207	0.211	0.3	0.349	0.221	0.217	0.377	0.345
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.316 to 0.557	0.316	0.403	0.399	0.551	0.512	0.384	0.401	0.444	0.514	0.409	0.404	0.557	0.512
MAE (select best)	0.202 to 0.377	0.202	0.233	0.229	0.372	0.345	0.225	0.228	0.3	0.349	0.237	0.235	0.377	0.345
IDP (select best)	92.7 to 100	-	95.4	96	100	100	92.7	98.3	100	100	94.5	95.3	100	100
RMSE (select no albumin)	0.321 to 0.557	0.321	0.409	0.401	0.551	0.512	0.398	0.402	0.444	0.514	0.413	0.409	0.557	0.512
MAE (select no albumin)	0.207 to 0.377	0.207	0.243	0.23	0.372	0.345	0.245	0.228	0.3	0.349	0.246	0.237	0.377	0.345

IDP (select no albumin)	59.1 to 100	-	71.8	100	100	100	59.1	100	100	100	67.8	100	100	100

Calibrated stopping threshold for superiority: 0.995420 (re-used from the simulations of the primary design with the primary assumptions without re-calibration).
Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S14. Performance metrics of the primary *INCEPT-Albumin* domain design with higher proportion of zeroes

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	13.3 to 13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3
Mean number of days (albumin arm)	8.1 to 18.2	13.3	14.3	12.3	18.1	8.3	14.2	12.1	18.2	8.1	14.2	12.3	17.9	8.3
Sample size – mean	1137 to 3616.1	3007.8	3495.8	3275.9	1137.4	1137	3521.5	2995	1137	1137	3616.1	3199.9	1137.7	1137
Sample size –SD	0 to 1831.4	1127.4	1775.5	1656.1	10.6	0.787	1741.7	1561.5	2.8	1.4	1831.4	1591.4	15	0
Sample size – median	1137 to 3135	2637	3135	2886	1137	1137	3135	2637	1137	1137	3135	2886	1137	1137
Sample size – P25	1137 to 2136	2136	2136	2136	1137	1137	2136	1635	1137	1137	2136	1887	1137	1137
Sample size – P75	1137 to 4887	3387	4635	4386	1137	1137	4635	3885	1137	1137	4887	4137	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1137 to 10000	10000	10000	10000	1887	1386	10000	9636	1386	1386	10000	9387	1887	1137
Total DAWOLS - mean	12155.5 to 50029	40037.9	48447.9	42185.1	17887.2	12270.2	48575.5	38320	17942.3	12155.5	50029	41248.4	17772.9	12323.2
Total DAWOLS – SD	379.7 to 25402.9	15026.3	24674.2	21401.1	486.8	397.3	24104.3	20067.5	425.7	426.1	25402.9	20578.2	516.7	379.7
Total DAWOLS – median	12155 to 43672.5	34952	43030	37193	17881	12270	42826	33777	17943	12155	43672.5	36807	17763	12322
Total DAWOLS – P25	11868 to 30238.5	29127	29686	26764	17574	12003	29755	21952.2	17656	11868	30238.5	24873	17453	12068
Total DAWOLS – P75	12440 to 66193.5	45396	64169.2	55902.2	18193	12536	63834	50182	18228	12440	66193.5	53931	18075	12577
Total DAWOLS – minimum	10322 to 16176	13674	14030	12936	15959	10568	13986	12965	16176	10322	14001	13164	15883	10642
Total DAWOLS – maximum	14007 to 141032	134588	141032	127855	29784	14301	140102	125420	22879	15335	140821	122036	30156	14007

Mean DAWOLS – mean	10.7 to 15.8	13.3	13.9	12.9	15.7	10.8	13.8	12.8	15.8	10.7	13.8	12.9	15.6	10.8
Mean DAWOLS – SD	0.246 to 0.405	0.248	0.255	0.255	0.403	0.349	0.246	0.27	0.372	0.375	0.254	0.252	0.405	0.334
Mean DAWOLS – median	10.7 to 15.8	13.3	13.9	12.9	15.7	10.8	13.8	12.8	15.8	10.7	13.8	12.9	15.6	10.8
Mean DAWOLS – P25	10.4 to 15.5	13.1	13.7	12.7	15.5	10.6	13.6	12.6	15.5	10.4	13.7	12.7	15.3	10.6
Mean DAWOLS – P75	10.9 to 16	13.5	14	13	16	11	13.9	13	16	10.9	14	13	15.9	11.1
Mean DAWOLS – minimum	9.1 to 14.2	12	12.3	11.4	14	9.3	12.3	11.4	14.2	9.1	12.3	11.6	14	9.4
Mean DAWOLS – maximum	12.3 to 17.4	14.5	15.2	14.3	17.4	12.4	15.4	14.1	17.3	12.6	15.3	14.3	17.4	12.3
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.05 to 1	0.05	0.719	0.755	1	1	0.606	0.875	1	1	0.677	0.723	1	1
Pr(equivalence)	0 to 0.95	0.95	0.281	0.245	0	0	0.394	0.125	0	0	0.323	0.277	0	0
Pr(max)	0 to 0.00013	0.00001	0.00002	0	0	0	0	0	0	0	0.00013	0	0	0
Pr(no albumin superior)	0 to 1	0.0264	0.00015	0.755	0	1	0.00021	0.875	0	1	0.00019	0.723	0	1
Pr(albumin superior)	0 to 1	0.0236	0.719	0.0001	1	0	0.606	0.00002	1	0	0.677	0.00009	1	0
Pr(none superior)	0 to 0.95	0.95	0.281	0.245	0	0	0.394	0.125	0	0	0.323	0.277	0	0
RMSE (superiority only)	0.406 to 0.782	0.782	0.421	0.412	0.585	0.535	0.413	0.406	0.487	0.538	0.444	0.427	0.591	0.538
MAE (superiority only)	0.213 to 0.627	0.627	0.213	0.213	0.398	0.36	0.214	0.216	0.329	0.363	0.228	0.223	0.399	0.364
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.324 to 0.591	0.324	0.419	0.414	0.585	0.535	0.399	0.417	0.487	0.538	0.429	0.421	0.591	0.538
MAE (select best)	0.204 to 0.399	0.204	0.238	0.235	0.398	0.36	0.232	0.235	0.329	0.363	0.244	0.243	0.399	0.364
IDP (select best)	93.3 to 100	-	95.3	96.1	100	100	93.3	98.1	100	100	94.2	95.3	100	100

RMSE (select no albumin)	0.328 to 0.591	0.328	0.424	0.417	0.585	0.535	0.41	0.419	0.487	0.538	0.432	0.426	0.591	0.538
MAE (select no albumin)	0.209 to 0.399	0.209	0.247	0.236	0.398	0.36	0.247	0.236	0.329	0.363	0.253	0.245	0.399	0.364
IDP (select no albumin)	60.6 to 100	-	71.9	100	100	100	60.6	100	100	100	67.7	100	100	100

Calibrated stopping threshold for superiority: 0.995420 (re-used from the simulations of the primary design with the primary assumptions without re-calibration).
Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S15. Performance metrics of the primary *INCEPT-Albumin* domain design with lower proportion of zeroes

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	15.7 to 15.8	15.7	15.7	15.7	15.7	15.7	15.7	15.7	15.8	15.8	15.8	15.7	15.7	15.7
Mean number of days (albumin arm)	10.5 to 20.6	15.7	16.7	14.7	20.5	10.7	16.6	14.5	20.6	10.5	16.7	14.8	20.3	10.8
Sample size – mean	1137 to 3441.5	2873.3	3326.3	3182.2	1137.1	1137	3349.5	2846.8	1137	1137	3441.5	3109.9	1137.6	1137
Sample size –SD	0.787 to 1716.4	1082.8	1658.7	1608	6.4	1.1	1645.1	1474.4	1.4	1.4	1716.4	1532	13	0.787
Sample size – median	1137 to 3135	2385	2886	2886	1137	1137	2886	2385	1137	1137	3135	2637	1137	1137
Sample size – P25	1137 to 2136	2136	2136	1887	1137	1137	2136	1635	1137	1137	2136	1887	1137	1137
Sample size – P75	1137 to 4635	3387	4386	4137	1137	1137	4386	3636	1137	1137	4635	4137	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1386 to 9885	9636	9636	9636	1635	1386	9387	9387	1386	1386	9885	9135	1887	1386
Total DAWOLS - mean	14891.2 to 55950.9	45201.5	54150.5	48675.6	20625.2	15026.3	54251.9	43270.9	20676.8	14891.2	55950.9	47620.1	20482.9	15079.6
Total DAWOLS – SD	379.6 to 27962.8	17038.5	27065.7	24670.6	451.4	402.6	26712.6	22499.3	395.5	432.1	27962.8	23517.7	499.2	379.6
Total DAWOLS – median	14891 to 50001.5	38473	47312	43551	20624	15027	46921	37656	20678	14891	50001.5	41339	20475	15080
Total DAWOLS – P25	14600 to 34722	33629	34335	29184	20330	14755	34186	24987	20409	14600	34722	29049	20178	14824
Total DAWOLS – P75	15183 to 74354	52244.2	71372	63799	20917.2	15297	71198.5	55968.5	20944	15183	74354	62983.2	20774	15335
Total DAWOLS – minimum	13007 to 19138	16665	16793	15757	18564	13296	16911	15664	19138	13007	16713	15835	18577	13360
Total DAWOLS – maximum	17986 to 162923	150083	157454	149060	30056	17986	154990	143910	25634	19327	162923	139697	34766	18391

Mean DAWOLS – mean	13.1 to 18.2	15.7	16.3	15.3	18.1	13.2	16.2	15.2	18.2	13.1	16.3	15.3	18	13.3
Mean DAWOLS – SD	0.243 to 0.388	0.247	0.251	0.252	0.383	0.354	0.243	0.271	0.347	0.38	0.251	0.249	0.388	0.334
Mean DAWOLS – median	13.1 to 18.2	15.7	16.3	15.3	18.1	13.2	16.2	15.2	18.2	13.1	16.3	15.3	18	13.3
Mean DAWOLS – P25	12.8 to 17.9	15.6	16.1	15.1	17.9	13	16	15	17.9	12.8	16.1	15.2	17.7	13
Mean DAWOLS – P75	13.4 to 18.4	15.9	16.4	15.4	18.4	13.5	16.3	15.4	18.4	13.4	16.4	15.5	18.3	13.5
Mean DAWOLS – minimum	11.4 to 16.8	14.5	14.8	13.9	16.3	11.7	14.9	13.8	16.8	11.4	14.7	13.9	16.3	11.8
Mean DAWOLS – maximum	14.7 to 19.8	16.9	17.5	16.5	19.8	14.7	17.5	16.9	19.7	14.8	17.6	16.8	19.7	14.8
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0496 to 1	0.0496	0.718	0.756	1	1	0.573	0.888	1	1	0.685	0.724	1	1
Pr(equivalence)	0 to 0.95	0.95	0.282	0.244	0	0	0.427	0.112	0	0	0.315	0.276	0	0
Pr(max)	0 to 0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr(no albumin superior)	0 to 1	0.0269	0.00009	0.756	0	1	0.00019	0.888	0	1	0.00014	0.723	0	1
Pr(albumin superior)	0 to 1	0.0227	0.718	0.00012	1	0	0.573	0.00002	1	0	0.685	0.00017	1	0
Pr(none superior)	0 to 0.95	0.95	0.282	0.244	0	0	0.427	0.112	0	0	0.315	0.276	0	0
RMSE (superiority only)	0.398 to 0.763	0.763	0.412	0.405	0.544	0.521	0.402	0.398	0.427	0.525	0.426	0.419	0.559	0.525
MAE (superiority only)	0.21 to 0.616	0.616	0.213	0.21	0.365	0.351	0.21	0.213	0.288	0.354	0.218	0.221	0.377	0.353
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.32 to 0.559	0.32	0.411	0.409	0.544	0.521	0.39	0.411	0.427	0.525	0.416	0.414	0.559	0.525
MAE (select best)	0.202 to 0.377	0.202	0.237	0.233	0.365	0.351	0.229	0.231	0.288	0.354	0.238	0.24	0.377	0.353
IDP (select best)	92.2 to 100	-	95.4	95.9	100	100	92.2	98.3	100	100	94.8	95.4	100	100

RMSE (select no albumin)	0.325 to 0.559	0.325	0.42	0.41	0.544	0.521	0.405	0.411	0.427	0.525	0.42	0.419	0.559	0.525
MAE (select no albumin)	0.208 to 0.377	0.208	0.249	0.233	0.365	0.351	0.249	0.231	0.288	0.354	0.245	0.242	0.377	0.353
IDP (select no albumin)	57.3 to 100	-	71.8	100	100	100	57.3	100	100	100	68.5	100	100	100

Calibrated stopping threshold for superiority: 0.995420 (re-used from the simulations of the primary design with the primary assumptions without re-calibration).
Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S16. Performance metrics of the primary *INCEPT-Albumin* domain design with lower mean number of days in those with >0 days

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	13.3 to 13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3
Mean number of days (albumin arm)	8 to 18.3	13.3	14.3	12.3	18.3	8.2	14.2	12.1	18.2	8	14.3	12.3	17.8	8.3
Sample size – mean	1137 to 3118.7	2638.6	3029.2	2874.4	1137	1137	3105	2616.5	1137	1137	3118.7	2789.9	1137.6	1137
Sample size –SD	0 to 1538.1	971.2	1498.1	1411.3	2.6	0	1492.7	1310.9	0.787	0.787	1538.1	1347.3	12.9	0
Sample size – median	1137 to 2637	2385	2637	2637	1137	1137	2637	2385	1137	1137	2637	2385	1137	1137
Sample size – P25	1137 to 1887	1887	1887	1887	1137	1137	1887	1635	1137	1137	1887	1635	1137	1137
Sample size – P75	1137 to 4137	2886	3885	3636	1137	1137	4137	3387	1137	1137	4137	3636	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1137 to 9387	8385	8886	8637	1635	1137	8637	8886	1386	1386	9387	8136	2136	1137
Total DAWOLS - mean	12137.8 to 43243.9	35137.3	42044.2	36988.6	17956	12251.9	42814.7	33448.8	17948.5	12137.8	43243.9	35932.9	17736	12309.3
Total DAWOLS – SD	354.3 to 21389.2	12945.6	20857.1	18234	426.5	373.2	20652.7	16845.6	381.5	399.8	21389.2	17410.8	484.6	354.3
Total DAWOLS – median	12138 to 37958	31035.5	36858	33211	17955	12251	36975	29930	17949	12138	37958	31208	17729	12309
Total DAWOLS – P25	11867 to 26320.8	25572	26089	23672	17670	12000	26221.8	20443	17691	11867	26320.8	21552	17429	12070
Total DAWOLS – P75	12407 to 57102	39601	54775.2	48187.5	18241	12503	56505.5	43416.2	18208	12407	57102	46872.2	18029	12549
Total DAWOLS – minimum	10438 to 16223	14084	14367	13124	16223	10517	14098	12792	16209	10438	14079	13162	15764	10770
Total DAWOLS – maximum	13831 to 128359	114137	124793	112863	26163	14071	120051	112637	21960	14609	128359	104749	33447	13831
Mean DAWOLS	10.7 to 15.8	13.3	13.9	12.9	15.8	10.8	13.8	12.8	15.8	10.7	13.9	12.9	15.6	10.8

– mean														
Mean DAWOLS – SD	0.238 to 0.391	0.243	0.251	0.249	0.373	0.328	0.238	0.264	0.335	0.352	0.25	0.245	0.391	0.312
Mean DAWOLS – median	10.7 to 15.8	13.3	13.9	12.9	15.8	10.8	13.8	12.8	15.8	10.7	13.9	12.9	15.6	10.8
Mean DAWOLS – P25	10.4 to 15.6	13.2	13.7	12.7	15.5	10.6	13.6	12.6	15.6	10.4	13.7	12.7	15.3	10.6
Mean DAWOLS – P75	10.9 to 16	13.5	14	13	16	11	13.9	12.9	16	10.9	14	13	15.9	11
Mean DAWOLS – minimum	9.2 to 14.3	12.3	12.6	11.4	14.3	9.2	12.4	11.3	14.3	9.2	12.4	11.6	13.9	9.5
Mean DAWOLS – maximum	12.2 to 17.3	14.5	15.1	14.1	17.3	12.4	15	14.1	17.2	12.2	15.3	14.2	17.2	12.2
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0472 to 1	0.0472	0.752	0.77	1	1	0.599	0.886	1	1	0.728	0.747	1	1
Pr(equivalence)	0 to 0.953	0.953	0.248	0.23	0	0	0.401	0.114	0	0	0.272	0.253	0	0
Pr(max)	0 to 0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr(no albumin superior)	0 to 1	0.0243	0.00006	0.77	0	1	0.00013	0.886	0	1	0.00011	0.747	0	1
Pr(albumin superior)	0 to 1	0.0229	0.752	0.00006	1	0	0.598	0.00003	1	0	0.728	0.00005	1	0
Pr(none superior)	0 to 0.953	0.953	0.248	0.23	0	0	0.401	0.114	0	0	0.272	0.253	0	0
RMSE (superiority only)	0.382 to 0.737	0.737	0.397	0.39	0.536	0.495	0.384	0.382	0.423	0.498	0.403	0.398	0.59	0.497
MAE (superiority only)	0.205 to 0.596	0.596	0.208	0.208	0.361	0.335	0.205	0.209	0.286	0.336	0.21	0.213	0.398	0.334
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.312 to 0.59	0.312	0.405	0.4	0.536	0.495	0.381	0.398	0.423	0.498	0.408	0.403	0.59	0.497
MAE (select best)	0.199 to 0.398	0.199	0.234	0.231	0.361	0.335	0.226	0.228	0.286	0.336	0.238	0.236	0.398	0.334
IDP (select best)	93.1 to 100	-	96	96.4	100	100	93.1	98.3	100	100	95.4	95.8	100	100
RMSE (select no albumin)	0.318 to 0.59	0.318	0.408	0.4	0.536	0.495	0.394	0.398	0.423	0.498	0.408	0.407	0.59	0.497
MAE (select no albumin)	0.205 to 0.398	0.205	0.241	0.23	0.361	0.335	0.245	0.228	0.286	0.336	0.239	0.237	0.398	0.334
IDP (select no albumin)	59.8 to 100	-	75.2	100	100	100	59.8	100	100	100	72.8	100	100	100

Calibrated stopping threshold for superiority: 0.995420 (re-used from the simulations of the primary design with the primary assumptions without re-calibration).
Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

Table S17. Performance metrics of the primary *INCEPT-Albumin* domain design with higher mean number of days in those with >0 days

Metric	Range	ND	B +1	B -1	B +5	B -5	Z +1	Z -1	Z +5	Z -5	M +1	M -1	M +5	M -5
Mean number of days (no albumin arm)	15.5 to 15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.5	15.6	15.6
Mean number of days (albumin arm)	10.4 to 20.4	15.6	16.5	14.6	20.3	10.6	16.4	14.4	20.4	10.4	16.5	14.7	20.3	10.7
Sample size – mean	1137 to 4000.9	3320.9	3870.1	3650.2	1137.6	1137	3856.2	3271.5	1137.1	1137.1	4000.9	3628.6	1137.6	1137
Sample size –SD	2.2 to 2030.9	1258.4	1976.1	1878	12.5	3.2	1941	1754.1	5	4.5	2030.9	1825.4	13.5	2.2
Sample size – median	1137 to 3636	2886	3387	3135	1137	1137	3387	2886	1137	1137	3636	3135	1137	1137
Sample size – P25	1137 to 2385	2385	2385	2385	1137	1137	2385	1887	1137	1137	2385	2136	1137	1137
Sample size – P75	1137 to 5385	3885	5136	4887	1137	1137	5136	4386	1137	1137	5385	4887	1137	1137
Sample size – minimum	1137 to 1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137	1137
Sample size – maximum	1386 to 10000	10000	10000	10000	1635	1386	10000	10000	1635	1635	10000	10000	1635	1386
Total DAWOLS - mean	14739.2 to 64319.7	51695.6	62303.6	55304.5	20378.6	14901.7	61872.6	49255.7	20485	14739.2	64319.7	55085.6	20380.9	14953.5
Total DAWOLS – SD	409.7 to 32716	19601.4	31885.7	28530	512.4	431.8	31220.5	26499.2	448.7	464.2	32716	27778.2	519.5	409.7
Total DAWOLS – median	14737 to 56549.5	44863	54689.5	48201.5	20372	14902	54129.5	43449.5	20484	14737	56549.5	48089	20372	14955
Total DAWOLS – P25	14426 to 38991	37734.8	38474	34988	20060	14610	38254	28375	20190	14426	38991	33429.8	20061	14679
Total DAWOLS – P75	15051 to 85489.8	59337.2	82674.5	73558.2	20680	15193	82081	65408.2	20778	15051	85489.8	73018.5	20682	15228
Total DAWOLS – minimum	12681 to 18404	15885	16357	15514	18150	13014	16377	15280	17963	12681	16602	15725	18404	13126
Total DAWOLS – maximum	18273 to 164767	158003	164372	155439	30222	19013	164767	155153	30592	21643	164514	154779	30239	18273
Mean DAWOLS	13 to 18	15.6	16.1	15.1	17.9	13.1	16	15	18	13	16.1	15.2	17.9	13.2

– mean														
Mean DAWOLS – SD	0.249 to 0.405	0.249	0.257	0.259	0.403	0.378	0.25	0.278	0.385	0.405	0.255	0.252	0.403	0.36
Mean DAWOLS – median	13 to 18	15.6	16.1	15.1	17.9	13.1	16	15	18	13	16.1	15.2	17.9	13.2
Mean DAWOLS – P25	12.7 to 17.8	15.4	15.9	15	17.6	12.8	15.9	14.9	17.8	12.7	15.9	15	17.6	12.9
Mean DAWOLS – P75	13.2 to 18.3	15.7	16.3	15.3	18.2	13.4	16.2	15.2	18.3	13.2	16.2	15.3	18.2	13.4
Mean DAWOLS – minimum	11.2 to 16.2	14	14.4	13.6	16	11.4	14.4	13.4	15.8	11.2	14.6	13.8	16.2	11.5
Mean DAWOLS – maximum	14.6 to 19.7	17	17.6	16.7	19.7	14.7	17.4	16.7	19.7	14.8	17.6	16.7	19.6	14.6
Pr(conclusive)	0.998 to 1	1	0.999	1	1	1	0.999	1	1	1	0.998	1	1	1
Pr(superiority)	0.0523 to 1	0.0523	0.679	0.728	1	1	0.585	0.878	1	1	0.636	0.667	1	1
Pr(equivalence)	0 to 0.948	0.948	0.32	0.271	0	0	0.414	0.122	0	0	0.362	0.333	0	0
Pr(max)	0 to 0.00246	0.00013	0.00131	0.0003	0	0	0.00074	0.0002	0	0	0.00246	0.00005	0	0
Pr(no albumin superior)	0 to 1	0.0293	0.00024	0.728	0	1	0.00026	0.878	0	1	0.00028	0.667	0	1
Pr(albumin superior)	0 to 1	0.023	0.679	0.00016	1	0	0.585	0.00006	1	0	0.635	0.00014	1	0
Pr(none superior)	0 to 0.948	0.948	0.321	0.272	0	0	0.415	0.122	0	0	0.364	0.333	0	0
RMSE (superiority only)	0.424 to 0.789	0.789	0.433	0.427	0.558	0.565	0.424	0.425	0.496	0.569	0.447	0.452	0.557	0.568
MAE (superiority only)	0.215 to 0.62	0.62	0.216	0.215	0.378	0.382	0.215	0.22	0.335	0.385	0.223	0.239	0.377	0.383
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.325 to 0.569	0.325	0.424	0.425	0.558	0.565	0.406	0.434	0.496	0.569	0.425	0.428	0.557	0.568
MAE (select best)	0.202 to 0.385	0.202	0.24	0.24	0.378	0.382	0.233	0.238	0.335	0.385	0.241	0.246	0.377	0.383
IDP (select best)	92.3 to 100	-	94.5	95.4	100	100	92.3	98.1	100	100	93.7	94.3	100	100
RMSE (select no albumin)	0.33 to 0.569	0.33	0.431	0.427	0.558	0.565	0.418	0.434	0.496	0.569	0.428	0.433	0.557	0.568

MAE (select no albumin)	0.208 to 0.385	0.208	0.252	0.241	0.378	0.382	0.251	0.239	0.335	0.385	0.247	0.248	0.377	0.383
IDP (select no albumin)	58.5 to 100	-	67.9	100	100	100	58.5	100	100	100	63.5	100	100	100

Calibrated stopping threshold for superiority: 0.995420 (re-used from the simulations of the primary design with the primary assumptions without re-calibration).
Abbreviations: DAWOLS: days alive without life support (at day 30); IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

14.6 | Appendix 6: variable definitions

This appendix includes definitions of all domain-specific variables (i.e., all variables not defined in the core protocol), except domain-specific clinical outcomes (section 6.6), domain-specific safety outcomes (section 6.7), and domain-specific feasibility outcomes (section 6.8).

Screening and baseline variables

- Lowest plasma albumin within the last 24 hours: g/L, lowest registered plasma albumin measured in the 24 hours prior to randomisation.
- IV crystalloid volumes within the last 24 hours: mL, total volume of IV crystalloids (e.g., saline, Ringer's solutions, Hartmann's solution or Plasmalyte™) administered to the patient in the 24 hours prior to randomisation.
- Primary cause of shock
    - Septic: yes/no, shock caused by severe infection (sepsis[82]).
    - Cardiogenic: yes/no, shock caused by inadequate heart function.
    - Haemorrhagic shock or traumatic shock: yes/no, shock caused by bleeding, or resulting from trauma.
    - Other type of shock: yes/no:
        - Neurogenic shock caused by damage to the nervous system.
        - Anaphylactic shock resulting from a severe allergic reaction.
        - Burn shock due to severe burn injury.
        - Obstructive shock due to, e.g., tension pneumothorax, massive pulmonary embolism, pericardial tamponade.
- Traumatic brain injury: yes/no, suspected or documented head trauma injury leading to brain damage.
- Use of albumin during the current ICU stay: yes/no, administration of albumin (any concentration and volume) during the current ICU stay.
- Known pregnancy: yes/no, documented pregnancy.
- Religious objection to the administration of albumin, yes/no, patient or guardian refusal to receive albumin due to religious beliefs.
- Known allergy to albumin: yes/no, documented allergy to any albumin solutions.

- Inclusion in another interventional trial or *INCEPT* domain where co-enrolment with the *INCEPT-Albumin* domain is not permitted: yes/no, documented inclusion in a trial/domain where it is known that co-enrolment in INCEPT-Albumin is not permitted (after a formal evaluation).

Variables collected daily until 90 days after inclusion in the domain

- Albumin volumes and concentrations: mL, volume of albumin administered for each of the concentrations 4% and 5% combined, and 20% or higher concentration, respectively.
- Total fluid input: mL, total volume of fluids administered to the patient on that day.
- Total fluid balance: mL, net fluid balance calculated as total fluid input minus total fluid output.
- Total volume of packed red blood cells, mL.
- Protocol violations, yes/no, any violation of the protocol as specified in section 6.8.

Process data and protocol adherence

- Separation in albumin volumes: mL, total volume of albumin (all concentrations combined) during ICU stay in the two intervention arms.
- Time to completion of the feasibility phase: days, time from randomisation of the first participant until the first 200 participants have completed the maximal 90 days intervention period.
- Protocol violations: percentage of patients with a protocol violation in the two intervention arms:
    - *Albumin arm*: No albumin given during resuscitation or as substitution in case of suspected or overt albumin loss or plasma albumin levels ≤25 g/L.
    - *No albumin arm*: Albumin given without one of the extenuating circumstances occurring i.e., large volume ascites drainage, spontaneous bacterial peritonitis, or hepatorenal syndrome.
- Recruitment proportion: percentage of patients screened in INCEPT who are included in *INCEPT-Albumin* during the feasibility phase.

- Proportion of participants without consent to the use of data: percentage of patients randomised in *INCEPT-Albumin* for whom consent for the use of data is not obtained during the feasibility phase.
- Retention proportion: percentage of patients randomised in *INCEPT-Albumin* who stayed in the domain until the end of the 90-day intervention period during the feasibility phase.