

The Intensive Care Platform Trial (INCEPT)

INCEPT-Thromboprophylaxis

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1 | Abstract

Background
Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is a common and potentially serious complication in intensive care unit (ICU) patients. International guidelines recommend pharmacological thromboprophylaxis, with a preference for low-molecular-weight heparin (LMWH). Despite thromboprophylaxis ICU patients get VTE, with estimates ranging from 3% to 26% of patients. This risk suggests that higher prophylactic doses of LMWH might be beneficial. At the same time, ICU patients may also bleed (estimates range from 3 to 10% of patients). Therefore, thromboprophylaxis is about striking the right balance: higher LMWH doses may reduce VTE events but increase bleeding and vice versa. Currently, there is insufficient evidence on the optimal dose, guidelines give no dose recommendations, and there appears to be practice variation. Determining the LMWH dosing strategy that most effectively balances the risks of VTE and bleeding has potential to improve outcomes in ICU patients.

Objectives
We aim to assess the effects of a fixed low, fixed intermediate, and weight-adjusted LMWH dose for thromboprophylaxis on days alive out of hospital at 30 days and other patient-important outcomes in acutely admitted, adult ICU patients. We hypothesise that the weight-adjusted dose will be superior to both fixed low and fixed intermediate dose LMWH regarding days alive out of hospital at 30 days, and that the fixed low and intermediate dose LMWH will be practically equivalent.

Design
INCEPT-Thromboprophylaxis will be an investigator-initiated, open-label domain with an integrated feasibility phase on the pragmatic, parallel-group, randomised, embedded, multifactorial, international, adaptive *Intensive Care Platform Trial (INCEPT)*. The domain will employ adaptive stopping and arm dropping for superiority/inferiority, stopping for practical equivalence, and restricted response-adaptive randomisation.

Inclusion and exclusion criteria
Acutely admitted adult ICU patients will be screened if all intervention arms are considered clinically appropriate and there is a decision by the treating clinician to start thromboprophylaxis with LMWH, or to continue LMWH thromboprophylaxis. We will exclude patients who have received more than one prophylactic dose of anticoagulation during the current ICU stay, patients with known or suspected previous adverse reactions to heparin, patients with a known pregnancy, patients who receive mechanical circulatory support, patients who received solid organ transplant during current hospital admission, patients weighing <40kg, and patients who are included in

another interventional trial or *INCEPT* domain where co-enrolment with *INCEPT-Thromboprophylaxis* is not permitted.

Interventions and comparisons

The intervention is LMWH for thromboprophylaxis, administered in either a fixed low, fixed intermediate, or weight-adjusted dose. Four LMWH types will be used: enoxaparin, tinzaparin, dalteparin, or nadroparin. Each participating site will select one preferred LMWH type prior to patient enrollment. Sites may change selected LMWH during the domain conduct.

The intervention period is up 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. There will be no common control arm, and all interventions will be simultaneously compared.

Outcomes

The primary outcome guiding all adaptations is days alive out of hospital 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 days mortality; days alive without life support at day 30 and 90; days alive and out of hospital at day 90; days free of delirium at day 30; and 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. Additional domain-specific outcomes will be: VTE and major bleeding during hospital stay after 30 and 90 days, and one or more domain-specific safety outcomes including serious adverse reactions (severe anaphylactic reaction to LMWH and heparin-induced thrombocytopenia [HIT]) and suspected unexpected serious adverse reactions at day 30 and 90.

Statistics and adaptation rules

This domain will use Bayesian statistical methods with the primary analyses conducted in the intention-to-treat population and using neutral, weakly informative priors. Adaptive analyses will be conducted after follow-up and data collection concludes for 1,500 participants and every subsequent 500 participants up to a maximum of 10,000 participants.

The domain uses constant, symmetrical stopping rules for inferiority/superiority calibrated to keep the type 1 error rate (the probability of erroneously declaring one arm overall superior) below 5% across a range of realistic scenarios. The domain will be stopped for practical equivalence if there is >90% probability that the largest absolute mean difference between all remaining arms at any adaptive analysis is less than 1 day.

Equal initial allocation percentages will be used followed by restricted response-adaptive randomisation with minimum allocation probabilities of 25% to each arm (rescaled proportionally if one arm is dropped early).

Domain design performance metrics

Performance metrics have been evaluated assuming a mean number of 10.3 days alive out of hospital at 30 days for the primary and guiding outcome and 15 scenarios with no, small, and large differences between arms corresponding to differences of 0, 1, and 2 days in either direction in different combinations. The expected (mean) sample sizes under these scenarios range from 2,265 to 4,892 respectively. The probabilities of conclusiveness (i.e., superiority/inferiority or equivalence) are ~100% in all scenarios, and the probabilities of superiority (power) range from 72.1% to 99.9% in scenarios with a single superior arm.

Estimated timeline

- Third quarter, 2025: domain approved and first participant randomised
- Second quarter, 2026: feasibility phase analysis concluded
- Fourth quarter, 2028: expected inclusion of the last participant if the domain continues to the expected sample size in the scenario assessed leading to the largest expected sample size.
- Third quarter, 2030: expected inclusion of the last participant if the domain continues to the maximum sample size (n = 10,000)
- Approximately 6 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

The *INCEPT-Thromboprophylaxis* domain is funded by a grant from the *Novo Nordisk Foundation* and the *Netherlands Thrombosis Foundation*.

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. The statistical analysis plan for the domain is contained in this domain-specific appendix.

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3 | Abbreviations

AE: *adverse event*
AKI*: acute kidney injury*
APTT: *activated partial thromboplastin time*
ATC code: *Anatomical therapeutic chemical code*
CONSORT-ACE: *Adaptive designs CONSORT Extension*
CONSORT: *Consolidated Standards of Reporting Trials statement*
CrI: *credible interval*
CT: *computed tomography*
CTIS: *Clinical Trials Information System*
CVC: *Central venous catheter*
DeIC: *Danish e-infrastructure Consortium*
DVT: *deep vein thrombosis*
eGFR*: estimated glomerular filtration rate*
EMPRESS: *Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis trial*
EUCT number: *European Union Clinical Trials Information System (CTIS) number*
HCG: *human chorionic gonadotropin*
HIT: *Heparin-induced thrombocytopenia*
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*
kg: *kilogram*
L: *litre*
LMWH: *Low-molecular-weight heparin*
MAE: *median absolute error*
MD: *mean difference*
mmHg: *millimetres of mercury*
mmol: *millimoles*
MRI: *magnetic resonance imaging*
OR: *odds ratio*
P25: *25th percentile*
P75: *75th percentile*

PE: *pulmonary embolism*
PP: *per-protocol*
Pr: *probability*
PT: *prothrombin time*
RCT: *randomized controlled 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*
SmPC: *summary of product characteristics*
SMS-ICU: *Simplified Mortality Score for the Intensive Care Unit*
SPC: *Summary of product characteristics*
SPIRIT: *Standard Protocol Items: Recommendations for Interventional Trials statement*
SUSAR: *suspected unexpected serious adverse reaction*
UFH: *unfractionated heparin*
VTE: *venous thromboembolism*
YYYY-MM-DD*: year, month, date*
µmol: *micromoles*

4 | Objectives and lay description

4.1 | Objectives

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially serious complication in intensive care unit (ICU) patients. Major clinical guidelines conditionally recommend pharmacological thromboprophylaxis in ICU patients without contraindications, with a preference for low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) based on moderate certainty evidence [1–3]. Despite thromboprophylaxis, ICU patients face a substantial residual VTE risk, with estimates ranging from 3% to 26% in a recent systematic review [4]. This risk suggests that higher LMWH doses might be beneficial. At the same time, ICU patients also face a substantial bleeding risk of 3 to 10% [5–7]. Therefore, thromboprophylaxis is about striking the right balance: higher LMWH doses may reduce VTE risk, whereas lower doses might limit bleeding complications. Currently, there is insufficient evidence on the optimal dose [8], guidelines offer no dose recommendations [1–3], and there appears to be practice variation [9]. Determining the LMWH dosing strategy that most effectively balances the risks of VTE and bleeding has potential to improve outcomes in ICU patients.

With the *INCEPT-Thromboprophylaxis* domain we aim to assess the effects of a fixed low, fixed intermediate, and weight-adjusted LMWH dose for thromboprophylaxis on days alive out of hospital at 30 days and other patient-important outcomes in acutely admitted, adult ICU patients. We hypothesise that the weight-adjusted dose will be superior to both fixed low and fixed intermediate dose LMWH regarding days alive out of hospital at 30 days, and that the fixed low and intermediate dose LMWH will be practically equivalent.

4.2 | Lay description

The results of *INCEPT-Thromboprophylaxis* will help us prevent blood clots and bleeding in intensive care unit (ICU) patients.

Patients in ICUs have a high risk of developing blood clots (deep vein thrombosis). Development of a blood clot in the veins of the legs (thrombosis) may pose a serious threat. When the blood clot breaks loose it may travel to the vessels of the lungs. This is called pulmonary embolism, which can be life-threatening. Patients admitted to ICU are at high risk of developing thrombosis. About one out of 10 ICU patients develop a blood clot.

Clinical practice guidelines recommend use of blood-thinners in all ICU patients to prevent formation of blood clots. Specifically, they recommend a blood-thinning drug called low-

molecular-weight-heparin. Blood-thinners reduce the risk of blood clots. On the other hand, one out of 10 to 20 ICU patients will develop bleeding, and blood-thinners increase this risk. Therefore, using blood-thinners is a balancing act. The optimal dose should be just high enough to prevent blood clots, but not so high that bleeding occurs. We are uncertain about the optimal dose of blood-thinners in ICU patients.

The *INCEPT-Thromboprophylaxis* sub-trial (domain) aims to find the best dose of blood-thinners for preventing both blood clots and bleeding in ICU patients. Patients will be randomly assigned to one of three doses. There will be a fixed low dose, a fixed intermediate dose, and a weight-adjusted dose. All these doses are used in current clinical practice, but we do not know which dose is the best option. We assume that the use of a weight-adjusted dose will strike the best balance in preventing both blood clots and bleeding, and that this will translate into other patient-important outcomes, in particular improved survival and a shorter hospital stay. The results of this research will help us improve the safety and effectiveness of this preventive treatment.

5 | Background

5.1 | Venous thromboembolism in ICU patients

VTE includes DVT and PE and can constitute a severe complication of critical illness. VTE is associated with short-term adverse outcomes such as unexplained clinical deterioration and death, but also to long-term sequelae including post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension [10–12]. VTE has a multifactorial origin that usually results from a combination of factors that predispose to endothelial damage, stasis of blood and a procoagulant state [13]. A recent systematic review with meta-analysis identified nine factors associated with an increased risk for developing VTE: obesity, active malignancy, history of VTE, recent surgery, sepsis, lack of the use of pharmacologic thromboprophylaxis, central venous catheter, invasive mechanical ventilation, and administration of vasopressors [4]. ICU patients will typically be exposed to multiple of these factors. This translates into a particular high risk of VTE, and the American Society of Hematology, the United Kingdom National Institute for Health and Care Excellence, and the European Society of Anaesthesiology and Intensive Care all strongly recommend pharmacological thromboprophylaxis for all ICU patients without contraindications (moderate certainty of evidence) [1–3]. Although in theory any anticoagulant could be used for prophylaxis, most guidelines suggest the use of low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) or other anticoagulants (moderate certainty of evidence) [1–3]. Guideline recommendations are summarized in **Table 1** and the evidence base is discussed in depth in section 5.2.

Despite thromboprophylaxis, ICU patients face a substantial residual VTE risk, with estimates ranging from 3% to 26% in a recent systematic review [4]. This risk suggests that higher LMWH dosing might be beneficial. At the same time, ICU patients also face a substantial bleeding risk of 3 to 10% [5–7]. Therefore, thromboprophylaxis is about finding the right balance: higher LMWH doses may reduce VTE risk, whereas lower doses might limit bleeding complications. Guidelines provide no specific recommendations on LMWH type or dose even though there is no unambiguous definition on what entails a ‘standard dose’. A 2022 network meta-analysis that summarised all available data (44 trials that had randomised 90,095 participants) on thromboprophylaxis in non-surgical acutely ill hospitalised patients (excluding COVID-19), found that only 13 RCTs (n = 1390) had directly compared one or more LMWH doses, of which only 5 (n = 412) had been conducted in ICU patients [8]. A survey that was conducted in preparation for this domain reported considerable practice variation regarding LMWH dosing within and between ICUs [9]. Taken together, the lack of a standard dose, practice variation, and risks of both VTE and bleeding, there is an unmet clinical need to determine the optimal prophylactic dosing strategy for LMWH in ICU patients.

Table 1. Summary of international guideline recommendations

Guideline / Recommendation	NICE	ESAIC	ASH
Use pharmacological thromboprophylaxis in ICU patients without contraindications	Yes	Yes	Yes
Preferred anticoagulant(s) for ICU patients	LMWH	Prefer LMWH over UFH (strong recommendation, moderate certainty)	Prefer LMWH over UFH (conditional recommendation, moderate certainty)
Adaptations in ICU patients with severe renal insufficiency	Reduce the dose based on multidisciplinary or senior opinion, or local protocols	Administer UFH or dalteparin (conditional recommendation, low certainty)	-
Recommendation to use mechanical thromboprophylaxis in ICU patients	Only if pharmacological thromboprophylaxis is contraindicated	Only if pharmacological thromboprophylaxis is contraindicated (strong recommendation, low certainty)	Only if pharmacological thromboprophylaxis is contraindicated (conditional recommendation, moderate certainty)

Abbreviations: ASH: American Society of Hematology [1] ; ESA: European Society of Anaesthesiology [2]; NICE: National Institute for Health and Care Excellence (United Kingdom) [3]; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin.

5.2 | Domain rationale and ethical justification

Careful consideration of the balance between the benefits (VTE prevention) and potential harms (i.e., bleeding) associated with the use of anticoagulants is essential when evaluating the most appropriate dosing of thromboprophylaxis for ICU patients. A recent network meta-analysis suggested that a fixed intermediate dose LMWH may confer the best balance between benefits and harms for the prevention of VTE in comparison to a low dose LMWH, but the certainty of evidence was low due to imprecision and inconsistency (due to between-study heterogeneity) [8]. In addition, these findings were derived from RCTs that mainly included acutely ill patients in general wards, and generalization to ICU patients should be done cautiously. Not only is the risk of VTE increased in ICU patients, but the risk of bleeding is also increased [14].

Rationale for LMWH

As discussed in section 5.1 and summarised in **Table 1**, major international guidelines suggest the use of low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) as pharmacological thromboprophylaxis for ICU patients without contraindications (moderate certainty of evidence) [1–3]. Evidence from systematic reviews suggests that LMWHs reduce the

relative risk of VTE by approximately 20-35% as compared to UFH [15,16]. While direct comparisons of LMWH to placebo are rare in ICU patients, trials in general medical patients suggest an even larger relative risk reduction when comparing to placebo, up to 40-60% [17]. Bleeding risks appear similar between LMWH and UFH in ICU patients, whereas UFH is associated with higher bleeding risks in general medical patients [8,15,16]. The extent to which LMWH prophylaxis increases bleeding risk compared to placebo is uncertain, since only one RCT has directly compared LMWH to placebo in ICU patients [18]. Overall, LMWH seems to be superior to UFH for reduction of VTE risk whereas bleeding risks appear to be similar in ICU patients.

Alternatives to LMWH or UFH exist, but all face limitations in ICU patients. Fondaparinux, a synthetic Factor Xa inhibitor, is a possible alternative to LMWH. However, it has only been assessed in a single RCT in general medical patients and is contraindicated in renal failure [19]. Direct oral anticoagulants (DOACs) also seem appealing, but there is minimal evidence on their safety and efficacy in ICU patients [20]. Moreover, when used for thromboprophylaxis in general medical patients, DOACs had a similar efficacy but higher risk of bleeding compared to LMWHs, implicating an overall unfavorable profile, especially in patients with increased risk of bleeding, including ICU patients [21]. Other factors that may limit the use of DOACs in the ICU setting include uncertain bioavailability with enteral administration and limited clinical experience in patients with acute renal failure. In summary, LMWHs are currently the preferred pharmacological prophylactic agent for ICU patients requiring VTE prevention.

Rationale for focusing on the LMWH dose

Guidelines provide no specific LMWH type or dose recommendations even though there is no unambiguous definition on what entails a ‘standard dose’. Multiple LMWHs and dosages are registered for thromboprophylaxis across various countries, as outlined in the summary of product characteristics (SmPC) [22–27]. Adjustment of thromboprophylaxis according to weight is recommended in some of these SmPCs [22,24,26]. Further, while most ICUs that participated in the survey on thromboprophylaxis indicated the use of fixed dose LMWH regimes, 47% additionally reported the use of some form of adjustment according to weight, suggesting different approaches are used in a single ICU [9].

Only 5 RCTs (n = 412) have directly compared the effects of different LMWH types and doses in ICU patients without COVID-19 and their results are limited by imprecision and use of surrogate outcomes [8,28–31]. Two of these RCTs assessed weight-adjusted dosing [29,31]. Increased body mass index (BMI) has been associated with thromboprophylaxis failure in ICU patients, which could imply underdosing in overweight patients when using fixed-dose regimens [32]. Hypothetically, this could be amended by weight-adjusted dosing. However, the evidence in favour of this stems from predominantly small trials investigating subgroups of ICU patients (including patients with COVID-19) that often used anti-Xa levels as a surrogate outcome

[29,31,33]**.** Thus, while weight-adjusted dosing may in theory be beneficial, the evidence is insufficient and inconclusive.

RCTs on thromboprophylaxis in ICU patients with COVID-19 have provided results that may to some extent be generalizable to the 'general' ICU population. A trial by Perepu and colleagues (n = 173) randomized patients to enoxaparin 40 mg versus enoxaparin 1 mg/kg, and found no statistically significant differences in arterial thromboembolism (odds ratio [OR] 1.69; 95% confidence interval [CI] 0.39 to 7.29), venous thromboembolism (OR 1.79; 95% CI 0.51 to 6.25), or bleeding outcomes (OR 0.99; 95% CI 0.14 to 7.14), with results limited by substantial uncertainty due to imprecision [34]. The ATTAC, ACTIV-4, and REMAP-CAP multiplatform collaborative RCT (n = 1,098) that assessed several doses of thromboprophylaxis versus therapeutic dose anticoagulation concluded that showing superiority of therapeutic dose anticoagulation was futile (posterior probability of futility [defined as an OR <1.2] of 99.9% with regard to its primary outcome 'organ support-free days' [OR 0.83 (95% CI 0.67 to 1.03]) – and with a numerically higher incidence of major bleeding (3.8% versus 2.3%) [6]. The INSPIRATION trial (n = 562) found uncertain benefits of intermediate dose (enoxaparin 1mg/kg) versus standard-dose prophylaxis (enoxaparin 40mg) with regard to a composite outcome of mortality, venous and arterial thromboembolism and dependence on life support (OR 1.06; 95% CI 0.76 to 1.48) [35]. The HEP-COVID trial (n = 253, of which 32.8% of patients received ICU-level care) that compared standard or intermediate dose prophylaxis (defined as UFH up to 22,500 IU; enoxaparin 30-40mg once or twice daily, and dalteparin 2,500-5,000 IU once daily) to therapeutic dose (enoxaparin 1 mg/kg twice daily), found a lower composite of death, venous and arterial thromboembolism in the therapeutic dose arm (28.7% vs 41.9%; relative risk [RR] 0.68; 95% CI 0.49 to 0.96), but at the cost of an estimate for risk of major bleeding that was mostly compatible with harm (4.7% versus 1.6%; RR 2.88; 95% CI 0.59 to 14.02) [36]. The COVI-DOSE trial (n = 1,000, of whom 19.9% received ICU level care) that compared a fixed to a weight-adjusted LMWH dose, estimated an uncertain decrease in VTE events in the weight-adjusted arm (2.1% versus 1.2%; subdistribution hazard ratio 0.59; 95% CI 0.22 to 1.63) that was offset by an increased risk of clinically relevant non-major bleeding events (5.9% versus 3.1%; subdistribution hazard ratio 1.95; 95% CI: 1.05 to3.63) [37]. Finally, the ANTICOVID trial (n = 334) assessing tinzaparin 3,500 IU, 7,000 IU, and 175 IU/kg found no statistically significant differences between its arms with regard to the hierarchical primary outcome (all-cause mortality followed by time to clinical improvement at day 28) but the tinzaparin 7,000 IU arm performed best with regard to the secondary composite outcome of mortality, VTE, and major bleeding (absolute difference −13.5; 95% CI −2.6 to −24.3) [33].

Summary

In summary, only 5 RCTs (n = 412) have directly compared different LMWH doses for thromboprophylaxis in ICU patients *without* COVID-19 with inconclusive results. RCTs in ICU patients *with* COVID-19 generally have not found benefit of high ('therapeutic') dose LMWH for thromboprophylaxis over other doses. Several factors limit the extrapolation of results in ICU patients with COVID-19, such as the fact that pulmonary embolism in COVID-19 may be due to

lung microvascular thrombosis which – in theory – is not preventable by anticoagulation; the level of uncertainty around estimates in most trials; the use of composite outcomes that often included arterial events; and the use of heterogeneous treatment arms that often included both LMWH and UFH ('thromboprophylaxis according to local practice') [38,39]. Nevertheless, assuming the bleeding risk in ICU patients *without* COVID-19 is more or less similar to that of patients *with* COVID-19, we deem it unlikely that benefits of high ('therapeutic') dose anticoagulation for thromboprophylaxis will outweigh the bleeding risk. This leaves open the question whether a low, intermediate, or weight-adjusted LMWH dose offers the best balance between benefits and harms. Based on our documentation of clinical practice [9], we expect that participation in *INCEPT-Thromboprophylaxis* will increase the probability that participants receive weight-adjusted dose LMWH compared to current clinical practice, and therefore benefit because the hypothesis of *INCEPT-Thromboprophylaxis* is that weight-adjusted dose will be superior compared to the fixed low and intermediate dose LMWH.

The *INCEPT-Thromboprophylaxis* domain will be conducted according to high methodological standards assessing the benefits and harms of these three LMWH dosing strategies on patient-important outcomes. The adaptive design will both increase individual participants' chances of being allocated to the interventions that are more likely to be better and increase the probability that the trial results will be conclusive and thus inform clinical guidelines and practice [40,41]. 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-Thromboprophylaxis will be an investigator-initiated, open-label domain with an integrated feasibility phase on the pragmatic, parallel-group, randomised, embedded, multifactorial, international, adaptive *Intensive Care Platform Trial (INCEPT).* The domain compares three intervention arms: fixed low dose, fixed intermediate dose, and weight-adjusted dose of LMWH for thromboprophylaxis in adult, acutely admitted ICU patients. All interventions will be simultaneously compared. The domain will employ adaptive stopping and arm dropping for superiority/inferiority, stopping for practical equivalence, and restricted response-adaptive randomisation.

The maximum sample size will be 10,000 participants, which is required to ensure >99% probability of the domain being conclusive, i.e., ultimately fulfilling the criteria for superiority or practical equivalence, across a range of plausible clinical scenarios evaluated (detailed in section 7.10 and appendix 1, section 14.1). The expected sample sizes across the clinical scenarios evaluated range from 2,265 to 4,892 participants (section 7.10). With an assumed inclusion rate of 10 participants per day after conclusion of the feasibility phase, based on the inclusion rate of a comparable previous trial [42], the domain is expected to conclude enrolment within a realistic and feasible timeframe of approximately 3 years if the final sample size matches the upper limit of the range of expected sample sizes across the clinical scenarios evaluated, and approximately 5 years if the domain continues until enrolment of the maximum sample size.

This domain-specific appendix describes all required items included in the *Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 statement* and the relevant items from the *Consolidated Standards of Reporting Trials (CONSORT) Adaptive designs CONSORT Extension (ACE)* checklist, except those already covered by the core protocol and where no domain-specific adaptations are made (appendix 2, section 14.2); for these points, the checklists refer back to the core protocol [43,44].

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 of the following criteria must be fulfilled:

- All interventions in this domain are considered clinically appropriate.
- Decision by the treating clinician to start thromboprophylaxis with LMWH, or to continue LMWH prophylaxis.

Domain-specific exclusion criteria:
We will exclude patients who fulfil any of the following criteria:

- More than one prophylactic dose of anticoagulation administered during current ICU stay (including ICU days in other hospitals).
- Known or suspected previous adverse reaction to any type of heparin, including allergy and HIT.
- Known pregnancy.
- Mechanical circulatory support.
- Solid organ transplant during current hospital admission.
- Weight <40kg.
- Inclusion in another interventional trial or *INCEPT* domain where co-enrolment with the *INCEPT-Thromboprophylaxis* domain is not permitted.

Extended definitions of in- and exclusion criteria are suppled in appendix 3, section 14.3.

Participants that have previously been randomised to this domain cannot be included and randomised in the domain again. A flowchart as illustrated in
Figure S2 (appendix 4, section 14.4) will summarise screening, randomisation, and data availability in the analyses.

6.3 | Interventions

Intervention period
The intervention period is up to maximum 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.

Interventions
The intervention of interest is LMWH for thromboprophylaxis, administered in either a fixed low, fixed intermediate, or weight-adjusted dose (**Table 2**).

Table 2. Interventions

Intervention	*Weight (kg)*	Enoxaparin Dose (mg)	Tinzaparin Dose (IU)	Dalteparin Dose (IU)	Nadroparin Dose (IU)
Fixed low dose	*All*	40	2500	2500	2850
Fixed intermediate dose	*All*	60	4500	5000	5700
Weight-adjusted dose[1]	*≥40 - 50*	40	2500	2500	2850
	≥50 - 60	40	2500	2500	3800
	≥60 - 70	40	4500	5000	3800
	≥70 - 80	60	4500	5000	3800
	≥80 - 90	60	4500	5000	5700
	≥90 - 100	80	7000	7500	5700
	≥100 - 110	80	7000	7500	7600
	≥110 - 120	80	8000	7500	7600
	≥120	100	8000	10000	7600

Abbreviations: IU: international units, kg: kilogram, mg: milligram.

[1] Actual body weight, measured or estimated at screening.

Rationale for the use of different LMWHs

LMWHs differ in mean molecular weights, mix of polysaccharide chain lengths, and pharmacological properties [45]. This is caused by the process of depolymerization of native heparin which is different for each product; the LMWHs are, therefore, classified as separate drugs [46]. As such, each LMWH currently on the market has been trialed for different indications and sometimes in different doses. Not all LMWHs are registered for thromboprophylaxis in all countries and preferences may differ at country or even at hospital level. Whereas this practice heterogeneity forms the rationale for the current trial, it also poses challenges regarding feasibility and generalizability. Ideally, one would prefer to include all different types of LMWHs to generate a widely generalizable result, however, there is only limited data to build on regarding the interchangeability of different LMWH types and doses.

To facilitate generalizable results that are applicable to 'the real world' and to lower barriers to participation, we opt to include four types of LMWHs in this trial: enoxaparin, dalteparin, tinzaparin, and nadroparin. We chose these types based on the results of an international survey that was conducted to inform this trial [9]. Although other LMWHs exist (such as certoparin, bemiparin, and reviparin), we expect to have included the most frequently used LMWHs in the parts of the world where this trial is expected to run.

Rationale for the doses in each arm

As stated previously, it is challenging to categorize LMWHs according to dose and type because of a paucity of direct comparisons and inherent differences between different LMWHs. Since we intend to use the four LMWHs in each of the three study arms, and we wish to minimise the

amount of within-arm heterogeneity, we established the dose categorisation based on two principles:

1) Alignment with clinical practice: this was informed by survey results [9], national summary of product characteristics [22–27,47,48], and the clinical experience of the domain management committee. This was the primary guiding principle for the dose categorization.
2) Proportionality to the recommended therapeutic dose: whereas for each LMWH there is a well-defined therapeutic weight-adjusted dose, but no such weight-adjusted dosing recommendations exist for prophylactic use. We therefore expressed the prophylactic dose as a percentage of the recommended therapeutic dose, for each LMWH type and dose (**Figure S3** and **Figure S4,** Appendix 5, section 14.5). For example: the recommended prophylactic dose of dalteparin is 2500 or 5000 IU once daily. The recommended therapeutic dose is 200 IU / kg once daily. An 80 kg patient would thus be prescribed 200 IU * 80 kg = 16.000 IU once daily. Prophylactic dalteparin doses of 2500 or 5000 IU would in this case respectively imply a ratio of (2500 / 16.000) * 100 = 15.6% and (5000 / 16.000) *100 = 31.3%. We used this ratio as a crude guidance for the dosing categorization by aiming for roughly comparable ratios between the doses of the different LMWHs in each arm.

Additionally, in the weight-adjusted intervention arm we applied rounding of doses to comply with contents available in prefilled syringes, to reduce the risk of errors while preparing and administering LMWH to patients.

By adhering to these principles, we designed the domain with the intention that each intervention arm includes *commonly use*d *LMWH doses* that are *comparable between LMWH types*.

Trial sites and choice of LMWH

Each trial site may use its own preferred LMWH, provided it is one of the four pre-specified options: dalteparin, enoxaparin, nadroparin, or tinzaparin. This choice should be guided by local clinical practice and national regulatory requirements. Once a site has established its preferred LMWH, we recommend maintaining consistent use of that specific LMWH type throughout the trial for all enrolled patients at that location. Switching LMWHs during the trial is possible, but preferably if all newly included patients at that site receive the new LMWH type from that point onwards. Incidental treatment of patients with 'non preferred' LMWHs is allowed but discouraged.

Permitted deviations in the delivery of the allocated intervention

Dose adjustment or temporarily halting of the intervention is allowed in case of acute and/or chronic kidney injury, renal replacement therapy, thrombocytopenia, invasive procedures, use of

thrombolysis, and active (major) bleeding. The decision to adjust or withhold one or more doses of trial medication is at the discretion of the treating clinician. We provide suggested dose adjustment strategies in **Table S13**, but other deviations are allowed, both with respect to using other triggers for dose adjustment (for example using an estimated glomerular filtration rate [eGFR] cut-off of 30 instead of 20 ml/minute) and also using alternative adjusted doses. In case of the start of therapeutic anticoagulation (e.g., treatment of VTE or atrial fibrillation) or in case of a serious adverse reaction (serious allergy or HIT as defined in section 6.7), the intervention should be permanently stopped (**Table S13**).

Deviation from the allocated intervention for indications not listed in **Table S13** will be considered a protocol violation.

Preparation and administration

- Enoxaparin (anatomical therapeutic chemical (ATC) code B01AB05): solution for injection in a pre-filled syringe, should be injected subcutaneously once daily.
- Tinzaparin (ATC code B01AB10): solution for injection in a pre-filled syringe, should be injected subcutaneously once daily.
- Dalteparin (ATC code B01AB04): solution for injection in a pre-filled syringe, should be injected subcutaneously once daily.
- Nadroparin (ATC code B01AB06): solution for injection in a pre-filled syringe, should be injected subcutaneously once daily.

Availability of these four different types of LMWH and packaging varies by country [22–27,47,48]. Other solutions are permitted as long as the final dose is administered according to the protocol. Some of the weight-adjusted doses may require simultaneous (partial) administration of multiple syringes; for example, the tinzaparin 7,000 IU will require administration of two syringes of 3,500 IU.

Intervention accountability

All trial interventions are routinely used for in-hospital prophylaxis of patients at risk of VTE. We will use shelf-medication provided by the participating sites' pharmacies. The use of biosimilar LMWHs subject to stricter monitoring per the European Medicines Agency's *"List of medicines under additional monitoring"* [49] is not allowed and will be assessed at site initiation and systematically and regularly during domain conduct. The trial medication will only be handled by trial staff, who are trained in the trial-related procedures, or by the clinical staff, who are trained and certified for the caring of these patients.

Co-interventions
All participants randomised in the domain are allowed to receive antiplatelet agents at the discretion of the treating clinicians.

Drug traceability measures
The registration of the BATCH/LOT numbers, the expiry dates of the LMWHs used, and the identity of the clinician administering the trial interventions will be registered as per standard practice at the sites (e.g., in the electronic patient records). Consequently, these data will not be registered in the eCRF but registered according to usual clinical practice and applicable local regulations. We believe that this is a safe procedure because the LMWHs used in the *INCEPT-Thromboprophylaxis* domain are 1) shelf-medication from the hospitals' pharmacies, 2) well-known drugs that have been in clinical use for many years, and 3) the safety of single doses cannot be questioned. The same procedure was approved in the *COVID STEROID* [50], *COVID STEROID 2* [51], and *CLASSIC* trials [52], and the *INCEPT-Albumin* domain [53].

6.4 | Randomisation and stratification

Randomisation will initially be stratified for site and history of VTE (yes/no) [54]. Simple (unstratified), restricted response-adaptive randomisation will be used following the first adaptive analysis [40].

6.5 | Justification for using an open-label design

The *INCEPT-Thromboprophylaxis* domain will be conducted as open-label. The availability of LMWH and packaging varies by country [22–27,47,48]. Not all LMWHs are registered or marketed in every participating country, and therefore this domain will allow the use of four types, as discussed in section 6.3. Blinding is logistically impractical due to the application of four different types of LMWH, the use of a weight-adjusted arm, and reduced dosing with increased risk of bleeding or accumulation. Moreover, we expect that forcing sites to switch from their preferential LMWH to another for the purpose of participating in an RCT will be a barrier to participation. An additional advantage of this approach (i.e., allowing sites to use the LMWH of their preference) is that it will increase generalisability and implementation of the trial results. Additionally, including all four LMWHs as potential interventions in the domain is warranted to be able to recruit as many sites within our network as possible to finish the domain within a reasonable timeframe. Although the primary outcome (days alive out of hospital at day 30) may be affected by the clinician's knowledge of the intervention, we consider the risk of substantial effects on the primary outcome and most secondary outcomes to be unlikely. Moreover, as blinding is costly and time-consuming for clinical personnel, we consider an open-label domain, which will enrol more patients at the same cost, more ethical, as it allows the final domain to be larger and thus have a higher chance of

providing clinically conclusive results. Due to the use of response-adaptive randomisation and regular adaptive analyses, the statistical team will not be blinded; however, persons participating in data handling and statistical analyses will not be permitted to enrol patients or register outcome data.

6.6 | Outcomes

Primary and guiding outcome

The primary and guiding outcome will be days alive out of hospital at day 30 with non-survivors assigned 0 days [55].

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 30 and 90; days alive out of hospital at day 90; days free of delirium at day 30; health-related quality of life (HRQoL; evaluated using EQ5D-5L index values and EQ VAS [56]) and cognitive function (evaluated using the Montreal Cognitive Assessment test 5-minute version [Mini MoCA] at 180 days [57–59]); the domain-specific secondary outcomes VTE and major bleeding during hospital stay for a maximum of 30 and 90 days (**Table 3**); and one or more domain-specific safety outcomes as specified in section 6.7, **Table 4.**

Table 3. Domain-specific secondary outcomes

Name	Definition/operationalisation/data collection	Remarks
Venous thromboembolism	**Definition:** Any DVT of the lower or upper extremity **OR** any PE. • DVT is defined as proximal or distal DVT of the lower extremities (including the iliac, femoral, popliteal, and distal deep veins), or proximal or distal DVT of the upper extremity (including the internal jugular, brachiocephalic, subclavian, axillary, ulnar and radial veins). A diagnosis of DVT may be established based on either point-of-care ultrasound, compression ultrasound, venography, computed tomography (CT), or magnetic resonance imaging (MRI). • PE is defined as thrombosis within the pulmonary vasculature (central, lobar, segmental, and subsegmental arteries). A diagnosis of PE may be established by CT angiography or high probability ventilation-perfusion scan.	Requesting diagnostic tests will be left to the discretion of the treating clinician. Systematic screening of all patients for DVT (i.e. regardless of clinical signs or symptoms) using compression ultrasound or any other imaging modality will not be allowed. Participating sites will be informed of this requirement before domain initiation. VTE will only be registered in-hospital.

	Operationalisation: • Binary (yes/no) **Data collection:** In case of a VTE the following additional data will be collected: 1. The anatomical location (according to the above definition of DVT and PE) 2. The presence of a central venous catheter (any venous catheter positioned in the internal jugular vein, subclavian vein or femoral vein) 3. The imaging modality used to detect the event (according to the above definition of DVT and PE) 4. The operator (ICU versus radiology professional) 5. Start of treatment with therapeutic dose anticoagulation (for definitions, see appendix 3, section 14.3) < 24h after diagnosis	
Major bleeding	**Definition:** Major bleeding is 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). **Operationalisation:** • Binary (yes/no) **Data collection:** • In case of major bleeding, data will be collected on which of the above criteria was met, and in case of a symptomatic bleeding in a critical area or organ: which one.	The components of this outcome are based on guidance by the International Society on Thrombosis and Haemostasis, with adaptations to the ICU environment. [60,61]. Major bleedings will only be registered in-hospital.

Variants of INCEPT core outcomes

For the days alive without life support, days alive out of hospital, and days free of delirium outcomes at all timepoints, the penalised values (non-survivors assigned 0 days) will be the primary definitions [55].

6.7 | Benefit-risk assessment and safety outcomes

Risk classification

We consider this domain to be at low risk regarding safety reporting (corresponding to risk level 1 in the Danish Medicines Agency's guidance on risk adaptations to adverse event recording ([62]) in accordance with EU regulations (Regulation EU No 536/2014 [63]) for the following reasons:

- The investigational medicinal products (enoxaparin, tinzaparin, dalteparin, and nadroparin) all have marketing authorisations in Europe. Participating sites in each country will only use products with marketing authorisation in those specific countries.
- The interventions are considered part of standard care for ICU patients.
- The safety profiles for the interventional drugs are well-known, including rare adverse effects, and none of the included investigational medical products are subject to stricter reporting requirements in Denmark ([62]), the Netherlands, and Sweden. The use of biosimilar LMWHs subject to stricter monitoring per the European Medicines Agency "List of medicines under additional monitoring" [49] is not allowed (see 6.3 intervention accountability).
- The probability of discovering new safety signals is expected to be minimal.

Domain-specific safety outcomes

The serious adverse reactions (SARs) listed in **Table 4** 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'* outcomes. Investigators will always be able to report any SAEs immediately at their own discretion; these will be reported descriptively, but not included in the *'one or more domain-specific safety outcomes'* outcomes.

Follow-up for safety outcomes will be the hospital period, with a maximum of 30 (matching the primary and guiding outcome) and 90 days (matching the maximum intervention period) for all participants.

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 as the domain-specific safety outcomes are expected to occur during hospital admission.

Table 4. Domain-specific serious adverse reactions

Name	Definition/operationalisation	Remarks
Severe anaphylactic reaction to LMWH	**Definition:** 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 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. **Operationalisation:** Binary (yes/no)	Severe anaphylactic reactions will only be registered in the ICU (truncated to the maximum follow-up periods of 30 and 90 days) as the allocated intervention is limited to participating ICUs and severe anaphylactic reactions occurs shortly after the exposure.
Heparin-induced thrombocytopenia (HIT)	**Definition:** Testing for HIT in case of clinical suspicion will be left to the discretion of the treating physician. Definite HIT: Positive serotonin release assay or equivalent functional HIT confirmatory test. Possible HIT: Positive enzyme-linked immunosorbent assay (ELISA) or quantitative rapid immunoassay without functional HIT confirmatory test AND study medication is stopped. **Operationalisation:** Categorical (definite HIT, possible HIT, no HIT); when analysed as part of the *'one or more domain-specific safety outcomes'* outcomes, both definite HIT and possible HIT will be included. Details on each category will be presented descriptively.	HIT will only be registered in the ICU (truncated to the maximum follow-up periods of 30 and 90 days) as any HIT related to the allocated intervention is unlikely to occur after ICU discharge. Should LMWH be continued outside the domain, HIT testing will be at the discretion of the treating clinician.

Benefit-risk assessment

This domain is considered to be at risk level 1 and therefore the potential for any additional unexpected risks is expected to be very low. All types of LMWH used in this domain are currently applied in clinical practice, both in- and outside of the ICU, and also in higher ('therapeutic') doses, for example in the treatment of VTE or prevention of stroke in atrial fibrillation. As such, there is widespread experience with all four types of LMWH in the dose ranges (and even beyond) that are tested in this domain, albeit not always for prophylactic indications.

The aim of thromboprophylaxis is to reduce the risk of VTE, which may come at the cost of an increased risk of bleeding. Indeed, the risks of VTE and bleeding are the main considerations when weighing benefits and harms of different doses of LMWH for thromboprophylaxis. Other harms such as allergy, HIT, and idiosyncratic drug reactions are rare and only to a limited extent dose dependent. These will therefore generally not influence the eventual decision to treat patients with a higher LMWH dose. A network meta-analysis found a dose-response effect for both VTE and bleeding in a dataset comprised mainly of acutely ill hospitalized patients and suggested intermediate doses of LMWH performed better than low doses [8]. As discussed in section 5, there are only very sparse data on the optimal LMWH dose for prophylaxis in ICU patients, and this fact forms the rationale for this domain. Both VTE and bleeding are included as domain-specific secondary outcomes. Although not the primary or guiding outcome, the independent data monitoring and safety committee (IDMSC) assessments will include periodical review of VTE and bleeding events since both may also be regarded important safety outcomes.

LMWH dose-changes as a result of randomisation will occur: participants may be changed from a low to an intermediate or weight-based dose, or vice versa. This practice is not expected to present a meaningful risk to patients. There is no evidence to suggest that the act of changing the low-molecular-weight heparin dose is, in itself, associated with a (temporarily) increased risk of venous thromboembolism or bleeding. In daily clinical practice dose changes are common: doses are skipped due to interventions; doses may be increased or decreased when patients are transferred from the ward to the ICU or from one hospital to another; and dose changes are made when patients develop thrombosis and are given therapeutic dose low-molecular-weight heparin. Acute ICU admission (the target population of the domain) is caused by a shift in patient status (now acutely, critically ill) and is therefore associated with a re-evaluation of the indication and dosing of LMWH by the admitting ICU clinician. This occurs both for patients who are newly admitted to hospital and for those who are transferred from a regular ward. In many years of clinical experience with low-molecular-weight heparin no safety signals have emerged to suggest that this is unsafe.

The application of frequent adaptive analyses (guiding response-adaptive randomisation and potential arm-dropping) constitutes a benefit for the participants in this domain of INCEPT as they may have a higher chance of being randomised to the more favourable interventions after the first adaptive analyses and as an intervention arm is stopped as soon as there is sufficient evidence that it is inferior.

6.8 | End of domain

When the domain is closed, the competent authorities will be notified, and results 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 intervention period, defined as one or more doses of trial medication not administered per protocol (i.e., withheld for reasons other than those described in section 6.3 and **Table S13** (appendix 6, section 14.6).

Deviations in the delivery of the allocated intervention are allowed for several reasons per discretion of the treating physician, as explained in section 6.3.

Protocol adherence at each *INCEPT-Thromboprophylaxis* 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 hotline will enable discussion at any time between the clinical team and the *INCEPT* and the *INCEPT-Thromboprophylaxis* domain teams regarding the protocol.

Feasibility and separation
The *INCEPT-Thromboprophylaxis* domain will include an initial, integrated feasibility phase. Feasibility will be assessed after data collection of all feasibility outcomes (**Table 5**) for the first 300 participants has been completed. While clinical outcomes will be collected, only feasibility outcomes will be analysed after the feasibility phase. Feasibility will be assessed across all arms (i.e., not stratified by allocation), except for the feasibility outcomes related to separation within and between arms. Inclusion and delivery of the trial interventions will continue according to the approved domain specific appendix until a final decision from the feasibility phase has been made and implemented. The sample size for the integrated feasibility phase has been determined based on practical considerations [64] , sample sizes in other pilot/feasibility trials [65], and the expected precision for the estimates of the outcomes [66].

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. If changes to the protocol are deemed necessary, inclusion in the domain will be paused if required until the competent authorities have approved the applied changes. The domain will not pause inclusion while feasibility outcomes are being collected or evaluated.

No analyses of the clinical outcomes will be conducted before the feasibility phase has concluded. If the domain is stopped due to infeasibility, all included participants at that time-point will continue receiving the allocated trial interventions and follow-up, and analyses of clinical outcomes by treatment allocation will be conducted after follow-up has been completed for all included participants. If the domain is modified after the feasibility phase, a subsequent assessment of feasibility following these changes may be planned at discretion of the domain management committee after consulting the IDMSC.

The following feasibility and separation outcomes will be assessed for the full population (i.e., not stratified by treatment allocation unless otherwise stated) after the data collection for all feasibility outcomes for the first 300 participants has been completed.

Table 5. Domain-specific feasibility outcomes

Name	**Definition/operationalisation**	**Feasibility criteria**	**Expected precision**
Time to completion of the feasibility phase	Time to enrolment of the number of participants required for feasibility assessment.	<8 months	-
Recruitment proportion	Proportion of patients screened for *INCEPT-Thromboprophylaxis* who are included in the domain (the number of patients who are included in the domain divided by the number of patients screened for the domain).	≥50 %	44% to 56%
Proportion of participants without consent to continued collection of data	Proportion of participants for whom any consenting party do not consent to the continued collection of data (the number of participants for whom any consenting party do not consent to the continued collection of data divided by the number of randomised participants).	<5%	3% to 8%
Protocol adherence	Proportion of participants without protocol violations.	≥75%	70% to 80%
Retention proportion	Proportion of participants with data on the primary/guiding outcome within the outcome-data lag period.	≥95%	92% to 97%
Separation between the fixed low dose and the weight-adjusted dose arm	Proportion of participants in the weight-adjusted arm who, according to the participant's weight at baseline and the type of LMWH used on the participant's first day of domain participation, were to receive a different dose than they would receive of the same type of LMWH in the fixed low dose arm.	≥20%	16% to 25%

Separation between the fixed intermediate dose and the weight-adjusted dose arm	Proportion of participants in the weight-adjusted arm who, according to the participant's weight at baseline and the type of LMWH used on the participant's first day of domain participation, were to receive a different dose than they would receive of the same type of LMWH in the fixed intermediate dose arm.	≥20%	16% to 25%

For all binary feasibility outcomes, the expected precision of the proportions presented are the 95% confidence intervals (CIs; rounded) that would be obtained with 300 participants and a proportion matching the thresholds used to define the feasibility criteria calculated using the Clopper-Pearson method.

7 | Statistics and simulation

7.1 | Overall principles

The *INCEPT-Thromboprophylaxis* domain will be conducted using Bayesian statistical methods and adaptive stopping, arm dropping, and response-adaptive randomisation.

7.2 | Analysis sets and estimands

Analysis sets
All primary analyses of the *INCEPT-Thromboprophylaxis* 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 (the ITT population, except those with one or more protocol violations).

Estimands
The primary estimands [67,68] in the *INCEPT-Thromboprophylaxis* domain are the sample-average pairwise mean differences in the days alive out of hospital at day 30 between low, intermediate, and weight-adjusted dose LMWH regardless of protocol adherence with non-survivors assigned 0 days in acutely admitted adult ICU patients with an indication for thromboprophylaxis with LMWH (**Table 6**).

Table 6. Key attributes of the primary estimand

Attribute	Description
Population	Acutely admitted adult ICU patients with an indication for thromboprophylaxis with LMWH.
Interventions (*treatment conditions*)	LMWH for thromboprophylaxis, administered in either a fixed low, fixed intermediate, or weight-adjusted dose.
Outcome (*endpoint*)	Days alive out of hospital at day 30.
Summary measure	Sample-average pairwise mean differences.
Handling of intercurrent events	Participants analysed as randomised (i.e., according to the ITT principle) regardless of protocol adherence. Non-survivors assigned 0 days alive and out of hospital at day 30.

Key attributes of the primary estimands in the *INCEPT-Thromboprophylaxis* domain summarised according to recommendations [67,68].

Key attributes of additional, secondary estimands and sensitivity analyses are described in the applicable sections of this appendix and in the core protocol.

7.3 | Adaptive analyses and adaptation rules

Timing

The first adaptive (interim) analysis will be conducted after an initial *burn-in* period of 1,500 participants, followed by subsequent adaptive analyses after each additional 500 participants until a maximum sample size of 10,000 participants.

When the prespecified number of participants has been randomised and completed their *outcome-data lag* period (consisting of the 30-day follow-up duration for the primary and guiding outcome and a data collection and validation period of 15 days), an adaptive analysis will be conducted on the third occurring 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 and arm dropping rules will be used in the *INCEPT-Thromboprophylaxis* domain:

Superiority/inferiority:

Constant, symmetrical stopping/arm dropping rules for superiority/inferiority of 99.5% and 0.5%, respectively, will be used. The stopping rules for superiority/inferiority have been calibrated to ensure a type 1 error rate (the probability of erroneously declaring one arm overall superior) for the primary outcome below 5.0% across a range of realistic scenarios including the scenario where all arms are identical.

Practical equivalence:

The domain will be stopped for practical equivalence if there is >90% probability that the mean difference between the best and worst remaining arms is <1 day in any adaptive analysis. After domain conclusions we will also present pairwise probabilities of practical equivalence according to the same difference.

Futility:

No stopping rules for futility will be used in this domain, as there is no common control.

Stopping and communication of results

This will be handled as described in the *INCEPT* core protocol. If the domain is stopped, the reason (superiority or practical equivalence) will be openly communicated to the participating sites. It may also be communicated externally. Similarly, decisions to drop an arm (before the domain is stopped) will be communicated openly to the participating sites and may also be communicated

externally. Additional analysis details including exact probabilities, estimates, and uncertainty measures will not be communicated before all randomised 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, all participants still active in the domain may be switched to the superior intervention at the discretion of the treating clinicians. Similarly, if an arm is dropped for inferiority, participants active and randomised to that arm may be switched to another dose at the discretion of the treating clinicians. While this will lead to protocol violations in these participants, such actions are accepted for ethical reasons. If the domain is stopped for practical equivalence, all active participants should continue the allocated intervention. In case of any other important safety signals or other results that are asserted to require immediate communication, this will be done in an appropriate format without unnecessary delay as decided by the domain and platform management committees.

Primary and guiding outcome

The primary outcome, days alive out of hospital at day 30, will also be the guiding outcome on which all adaptation rules are based [40,69]. Non-survivors will be assigned 0 days [55].

7.4 | Randomisation profiles and rules

Initial stratified randomisation will use equal allocation probabilities and varying block sizes [54]. Simple (unstratified), restricted response-adaptive randomisation following the first adaptive analysis will use minimum allocation probabilities of 25% in each arm (rescaled to 37.5% if one arm is dropped and two arms remain) [40].

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, and results from the adaptive analyses will be reported as illustrated in **Table S14** to **Table S16** (appendix 7, section 14.7). Analyses will be adjusted for the baseline variables outlined in the core protocol and the following additional stratification/anticipated prognostic baseline variables: history of VTE (yes/no) and use of antiplatelet medication (yes/no).

Initially, the low dose LMWH arm will be the reference term in all analyses. If this arm is dropped in an adaptive analysis, the intermediate dose LMWH arm will subsequently be used as the reference.

Analyses will primarily use neutral, weakly informative priors, supplemented with sensitivity analyses using neutral, more informative (sceptical) priors; neutral, less informative priors; and

evidence-based priors for the outcomes where relevant external evidence is available at the time of conduct of these analyses.
Results will be presented as sample-average estimates in each intervention group. and sample-average intervention effects (i.e., pairwise mean differences [MDs], ratios of means [RoMs], risk differences [RDs], and relative risks [RRs]), with the absolute summary measures (MDs/RDs) being the primary. Results will be summarised numerically and visualised as outlined in the core protocol.

In addition, probabilities of overall superiority with each arm and pairwise superiority/inferiority between arms for all outcomes, and probabilities of practical equivalence between all arms and all active arms at the last adaptive analysis for the primary and guiding outcome will be presented.

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. Baseline characteristics considered for these analyses are displayed in **Table 7**.

Table 7. Heterogeneity of intervention effects on the primary outcome will be analysed according to the following baseline characteristics

Baseline characteristics	Definition	Expected direction of interaction
Disease severity	Baseline disease severity according to the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU; assessed on the continuous scale) [70].	Larger beneficial effects of the weight-based dose compared to the other two doses in patients with more severe disease. Similar effects of fixed low versus intermediate dose irrespective of severity.
Risk of VTE	Baseline risk of VTE according to a modified version of the 'Predicting the Risk of Venous Thromboembolism in Critically Ill Patients' score (PROVE-IT; assessed on the continuous scale).[1]	Larger beneficial effects of the weight-based dose compared to the other two doses in patients with higher risk of VTE. Similar effects of fixed low versus intermediate dose irrespective of VTE risk.
Renal function	Highest plasma creatinine in the 24 hours prior to randomisation (assessed on the continuous scale).	No substantial differences between any arms.

Platelet count	Lowest platelet count in the 24 hours prior to randomisation (assessed on the continuous scale).	No substantial differences between any arms.

[1] The PROVE-IT score has been submitted for publication but is not yet publicly available. See appendix 8, section 14.8 for more details.

Directions of heterogeneity in intervention effects are expected to be in the same directions on both the absolute and relative scales.

Analyses of heterogeneity in intervention effects for continuous baseline variables
The analyses of heterogeneity in intervention effects according to the continuous baseline variables listed above will be performed using linear regression for the primary outcome (days alive and out of hospital at day 30). The analyses will be conducted using models similar to the primary analysis model, but also including main effect terms for the baseline variable of interest and the baseline variable of interest squared, and interaction terms between the baseline variable of interest and the baseline variable of interest squared and the intervention effect indicators. We expect that the distributions of the risks of VTE (the modified PROVE-IT score), plasma creatinine, and platelet counts will be substantially right-skewed and will, thus, log2-transform the values prior to modelling. All continuous baseline variables used in the HTE analyses will be mean-centered before being entered in the models (after log2-transformation) with presentation of results on the actual scale.
The resulting models will be used to make predictions of the expected probabilities in each intervention group across a grid of values for the baseline variable of interest (covering the full range of values) as previously described [71]. Average predictions made at each grid point by using the model fit with full dataset with the covariate of interest set to the grid value, the intervention indicator first set to fixed low dose LMWH, then fixed intermediate dose LMWH, and then weight-adjusted LMWH, and all other baseline covariates at their original values. The posterior distributions of averages (means) of these predictions across all participants will be used to visualise the expected means of the primary outcome across the range of values for the baseline covariate of interest and further be used to calculate the expected average absolute and relative differences (for pair-wise comparisons between all three intervention groups) across the same range, which will also be visualised. Median posterior values will be used for point estimates with 95% percentile-based credible intervals (CrI) overlain along with visual presentations of the overall distributions of the baseline covariate of interest; the axis corresponding to the baseline covariate may be 'compressed' using an appropriate transformation to avoid giving undue space to rare values which may visually mislead. The results will be interpreted probabilistically across the range of values as a continuous measure of evidence.

Interactions with other domains
No assessment of interactions with other domains is planned.

7.7 | Priors

The exact priors are presented in appendix 9, section 14.9. The adaptive and final, primary analyses will be conducted using neutral, weakly informative priors for the intervention effects and all additional model terms, including adjustment variables. Sensitivity analyses using neutral, more informative (sceptical) priors, and using neutral, less informative priors for the intervention affects across all outcomes will be conducted.

In addition, sensitivity analyses may be conducted using evidence-based priors based on external evidence from an updated systematic review and meta-analysis at the time of conducting the final analyses. These sensitivity analyses will only be conducted for the outcomes and comparisons where sufficient, relevant external evidence is available, and none of these sensitivity analyses will be conducted if no or very limited external evidence (e.g., evidence so weak that the sensitivity analyses are not expected to provide any additional insights due to similarity with the other planned analyses and priors). At the time of writing, the external evidence is too insufficient for the specification of such analyses to be sensible (an overview is provided in appendix 9, section 14.9). The most recent evidence on the effects of thromboprophylaxis is summarised by three network meta-analyses, in postoperative surgical patients (78 trials enrolling a total of 60,068 participants for 6 comparisons) [72], acutely ill medical patients (44 trials enrolling a total of 90,095 participants for 13 comparisons) [8], and ICU patients (13 trials enrolling a total of 9,619 participants for 5 comparisons) [16], respectively. Two of these network meta-analyses were unable to estimate treatment effects on mortality because of a lack of data [16,72]. In acutely ill patients the effects of intermediate versus low-dose LMWH on mortality was uncertain due to substantial imprecision (OR 0.72; 95% CrI 0.46 to 1.1), and there were no data on comparisons of either intermediate or low-dose LMWH with weight-adjusted dose LMWH [8]. Two analyses reported the effects of a low versus a higher LMWH dose on VTE in surgical patients (OR 1.75; 95% CrI 0.79 to 3.85; moderate certainty of evidence [72]) and acutely ill medical patients (OR 1.25; 95% CrI 0.77 to 2.09; low certainty of evidence [8]). Two analyses reported effect of a low versus a higher on bleeding in surgical patients (OR 0.53; 95% CrI 0.30 to 0.94; moderate certainty of evidence [72]) and acutely ill medical patients (OR 0.77; 95% CrI 0.36 to 1.52; low certainty of evidence [8]). However, neither provided comparisons against a weight-adjusted dose [8,72].

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 [73] as outlined in the core protocol. These imputation models will include all outcomes which are available at time of analysis, all adjustment variables, and all baseline variables listed in **Table S14** (appendix 7, section 14.7), excluding SMS-ICU, predicted mortality, and predicted VTE incidence 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 in the ITT population only, except where otherwise noted. All analysis choices will reflect the corresponding choices from the primary analysis except where 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:
    - All clinical outcomes: per-protocol analysis, neutral, weakly informative priors.
- Sensitivity analyses:
    - All clinical outcomes: neutral, more informative (sceptical) priors; neutral, less informative priors; and evidence-based priors where relevant evidence is available.
    - Major bleeding: analysis restricted to participants who received the last dose of study medication ≤24 hours.
    - Days alive without life support and days alive out of hospital after 30 and 90 days and days free of delirium at 30 days: using the actual values without penalisation of death to 0 days.
    - Health-related quality of life (EQ-5D-5L index values and EQ VAS at day 180): analysis conducted in survivors only and analysis conducted in all participants using the national value set applicable to most participants [74].
    - Cognitive function (Mini MoCA at 180 days): analysis conducted in survivors only
    - All clinical outcomes: best-worst/worst-best case analyses.

7.10 | Simulations and performance metrics (including sample sizes)

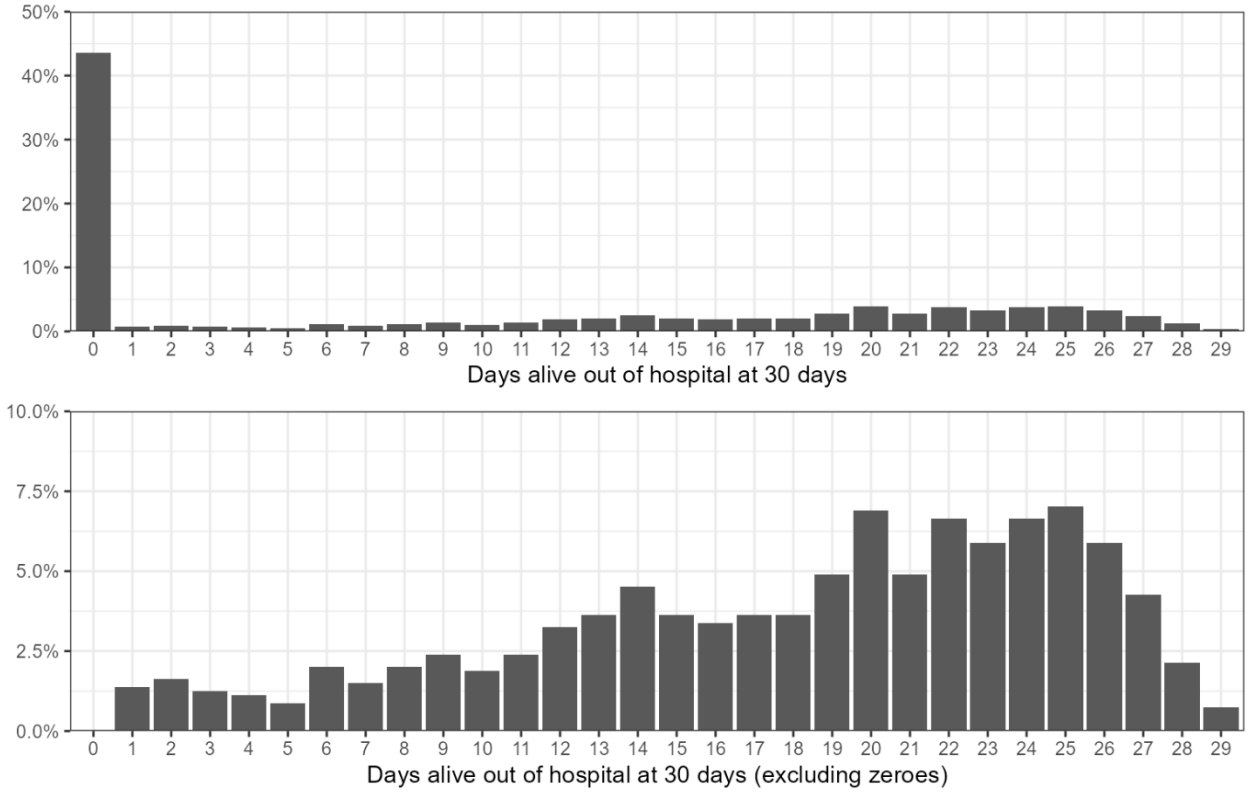
Performance metric evaluation, assumptions, and clinical scenarios

The final domain design has been developed and evaluated using statistical simulation as recommended [40], according to the principles described elsewhere [75]. The evaluations used 100,000 simulations under multiple clinical scenarios to assess multiple performance metrics. These included Bayesian analogues of type 1 error rates (probabilities of erroneously declaring

one arm overall superior) and power (the probability of stopping for superiority in scenarios with specific differences between any arms) for the primary and guiding outcome [40].

For evaluating the performance metrics, we used the distribution of days alive out of hospital at day 30 (with non-survivors assigned 0 days) from the *AFIB-ICU* cohort study [76] as the reference distribution. We began by informally comparing the distributions of days alive and out of hospital at day 30 between the *AFIB-ICU* and *Simple Intensive Care Studies (SCS)* cohorts [76,77]. Finding them comparable, we used the *AFIB-ICU* cohort distribution as the basis for the simulations. The distribution ranges from 0 days (minimum) to 29 days (maximum, as all participants were in the hospital on the first day, which will also be the case for the *INCEPT-Thromboprophylaxis* domain), and is shown in **Figure 1.**

Figure 1. Distribution of days alive out of hospital at day 30 in the *AFIB-ICU* cohort



Distribution of days alive out of hospital at 30 days in the *AFIB-ICU* cohort [76] with non-survivors assigned 0 days [55]. The upper subplot contains the entire distribution, while the lower subplot presents all values >0 to better visualise this part of the distribution.

The distribution is substantially zero-inflated with a peak at 0 days and was thus modelled using a two-part distribution (a 'hurdle-beta' distribution). A binomial distribution handled the probability of having either 0 or >0 days, with 0 days constituting who died within 30 days and were assigned 0 and those who were still in the hospital at day 30 without previous discharge. The rest of the distribution (i.e., the distribution in those with >0 days) was modelled using a beta-distribution (on

the proportion scale after dividing by the maximum value, 29 days, plus a small offset of 0.01 days to avoid having to use a third sub-distribution to handle the maximum possible value of 29 days). In summary, 43.6% of the *AFIB-ICU* cohort population had a value of 0 days (22.3% due to being dead at day 30). The overall estimated mean according to the combined distributions was 10.04 days (rounded to 10 days below; raw mean 10.2 days), with an estimated mean of approximately 18 days in those with >0 days (based on the beta distribution) and a variance of 0.058207 (calculated on the proportion out of the maximum number of days scale, so the variance is on the proportion^2 scale).

The joint distributions were used to simulate data under different clinical scenarios, with the randomly generated data being on the proportion scale converted back to number of days and rounded up to the nearest whole number of days. Upwards rounding was used to ensure that zeroes were only generated by the binomial sub-distribution and that all simulated outcome data were whole numbers, matching data registration in *INCEPT*. In the different clinical scenarios, differences were simulated by changing the overall mean value according to a desired value, without changing the variance of the beta distribution. The changes in the overall means were achieved by changing the mean proportion of days in those with >0 days, as we expect that the different interventions will mostly affect this part of the distribution (thus, if the total difference is 1 day, then the change in the part of the distribution constituting those with >0 days will correspond to a difference in the mean of 1.77 days). Due to rounding, the overall means of data simulated from the specified distributions differ slightly from the overall mean of the reference distribution (appendix 1, section 14.1).

Performance metrics were assessed under a total of 15 realistic scenarios, constituting all unique combinations of the reference distribution in one arm and no/small/large differences in the other arms in both directions. This included a *null scenario* with identical distributions in all arms and 14 scenarios with differences present. As all arms are compared simultaneously (with no arm considered a common control arm), it does not matter which arm is which for simulation-based performance evaluation. As such, arms are denoted A, B, and C in all results without these directly corresponding to any specific arm in the domain, and without simulation of the same combinations of differences in arms B and C, as this would lead to similar results.

Combinations of the following differences in both directions were assessed:

- No difference: the distribution described above was used without any changes.
- Small difference: the distribution described above was changed to obtain an approximate difference of +/- 1 day in the overall mean values. This corresponds to a relative difference of approximately 10% and is similar to the threshold used for practical equivalence, and thus reflects what we consider to be the minimum clinically important difference.

- Large difference: as above, but with a difference of +/- 2 days in the overall mean values, i.e., twice as large as the minimum clinically important difference and the threshold for practical equivalence and corresponding to a relative difference of 20%.

For the primary simulations, we assumed constant inclusion rates of 10 participants/day throughout the domain, with combined follow-up, data collection, and data verification lags of 15 days. During simulations, draws from the posterior distributions in each arm were generated from normal distributions with means corresponding to the currently estimated raw mean in each arm and standard deviations (SDs) corresponding to the standard errors of the means. These were calculated as the *SD/square root(number of participants in the arm – 1)* in each arm, to correspond to the linear regression models used in the actual analyses. Completely uninformative (i.e., improper) priors were used during simulations for simplicity. Although very weakly informative priors will be used in the actual analyses, the influence of this discrepancy will be minimal and negligible due to the accrued sample size at the time of the first adaptive analysis.

The following performance metrics [40] were assessed: sample size, total event count, total event rate, probability of conclusiveness, decision probabilities, probabilities of selecting each arm, root mean squared errors (RMSE) and median absolute errors (MAE) for the estimated mean number of days in the selected arm, and ideal design percentages (IDP) [40,78,79]. The expected (mean) sample sizes and the probabilities of conclusiveness were prioritised when deciding on the final domain design due to multiple ethical, practical, and economical considerations. We believe that the final design chosen will maximise the probability of a conclusive result within a feasible and reasonable timeframe, ensuring that care can be improved for future patients.

RMSE, MAE, and IDP were calculated in multiple ways:

1) For simulations ending in superiority only
   AND
2) Assuming that the best arm (the intervention with highest probability of being superior in the final analysis) was selected in simulations not ending with superiority.

First, the primary candidate design was evaluated, with stopping rules for superiority/inferiority calibrated to keep the type 1 error rate (the probability of erroneously declaring one superior) in the scenario with no differences present at approximately 5% (i.e., 4.9-5.0%) based on 100,000 simulations.
Several design variants were also assessed, with key design choices varied and the calibration procedure repeated in each of these scenarios [75]. These design choices included different randomisation strategies (fixed and less restricted randomisation); a different frequency for the adaptive analyses; and a stricter threshold for practical equivalence. Following these comparisons, we selected the primary candidate design and assessed the type 1 error rates (the probabilities of

erroneously declaring one arm superior) in scenarios where differences between arm were present among some or all arms and re-calibrated the stopping rules accordingly to ensure that these probabilities were <5% in all scenarios assessed. This was followed by multiple sensitivity analyses of assumptions (using the same re-calibrated stopping rules in all sensitivity analyses), assessing different underlying outcome distributions (with differences on both parts of the combined distribution and in both directions assessed) and different inclusion rates (in both directions). Key performance metrics are presented in **Table 8**; all performance metrics for the final design and all sensitivity analyses of design choices and assumptions are presented in Table **Table S1** to **Table S12** (appendix 1 section 14.1) The mean (expected) sample sizes for the final design under the scenarios investigated range from 2,265 to 4,899 participants, with probabilities of conclusiveness (i.e., superiority or practical equivalence) of ~100% in all scenarios for the primary design with the primary assumptions. The probabilities of correctly concluding superiority (power) range from 72.1% to 99.9% in scenarios where one single arm was superior.

Table 8. Key performance metrics of the final domain design under the primary assumptions

Metric	No differences	Ranges across scenarios with differences
Sample size – mean [25; 50; 75%-percentiles]	4,867 [3,950; 4,450; 5,450]	2,265 to 4,892 [1,950 to 3,450; 1,950 to 4,950; 2,450 to 5,950]
Mean number of days alive out of hospital at 30 days – mean [25; 50; 75%-percentiles]	10.3 days [10.2; 10.3; 10.4]	9.0 to 11.9 (days) [8.9 to 11.8; 9.0 to 11.9; 9.2 to 12.1]
Probability of conclusiveness	~100.0%	~100.0% to ~100.0%
Probability of superiority	0.9%	4.0% to 99.9%
Probability of practical equivalence	99.1%	0.1% to 96.0%
Probability of inconclusiveness	~0.0%	~0.0% to ~0.0%
Probability of erroneous superiority	0.1%	~0.0% to 4.6%
Root mean squared error (for estimated mean number of days in the superior arm, for simulations stopped for superiority only)	0.7 days	0.3 to 0.6 (days)
Ideal design percentage (for simulations stopped for superiority only)	-	100.0% to 100.0%

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 can be interpreted as a type 1 error rate in the scenario with no difference and as the power in the scenario with differences present [40,75]. The probability of inconclusiveness refers to the proportion of simulations stopped at the maximum sample size (10,000) without triggering any stopping rule. The probability of erroneous superiority refers to the probabilities of declaring one arm overall superior if it is not a single superior arm (i.e., if the arm is inferior to one or more other arms or if the arm is superior to one arm but equivalent to another arm). Ideal design percentages are calculated as described elsewhere [40,78,79]; this measure cannot be calculated in the scenario where no differences between arms are present.

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 3, section 14.3):

Site-specific variables:

- Site-preferred LMWH.

Screening variables:

- All interventions in this domain are considered clinically appropriate.
- Decision by the treating clinician to start thromboprophylaxis with LMWH, or to continue LMWH prophylaxis.
- More than one prophylactic dose of anticoagulation administered during current ICU stay, including ICU days in other hospitals.
- Known or suspected previous adverse reaction to any type of heparin, including allergy and HIT.
- Known pregnancy.
- Mechanical circulatory support.
- Solid organ transplant during current hospital admission.
- Weight <40kg.
- Inclusion in another interventional trial or *INCEPT* domain where co-enrolment with the *INCEPT-Thromboprophylaxis* domain is not permitted.

Baseline variables:

- History of VTE.
- Lowest platelet count in the 24 hours prior to randomisation.
- Presence of a central venous catheter.
- Suspected sepsis.
- Use of antiplatelet medication.

Variables collected daily until 90 days after domain inclusion:

- Severe anaphylactic reaction to LMWH (in participating ICUs).
- HIT (in participating ICUs).
- VTE (in hospital).
- Major bleeding (in hospital).

- Administration of the site-preferred LMWH in the allocated dose (in participating ICUs).
  If administration of the site-preferred LMWH in the allocated dose is answered 'no':
- Administered LMWH.

  If administered LMWH is answered 'enoxaparin', 'dalteparin', 'tinzaparin', or 'nadroparin'
- Deviation from the allocated dose.

  If deviation from the allocated dose is answered 'yes' and the administered LMWH is answered 'enoxaparin':
- Administered dose in mg

  If deviation from the allocated dose is answered 'yes' and the administered LMWH is answered either 'dalteparin', 'tinzaparin', or 'nadroparin':
- Administered dose in IU.

  If deviation from the allocated dose is answered 'yes' or if the administered LMWH is answered 'none':
- Reason for deviation, one or more of the following:
  - Acute or chronic kidney injury: yes/no, as judged by treating clinician.
  - Renal replacement therapy: yes/no, as defined in core protocol.
  - Invasive procedure: yes/no, as judged by the treating clinician.
  - Thrombocytopenia: yes/no, as judged by the treating clinician.
  - Use of thrombolysis: yes/no, as judged by the treating clinician.
  - Active bleeding: yes/no, active bleeding as judged by the treating clinician.
  - Start of therapeutic anticoagulation, e.g. for VTE or atrial fibrillation: yes/no, start of anticoagulation treatment, e.g. for treatment of VTE or atrial fibrillation.
  - Serious adverse reaction: yes/no, severe anaphylactic reaction or HIT, as defined in section 6.7.
  - Dose adjustment (or temporary withholding of daily dose) for another reason: yes/no, this constitutes a protocol violation.

Domain-specific and safety outcomes:
As defined in section 6.6 and section 6.7 including follow-up time-points.

Feasibility outcomes:
As defined in section 6.9.

The data collected will be presented as outlined in the core protocol and illustrated in **Table S14** to **Table S16** (appendix 7, section 14.7).

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 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 trials will be continuously updated and available at the *INCEPT* website, including any formal co-enrolment agreements. Co-enrolment with all other *INCEPT* domains active at the time of writing is permitted.

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 will be made before enrolment of the first participant.

No collaboration between the *INCEPT-Thromboprophylaxis* 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-Thromboprophylaxis* domain at the time of writing and planned future stakeholder involvement in the domain according to the research stages described by Pii and colleagues [80]. 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 existing research panels in Denmark, the Netherlands, and Sweden, to which all stakeholders were affiliated. Stakeholders consisted of 9 ICU survivors (Denmark 1, Netherlands 4, Sweden 4), 4 family members (Denmark 1, Netherlands 1, Sweden 2), 5 clinical nurses (Denmark 1, Netherlands 1, Sweden 3), and 2 clinical doctors (Denmark 1, Sweden 1) not involved in the planning or daily management of *INCEPT-Thromboprophylaxis*. Stakeholders were involved in discussions of *INCEPT-Thromboprophylaxis* domain outcomes including inputs to the primary/guiding outcome. Moreover, stakeholders could suggest potential additional domain-specific secondary outcomes. During these discussions, we found that stakeholders have different risk perceptions of different outcomes, with some most fearing the bleeding outcomes whereas others put more emphasis on thrombosis.

Recruitment (recruitment strategy and recruitment)
All abovementioned stakeholders participated in group discussions. We explored participants' perspective on the lay summary within the domain specific appendix and written information materials for INCEPT-Thromboprophylaxis to be used in the informed consent process. The information materials were translated for the purpose of stakeholder discussions.

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

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 heterogeneous intervention effects according to the presence of thrombocytopenia and kidney injury; and on the variability of LMWH effects with respect to peak anti-Xa measurements. These will be conducted alongside *INCEPT-Thromboprophylaxis* and are not part of the present domain specific appendix but will have specific protocols written and approved by the competent authorities before any enrolments; the protocols will be made publicly available prior to data analysis.

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)
Danny McAuley
Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast
Belfast, United Kingdom

IDMSC clinician
Christian Hassager
Department of Cardiology, Rigshospitalet and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

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 meetings according to the requirements outlined in the core protocol.

The IDMSC will at least meet once yearly to review safety data. 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. Additionally, for the annual safety meetings, the IDMSC will receive data regarding recruitment, protocol adherence/violations, and separation. Although not the guiding outcome, the IDMSC assessments will include review of VTE and bleeding events since both are also important safety outcomes.

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.*
Karina Meijer: *speaker fees from Alexion, participation in trial steering committees for Bayer and Astra Zeneca, consulting fees from Therini, participation in data monitoring and endpoint adjudication committee for Octapharma. All payments are to my institution*

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 *Savværkejer Jeppe Juhl og hustru Ovita Juhls Mindelegat*, *Grosserer Jakob Ehrenreich og Hustru Grete Ehrenreichs Fond*, and *Dagmar Marshalls Fond*.

The *INCEPT-Thromboprophylaxis* domain is funded by a grant from the *Novo Nordisk Foundation* and by the *Netherlands Thrombosis Foundation*.

Additional funding will be sought for *INCEPT* in general and for the *INCEPT-Thromboprophylaxis* domain.

Simulations were performed on the *UCloud* (docs.cloud.sdu.dk) 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 they have ownership of the data.

We thank Mik Wetterslev for sharing the *AFIB-ICU* cohort data to inform domain design simulations [76].

11.3 | Compensation

In *INCEPT-Thromboprophylaxis*, trial sites will receive case money according to the number of participants enrolled and followed up to support the salaries of dedicated trial staff. The compensation model will follow specifications from the *INCEPT* management committee, with an updated version 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 after 30-day follow-up concludes and later after follow-up for all outcomes conclude. 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 [81] by the platform and domain management committees according to the individual authors' contributions. 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 [42,52,82,83]

11.5 | Estimated timeline

- Third quarter, 2025: domain approved and first participant randomised
- Second quarter, 2026: feasibility phase analysis concluded
- Fourth quarter, 2028: expected inclusion of the last participant if the domain continues to the expected sample size in the scenario assessed leading to the largest expected sample size.
- Third quarter, 2030: expected inclusion of the last participant if the domain continues to the maximum sample size (n = 10,000)
- Approximately 6 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 1.2, 2026-04-01:

- Added the *Netherlands Thrombosis Foundation* as funder (section 1 and section 11.2).
- Added statement that the use of biosimilar LMWHs subject to stricter monitoring, which is not allowed, will be assessed not only at site initiation, but also systematically and regularly during domain conduct (section 6.3).
- Clarifications with regards to what is included in the *'one or more domain-specific safety outcomes'* outcomes (section 6.7), matching most recent version of the core protocol.
- Clarifications to justification for period of registration of HIT and handling of possible versus definitive HIT events in the *'one or more domain-specific safety outcomes'* outcomes (Table 4, section 6.7).
- Updates and clarifications of domain-specific feasibility outcomes (Table 5, section 6.9): clarification regarding 'recruitment proportion', consent to use of data replaced with consent to continued collection of data, and clarifications regarding how the separation-focused feasibility outcomes will be calculated.
- Correction of typo in stopping rule for inferiority in section 7.3 (unchanged in all other places, where it was correct).
- Added erroneously missing variable (sex) to the general model formula for analyses outlined in appendix 9, section 14.9 (the inclusion of this variable is defined in the core protocol).
- Clarifications and additional details on data the domain IDMSC will review at the annual meetings in addition to safety data and updates on how this will be presented (section 10.2).
- Minor corrections, updates, and semantic edits in multiple places not leading to any changes in meaning.

Version 1.1, 2025-08-20:

- Added specification in Section 6.6, Table 3, that systematic screening for DVT will not be allowed within the study protocol.
- Added consideration to the risk-benefit assessment in Section 6.7 explaining why the dose change in itself is not expected to present a meaningful risk to participants.

Version 1.0, 2025-06-25: first version submitted for approval.

13 | References

1. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Advances 2018;2:3198–225. https://doi.org/10.1182/bloodadvances.2018022954.

2. Bounes F, Ferrandis R, Frere C, Helms J, Llau JV. European guidelines on peri-operative venous thromboembolism prophylaxis: first update.: Chapter 4: Prophylaxis in critical care patients. European Journal of Anaesthesiology | EJA 2024;41:582. https://doi.org/10.1097/EJA.0000000000002011.

3. National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. 2018;Available from: https://www.nice.org.uk/guidance/ng89.

4. Tran A, Fernando SM, Rochwerg B, Cook DJ, Crowther MA, Fowler RA, et al. Prognostic Factors Associated With Development of Venous Thromboembolism in Critically Ill Patients—A Systematic Review and Meta-Analysis. Critical Care Medicine 2022;50:e370. https://doi.org/10.1097/CCM.0000000000005382.

5. Dalteparin versus Unfractionated Heparin in Critically Ill Patients. The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. New England Journal of Medicine 2011;364:1305–14. https://doi.org/10.1056/nejmoa1014475.

6. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. New England Journal of Medicine 2021;385:777–89. https://doi.org/10.1056/nejmoa2103417.

7. Vigneron C, Devautour C, Charpentier J, Birsen R, Jamme M, Pène F. Severe bleeding events among critically ill patients with haematological malignancies. Annals of Intensive Care 2024;14:155. https://doi.org/10.1186/s13613-024-01383-2.

8. Eck RJ, Elling T, Sutton AJ, Wetterslev J, Gluud C, van der Horst ICC, et al. Anticoagulants for thrombosis prophylaxis in acutely ill patients admitted to hospital: systematic review and network meta-analysis. BMJ 2022;e070022. https://doi.org/10.1136/bmj-2022-070022.

9. Heijkoop ÈRH, Keus F, Møller MH, Perner A, Morgan M, Abdelhadi A, et al. Preferences for thromboprophylaxis in the intensive care unit: An international survey. Acta Anaesthesiologica Scandinavica 2025;69:e70009. https://doi.org/10.1111/aas.70009.

10. Minet CC, Potton L, Bonadona AA, Hamidfar-Roy RR, Somohano CA, Lugosi M, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Critical care (London, England) 2015;19:287. https://doi.org/10.1186/s13054-015-1003-9.

11. Makedonov I, Kahn SR, Abdulrehman J, Schulman S, Delluc A, Gross P, et al. Prevention of the Postthrombotic Syndrome with Anticoagulation: A Narrative Review. Thromb Haemost 2022;122:1255–64. https://doi.org/10.1055/a-1711-1263.

12. Luijten D, Talerico R, Barco S, Cannegieter SC, Delcroix M, Ende-Verhaar YM, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: an updated systematic review and meta-analysis. European Respiratory Journal [Internet] 2023 [cited 2024 Nov 15];62. Available from: https://publications.ersnet.org/content/erj/62/1/2300449. https://doi.org/10.1183/13993003.00449-2023.

13. Anderson FA, Spencer FA. Risk Factors for Venous Thromboembolism. Circulation 2003;107:I–9. https://doi.org/10.1161/01.CIR.0000078469.07362.E6.

14. Darzi AJ, Karam SG, Charide R, Etxeandia-Ikobaltzeta I, Cushman M, Gould MK, et al. Prognostic factors for VTE and bleeding in hospitalized medical patients: A systematic review and meta-analysis. Blood 2020;135:1788–810. https://doi.org/10.1182/BLOOD.2019003603.

15. Beitland S, Sandven I, Kjaervik LK, Sandset PM, Sunde K, Eken T. Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in intensive care patients: a systematic review with meta-analysis and trial sequential analysis. Intensive care medicine 2015;41:1209–19. https://doi.org/10.1007/s00134-015-3840-z.

16. Fernando SM, Tran A, Cheng W, Sadeghirad B, Arabi YM, Cook DJ, et al. VTE Prophylaxis in Critically Ill Adults: A Systematic Review and Network Meta-analysis. Chest 2022;161:418–28. https://doi.org/10.1016/j.chest.2021.08.050.

17. Alikhan R, Bedenis R, Cohen AT. Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction). The Cochrane database of systematic reviews 2014;5:CD003747. https://doi.org/10.1002/14651858.CD003747.pub4.

18. Fraisse F, Holzapfel L, Coulaud JM, Simonneau G, Bedock B, Feissel M, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. American Journal of Respiratory and Critical Care Medicine 2000;161:1109–14. https://doi.org/10.1164/ajrccm.161.4.9807025.

19. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ (Clinical research ed.) 2006;332:325–9. https://doi.org/10.1136/bmj.38733.466748.7C.

20. Chi G, Gibson CM, Kalayci A, Cohen AT, Hernandez AF, Hull RD, et al. Extended-duration betrixaban versus shorter-duration enoxaparin for venous thromboembolism prophylaxis in critically ill medical patients: an APEX trial substudy. Intensive Care Medicine 2019;45:477–87. https://doi.org/10.1007/s00134-019-05565-6.

21. Neumann I, Izcovich A, Zhang Y, Rada G, Kahn SR, Spencer F, et al. DOACs vs LMWHs in hospitalized medical patients: A systematic review and meta-analysis that informed 2018 ASH guidelines. Blood Advances 2020;4:1512–7. https://doi.org/10.1182/bloodadvances.2019000840.

22. Swedish Medical Products Agency. Sök läkemedelsfakta [Internet]. https://www.lakemedelsverket.se/sv [cited 2025 Apr 21];Available from: https://www.lakemedelsverket.se/sv/sok-lakemedelsfakta.

23. Estonia State Agency of Medicines. Register of Medicinal Products [Internet]. [cited 2025 Apr 21];Available from: https://www.ravimiregister.ee/en/default.aspx?pv=HumRavimid.Ravim&vid=3d9b5346-a2e8-41b8-85dd-97a0455ea53a.

24. Finnish Medicines Agency. FimeaWeb [Internet]. Fimea [cited 2025 Apr 21];Available from: https://fimea.fi/databases_and_registers/fimeaweb.

25. College ter Beoordeling van Geneesmiddelen. Geneesmiddeleninformatiebank [Internet]. 2014 [cited 2025 Apr 21];Available from: https://www.geneesmiddeleninformatiebank.nl.

26. Norwegian Medicines Agency. Legemiddelsøk [Internet]. Legemiddelsøk [cited 2025 Apr 21];Available from: https://www.legemiddelsok.no:443/.

27. Danish Medicines Agency. Laegemiddelstyrelsen [Internet]. [cited 2025 Apr 21];Available from: https://www.produktresume.dk/AppBuilder/search?utf8=%E2%9C%93&id=&type=&q=&button=search.

28. Takkuner O, Alaspaa A, Heinonen P, Huotilainen H, Hynninen M. Comparison of two low-molecular weight heparins (dalteparin and enoxaparin) in the prevention of thromboembolism in intensive care patients. European Journal of Anaesthesiology 1996;13:192.

29. Robinson S, Zincuk A, Strom T, Larsen TB, Rasmussen B, Toft P, et al. Enoxaparin, effective dosage for intensive care patients: double-blinded, randomised clinical trial. Critical care (London, England) 2010;14:R41. https://doi.org/10.1186/cc8924.

30. Abbas MS. Bemiparin versus enoxaparin in the prevention of venous thromboembolism among intensive care unit patients. Indian Journal of Critical Care Medicine 2017;21:419–23. https://doi.org/10.4103/ijccm.IJCCM.

31. Robinson S, Zincuk A, Larsen UL, Ekstrøm C, Nybo M, Rasmussen B, et al. A comparative study of varying doses of enoxaparin for thromboprophylaxis in critically ill patients: A double-blinded, randomised controlled trial. Critical Care 2013;17:R75. https://doi.org/10.1186/cc12684.

32. Lim W, Meade M, Lauzier F, Zarychanski R, Mehta S, Lamontagne F, et al. Failure of anticoagulant thromboprophylaxis: Risk factors in medical-surgical critically Ill patients. Critical Care Medicine 2015;43:401–10. https://doi.org/10.1097/CCM.0000000000000713.

33. Labbé V, Contou D, Heming N, Megarbane B, Razazi K, Boissier F, et al. Effects of Standard-Dose Prophylactic, High-Dose Prophylactic, and Therapeutic Anticoagulation in Patients With Hypoxemic COVID-19 Pneumonia: The ANTICOVID Randomized Clinical Trial. JAMA Internal Medicine 2023;183:520–31. https://doi.org/10.1001/jamainternmed.2023.0456.

34. Perepu US, Chambers I, Wahab A, Ten Eyck P, Wu C, Dayal S, et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial. Journal of Thrombosis and Haemostasis 2021;19:2225–34. https://doi.org/10.1111/jth.15450.

35. Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality among Patients with COVID-19 Admitted to the Intensive Care Unit. JAMA 2021;325:1620–30. https://doi.org/10.1001/jama.2021.4152.

36. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients with COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Internal Medicine 2021;181:1612–20. https://doi.org/10.1001/jamainternmed.2021.6203.

37. Zuily S, Lefèvre B, Sanchez O, Vendin OE de, Ciancio G de, Arlet JB, et al. Effect of weight-adjusted intermediate-dose versus fixed-dose prophylactic anticoagulation with low-molecular-weight heparin on venous thromboembolism among noncritically and critically ill patients with COVID-19: the COVI-DOSE trial, a multicenter, randomised, open-label, phase 4 trial. eClinicalMedicine [Internet] 2023 [cited 2023 Dec 5];60. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00208-0/fulltext#tbl1. https://doi.org/10.1016/j.eclinm.2023.102031.

38. Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. BMJ 2010;341:c3920. https://doi.org/10.1136/bmj.c3920.

39. Ten Cate H. Surviving Covid-19 with Heparin? The New England journal of medicine 2021;385:845–6. https://doi.org/10.1056/NEJMe2111151.

40. Granholm A, Kaas-Hansen BS, Lange T, Schjørring OL, Andersen LW, Perner A, et al. An overview of methodological considerations regarding adaptive stopping, arm dropping, and randomization in clinical trials. Journal of Clinical Epidemiology 2023;153:45–54. https://doi.org/10.1016/j.jclinepi.2022.11.002.

41. Granholm A, Alhazzani W, Derde LPG, Angus DC, Zampieri FG, Hammond NE, et al. Randomised clinical trials in critical care: past, present and future. Intensive Care Med 2022;48:164–78. https://doi.org/10.1007/s00134-021-06587-9.

42. Krag M, Marker S, Perner A, Wetterslev J, Wise MP, Schefold JC, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. New England Journal of Medicine 2018;379:2199–208. https://doi.org/10.1056/NEJMoa1714919.

43. Chan AW, Boutron I, Hopewell S, Moher D, Schulz KF, Collins GS, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. BMJ 2025;389:e081477. https://doi.org/10.1136/bmj-2024-081477.

44. Dimairo M, Pallmann P, Wason J, Todd S, Jaki T, Julious SA, et al. The Adaptive designs CONSORT Extension (ACE) statement: a checklist with explanation and elaboration guideline for reporting randomised trials that use an adaptive design. BMJ 2020;369:m115. https://doi.org/10.1136/bmj.m115.

45. Merli GJ, Groce JB. Pharmacological and clinical differences between low-molecular-weight heparins implications for prescribing practice and therapeutic interchange. P and T 2010;35:95–105.

46. Nightingale SL. From the Food and Drug Administration. JAMA 1993;270:1672.

47. Therapeutic Goods Administration. Australian Register of Therapeutic Goods [Internet]. [cited 2025 Apr 21];Available from: https://www.tga.gov.au/resources/artg.

48. US Food and Drug Administration. FDA Label Search [Internet]. [cited 2025 Apr 21];Available from: https://nctr-crs.fda.gov/fdalabel/ui/search.

49. List of medicines under additional monitoring | European Medicines Agency (EMA) [Internet]. 2025 [cited 2025 Feb 17];Available from: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/medicines-under-additional-monitoring/list-medicines-under-additional-monitoring.

50. Munch MW, Meyhoff TS, Helleberg M, Kjær MBN, Granholm A, Hjortsø CJS, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: The COVID STEROID randomised, placebo-controlled trial. Acta Anaesthesiologica Scandinavica 2021;65:1421–30. https://doi.org/10.1111/aas.13941.

51. The COVID STEROID 2 Trial Group. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. JAMA 2021;326:1807–17. https://doi.org/10.1001/jama.2021.18295.

52. Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. New England Journal of Medicine 2022;386:2459–70. https://doi.org/10.1056/NEJMoa2202707.

53. INCEPT platform. INCEPT-Albumin protocol [Internet]. 2025 [cited 2025 Apr 22];Available from: https://incept.dk/albumin/.

54. Altman DG, Bland JM. How to randomise. BMJ 1999;319:703–4. https://doi.org/10.1136/bmj.319.7211.703.

55. Granholm A, Kaas-Hansen BS, Lange T, Munch MW, Harhay MO, Zampieri FG, et al. Use of days alive without life support and similar count outcomes in randomised clinical trials – an overview and comparison of methodological choices and analysis methods. BMC Medical Research Methodology 2023;23:139. https://doi.org/10.1186/s12874-023-01963-z.

56. Herdman M, Gudex C, Lloyd A, Janssen Mf, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36. https://doi.org/10.1007/s11136-011-9903-x.

57. MoCA Test Inc. MoCA Cognition 2023 [cited 2025 Mar 5];Available from: https://mocacognition.com/.

58. Nasreddine ZS. MoCA Test: Validation of a five-minute telephone version. Alzheimer's & Dementia 2021;17:e057817. https://doi.org/10.1002/alz.057817.

59. Kjær MBN, Bruun CRL, Granholm A, Møller MH, Rasmussen BS, Mortensen CB, et al. A Core Outcome Set for Adult General ICU Patients. Critical Care Medicine 2025;53:e575–89. https://doi.org/10.1097/CCM.0000000000006556.

60. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of thrombosis and haemostasis : JTH 2005;3:692–4. https://doi.org/10.1111/j.1538-7836.2005.01204.x.

61. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. Journal of thrombosis and haemostasis : JTH 2010;8:202–4. https://doi.org/10.1111/j.1538-7836.2009.03678.x.

62. Lægemiddelstyrelsen (The Danish Medicines Agency). Medicines with stricter reporting requirements for doctors, dentists, veterinarians, midwives and prescribing pharmacists [Internet]. 2024 [cited 2025 Jun 12];Available from: https://laegemiddelstyrelsen.dk/en/sideeffects/side-effects-of-medicines/medicines-with-stricter-reporting-requirements/.

63. Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use [Internet]. 2017 [cited 2024 Jul 30];Available from: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en.

64. Pilot Studies: Common Uses and Misuses [Internet]. NCCIH [cited 2024 Sep 9];Available from: https://www.nccih.nih.gov/grants/pilot-studies-common-uses-and-misuses.

65. Totton N, Lin J, Julious S, Chowdhury M, Brand A. A review of sample sizes for UK pilot and feasibility studies on the ISRCTN registry from 2013 to 2020. Pilot and Feasibility Studies 2023;9:188. https://doi.org/10.1186/s40814-023-01416-w.

66. Teresi JA, Yu X, Stewart AL, Hays RD. Guidelines for Designing and Evaluating Feasibility Pilot Studies. Medical Care 2022;60:95. https://doi.org/10.1097/MLR.0000000000001664.

67. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials 2020 [Internet]. 2020 [cited 2025 Mar 26];Available from: https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials-scientific-guideline.

68. Kahan BC, Hindley J, Edwards M, Cro S, Morris TP. The estimands framework: a primer on the ICH E9(R1) addendum. BMJ 2024;384:e076316. https://doi.org/10.1136/bmj-2023-076316.

69. Granholm A, Jensen AKG, Lange T, Kaas-Hansen BS. adaptr: an R package for simulating and comparing adaptive clinical trials. Journal of Open Source Software 2022;7:4284. https://doi.org/10.21105/joss.04284.

70. Granholm A, Perner A, Krag M, Hjortrup PB, Haase N, Holst LB, et al. Development and internal validation of the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU). Acta Anaesthesiologica Scandinavica 2018;62:336–46. https://doi.org/10.1111/aas.13048.

71. Granholm A, Munch MW, Meier N, Sjövall F, Helleberg M, Hertz FB, et al. Empirical meropenem versus piperacillin/tazobactam for adult patients with sepsis (EMPRESS) trial: Protocol. Acta Anaesthesiologica Scandinavica 2024;68:1107–19. https://doi.org/10.1111/aas.14441.

72. Marcucci M, Etxeandia-Ikobaltzeta I, Yang S, Germini F, Gupta S, Agarwal A, et al. Benefits and harms of direct oral anticoagulation and low molecular weight heparin for thromboprophylaxis in patients undergoing non-cardiac surgery: systematic review and network meta-analysis of randomised trials. BMJ 2022;376:e066785. https://doi.org/10.1136/bmj-2021-066785.

73. Vesin A, Azoulay E, Ruckly S, Vignoud L, Rusinovà K, Benoit D, et al. Reporting and handling missing values in clinical studies in intensive care units. Intensive Care Med 2013;39:1396–404. https://doi.org/10.1007/s00134-013-2949-1.

74. Devlin N, Parkin D, Janssen B. Methods for Analysing and Reporting EQ-5D Data [Internet]. Cham: Springer International Publishing; 2020 [cited 2024 Sep 2]. Available from: https://link.springer.com/10.1007/978-3-030-47622-9. https://doi.org/10.1007/978-3-030-47622-9.

75. Granholm A, Jensen AKG, Lange T, Perner A, Møller MH, Kaas-Hansen BS. Designing and evaluating advanced adaptive randomised clinical trials: a practical guide [Internet]. 2025 [cited 2025 Mar 26];Available from: http://arxiv.org/abs/2501.08765. https://doi.org/10.48550/arXiv.2501.08765.

76. Wetterslev M, Hylander Møller M, Granholm A, Hassager C, Haase N, Lange T, et al. Atrial Fibrillation (AFIB) in the ICU: Incidence, Risk Factors, and Outcomes: The International AFIB-ICU Cohort Study*. Critical Care Medicine 2023;51:1124. https://doi.org/10.1097/CCM.0000000000005883.

77. Hiemstra B, Koster G, Wiersema R, Hummel YM, van der Harst P, Snieder H, et al. The diagnostic accuracy of clinical examination for estimating cardiac index in critically ill patients: the Simple Intensive Care Studies-I. Intensive Care Medicine 2019;45:190–200. https://doi.org/10.1007/s00134-019-05527-y.

78. Viele K, Saville BR, McGlothlin A, Broglio K. Comparison of response adaptive randomization features in multiarm clinical trials with control. Pharmaceutical Statistics 2020;19:602–12. https://doi.org/10.1002/pst.2015.

79. Viele K, Broglio K, McGlothlin A, Saville BR. Comparison of methods for control allocation in multiple arm studies using response adaptive randomization. Clinical Trials 2020;17:52–60. https://doi.org/10.1177/1740774519877836.

80. Pii KH, Schou LH, Piil K, Jarden M. Current trends in patient and public involvement in cancer research: A systematic review. Health Expect 2019;22:3–20. https://doi.org/10.1111/hex.12841.

81. International Committee of Medical Journal Editors. Defining the Role of Authors and Contributors [Internet]. [cited 2025 Mar 19];Available from: https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

82. Schjørring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, et al. Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. New England Journal of Medicine 2021;384:1301–11. https://doi.org/10.1056/NEJMoa2032510.

83. Andersen-Ranberg NC, Poulsen LM, Perner A, Wetterslev J, Estrup S, Hästbacka J, et al. Haloperidol for the Treatment of Delirium in ICU Patients. New England Journal of Medicine 2022;387:2425–35. https://doi.org/10.1056/NEJMoa2211868.

84. Food and Drug Administration. Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry [Internet]. 2020 [cited 2025 Apr 22];Available from:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry.

85. Beta distribution [Internet]. In: Wikipedia. 2025 [cited 2025 Apr 22]. Available from: https://en.wikipedia.org/w/index.php?title=Beta_distribution&oldid=1284886665.

86. Delignette-Muller ML, Dutang C. **fitdistrplus** : An *R* Package for Fitting Distributions. J. Stat. Soft. [Internet] 2015 [cited 2025 Apr 22];64. Available from: http://www.jstatsoft.org/v64/i04/. https://doi.org/10.18637/jss.v064.i04.

87. Nørskov AK, Lange T, Nielsen EE, Gluud C, Winkel P, Beyersmann J, et al. Assessment of assumptions of statistical analysis methods in randomised clinical trials: the what and how. BMJ Evidence-Based Medicine 2021;26:121–6. https://doi.org/10.1136/bmjebm-2019-111268.

88. Granholm A, Lange T, Harhay MO, Jensen AKG, Perner A, Møller MH, et al. Effects of duration of follow-up and lag in data collection on the performance of adaptive clinical trials. Pharmaceutical Statistics 2024;23:138–50. https://doi.org/10.1002/pst.2342.

89. Gramacy RB. Surrogates [Internet]. In: Chapter 5 Gaussian Process Regression. [cited 2025 Apr 22]. Available from: https://bookdown.org/rbg/surrogates/chap5.html.

90. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, Van Bentum-Puijk W, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. Annals ATS 2020;17:879–91. https://doi.org/10.1513/AnnalsATS.202003-192SD.

91. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332. https://doi.org/10.1136/bmj.c332.

92. Atiq F, van den Bemt PMLA, Leebeek FWG, van Gelder T, Versmissen J. A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency. European journal of clinical pharmacology 2015;71:921–9. https://doi.org/10.1007/s00228-015-1880-5.

93. Mahe I, Aghassarian M, Drouet L, Bal dit-Sollier C, Lacut K, Heilmann JJ, et al. Tinzaparin and enoxaparin given at prophylactic dose for eight days in medical elderly patients with impaired renal function. A comparative pharmacokinetic study. Thrombosis and haemostasis 2007;98:581–6. https://doi.org/10.1160/TH06.

94. Projean D, Lalonde S, Morin J, Nogues E, Séguin A, Vincent A, et al. Study of the bioaccumulation of tinzaparin in renally impaired patients when given at prophylactic doses - The STRIP study. Thrombosis Research 2019;174:48–50. https://doi.org/10.1016/j.thromres.2018.11.031.

95. James Douketis, MD F, Deborah Cook, MD, MSc F, Maureen Meade, MD F, Gordon Guyatt, MD F, William Geerts, MD F, Yoanna Skrobik, MD F, et al. Prophylaxis Against Deep Vein Thrombosis in Critically Ill Patients With Severe Renal Insufficiency With the Low-Molecular-Weight Heparin Dalteparin. Archives of internal medicine 2008;168:1805–12.

96. Eck RJ, van de Leur JJCM, Wiersema R, Cox EGM, Bult W, Spanjersberg AJ, et al. Trough anti-Xa activity after intermediate dose nadroparin for thrombosis prophylaxis in critically ill patients with COVID-19 and acute kidney injury. Sci Rep 2022;12:17408. https://doi.org/10.1038/s41598-022-21560-2.

97. Hene IZ, Wiertz NR, Van Schilfgaarde M, Wester JPJ, Leyte A OVSH. Nadroparin anticoagulation in continuous venovenous hemofiltration (CVVH): kinetics and extracorporeal removal. Intensive CareMed 35:S44 2009;

98. Atiq F, van den Bemt PMLA, Leebeek FWG, van Gelder T, Versmissen J. No accumulation of a prophylactic dose of nadroparin in moderate renal insufficiency. The Netherlands journal of medicine 2015;73:373–8.

99. Eck RJ, Hulshof L, Wiersema R, Thio CHL, Hiemstra B, van den Oever NCG, et al. Incidence, prognostic factors, and outcomes of venous thromboembolism in critically ill patients: data from two prospective cohort studies. Critical Care 2021;25:1–9. https://doi.org/10.1186/s13054-021-03457-0.

100. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Critical Care Medicine 2003;31:1250. https://doi.org/10.1097/01.CCM.0000050454.01978.3B.

101. Austin PC, Steyerberg EW. The Integrated Calibration Index (ICI) and related metrics for quantifying the calibration of logistic regression models. Statistics in Medicine 2019;38:4051–65. https://doi.org/10.1002/sim.8281.

102. Mortensen CB, Andersen-Ranberg NC, Poulsen LM, Granholm A, Rasmussen BS, Kjær MBN, et al. Long-term outcomes with haloperidol versus placebo in acutely admitted adult ICU patients with delirium. Intensive Care Med 2024;50:103–13. https://doi.org/10.1007/s00134-023-07282-7.

103. Granholm A, Munch MW, Møller MH, Lange T, Perner A. Choice of priors: how much scepticism is appropriate? Intensive Care Med 2022;48:372–3. https://doi.org/10.1007/s00134-021-06613-w.

104. Granholm A, Lange T, Harhay MO, Perner A, Møller MH, Kaas-Hansen BS. Effects of sceptical priors on the performance of adaptive clinical trials with binary outcomes. Pharmaceutical Statistics 2024;23:728–41. https://doi.org/10.1002/pst.2387.

14 | Appendices

14.1 | Appendix 1: 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 [71] and the *INCEPT-Albumin* domain [53].
Simulations were conducted in R v4.5.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the *adaptr* package (inceptdk.github.io/adaptr) v1.4.0 [69]. We conducted 100,000 simulations for each design considered as recommended [84] and described in the core protocol.

Model and priors
Data generation model
As described in section 7.10, the expected reference distribution for the primary and guiding outcome (days alive out of hospital at 30 days [DAOH30]) was based on the distribution of the same outcome in the *AFIB-ICU* cohort population (1,414 participants with available data) [76]. The distribution ranged from 0 (minimum) to 29 (maximum) days, due to all participants being in the hospital at the time of inclusion. Non-survivors were assigned 0 days [55]. As illustrated in **Figure 1** in section 7.10, the distribution was substantially zero-inflated with 43.6% 0'es, of which 22.3% were due to mortality at day 30 [76]. The overall mean was 10.2 days, with a mean of 18.1 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 (43.6% 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 [85]. We fitted a beta distribution to the subset of the *AFIB-ICU* population with >0 days using the *fitdistrplus* R package v1.1-11 [86] after dividing the DAOH30 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 was no maximum-inflation, a three-part model [55] was not used). The estimated mean proportion was 0.61 (corresponding to 17.8 days in those with >0 days, and 10.04 [shortened to 10 below] days in the full distribution including those with 0 days) and the estimated variance on the proportion scale was 0.058207 (standard deviation [SD] 0.2413).
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 one arm during the simulations. Similarly, the proportion of zeroes were unchanged during simulations, while the mean number of days in those with >0 days were changed according to different scenarios in the two arms other arms, with the *beta* model variance unchanged in all clinical scenarios simulated. This was done as the overall changes in the number of DAOH30 are what drives the simulation results, and as we expect that differences mediated by the intervention will primarily be on the number of days alive out of hospital in those with >0 days and not on the proportion of zeroes. 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 **Table S1** to **Table S12** below.

Analysis model and priors

During simulations, a simple model using a normal distribution for the posterior mean number of DAOH30 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 uncertainty in this estimate [55] 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) [55,87].

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 weakly informative priors for the intervention effects (section 7.7 and appendix 8, section 14.8) will be used to stabilise and the speed up the Markov chain Monte Carlo sampling. However, these priors are so weak that they 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 for all adaptations and decision rules.

Timing of analyses

The first adaptive analyses were conducted once data for the primary and guiding outcome data were available for 1,500 simulated participants, with subsequent analyses after each additional 500 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 10 participants per day, on previous trials by our group in which overall inclusion rates have been approximately constant after initiation of most sites, e.g., *SUP-ICU* [42], *HOT-ICU* [82], *COVID STEROID 2* [51], *CLASSIC* [52], and *AID-ICU* [83]. 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 [88].

Scenarios

The performance of the *INCEPT-Thromboprophylaxis* domain design was evaluated under a number of realistic clinical scenarios as described in section 7.10:

- No difference (null scenario): identical distributions in all three arms (all MDs 0 days)
- 14 scenarios with small and large differences present between some or all arms: one arm with the reference distribution as described above, and in the other two arms, all unique combinations of no difference (MD 0 days), small positive difference (MD ~1 day), small negative difference (MD ~-1 day), large positive difference (MD ~2 days), and large negative difference (MD ~-2 days). The small and large differences correspond to relative differences of approximately 10% and 20%, respectively.

As all arms are compared simultaneously with no arm being designated as the control arm, it did not matter which arm is which for the purposes of the simulations. Thus, only unique combinations of the differences were assessed. Arms were denoted A (always using the reference distribution), B and C in the simulations. Below, scenarios are denoted as ND (null scenario, no differences) and then as the simulated arm names and (approximate) differences, e.g., “B +1 C -2” for a scenario with a small positive mean difference of 1 day in arm B compared with arm A and a large negative mean difference of 2 days in arm C compared with arm A.

Adaptation rules

Constant, symmetrical stopping thresholds for superiority and inferiority were used for all trial designs assessed; thresholds for superiority are reported below, with all stopping thresholds for

inferiority defined as 1 minus the stopping threshold for superiority. Stopping thresholds were calibrated to control type 1 error rates as described below.
Simulations were stopped for practical equivalence according to the stopping rules described in section 7.3. The initial and subsequent allocation rules were as outlined in section 7.4.

Performance metrics

Multiple performance metrics [40,69,75] 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 out of hospital (total number of days in all arms in the simulations; same summary measures as for #1)
3) Mean number of days alive out of hospital (mean number of days across all arms in the simulations, i.e., total number of days alive out of hospital/sample size; 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 differences present and the power in scenarios with differences present [40].
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(maximum): 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(arm A/B/C superior): the probabilities of declaring arm A/B/C superior, i.e., the proportion of simulations with the A/B/C arm triggering the stopping rule for superiority. Repeated for each arm.
9) Pr(no arm 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.
10) Pr(erroneous superiority): the combined probabilities of declaring overall superiority for any arm that is not the single superior arm in a scenario.
11) RMSE (superiority only): the root mean squared error (RMSE) of the estimated versus the true simulated mean number of days alive out of hospital in the superior arm (only calculated for simulations 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 out of hospital in the superior arm (only calculated for simulations stopped for superiority; days).
13) IDP (superiority only): the ideal design percentage (IDP, %) [40,78,79], for simulations ending in superiority only. The IDP is 100% for a design that always ends selecting the best

arm and lower otherwise, with selection of a substantially inferior arm affecting the IDP more than selection of slightly inferior arm and can only be calculated for scenarios with differences between arms.

14) RMSE (select best arm in inconclusive simulations): the RMSE of the estimated versus the true simulated mean number of days alive out of hospital 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 out of hospital 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.

Final design and variants

Evaluation process

Results from the simulation-based evaluation of the final *INCEPT-Thromboprophylaxis* domain design (**Table S1**) and several variants (**Table S2** to **Table S12**) are summarised here. Details are included in the tables, including the range of metrics across all scenarios evaluated and the *actual* overall means in each arm in each scenario. First, the primary candidate design was evaluated with probability thresholds *calibrated* to obtain a probability of ultimately stopping for superiority of approximately 5% in the scenario without differences, corresponding to the domain-wise type 1 error rate in this scenario [40,75]. Calibration was performed using a Gaussian process-based Bayesian optimisation algorithm [89] 100,000 simulations for each evaluation step, and a tolerance range of 4.9-5.0% for the probability of superiority in the scenario without differences. Second, we conducted sensitivity analyses of several design variants. As the design choices varied in these analyses were fixed, stopping rules for superiority and inferiority were re-calibrated in these scenarios as described above. Third, we decided to proceed with the overall initial design, but manually re-calibrated stopping rules to ensure that the type 1 error rate, defined as the probability of erroneously declaring one arm as overall superior (i.e., if the arm is truly inferior to one or more arms or exactly equivalent to one or more arms, even if one arm is inferior to two equivalent arms), was below 5% in all the scenarios assessed.

Fourth, we conducted a number of sensitivity analyses of assumptions, which are by definition not controllable by us. Here, we used the final design with the re-calibrated stopping rules described above, without further re-calibration due to the assumed values inherently being unknown [75]. As stopping rules are not re-calibrated in these sensitivity analyses, the probabilities of erroneous superiority decisions may deviate from the tolerated maximum used for the manual re-calibration, and this is a central reason for doing these sensitivity analyses. Except where noted otherwise, all

design choices and assumptions reflect those from the primary trial design. Of note, results from the initial primary design can sensibly be compared to the results of the first set of sensitivity analysis of design choices due to the use of the same calibration strategy (i.e., stopping rules for each variant re-calibrated in the scenario with no differences present). Similarly, results from the final primary design can be sensibly compared to the results of the second set of sensitivity analyses assessing assumptions due to the use of the same manually re-calibrated stopping rules. However, results from the different sets of simulations are not directly comparable due to different calibration targets (i.e., the first sets of simulations were all calibrated to keep type 1 error rates at or below 5% in the scenario with no differences present, whereas the second set of simulations used stricter stopping rules calibrated to keep type 1 error rates at or below 5% across all scenarios assessed, as described above).

Results

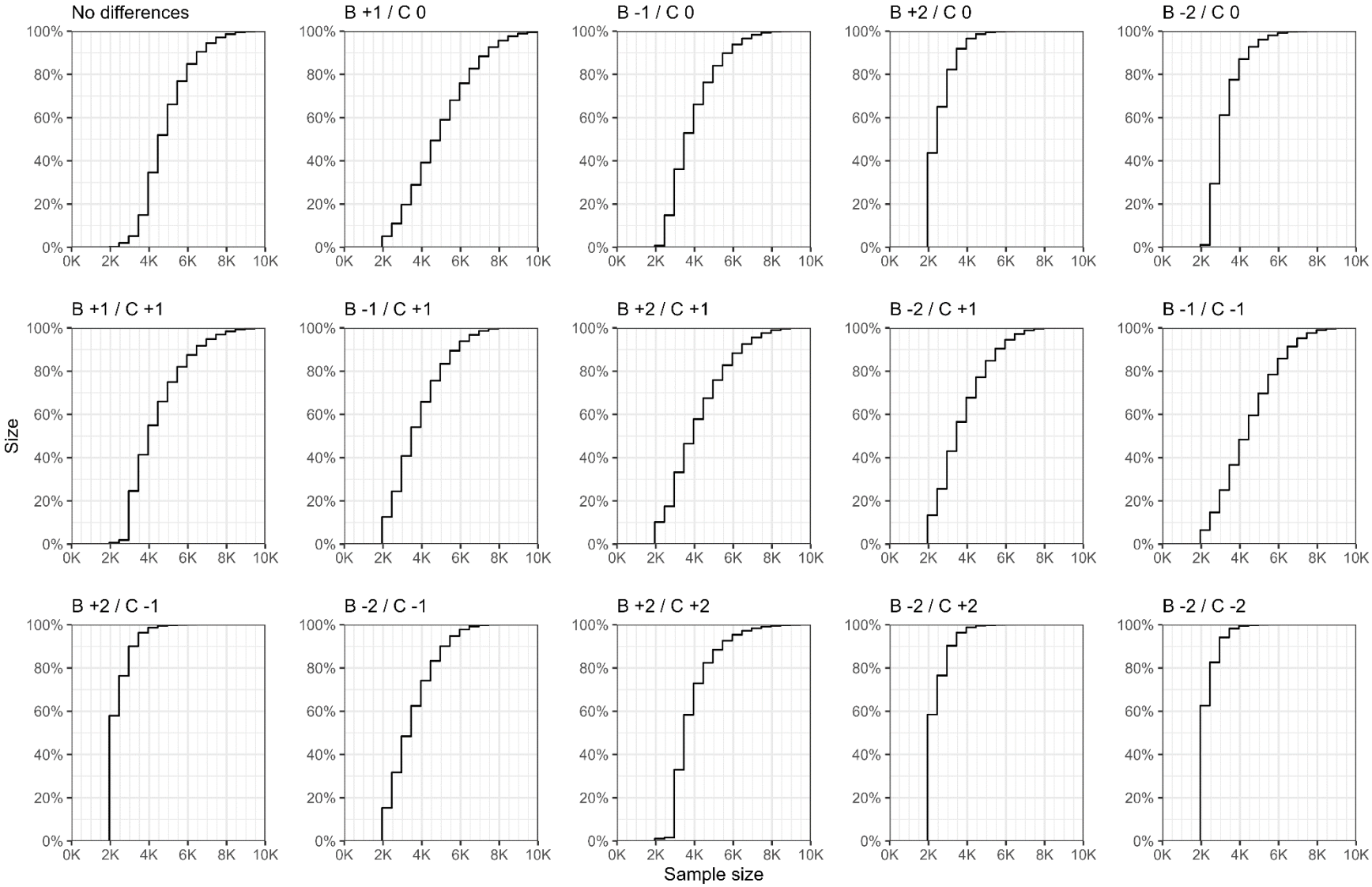
First, the initial primary domain design was evaluated with stopping rules calibrated to keep the type 1 error rate at approximately 5% in the scenario without differences (**Table S1**). Across all scenarios, the mean (expected) sample sizes ranged from 2,075 to 4,119 participants, with maximum observed sample sizes ranging from 4,950 to 8,450. The probabilities of conclusiveness were approximately 100% in all scenarios. The probabilities of erroneous superiority decisions ranged from ~0.0% to 14.2%, with the highest probabilities observed in scenarios with one inferior arm and two better but identical arms where this ranged from 12.6% to 14.2%. IDPs when selecting the best remaining arm if not stopped for superiority ranged from 96.4% to 100.0% across the scenarios with differences present. Second, a sensitivity analysis using fixed, equal (33.3%:33.3%:33.3%) allocation probabilities (rescaled to 50%:50% when one arm is dropped) was conducted (**Table S2**). Results were largely similar to the initial primary design results; mean (expected) sample sizes ranged from 2,088 to 4,177 participants, but maximum observed sample sizes were increased and ranged from 5,450 to 8,950. Probabilities of conclusiveness were approximately 100% in all scenarios. Probabilities of erroneous superiority conclusions ranged from ~0.0% to 12.9%. IDPs were largely unchanged.

Third, a sensitivity analysis using less restricted response-adaptive randomisation (minimum allocation probabilities of 20% instead of 25%; rescaled to 30% when one arm is dropped) was evaluated (**Table S3**). The expected (mean) and maximum sample sizes were overall largely similar, as were IDPs. The probabilities of conclusiveness remained at approximately 100% across all scenarios, with probabilities of erroneous superiority conclusions ranging from ~0.0% to 14.9%.

Fourth, a sensitivity analysis using a higher probability threshold for stopping for practical equivalence (>95% probability of the differences between all remaining arms being <1 day in any analysis) was conducted (**Table S4**). This led to some increases in mean (expected) sample sizes depending on the scenario assessed (range 2,094 to 5,114 participants), with maximum observed sample sizes ranging from 4,950 to 10,000 participants. The probabilities of conclusiveness remained at approximately 100% across scenarios. IDPs were higher, as this design is more likely

to select an arm due to stopping for superiority. The probabilities of erroneous superiority conclusions ranged from ~0.0% to 14.6%.
Fifth, a sensitivity analysis with more frequent adaptive analyses (first analysis after 1,500 participants, subsequent analyses after each additional 250 participants) was conducted (**Table S5**). Mean (expected) sample sizes slightly decreased (2,054 to 3,958 participants), while maximum observed sample sizes ranged from 4,700 to 8,450 participants. Probabilities of conclusiveness remained at approximately 100% across all scenarios, while IDPs where slightly worse in the worst scenarios when selecting the best remaining arm in simulations not stopped for superiority. The probabilities of erroneous superiority conclusions ranged from ~0.0% to 14.3%
Sixth, based on the comparisons above, we decided to proceed with the initial primary trial design, but manually re-calibrated the stopping rules to obtain probabilities of erroneous superiority conclusions below 5% in all scenarios assessed (**Table S6**). The resulting stopping thresholds were 0.995 for superiority and 0.005 for inferiority. The mean (expected) sample sizes ranged from 2,265 to 4,892 participants, with maximum observed sample sizes ranging from 5,950 to 10,000. The probabilities of conclusiveness were approximately 100% in all scenarios. The probabilities of erroneous superiority decisions ranged from ~0.0% to 4.6% (0.9% in the scenario with no differences present). IDPs when selecting the best remaining arm if not stopped for superiority ranged from 97.8% to 100.0% across the scenarios with differences present. **These results are the performance metrics for the final domain design under the primary assumptions.** The empirical cumulative distributions for the sample sizes with the final design with the re-calibrated stopping rules are presented in **Figure S1** below. Seventh, a sensitivity analysis assuming a higher, constant inclusion rate (15 participants/day) was conducted (Table S7). Sample sizes were slightly increased, while other performance metrics were largely unchanged. Eight, a sensitivity analysis assuming a lower, constant inclusion rate (5 participants/day) was conducted (**Table S**8). Sample sizes were slightly decreased, while other performance metrics were largely unchanged.
Ninth, a sensitivity analysis assuming a higher proportion of zeroes in the reference distribution (50%, with the mean value in those with >0 days unchanged, leading to an overall mean of 8.9 days in the “ideal” overall distribution (which differs slightly from the actual distributions due to rounding) was evaluated (**Table S9**; no re-calibration). Performance metrics were essentially unchanged.
Tenth, a sensitivity analysis 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 11.6 days in the “ideal” overall distribution (which differs slightly from the actual distributions due to rounding) was evaluated (**Table S10;** no re-calibration). Performance metrics were essentially unchanged.

Figure S1. Empirical cumulative distribution functions for sample sizes



Empirical cumulative distribution functions for sample sizes in the final primary trial design with manually calibrated stopping rules based on the 15 clinical scenarios assessed, designated as described elsewhere in the section, i.e., the approximate differences in the overall mean number of days alive out of hospital at day 30 in arms B and C are denoted in the titles of each subplot. 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.

Eleventh, a sensitivity analysis assuming a lower mean number of days in those with >0 days in the reference distribution (14 days, with the proportion of zeroes unchanged, leading to an overall mean of 7.9 days in the "ideal" overall distribution (which differs slightly from the actual distributions due to rounding) was evaluated (**Table S11**; no re-calibration). Sample sizes were smaller (expected [mean] sample sizes of 2,064 to 3,919 participants), probabilities of erroneous superiority conclusions ranged from ~0.0% to 4.0%, and other performance metrics were similar. Finally, a sensitivity analysis assuming a higher mean number of days in those with >0 days in the reference distribution (2 days, with the proportion of zeroes unchanged, leading to an overall mean of 12.4 days in the "ideal" overall distribution (which differs slightly from the actual distributions due to rounding) was evaluated (**Table S12;** no re-calibration). Sample sizes were larger in some scenarios (expected [mean] sample sizes of 2,639 to 6,288 participants), probabilities of conclusiveness ranged from 95.0% to ~100.0%, probabilities of erroneous superiority conclusions ranged from ~0.0% to 5.08%, and other performance metrics were similar

To summarise, when comparing the initially proposed trial design to other design variants (with calibration for each design, as described above), none of the evaluated design variants (fixed, equal randomisation; less restricted response-adaptive randomisation; a higher probability threshold for practical equivalence; and more frequent analyses) had substantial impact on performance metrics. Accordingly, we considered the initial primary design to strike an adequate balance between the ethical arguments of using response-adaptive randomisation (and the benefits observed in the average scenario) and the arguments for fixed, equal allocation (including the potential consequences of response-adaptive randomisation in the worst-case scenario). This includes considerations regarding how unrestricted or less restricted response-adaptive randomisation may potentially prematurely affect equipoise and willingness to enrol. We opted to keep the 90% probability threshold for practical equivalence considering the potential sample size increases associated with raising it. This threshold is also used in the *INCEPT-Albumin* domain and other trials [53,71,90]. More frequent analyses led to slightly lower mean sample sizes, but slightly worse IDPs. Because of this – and practical reasons, including the expected inclusion rates – we preferred analyses after every 500 participants. Consequently, we proceeded with the initially proposed trial design, and manually re-calibrated the stopping thresholds to keep the probabilities of erroneous superiority conclusions below 5% in all scenarios evaluated, leading to the final primary design. We then conducted sensitivity analyses of important, uncontrollable assumptions using the final primary design including the final stopping rules. Results of the sensitivity analyses of assumed inclusion rates were similar to the results under the primary assumption. Results of sensitivity analyses of changed reference distributions were considered acceptable; changing the proportion of zero days had no substantial impact, while changing the mean number of days in those with >0 days had some influence on expected sample sizes, probabilities of conclusiveness, and probabilities of erroneous superiority conclusions, all which we were found to be acceptable. In conclusion, we consider the final, primary *INCEPT-Thromboprophylaxis* domain design to have acceptable performance metrics and to be either

comparable or superior to the most obvious alternative design choices, with robust results across all sensitivity analyses of the underlying assumptions.

Table S1. Performance metrics of the initial primary *INCEPT-Thromboprophylaxis* domain design without rounding of stopping rules

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	10.3 to 10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3
Mean number of days (arm B)	8.3 to 12.3	10.3	11.3	9.3	12.3	8.3	11.3	9.3	12.3	8.3	9.3	12.3	8.3	12.3	8.3	8.3
Mean number of days (arm C)	8.3 to 12.3	10.3	10.3	10.3	10.3	10.3	11.3	11.3	11.3	11.3	9.3	9.3	9.3	12.3	12.3	8.3
Sample size - mean	2074.9 to 4118.7	4118.7	3543.9	3295.9	2232.1	3051.6	3645.5	2969.4	3200.7	2948.7	3255.4	2127.9	2779.7	3561.2	2125.8	2074.9
Sample size - SD	305.5 to 1218.8	1023.1	1218.8	850.1	490.6	691.8	952.9	950.2	1090.8	941.2	1048.8	389.7	820.8	872.7	388.6	305.5
Sample size - median	1950 to 3950	3950	3450	2950	1950	2950	3450	2950	2950	2950	2950	1950	2450	3450	1950	1950
Sample size - P25	1950 to 3450	3450	2450	2450	1950	2450	2950	1950	2450	1950	2450	1950	1950	2950	1950	1950
Sample size - P75	1950 to 4950	4950	4450	3950	2450	3450	3950	3450	3950	3450	3950	1950	3450	3950	1950	1950
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	4950 to 8450	8450	8450	7450	6450	6450	8450	6950	7950	6450	7950	5950	5950	7950	6450	4950
Total DAOH - mean	18712.5 to 42498	42496.3	38077.5	33228.4	24650.5	30185	40423.9	31228.7	36917.5	30379.7	31702	22809.9	26397	42498	22138.9	18712.5
Total DAOH - SD	2912.9 to 13208.7	10593.6	13208.7	8650	5617	7166.5	10620.6	10375.1	12976.7	10289.7	10330.4	4487.5	8147.6	10756.8	4483.2	2912.9
Total DAOH - median	17647 to 41148	41148	36852	30289	21746	29084	38182.5	30562	34194	29888	29229	20949	23565	40906.5	20291	17647
Total DAOH - P25	17317 to 35377	35377	26553	25419	21267	24201	32744	20689	27025	19979	23576	20553	18517	35051	19903	17317
Total DAOH - P75	18097 to 50347.2	50347.2	47588	39200	27062	34227	44974	36885	45573	36156	38634	21620.2	32501	47479	20933	18097
Total DAOH - minimum	15843 to 20513	18568	18885	18090	19469	17342	19787	18271	20153	17675	16541	18724	16570	20513	18223	15843
Total DAOH - maximum	46378 to 96246	86899	91672	74966	73560	66824	93648	74355	93763	70671	77887	68629	59087	96246	71315	46378
Mean DAOH - mean	9 to 11.9	10.3	10.7	10.1	11	9.9	11.1	10.5	11.5	10.2	9.7	10.7	9.5	11.9	10.4	9

Mean DAOH - SD	0.169 to 0.279	0.169	0.2	0.194	0.248	0.211	0.199	0.239	0.247	0.279	0.192	0.258	0.227	0.224	0.274	0.216
Mean DAOH - median	9 to 11.9	10.3	10.7	10.1	11	9.9	11.1	10.5	11.5	10.3	9.7	10.7	9.5	11.9	10.4	9
Mean DAOH - P25	8.9 to 11.8	10.2	10.6	9.9	10.9	9.7	11	10.3	11.3	10.1	9.6	10.5	9.3	11.8	10.2	8.9
Mean DAOH - P75	9.2 to 12.1	10.4	10.9	10.2	11.2	10	11.2	10.6	11.7	10.4	9.9	10.9	9.6	12.1	10.6	9.2
Mean DAOH - minimum	8.1 to 10.5	9.5	9.7	9.2	10	8.9	10.1	9.4	10.3	9.1	8.5	9.6	8.5	10.5	9.3	8.1
Mean DAOH - maximum	9.9 to 12.9	11.1	11.6	10.9	12.1	10.7	11.9	11.4	12.5	11.3	10.6	11.7	10.3	12.9	11.6	9.9
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0498 to 0.999	0.0498	0.745	0.129	0.999	0.124	0.139	0.812	0.807	0.812	0.749	0.999	0.815	0.142	0.999	0.999
Pr(equivalence)	0.00096 to 0.95	0.95	0.255	0.871	0.00139	0.876	0.861	0.188	0.193	0.188	0.251	0.00099	0.185	0.858	0.00096	0.0014
Pr(maximum)	0 to 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.0166	0.00021	0.0636	0	0.0621	0.00001	0.00042	0	0.00026	0.749	0	0.815	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.0162	0.744	0	0.999	0	0.0693	0	0.806	0	0.00014	0.999	0	0.0715	0	0
Pr(arm C superior)	0 to 0.999	0.017	0.00025	0.0649	0	0.0622	0.0694	0.812	0.00066	0.812	0.00007	0	0.00019	0.0702	0.999	0
Pr(no arm superior)	0.00096 to 0.95	0.95	0.255	0.871	0.00139	0.876	0.861	0.188	0.193	0.188	0.251	0.00099	0.185	0.858	0.00096	0.0014
Pr(erroneous superiority)	0 to 0.142	0.0498	0.00046	0.129	0	0.124	0.139	0.00042	0.00066	0.00026	0.00021	0	0.00019	0.142	0	0
RMSE (superiority only)	0.341 to 0.664	0.664	0.353	0.541	0.418	0.547	0.548	0.365	0.385	0.36	0.344	0.431	0.341	0.594	0.426	0.377
MAE (superiority only)	0.195 to 0.559	0.559	0.196	0.425	0.276	0.438	0.418	0.214	0.22	0.211	0.195	0.289	0.203	0.458	0.287	0.256
IDP (superiority only)	99.9 to 100	-	99.9	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.301 to 0.431	0.301	0.354	0.304	0.419	0.307	0.305	0.37	0.387	0.369	0.343	0.431	0.352	0.327	0.427	0.377
MAE (select best)	0.184 to 0.289	0.199	0.213	0.187	0.276	0.192	0.184	0.228	0.235	0.228	0.208	0.289	0.221	0.196	0.287	0.256
IDP (select best)	96.4 to 100	-	96.4	99.8	100	100	99.8	98.3	98.4	98.9	96.8	100	98.4	100	100	100

Calibrated stopping threshold for superiority: 0.977523.

Abbreviations: 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 S2. Performance metrics of the initial primary *INCEPT-Thromboprophylaxis* domain design if using fixed, equal allocation

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	10.3 to 10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3
Mean number of days (arm B)	8.3 to 12.3	10.3	11.3	9.3	12.3	8.3	11.3	9.3	12.3	8.3	9.3	12.3	8.3	12.3	8.3	8.3
Mean number of days (arm C)	8.3 to 12.3	10.3	10.3	10.3	10.3	10.3	11.3	11.3	11.3	11.3	9.3	9.3	9.3	12.3	12.3	8.3
Sample size - mean	2087.8 to 4177.3	4177.3	3639.7	3324.3	2259.1	3061.6	3662.8	3024.9	3262.9	2996.4	3350.2	2143.6	2823.1	3572.3	2141.9	2087.8
Sample size - SD	323.5 to 1273.8	1025.4	1273.8	845.4	523	690.8	938.4	969.2	1113.9	959.3	1106.2	409.4	841	865.3	407.6	323.5
Sample size - median	1950 to 3950	3950	3450	2950	1950	2950	3450	2950	2950	2950	3450	1950	2450	3450	1950	1950
Sample size - P25	1950 to 3450	3450	2450	2950	1950	2450	2950	1950	2450	1950	2450	1950	1950	2950	1950	1950
Sample size - P75	1950 to 4950	4950	4450	3950	2450	3450	3950	3450	3950	3450	3950	1950	3450	3950	1950	1950
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	5450 to 8950	8450	8950	7450	6950	6450	8450	6950	7450	6950	7950	5450	6450	7450	5950	5450
Total DAOH - mean	18797.1 to 43097.1	43097.1	38913.1	33470.2	24882.6	30285.3	40564	31703.6	37501	30784.2	32459.9	22945.7	26719.3	42630.3	22279.6	18797.1
Total DAOH - SD	2996 to 13636.1	10618.5	13636.1	8567.5	5845.7	7153.5	10424.2	10457.7	13108.9	10374.5	10743.5	4616.8	8242.4	10661.5	4599.2	2996
Total DAOH - median	17659 to 41365	41365	36967	30454	21786	29100	38253.5	30672	34336	29992	31835.5	20965	23726	40929	20312	17659
Total DAOH - P25	17325 to 35600	35600	26825	28165.2	21289	24222	32771	20903.8	27414	20106	23675	20559	18579	35085	19910	17325
Total DAOH - P75	18146 to 50635.2	50635.2	47744	39336	27076	34253	45097	37042	45665	36196	38804	21762	32597	47530	21069.2	18146
Total DAOH - minimum	15803 to 20910	18700	19170	18046	19248	16975	19593	18324	20176	17810	17108	18750	16230	20910	17799	15803
Total DAOH - maximum	49036 to 97373	87782	97373	75484	75985	65119	93878	73265	88296	74320	77500	59928	61317	92777	66099	49036
Mean DAOH - mean	9 to 11.9	10.3	10.7	10.1	11	9.9	11.1	10.5	11.5	10.2	9.7	10.7	9.4	11.9	10.4	9

Mean DAOH - SD	0.167 to 0.261	0.167	0.193	0.196	0.239	0.211	0.201	0.226	0.234	0.261	0.185	0.249	0.216	0.224	0.261	0.212
Mean DAOH - median	9 to 11.9	10.3	10.7	10.1	11	9.9	11.1	10.5	11.5	10.2	9.7	10.7	9.4	11.9	10.4	9
Mean DAOH - P25	8.9 to 11.8	10.2	10.6	9.9	10.9	9.7	10.9	10.3	11.3	10	9.6	10.5	9.3	11.8	10.2	8.9
Mean DAOH - P75	9.1 to 12.1	10.4	10.8	10.2	11.2	10	11.2	10.6	11.6	10.4	9.8	10.9	9.6	12.1	10.6	9.1
Mean DAOH - minimum	8.1 to 10.7	9.6	9.8	9.2	9.9	8.7	10	9.4	10.3	9.1	8.8	9.6	8.3	10.7	9.1	8.1
Mean DAOH - maximum	10.1 to 12.7	11.1	11.6	11	12.1	10.8	12	11.3	12.3	11.2	10.6	11.7	10.3	12.7	11.3	10.1
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0494 to 0.999	0.0494	0.742	0.119	0.999	0.111	0.128	0.807	0.803	0.806	0.75	0.999	0.812	0.129	0.999	0.999
Pr(equivalence)	0.0009 to 0.951	0.951	0.258	0.881	0.00124	0.889	0.872	0.193	0.197	0.194	0.25	0.00096	0.188	0.871	0.0009	0.00134
Pr(maximum)	0 to 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.0165	0.00019	0.0595	0	0.0549	0	0.00034	0	0.00025	0.75	0	0.812	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.0161	0.742	0	0.999	0	0.0629	0	0.803	0	0.00012	0.999	0	0.0635	0	0
Pr(arm C superior)	0 to 0.999	0.0168	0.00014	0.0599	0	0.056	0.0648	0.806	0.00046	0.806	0.00012	0	0.0002	0.0655	0.999	0
Pr(no arm superior)	0.0009 to 0.951	0.951	0.258	0.881	0.00124	0.889	0.872	0.193	0.197	0.194	0.25	0.00096	0.188	0.871	0.0009	0.00134
Pr(erroneous superiority)	0 to 0.129	0.0494	0.00033	0.119	0	0.111	0.128	0.00034	0.00046	0.00025	0.00024	0	0.0002	0.129	0	0
RMSE (superiority only)	0.34 to 0.681	0.681	0.368	0.563	0.416	0.569	0.597	0.361	0.386	0.363	0.341	0.432	0.34	0.631	0.429	0.379
MAE (superiority only)	0.196 to 0.591	0.591	0.207	0.455	0.28	0.464	0.482	0.212	0.221	0.214	0.196	0.289	0.204	0.511	0.289	0.258
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.309 to 0.432	0.309	0.368	0.309	0.417	0.309	0.323	0.373	0.392	0.375	0.347	0.432	0.355	0.338	0.43	0.38
MAE (select best)	0.193 to 0.289	0.208	0.225	0.193	0.281	0.196	0.197	0.234	0.242	0.235	0.216	0.289	0.226	0.208	0.289	0.258
IDP (select best)	96.5 to 100	-	96.5	99.9	100	100	99.8	98.3	98.3	98.8	96.9	100	98.4	100	100	100

Calibrated stopping threshold for superiority: 0.980161 (re-calibrated due to changed design choice).

Abbreviations: 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 S3. Performance metrics of the initial primary *INCEPT-Thromboprophylaxis* domain design if using less restricted response-adaptive randomisation

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	10.3 to 10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3
Mean number of days (arm B)	8.3 to 12.3	10.3	11.3	9.3	12.3	8.3	11.3	9.3	12.3	8.3	9.3	12.3	8.3	12.3	8.3	8.3
Mean number of days (arm C)	8.3 to 12.3	10.3	10.3	10.3	10.3	10.3	11.3	11.3	11.3	11.3	9.3	9.3	9.3	12.3	12.3	8.3
Sample size - mean	2070.6 to 4144.2	4144.2	3528.8	3304.3	2222.7	3058.8	3667.8	2956	3188.8	2944.7	3240.8	2121.2	2764.4	3575.1	2120.6	2070.6
Sample size - SD	300.4 to 1234	1064.3	1234	879.8	483.5	711.5	997.3	958.8	1105.2	955.8	1056.5	383	822.9	910.3	384	300.4
Sample size - median	1950 to 3950	3950	3450	2950	1950	2950	3450	2950	2950	2950	2950	1950	2450	3450	1950	1950
Sample size - P25	1950 to 3450	3450	2450	2450	1950	2450	2950	1950	1950	1950	2450	1950	1950	2950	1950	1950
Sample size - P75	1950 to 4950	4950	4450	3950	2450	3450	4450	3450	3950	3450	3950	1950	3450	3950	1950	1950
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	4950 to 8950	8950	8950	7950	6950	6450	8450	6950	8450	6950	7950	5450	5950	7950	5950	4950
Total DAOH - mean	18690.6 to 42761.4	42761.4	38022.5	33333.3	24588.4	30256.9	40702.8	31152	36857.3	30400.6	31652.9	22757.6	26302.2	42674.4	22104.2	18690.6
Total DAOH - SD	2909.9 to 13465.2	11011.5	13465.2	8967.9	5610.6	7372.3	11141	10533.8	13228.6	10520.4	10485.7	4465.8	8231.8	11221.7	4480.3	2909.9
Total DAOH - median	17643 to 41222	41222	36840	30268.5	21736	29092	38219	30518	34171.5	29851.5	29195	20937	23502.5	40901	20285	17643
Total DAOH - P25	17315 to 35353	35353	26490	25336	21267	24179	32733	20642	23214	19947	23563	20545	18483	35039.8	19900.8	17315
Total DAOH - P75	18082 to 50614	50614	47657	39301.2	27081.2	34235	47399.5	36880	45650	36227.2	38706	21570	32469	47558	20900	18082
Total DAOH - minimum	15685 to 20731	18771	18740	17884	19401	16900	19812	18145	20133	17594	17145	18805	16377	20731	17945	15685
Total DAOH - maximum	47245 to 97668	92480	96568	81185	77545	66989	96193	75427	96362	75477	78524	61034	59825	97668	66933	47245

Mean DAOH - mean	9 to 11.9	10.3	10.8	10.1	11	9.9	11.1	10.5	11.5	10.3	9.8	10.7	9.5	11.9	10.4	9
Mean DAOH - SD	0.169 to 0.292	0.169	0.207	0.193	0.253	0.212	0.197	0.247	0.257	0.292	0.198	0.265	0.236	0.225	0.282	0.22
Mean DAOH - median	9 to 11.9	10.3	10.8	10.1	11	9.9	11.1	10.5	11.5	10.3	9.8	10.7	9.5	11.9	10.4	9
Mean DAOH - P25	8.9 to 11.8	10.2	10.6	10	10.9	9.7	11	10.3	11.3	10.1	9.6	10.5	9.3	11.8	10.2	8.9
Mean DAOH - P75	9.2 to 12.1	10.4	10.9	10.2	11.2	10	11.2	10.7	11.7	10.5	9.9	10.9	9.6	12.1	10.6	9.2
Mean DAOH - minimum	8 to 10.6	9.6	9.6	9.2	9.9	8.7	10.2	9.3	10.3	9	8.8	9.6	8.4	10.6	9.2	8
Mean DAOH - maximum	9.9 to 12.9	11.1	11.7	11	12.1	10.7	12.1	11.4	12.5	11.3	10.6	11.7	10.4	12.9	11.6	9.9
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.05 to 0.999	0.05	0.744	0.135	0.999	0.13	0.146	0.813	0.81	0.813	0.752	0.999	0.818	0.149	0.999	0.999
Pr(equivalence)	0.00094 to 0.95	0.95	0.256	0.865	0.00145	0.87	0.854	0.187	0.19	0.187	0.248	0.00094	0.182	0.851	0.00104	0.00131
Pr(maximum)	0 to 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.0167	0.0002	0.0668	0	0.0646	0	0.0004	0	0.00054	0.751	0	0.817	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.0166	0.743	0	0.999	0	0.0725	0	0.809	0	0.0002	0.999	0	0.0748	0	0
Pr(arm C superior)	0 to 0.999	0.0166	0.0002	0.0678	0	0.065	0.0735	0.813	0.00051	0.813	0.0001	0	0.00031	0.0743	0.999	0
Pr(no arm superior)	0.00094 to 0.95	0.95	0.256	0.865	0.00145	0.87	0.854	0.187	0.19	0.187	0.248	0.00094	0.182	0.851	0.00104	0.00131
Pr(erroneous superiority)	0 to 0.149	0.05	0.0004	0.135	0	0.13	0.146	0.0004	0.00051	0.00054	0.0003	0	0.00031	0.149	0	0
RMSE (superiority only)	0.333 to 0.649	0.649	0.364	0.523	0.412	0.532	0.559	0.362	0.376	0.358	0.333	0.424	0.344	0.581	0.424	0.379
MAE (superiority only)	0.188 to 0.536	0.536	0.201	0.398	0.273	0.411	0.416	0.21	0.215	0.208	0.188	0.286	0.203	0.431	0.285	0.254
IDP (superiority only)	99.9 to 100	-	99.9	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.291 to 0.425	0.291	0.357	0.298	0.413	0.303	0.315	0.368	0.379	0.366	0.336	0.424	0.351	0.324	0.425	0.38
MAE (select best)	0.181 to 0.287	0.188	0.21	0.181	0.273	0.188	0.188	0.225	0.23	0.224	0.204	0.287	0.217	0.193	0.285	0.255

IDP (select best)	96.5 to 100	-	96.5	99.8	100	100	99.8	98.3	98.4	98.8	96.9	100	98.4	100	100	100

Calibrated stopping threshold for superiority: 0.976345 (re-calibrated due to changed design choice).

Abbreviations: 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 S4. Performance metrics of the initial primary *INCEPT-Thromboprophylaxis* domain design with higher equivalence stopping probability threshold

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	10.3 to 10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3
Mean number of days (arm B)	8.3 to 12.3	10.3	11.3	9.3	12.3	8.3	11.3	9.3	12.3	8.3	9.3	12.3	8.3	12.3	8.3	8.3
Mean number of days (arm C)	8.3 to 12.3	10.3	10.3	10.3	10.3	10.3	11.3	11.3	11.3	11.3	9.3	9.3	9.3	12.3	12.3	8.3
Sample size - mean	2093.8 to 5114.1	5114.1	3993.7	3938.6	2267.7	3681	4346.2	3299.3	3558.4	3270.6	3643.7	2148.6	3053.2	4367.1	2149.3	2093.8
Sample size - SD	330.8 to 1545.5	1313.1	1545.5	1026.8	525.9	885.4	1173.9	1236.1	1415	1225	1335.9	415.7	1061.7	1153.1	418.4	330.8
Sample size - median	1950 to 4950	4950	3950	3950	1950	3450	3950	2950	3450	2950	3450	1950	2950	3950	1950	1950
Sample size - P25	1950 to 4450	4450	2950	3450	1950	2950	3450	1950	2450	1950	2450	1950	1950	3450	1950	1950
Sample size - P75	1950 to 5950	5950	4950	4450	2450	3950	4950	3950	4450	3950	4450	1950	3950	4950	1950	1950
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	4950 to 10000	10000	10000	9450	6450	7950	10000	8450	9450	7950	9450	5950	7450	9950	5950	4950
Total DAOH - mean	18890.5 to 52765.9	52765.9	42978.7	39827.8	25063	36679.4	48321.1	34831.7	41169.2	33895.5	35540.8	23048.8	29109.5	52409.3	22410.7	18890.5
Total DAOH - SD	3144 to 16825.7	13581.5	16751.9	10466.7	6016.3	9162.2	13113.4	13481.3	16825.7	13382.5	13151.9	4788.2	10534.2	14199	4822	3144
Total DAOH - median	17664 to 51533	51533	41869	38596	21806	34526	44489	31560	39479	30798	33671	20970	27837	48221	20317	17664
Total DAOH - P25	17327 to 44924	44924	30981	34105	21300	29534	38649.8	20946.8	27541	20136	24087	20562	18603.8	42811.2	19915	17327
Total DAOH - P75	18174 to 61475	61475	53664.2	45296	27270	40181	55294	42364	51743	41607	43790	21840	36479.5	59633	21153	18174
Total DAOH - minimum	15784 to 20809	18777	18984	17669	19506	17299	19794	18319	20138	17600	17134	18582	16586	20809	18049	15784
Total DAOH - maximum	46767 to 121384	104746	108377	95758	74178	81493	111408	92294	111965	86842	94293	66415	74071	121384	67002	46767

Mean DAOH - mean	9 to 12	10.3	10.7	10.1	11	9.9	11.1	10.5	11.5	10.3	9.7	10.7	9.5	12	10.4	9
Mean DAOH - SD	0.152 to 0.289	0.152	0.192	0.181	0.246	0.196	0.186	0.238	0.247	0.289	0.185	0.26	0.23	0.209	0.277	0.216
Mean DAOH - median	9 to 12	10.3	10.8	10.1	11	10	11.1	10.5	11.5	10.3	9.7	10.7	9.5	12	10.4	9
Mean DAOH - P25	8.9 to 11.9	10.2	10.6	10	10.9	9.8	11	10.4	11.4	10.1	9.6	10.5	9.3	11.9	10.2	8.9
Mean DAOH - P75	9.2 to 12.1	10.4	10.9	10.2	11.2	10.1	11.2	10.7	11.7	10.5	9.9	10.9	9.7	12.1	10.6	9.2
Mean DAOH - minimum	8.1 to 10.7	9.6	9.7	9.1	10	8.9	10.2	9.4	10.3	9	8.8	9.5	8.5	10.7	9.3	8.1
Mean DAOH - maximum	9.9 to 12.8	11.1	11.8	11	12	10.7	12	11.3	12.5	11.1	10.5	11.7	10.3	12.8	11.5	9.9
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.05 to 1	0.05	0.848	0.131	1	0.128	0.142	0.894	0.887	0.893	0.85	1	0.894	0.146	1	1
Pr(equivalence)	0.00003 to 0.95	0.95	0.152	0.869	0.00012	0.872	0.858	0.106	0.113	0.107	0.15	0.00003	0.106	0.854	0.00009	0.00012
Pr(maximum)	0 to 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 1	0.017	0.00021	0.0648	0	0.0645	0	0.00023	0	0.00031	0.849	0	0.894	0	0	1
Pr(arm B superior)	0 to 1	0.0166	0.848	0	1	0	0.0707	0	0.887	0	0.00012	1	0	0.0724	0	0
Pr(arm C superior)	0 to 1	0.0163	0.00022	0.0657	0	0.0636	0.0711	0.893	0.00064	0.892	0.00007	0	0.00027	0.0734	1	0
Pr(no arm superior)	0.00003 to 0.95	0.95	0.152	0.869	0.00012	0.872	0.858	0.106	0.113	0.107	0.15	0.00003	0.106	0.854	0.00009	0.00012
Pr(erroneous superiority)	0 to 0.146	0.05	0.00043	0.131	0	0.128	0.142	0.00023	0.00064	0.00031	0.00019	0	0.00027	0.146	0	0
RMSE (superiority only)	0.314 to 0.625	0.625	0.338	0.507	0.414	0.539	0.541	0.346	0.376	0.35	0.314	0.425	0.332	0.572	0.424	0.375
MAE (superiority only)	0.175 to 0.51	0.51	0.181	0.384	0.276	0.421	0.399	0.198	0.207	0.199	0.175	0.286	0.194	0.423	0.286	0.254
IDP (superiority only)	99.9 to 100	-	99.9	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.266 to 0.425	0.266	0.338	0.271	0.414	0.285	0.287	0.352	0.376	0.355	0.32	0.425	0.338	0.299	0.424	0.376
MAE (select best)	0.162 to 0.286	0.172	0.194	0.162	0.276	0.174	0.167	0.21	0.217	0.211	0.191	0.286	0.206	0.17	0.286	0.254
IDP (select best)	98.3 to 100	-	98.3	99.9	100	100	99.9	99.2	99.1	99.4	98.3	100	99.2	100	100	100

Calibrated stopping threshold for superiority: 0.980848 (re-calibrated due to changed design choice).

Abbreviations: 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 S5. Performance metrics of the initial primary *INCEPT-Thromboprophylaxis* domain design with more frequent adaptive analyses

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	10.3 to 10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3
Mean number of days (arm B)	8.3 to 12.3	10.3	11.3	9.3	12.3	8.3	11.3	9.3	12.3	8.3	9.3	12.3	8.3	12.3	8.3	8.3
Mean number of days (arm C)	8.3 to 12.3	10.3	10.3	10.3	10.3	10.3	11.3	11.3	11.3	11.3	9.3	9.3	9.3	12.3	12.3	8.3
Sample size - mean	2054 to 3958	3958	3408	3145.9	2196.7	2908.1	3449.3	2854.2	3057.9	2831.6	3121.3	2100.7	2663.7	3379.9	2098.3	2054
Sample size - SD	260.5 to 1150	970.1	1150	783.1	443.1	613.6	918.9	863.4	996.6	853	977.3	340.4	732.6	797.1	339.2	260.5
Sample size - median	1950 to 3950	3950	3200	2950	1950	2700	3200	2700	2950	2700	2950	1950	2450	3200	1950	1950
Sample size - P25	1950 to 3450	3450	2450	2450	1950	2450	2700	1950	2200	1950	2200	1950	1950	2950	1950	1950
Sample size - P75	1950 to 4450	4450	4200	3450	2200	3200	3950	3450	3700	3450	3700	1950	3200	3700	1950	1950
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	4700 to 8450	8200	8450	6950	6450	6200	8200	6700	7950	6450	7450	5700	5950	7700	5950	4700
Total DAOH - mean	18510.5 to 40836	40836	36604.4	31686.3	24248.4	28701.3	38214.8	29974.6	35220.4	29099.9	30379.4	22498.6	25247.2	40274.6	21823.3	18510.5
Total DAOH - SD	2485.1 to 12463.9	10041.6	12463.9	7959.3	5074	6362.4	10235	9423.9	11855.6	9332	9626.7	3922.6	7277.2	9825.8	3914.3	2485.1
Total DAOH - median	17662 to 40375	40375	34519.5	29659	21794	26817	35467	28178	33405	27426.5	28786	20968	23280	37928	20309	17662
Total DAOH - P25	17325 to 34668.8	34668.8	26471	25489.8	21294	24142	30393	20902	24795	20103.8	21887.8	20564	18591	34636	19913	17325
Total DAOH - P75	18157 to 47052	47052	44865	35930	25007.2	31698	43800	35830	42527.2	34476.5	36484	21778.2	29892	44520	21065	18157
Total DAOH - minimum	15748 to 20652	18560	18866	17969	19398	17274	19617	18124	20091	17652	17205	18800	16525	20652	18169	15748
Total DAOH - maximum	43762 to 95051	84383	89706	70708	72190	62833	90964	74928	91443	69344	74263	63650	58668	95051	65301	43762
Mean DAOH - mean	9 to 11.9	10.3	10.7	10.1	11	9.9	11.1	10.5	11.5	10.2	9.7	10.7	9.4	11.9	10.4	9

Mean DAOH - SD	0.172 to 0.274	0.172	0.202	0.195	0.246	0.212	0.202	0.237	0.248	0.274	0.194	0.255	0.225	0.226	0.267	0.216
Mean DAOH - median	9 to 11.9	10.3	10.7	10.1	11	9.9	11.1	10.5	11.5	10.2	9.7	10.7	9.5	11.9	10.4	9
Mean DAOH - P25	8.9 to 11.8	10.2	10.6	9.9	10.9	9.7	10.9	10.3	11.3	10	9.6	10.5	9.3	11.8	10.2	8.9
Mean DAOH - P75	9.2 to 12.1	10.4	10.9	10.2	11.2	10	11.2	10.6	11.7	10.4	9.9	10.9	9.6	12.1	10.6	9.2
Mean DAOH - minimum	8.1 to 10.6	9.5	9.7	9.2	9.9	8.9	10.1	9.3	10.3	9.1	8.8	9.6	8.5	10.6	9.3	8.1
Mean DAOH - maximum	10.1 to 12.9	11.1	11.6	10.9	12	10.8	12	11.3	12.5	11.2	10.6	11.7	10.4	12.9	11.4	10.1
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.05 to 0.998	0.05	0.724	0.129	0.998	0.125	0.14	0.795	0.791	0.794	0.729	0.998	0.796	0.143	0.998	0.998
Pr(equivalence)	0.00165 to 0.95	0.95	0.276	0.871	0.00247	0.875	0.86	0.205	0.209	0.206	0.271	0.00165	0.204	0.857	0.00179	0.00202
Pr(maximum)	0 to 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.998	0.0163	0.00022	0.0648	0	0.0618	0.00001	0.00048	0	0.00036	0.729	0	0.796	0	0	0.998
Pr(arm B superior)	0 to 0.998	0.0168	0.724	0	0.998	0	0.0697	0	0.79	0	0.00011	0.998	0	0.071	0	0
Pr(arm C superior)	0 to 0.998	0.0168	0.00014	0.0642	0	0.0627	0.0703	0.794	0.00054	0.794	0.00015	0	0.00023	0.0717	0.998	0
Pr(no arm superior)	0.00165 to 0.95	0.95	0.276	0.871	0.00247	0.875	0.86	0.205	0.209	0.206	0.271	0.00165	0.204	0.857	0.00179	0.00202
Pr(erroneous superiority)	0 to 0.143	0.05	0.00036	0.129	0	0.125	0.14	0.00048	0.00054	0.00036	0.00026	0	0.00023	0.143	0	0
RMSE (superiority only)	0.346 to 0.663	0.663	0.355	0.538	0.417	0.554	0.574	0.363	0.398	0.365	0.346	0.427	0.348	0.614	0.43	0.381
MAE (superiority only)	0.197 to 0.567	0.567	0.199	0.424	0.279	0.444	0.445	0.215	0.229	0.216	0.197	0.291	0.21	0.479	0.291	0.259
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.302 to 0.431	0.302	0.357	0.305	0.418	0.313	0.321	0.372	0.397	0.373	0.348	0.428	0.358	0.338	0.431	0.382
MAE (select best)	0.188 to 0.292	0.199	0.218	0.188	0.28	0.198	0.195	0.233	0.243	0.233	0.213	0.292	0.227	0.205	0.292	0.26
IDP (select best)	96 to 100	-	96	99.8	100	100	99.8	98	98	98.6	96.2	100	98.1	100	100	100

Calibrated stopping threshold for superiority: 0.980302 (re-calibrated due to changed design choice).
Abbreviations: 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 primary *INCEPT-Thromboprophylaxis* domain design with stricter stopping rules

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	10.3 to 10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3
Mean number of days (arm B)	8.3 to 12.3	10.3	11.3	9.3	12.3	8.3	11.3	9.3	12.3	8.3	9.3	12.3	8.3	12.3	8.3	8.3
Mean number of days (arm C)	8.3 to 12.3	10.3	10.3	10.3	10.3	10.3	11.3	11.3	11.3	11.3	9.3	9.3	9.3	12.3	12.3	8.3
Sample size - mean	2264.9 to 4891.8	4867.4	4891.8	3906.3	2563.4	3240.5	4375.8	3774.7	4129.4	3704.9	4411.6	2356.3	3464.3	3850.9	2349.8	2264.9
Sample size - SD	492.6 to 1796	1266	1796	1250	727.6	858.2	1432.1	1373.4	1564.3	1348.6	1552.9	594.8	1194.2	1090.3	587.8	492.6
Sample size - median	1950 to 4950	4450	4950	3450	2450	2950	3950	3450	3950	3450	4450	1950	3450	3450	1950	1950
Sample size - P25	1950 to 3950	3950	3450	2950	1950	2450	3450	2950	2950	2450	2950	1950	2450	2950	1950	1950
Sample size - P75	2450 to 5950	5450	5950	4450	2950	3450	5450	4450	4950	4450	5450	2450	4450	4450	2450	2450
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	5950 to 10000	10000	10000	10000	7950	7950	10000	8950	9950	8450	10000	6950	7950	10000	6950	5950
Total DAOH - mean	20515.4 to 52695.3	50219	52695.3	39360	28446.9	32118.2	48480.5	39990.6	47922.9	38653.4	43093.6	25444.2	33165.3	46028.9	24726.4	20515.4
Total DAOH - SD	4662.5 to 19449.3	13091.9	19449.3	12626.3	8305.4	8877.5	15866	14988	18601.2	14761.3	15279.7	6835.6	11851.4	13421.4	6767.4	4662.5
Total DAOH - median	17901 to 52108.5	46751	52108.5	35386	26873	29338	44042	36766	45398	35898.5	42751	21316	32256.5	41401	20634	17901
Total DAOH - P25	17437 to 40772	40772	37202	29680	21538	24468.8	36908	29872	33841	25764	30525.8	20705	23206	35406	20050	17437
Total DAOH - P75	22415 to 65243.2	56964	65243.2	45720	32994	34887	58034	48518	58730	47332	53541	27294.2	42019	52742	26622	22415
Total DAOH - minimum	15756 to 21021	18893	18871	18264	19460	17385	19749	18307	20154	17722	17090	18921	16463	21021	18192	15756
Total DAOH - maximum	55958 to 123552	105289	110593	101793	88224	82311	112845	96845	119164	92737	99482	77695	78895	123552	78957	55958
Mean DAOH - mean	9 to 11.9	10.3	10.8	10.1	11.1	9.9	11.1	10.6	11.6	10.4	9.8	10.8	9.5	11.9	10.5	9

Mean DAOH - SD	0.155 to 0.299	0.155	0.175	0.181	0.239	0.209	0.185	0.228	0.231	0.274	0.17	0.268	0.22	0.217	0.299	0.216
Mean DAOH - median	9 to 11.9	10.3	10.8	10.1	11.1	9.9	11.1	10.6	11.6	10.4	9.8	10.8	9.6	11.9	10.5	9
Mean DAOH - P25	8.9 to 11.8	10.2	10.7	10	10.9	9.8	11	10.4	11.4	10.2	9.7	10.6	9.4	11.8	10.3	8.9
Mean DAOH - P75	9.2 to 12.1	10.4	10.9	10.2	11.2	10	11.2	10.7	11.7	10.6	9.9	11	9.7	12.1	10.7	9.2
Mean DAOH - minimum	8.1 to 10.8	9.5	9.7	9.2	10	8.9	10.1	9.4	10.3	9.1	8.8	9.7	8.4	10.8	9.3	8.1
Mean DAOH - maximum	9.9 to 12.9	11.2	11.6	10.9	12.1	10.7	11.9	11.4	12.3	11.3	10.5	11.8	10.3	12.9	11.6	9.9
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.0088 to 0.999	0.0088	0.721	0.0408	0.999	0.0396	0.0447	0.771	0.765	0.769	0.728	0.999	0.777	0.0456	0.999	0.999
Pr(equivalence)	0.00073 to 0.991	0.991	0.279	0.959	0.00107	0.96	0.955	0.229	0.235	0.231	0.272	0.00105	0.223	0.954	0.00073	0.00095
Pr(maximum)	0 to 0.00046	0.00002	0.00046	0	0	0	0.00001	0	0	0	0.00001	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.00268	0.00001	0.0209	0	0.02	0	0.00004	0	0.0001	0.728	0	0.777	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.0033	0.721	0	0.999	0	0.0227	0	0.765	0	0.00001	0.999	0	0.0231	0	0
Pr(arm C superior)	0 to 0.999	0.00282	0.00001	0.0199	0	0.0196	0.022	0.771	0.00008	0.769	0.00001	0	0.00004	0.0225	0.999	0
Pr(no arm superior)	0.00073 to 0.991	0.991	0.279	0.959	0.00107	0.96	0.955	0.229	0.235	0.231	0.272	0.00105	0.223	0.954	0.00073	0.00095
Pr(erroneous superiority)	0 to 0.0456	0.0088	0.00002	0.0408	0	0.0396	0.0447	0.00004	0.00008	0.0001	0.00002	0	0.00004	0.0456	0	0
RMSE (superiority only)	0.306 to 0.72	0.72	0.318	0.576	0.395	0.603	0.593	0.338	0.345	0.338	0.306	0.406	0.332	0.637	0.403	0.362
MAE (superiority only)	0.162 to 0.595	0.595	0.164	0.453	0.252	0.485	0.461	0.181	0.183	0.184	0.162	0.267	0.184	0.5	0.266	0.238
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.248 to 0.407	0.248	0.315	0.266	0.395	0.277	0.272	0.345	0.353	0.348	0.304	0.407	0.337	0.286	0.403	0.363
MAE (select best)	0.169 to 0.267	0.17	0.178	0.169	0.253	0.181	0.173	0.201	0.206	0.204	0.174	0.267	0.199	0.184	0.266	0.239
IDP (select best)	97.8 to 100	-	97.8	99.9	100	100	99.8	98.4	98.4	98.8	98	100	98.5	100	100	100

Calibrated stopping threshold for superiority: 0.995 (manually re-calibrated).
Abbreviations: 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 final primary *INCEPT-Thromboprophylaxis* domain design with higher inclusion rate

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	10.3 to 10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3
Mean number of days (arm B)	8.3 to 12.3	10.3	11.3	9.3	12.3	8.3	11.3	9.3	12.3	8.3	9.3	12.3	8.3	12.3	8.3	8.3
Mean number of days (arm C)	8.3 to 12.3	10.3	10.3	10.3	10.3	10.3	11.3	11.3	11.3	11.3	9.3	9.3	9.3	12.3	12.3	8.3
Sample size - mean	2501.7 to 5158.2	5102.6	5158.2	4153.6	2808.5	3512.4	4616	4042.6	4398.3	3977.4	4671.8	2598	3730.8	4128.8	2590.4	2501.7
Sample size - SD	510.3 to 1792.9	1264	1792.9	1241.7	748.6	880.2	1423.8	1392	1572	1366	1560.7	621	1215.8	1095.5	614	510.3
Sample size - median	2175 to 5175	4680	5175	3675	2685	3180	4185	3675	4185	3675	4680	2175	3675	3675	2175	2175
Sample size - P25	2175 to 4185	4185	3675	3180	2175	2685	3675	3180	3180	3180	3675	2175	2685	3180	2175	2175
Sample size - P75	2685 to 6180	5685	6180	4680	3180	3675	5685	5175	5175	4680	5685	2685	4680	4680	2685	2685
Sample size - minimum	2175 to 2175	2175	2175	2175	2175	2175	2175	2175	2175	2175	2175	2175	2175	2175	2175	2175
Sample size - maximum	6180 to 10000	10000	10000	10000	9180	8175	10000	10000	10000	9180	10000	8175	8685	10000	7185	6180
Total DAOH - mean	22647.3 to 55543.9	52649.7	55543.9	41833.4	31149.7	34775.2	51125.4	42775.4	50986.7	41416.1	45614.4	28033.5	35675.9	49300.1	27230.7	22647.3
Total DAOH - SD	4829 to 19419.5	13071.5	19419.5	12548.5	8552.3	9106.5	15783.1	15192.8	18700	14946.2	15358.7	7140.9	12068.1	13484.2	7070.6	4829
Total DAOH - median	19941 to 54912	49159	54912	37812.5	29455	31686	46675	39246.5	48282	38335	45180.5	23735	34602	44282	22983	19941
Total DAOH - P25	19455 to 43222	43222	39771	32048	24015	26885	39805	32456	36533	31127.8	34802.8	23096	25430	38341	22369	19455
Total DAOH - P75	24552 to 68386.8	59407	68386.8	48209	35633	37406.2	61005.2	53740.2	62046	49977	55961	29990	44592	55736.2	29202	24552
Total DAOH - minimum	17884 to 23315	20843	21563	20297	21592	19311	22372	20645	22751	20045	19466	20976	18551	23315	20549	17884
Total DAOH - maximum	56708 to 123990	104677	110769	100470	99317	85134	113429	106031	119085	99479	98819	92805	82497	123990	79902	56708
Mean DAOH - mean	9 to 11.9	10.3	10.8	10.1	11.1	9.9	11.1	10.5	11.6	10.4	9.8	10.8	9.5	11.9	10.5	9

Mean DAOH - SD	0.151 to 0.285	0.151	0.169	0.175	0.23	0.201	0.179	0.22	0.223	0.264	0.164	0.256	0.212	0.209	0.285	0.205
Mean DAOH - median	9 to 11.9	10.3	10.8	10.1	11.1	9.9	11.1	10.6	11.6	10.4	9.8	10.8	9.5	11.9	10.5	9
Mean DAOH - P25	8.9 to 11.8	10.2	10.7	10	10.9	9.7	11	10.4	11.4	10.2	9.7	10.6	9.4	11.8	10.3	8.9
Mean DAOH - P75	9.2 to 12.1	10.4	10.9	10.2	11.2	10	11.2	10.7	11.7	10.5	9.9	10.9	9.7	12.1	10.7	9.2
Mean DAOH - minimum	8.2 to 10.7	9.6	9.8	9.2	9.9	8.9	10.2	9.5	10.5	9.2	8.8	9.6	8.5	10.7	9.4	8.2
Mean DAOH - maximum	9.9 to 12.8	11	11.5	10.8	12.1	10.7	11.9	11.3	12.3	11.2	10.5	11.8	10.3	12.8	11.7	9.9
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.00892 to 0.999	0.00892	0.72	0.042	0.999	0.0404	0.0458	0.773	0.765	0.768	0.73	0.999	0.776	0.0454	0.999	0.999
Pr(equivalence)	0.00088 to 0.991	0.991	0.279	0.958	0.00119	0.96	0.954	0.227	0.235	0.232	0.27	0.00113	0.224	0.955	0.00088	0.00103
Pr(maximum)	0 to 0.00036	0.00004	0.00036	0	0	0	0.00003	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.00279	0.00003	0.0214	0	0.0202	0	0.00003	0	0.00004	0.73	0	0.776	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.00316	0.72	0	0.999	0	0.0235	0	0.765	0	0.00001	0.999	0	0.0228	0	0
Pr(arm C superior)	0 to 0.999	0.00297	0.00004	0.0207	0	0.0202	0.0223	0.773	0.00007	0.768	0	0	0.00001	0.0227	0.999	0
Pr(no arm superior)	0.00088 to 0.991	0.991	0.28	0.958	0.00119	0.96	0.954	0.227	0.235	0.232	0.27	0.00113	0.224	0.955	0.00088	0.00103
Pr(erroneous superiority)	0 to 0.0458	0.00892	0.00007	0.042	0	0.0404	0.0458	0.00003	0.00007	0.00004	0.00001	0	0.00001	0.0454	0	0
RMSE (superiority only)	0.287 to 0.67	0.67	0.308	0.513	0.376	0.543	0.566	0.315	0.335	0.318	0.287	0.385	0.304	0.599	0.389	0.345
MAE (superiority only)	0.155 to 0.586	0.586	0.163	0.411	0.244	0.429	0.444	0.175	0.182	0.177	0.155	0.257	0.172	0.467	0.255	0.232
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.248 to 0.389	0.248	0.303	0.255	0.377	0.265	0.266	0.326	0.338	0.329	0.289	0.386	0.314	0.28	0.389	0.346
MAE (select best)	0.163 to 0.257	0.172	0.172	0.163	0.244	0.175	0.17	0.194	0.198	0.195	0.168	0.257	0.189	0.182	0.255	0.232
IDP (select best)	97.8 to 100	-	97.8	99.9	100	100	99.9	98.3	98.4	98.8	97.9	100	98.5	100	100	100

Calibrated stopping threshold for superiority: 0.995 (re-used from the final, primary design).

Abbreviations: 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 final primary *INCEPT-Thromboprophylaxis* domain design with slower inclusion rate

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	10.3 to 10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3	10.3
Mean number of days (arm B)	8.3 to 12.3	10.3	11.3	9.3	12.3	8.3	11.3	9.3	12.3	8.3	9.3	12.3	8.3	12.3	8.3	8.3
Mean number of days (arm C)	8.3 to 12.3	10.3	10.3	10.3	10.3	10.3	11.3	11.3	11.3	11.3	9.3	9.3	9.3	12.3	12.3	8.3
Sample size - mean	2026 to 4644	4644	4613.6	3670.9	2314.5	2962.9	4107.8	3498.4	3857.1	3417.5	4154.1	2107.4	3191.3	3580.7	2102.5	2026
Sample size - SD	472.4 to 1790.6	1272.9	1790.6	1271.2	703.9	859.5	1464	1362.5	1553	1339.5	1552.2	568.5	1178.3	1081.5	563.9	472.4
Sample size - median	1725 to 4225	4225	4225	3225	2225	2725	3725	3225	3725	3225	4225	1725	2725	3225	1725	1725
Sample size - P25	1725 to 3725	3725	3225	2725	1725	2225	2725	2225	2725	2225	2725	1725	2225	2725	1725	1725
Sample size - P75	2225 to 5725	5225	5725	4225	2725	3225	4725	4225	4725	4225	5225	2225	3725	4225	2225	2225
Sample size - minimum	1725 to 1725	1725	1725	1725	1725	1725	1725	1725	1725	1725	1725	1725	1725	1725	1725	1725
Sample size - maximum	6225 to 10000	10000	10000	10000	7225	8225	10000	8725	9725	8225	9725	7225	7725	9725	6725	6225
Total DAOH - mean	18359.6 to 49720.2	47913.2	49720.2	36999.9	25701.5	29403.5	45524.3	37107.6	44813.9	35721.3	40597.3	22772.2	30592.8	42852.2	22151.4	18359.6
Total DAOH - SD	4464.1 to 19393.6	13161	19393.6	12833.8	8030.8	8885.3	16218.4	14867.5	18469	14655	15269.7	6532.4	11691	13308.6	6490.2	4464.1
Total DAOH - median	15859 to 46717	44416	46717	33047.5	24376	26986	41424	34208.5	42586.5	33404	40344	18877	27031.5	38594	18286	15859
Total DAOH - P25	15423 to 38469	38469	34643.8	27329	19067	22057	31009	23825	31163	22991	27292	18314	21022	32622	17736	15423
Total DAOH - P75	20321 to 62399.5	54684.2	62399.5	43604	30358	32498	54198.8	45700	55831	44753	51193	24575	36997.5	49676	23984	20321
Total DAOH - minimum	13891 to 18612	16870	16831	15792	17186	15335	17560	16168	17401	15147	15106	16552	14492	18612	15800	13891
Total DAOH - maximum	56329 to 119238	104213	110682	100232	82515	82816	113328	93776	116170	90777	96424	80751	77639	119238	76144	56329
Mean DAOH - mean	9 to 11.9	10.3	10.8	10.1	11.1	9.9	11.1	10.6	11.6	10.4	9.8	10.8	9.5	11.9	10.5	9

Mean DAOH - SD	0.159 to 0.313	0.159	0.182	0.189	0.252	0.219	0.193	0.237	0.242	0.285	0.176	0.282	0.231	0.225	0.313	0.228
Mean DAOH - median	9.1 to 12	10.3	10.8	10.1	11.1	9.9	11.1	10.6	11.6	10.4	9.8	10.8	9.6	12	10.5	9.1
Mean DAOH - P25	8.9 to 11.8	10.2	10.7	10	10.9	9.8	11	10.4	11.4	10.2	9.7	10.6	9.4	11.8	10.3	8.9
Mean DAOH - P75	9.2 to 12.1	10.4	10.9	10.2	11.3	10	11.2	10.7	11.7	10.6	9.9	11	9.7	12.1	10.7	9.2
Mean DAOH - minimum	8.1 to 10.8	9.6	9.8	9.1	10	8.9	10.2	9.4	10.1	8.8	8.8	9.6	8.4	10.8	9.2	8.1
Mean DAOH - maximum	10.1 to 12.8	11.1	11.8	11	12.1	10.8	11.9	11.4	12.6	11.3	10.6	11.8	10.4	12.8	11.6	10.1
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.00857 to 0.999	0.00857	0.722	0.0418	0.999	0.0383	0.0448	0.772	0.767	0.769	0.732	0.999	0.781	0.044	0.999	0.999
Pr(equivalence)	0.00087 to 0.991	0.991	0.278	0.958	0.00125	0.962	0.955	0.228	0.233	0.231	0.268	0.00115	0.219	0.956	0.00117	0.00087
Pr(maximum)	0 to 0.00042	0.00004	0.00042	0	0	0	0.00004	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.00297	0.00002	0.021	0	0.0193	0	0.00005	0	0.00004	0.732	0	0.781	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.00266	0.722	0	0.999	0	0.0225	0	0.766	0	0	0.999	0	0.0222	0	0
Pr(arm C superior)	0 to 0.999	0.00294	0.00001	0.0208	0	0.019	0.0223	0.772	0.0001	0.769	0.00001	0	0.00001	0.0218	0.999	0
Pr(no arm superior)	0.00087 to 0.991	0.991	0.278	0.958	0.00125	0.962	0.955	0.228	0.233	0.231	0.268	0.00115	0.219	0.956	0.00117	0.00087
Pr(erroneous superiority)	0 to 0.0448	0.00857	0.00003	0.0418	0	0.0383	0.0448	0.00005	0.0001	0.00004	0.00001	0	0.00001	0.044	0	0
RMSE (superiority only)	0.337 to 0.784	0.784	0.339	0.616	0.422	0.644	0.627	0.357	0.361	0.352	0.337	0.427	0.352	0.711	0.427	0.377
MAE (superiority only)	0.17 to 0.672	0.672	0.17	0.479	0.266	0.512	0.466	0.191	0.188	0.187	0.173	0.281	0.192	0.547	0.279	0.253
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.26 to 0.428	0.26	0.334	0.276	0.422	0.282	0.276	0.367	0.372	0.368	0.328	0.428	0.359	0.298	0.428	0.377
MAE (select best)	0.172 to 0.281	0.178	0.184	0.175	0.266	0.182	0.172	0.214	0.216	0.215	0.181	0.281	0.211	0.19	0.28	0.253
IDP (select best)	97.9 to 100	-	97.9	99.9	100	100	99.9	98.4	98.5	98.8	98	100	98.6	100	100	100

Calibrated stopping threshold for superiority: 0.995 (re-used from the final, primary design).
Abbreviations: 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 final primary *INCEPT-Thromboprophylaxis* domain design with higher proportion of zeroes

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	9.1 to 9.2	9.2	9.2	9.1	9.1	9.1	9.2	9.1	9.1	9.2	9.1	9.2	9.1	9.2	9.2	9.1
Mean number of days (arm B)	7.1 to 11.1	9.2	10.1	8.2	11.1	7.1	10.1	8.1	11.1	7.2	8.1	11.1	7.1	11.1	7.2	7.1
Mean number of days (arm C)	7.1 to 11.1	9.2	9.2	9.1	9.1	9.1	10.1	10.1	10.1	10.1	8.1	8.1	8.1	11.1	11.1	7.1
Sample size - mean	2232.4 to 4870.9	4809.5	4870.9	3849.3	2580.7	3213.7	4373.9	3749.1	4171.4	3698.2	4314.2	2361.8	3402.8	3897.4	2358.5	2232.4
Sample size - SD	463.7 to 1777.9	1246.5	1777.9	1217.1	738.2	846.4	1425.2	1358	1584.1	1347.1	1506.2	599	1154.1	1114.8	597.7	463.7
Sample size - median	1950 to 4950	4450	4950	3450	2450	2950	3950	3450	3950	3450	3950	1950	2950	3450	1950	1950
Sample size - P25	1950 to 3950	3950	3450	2950	1950	2450	3450	2950	2950	2450	2950	1950	2450	2950	1950	1950
Sample size - P75	2450 to 5950	5450	5950	4450	2950	3450	4950	4450	5450	4450	5450	2450	3950	4450	2450	2450
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	5950 to 10000	10000	10000	9950	8950	7950	10000	8950	9950	8450	9950	7950	7950	10000	6950	5950
Total DAOH - mean	17592.7 to 46764	43989.5	46764	34275.9	25622	28084.8	43345.3	35322.6	43530	34248.9	37084.1	22740.5	28581.3	42031.5	22065.8	17592.7
Total DAOH - SD	3844.6 to 17176.3	11442.7	17176.3	10877	7555.4	7767.7	14128.3	13233	16983.7	13166.5	13061.9	6181.4	10107.7	12422.6	6172.9	3844.6
Total DAOH - median	15562 to 45988.5	41239	45988.5	31134	24069	25820	39435.5	32624	40945	31826.5	35110.5	19040	25980	37527	18376	15562
Total DAOH - P25	15141 to 35996	35996	33159	26145	19278	21500	33000	26239.8	30438	22772	25914	18425	20269	32086	17778	15141
Total DAOH - P75	19393 to 57997	50249	57997	40189	29611	30739	51171	42945	54648	42039.2	46626	24533.2	34237	47837.2	23839	19393
Total DAOH - minimum	13418 to 18791	16655	16749	15908	17100	15257	17770	16166	18190	15657	14890	16543	14408	18791	15799	13418
Total DAOH - maximum	48666 to 110464	93654	98873	88775	90678	72415	100725	86460	108017	82228	86274	79066	67170	110464	69714	48666
Mean DAOH - mean	7.9 to 10.8	9.1	9.6	8.9	9.9	8.7	9.9	9.4	10.4	9.2	8.6	9.6	8.4	10.8	9.3	7.9

Mean DAOH - SD	0.155 to 0.297	0.155	0.175	0.181	0.238	0.208	0.185	0.226	0.232	0.273	0.169	0.266	0.217	0.218	0.297	0.211
Mean DAOH - median	7.9 to 10.8	9.1	9.6	8.9	9.9	8.7	9.9	9.4	10.4	9.2	8.6	9.6	8.4	10.8	9.3	7.9
Mean DAOH - P25	7.7 to 10.6	9	9.5	8.8	9.8	8.6	9.8	9.2	10.2	9	8.5	9.4	8.2	10.6	9.1	7.7
Mean DAOH - P75	8 to 10.9	9.2	9.7	9	10.1	8.9	10	9.5	10.6	9.4	8.7	9.8	8.5	10.9	9.5	8
Mean DAOH - minimum	6.9 to 9.6	8.4	8.6	8.1	8.8	7.6	9	8.3	9.3	8	7.6	8.5	7.4	9.6	8.1	6.9
Mean DAOH - maximum	8.8 to 11.6	10	10.4	9.7	10.9	9.5	10.7	10.1	11.2	10	9.5	10.6	9.1	11.6	10.5	8.8
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.00886 to 0.999	0.00886	0.72	0.0417	0.999	0.0384	0.0463	0.771	0.762	0.771	0.731	0.999	0.779	0.0452	0.999	0.999
Pr(equivalence)	0.00083 to 0.991	0.991	0.28	0.958	0.00124	0.962	0.954	0.229	0.238	0.229	0.269	0.00105	0.221	0.955	0.00083	0.00093
Pr(maximum)	0 to 0.00029	0	0.00029	0	0	0	0.00004	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.00307	0	0.0212	0	0.0194	0	0.00001	0	0.00001	0.731	0	0.779	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.00293	0.72	0	0.999	0	0.0233	0	0.762	0	0.00001	0.999	0	0.0228	0	0
Pr(arm C superior)	0 to 0.999	0.00286	0	0.0205	0	0.019	0.023	0.771	0.00002	0.771	0	0	0.00002	0.0223	0.999	0
Pr(no arm superior)	0.00083 to 0.991	0.991	0.28	0.958	0.00124	0.962	0.954	0.229	0.238	0.229	0.269	0.00105	0.221	0.955	0.00083	0.00093
Pr(erroneous superiority)	0 to 0.0463	0.00886	0	0.0417	0	0.0384	0.0463	0.00001	0.00002	0.00001	0.00001	0	0.00002	0.0452	0	0
RMSE (superiority only)	0.308 to 0.708	0.708	0.318	0.569	0.396	0.59	0.593	0.344	0.358	0.336	0.308	0.409	0.323	0.662	0.411	0.36
MAE (superiority only)	0.162 to 0.602	0.602	0.164	0.444	0.256	0.473	0.452	0.187	0.19	0.182	0.162	0.27	0.179	0.524	0.269	0.239
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.247 to 0.412	0.247	0.315	0.265	0.397	0.275	0.27	0.349	0.361	0.347	0.307	0.41	0.332	0.293	0.412	0.36
MAE (select best)	0.169 to 0.27	0.169	0.178	0.17	0.257	0.181	0.169	0.205	0.209	0.204	0.174	0.27	0.198	0.188	0.27	0.24
IDP (select best)	97.9 to 100	-	97.9	99.9	100	100	99.9	98.4	98.4	98.9	98	100	98.6	100	100	100

Calibrated stopping threshold for superiority: 0.995 (re-used from the final, primary design).

Abbreviations: 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 final primary *INCEPT-Thromboprophylaxis* domain design with lower proportion of zeroes

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	11.9 to 11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9	11.9
Mean number of days (arm B)	9.9 to 13.9	11.9	12.9	10.9	13.9	9.9	12.9	10.9	13.9	9.9	10.9	13.9	9.9	13.9	9.9	9.9
Mean number of days (arm C)	9.9 to 13.9	11.9	11.9	11.9	11.9	11.9	12.9	12.9	12.9	12.9	10.9	10.9	10.9	13.9	13.9	9.9
Sample size - mean	2271.6 to 4816.1	4816.1	4786.9	3891.1	2512.2	3216.4	4247.5	3702.3	3999.9	3634.9	4403.2	2314.1	3459.6	3725.6	2311.9	2271.6
Sample size - SD	496.4 to 1752	1253.7	1752	1257.4	691.1	851	1404.4	1333.7	1485.8	1315.5	1552.5	558	1192.2	1018.4	556.5	496.4
Sample size - median	1950 to 4450	4450	4450	3450	2450	2950	3950	3450	3950	3450	4450	1950	3450	3450	1950	1950
Sample size - P25	1950 to 3950	3950	3450	2950	1950	2450	2950	2450	2950	2450	2950	1950	2450	2950	1950	1950
Sample size - P75	2450 to 5950	5450	5950	4450	2950	3450	4950	4450	4950	4450	5450	2450	4450	3950	2450	2450
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	5950 to 10000	10000	10000	9950	7950	7950	10000	8950	9450	8450	10000	6450	7950	9950	6950	5950
Total DAOH - mean	24151.6 to 59092	57268.1	59092	45324	31817.6	36932.2	53728.9	45025.4	52689.1	43605.6	49941.1	28605.6	38558.5	50365.1	27933.8	24151.6
Total DAOH - SD	5479.9 to 21732.4	14929.2	21732.4	14675.7	8987.2	10135.1	17771.3	16649	20009.7	16461.8	17724	7297	13701.3	14139.4	7285.5	5479.9
Total DAOH - median	20978 to 55791	53470	55791	40710	30487	33914	49844.5	41954	50974	41120	49721.5	24294	37620	46424	23626	20978
Total DAOH - P25	20506.8 to 46843	46843	42373	34258	24558	28225	37938	30147.8	38294	29215	34534.8	23747	27061	39802.8	23097	20506.8
Total DAOH - P75	26304 to 73842	65253	73842	52694	37437	40191	63285	54866	65585	53957	62083.2	30798	48991	54299	30168	26304
Total DAOH - minimum	18776 to 23902	22020	22328	21237	22382	20509	22756	21649	23226	20876	20395	21713	19687	23902	21375	18776
Total DAOH - maximum	63884 to 135986	121638	126108	115841	100244	95604	127807	109801	128404	105130	115377	83408	90549	135986	88198	63884
Mean DAOH - mean	10.6 to 13.5	11.9	12.3	11.6	12.6	11.5	12.6	12.1	13.1	11.9	11.3	12.3	11.1	13.5	12	10.6

Mean DAOH - SD	0.155 to 0.295	0.155	0.173	0.181	0.238	0.208	0.184	0.225	0.229	0.274	0.169	0.265	0.221	0.213	0.295	0.218
Mean DAOH - median	10.6 to 13.5	11.9	12.3	11.6	12.7	11.5	12.6	12.1	13.2	12	11.3	12.3	11.1	13.5	12	10.6
Mean DAOH - P25	10.5 to 13.4	11.8	12.2	11.5	12.5	11.3	12.5	12	13	11.8	11.2	12.1	11	13.4	11.8	10.5
Mean DAOH - P75	10.8 to 13.6	12	12.4	11.8	12.8	11.6	12.8	12.3	13.3	12.1	11.4	12.5	11.3	13.6	12.2	10.8
Mean DAOH - minimum	9.6 to 12.3	11.1	11.5	10.8	11.5	10.5	11.7	11.1	11.9	10.7	10.5	11.1	10.1	12.3	11	9.6
Mean DAOH - maximum	11.5 to 14.3	12.7	13.2	12.4	13.7	12.3	13.5	12.9	13.9	12.8	12.1	13.3	11.9	14.3	13.2	11.5
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.00934 to 0.999	0.00934	0.72	0.0422	0.999	0.0385	0.0451	0.775	0.767	0.77	0.729	0.999	0.778	0.0447	0.999	0.999
Pr(equivalence)	0.00095 to 0.991	0.991	0.279	0.958	0.00112	0.962	0.955	0.225	0.233	0.23	0.271	0.0011	0.222	0.955	0.00099	0.00095
Pr(maximum)	0 to 0.0002	0.00002	0.0002	0	0	0	0.00002	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.0031	0.00001	0.0217	0	0.0191	0	0.00005	0	0.00004	0.729	0	0.778	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.00304	0.72	0	0.999	0	0.0228	0	0.767	0	0.00001	0.999	0	0.0229	0	0
Pr(arm C superior)	0 to 0.999	0.0032	0.00002	0.0205	0	0.0194	0.0223	0.775	0.00004	0.77	0.00002	0	0.00001	0.0218	0.999	0
Pr(no arm superior)	0.00095 to 0.991	0.991	0.28	0.958	0.00112	0.962	0.955	0.225	0.233	0.23	0.271	0.0011	0.222	0.955	0.00099	0.00095
Pr(erroneous superiority)	0 to 0.0451	0.00934	0.00003	0.0422	0	0.0385	0.0451	0.00005	0.00004	0.00004	0.00003	0	0.00001	0.0447	0	0
RMSE (superiority only)	0.308 to 0.718	0.718	0.322	0.554	0.381	0.592	0.573	0.322	0.339	0.324	0.308	0.398	0.314	0.63	0.398	0.355
MAE (superiority only)	0.163 to 0.614	0.614	0.169	0.433	0.249	0.474	0.44	0.177	0.182	0.18	0.163	0.261	0.176	0.497	0.261	0.238
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.252 to 0.399	0.252	0.314	0.261	0.381	0.276	0.263	0.336	0.348	0.34	0.305	0.399	0.327	0.283	0.399	0.356
MAE (select best)	0.165 to 0.262	0.174	0.177	0.165	0.249	0.181	0.165	0.2	0.203	0.202	0.172	0.262	0.197	0.183	0.262	0.238
IDP (select best)	97.9 to 100	-	97.9	99.9	100	100	99.9	98.4	98.5	98.8	98	100	98.6	100	100	100

Calibrated stopping threshold for superiority: 0.995 (re-used from the final, primary design).

Abbreviations: 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 final primary *INCEPT-Thromboprophylaxis* domain design with lower mean number of days in those with >0 days

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	8.2 to 8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2	8.2
Mean number of days (arm B)	6.2 to 10.2	8.2	9.2	7.2	10.2	6.2	9.2	7.2	10.2	6.2	7.2	10.2	6.2	10.2	6.2	6.2
Mean number of days (arm C)	6.2 to 10.2	8.2	8.2	8.2	8.2	8.2	9.2	9.2	9.2	9.2	7.2	7.2	7.2	10.2	10.2	6.2
Sample size - mean	2063.8 to 3918.8	3793.1	3918.8	3110.5	2248.6	2646.1	3479.2	3133.8	3415.4	3092.8	3537	2138	2887.8	3206.2	2135.9	2063.8
Sample size - SD	278 to 1302.2	908.1	1302.2	921.1	478	701.8	1034	1020.5	1164.6	1009.9	1114.9	381.5	878.7	845	379.5	278
Sample size - median	1950 to 3950	3450	3950	2950	1950	2450	3450	2950	3450	2950	3450	1950	2950	2950	1950	1950
Sample size - P25	1950 to 2950	2950	2950	2450	1950	1950	2450	2450	2450	2450	2450	1950	1950	2450	1950	1950
Sample size - P75	1950 to 4950	4450	4950	3450	2450	2950	3950	3950	3950	3950	4450	1950	3450	3450	1950	1950
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	4450 to 8950	7950	8950	7450	5950	6450	8450	6950	7450	6450	7450	4950	5950	7950	5450	4450
Total DAOH - mean	14187.5 to 33764	31009.1	33764	24612.2	20034.5	20331.8	31050.2	26326.9	32196	25344.2	26907	18360.9	21292.7	31307.9	17693.8	14187.5
Total DAOH - SD	2061.9 to 11392.5	7462	11335.1	7370.7	4454.2	5763.3	9277.6	8974.6	11392.5	8896.8	8605	3583.8	6856	8617.9	3568.8	2061.9
Total DAOH - median	13450 to 33585	28710	33585	23335	17587	18847	29788	24752.5	31006	24026	26229	16779	21132.5	28825	16121	13450
Total DAOH - P25	13171 to 25188	24520	25188	19241	17148	14933	22490	19781	22793	18867	19033	16431	14353	24002	15780	13171
Total DAOH - P75	13823 to 42330.2	36021	42330.2	28059.2	21982	23026	35756	33045	38468	32162	33596	17564	25760.2	34228	16877	13823
Total DAOH - minimum	11921 to 17340	14719	15264	13852	15563	12905	15909	14063	15903	13677	13391	14891	12454	17340	14197	11921
Total DAOH - maximum	32786 to 80436	65734	76612	59196	54217	51267	76136	60864	73623	57180	58140	44839	46758	80436	49613	32786
Mean DAOH - mean	6.9 to 9.7	8.2	8.6	7.9	8.9	7.7	8.9	8.4	9.4	8.1	7.6	8.6	7.3	9.7	8.3	6.9

Mean DAOH - SD	0.148 to 0.263	0.148	0.164	0.172	0.213	0.212	0.176	0.214	0.22	0.263	0.159	0.227	0.206	0.208	0.246	0.185
Mean DAOH - median	6.9 to 9.7	8.2	8.6	7.9	8.9	7.7	8.9	8.4	9.4	8.2	7.6	8.6	7.4	9.7	8.2	6.9
Mean DAOH - P25	6.7 to 9.6	8.1	8.5	7.8	8.8	7.5	8.8	8.2	9.2	8	7.5	8.4	7.2	9.6	8.1	6.7
Mean DAOH - P75	7 to 9.9	8.3	8.7	8	9	7.8	9	8.5	9.5	8.3	7.7	8.7	7.5	9.9	8.4	7
Mean DAOH - minimum	6.1 to 8.9	7.4	7.8	7.1	8	6.6	8.2	7.2	8.2	7	6.9	7.6	6.4	8.9	7.3	6.1
Mean DAOH - maximum	7.7 to 10.6	8.9	9.3	8.7	9.8	8.4	9.7	9.1	10.2	9	8.3	9.5	8.1	10.6	9.4	7.7
Pr(conclusive)	1 to 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pr(superiority)	0.00742 to 0.999	0.00742	0.734	0.0348	0.999	0.0331	0.0378	0.779	0.778	0.774	0.739	0.999	0.784	0.0401	0.999	0.999
Pr(equivalence)	0.00075 to 0.993	0.993	0.266	0.965	0.00101	0.967	0.962	0.221	0.222	0.226	0.261	0.00075	0.216	0.96	0.00094	0.00094
Pr(maximum)	0 to 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pr(arm A superior)	0 to 0.999	0.00242	0	0.0173	0	0.0164	0	0	0	0.00001	0.739	0	0.784	0	0	0.999
Pr(arm B superior)	0 to 0.999	0.00259	0.734	0	0.999	0	0.0187	0	0.778	0	0	0.999	0	0.0196	0	0
Pr(arm C superior)	0 to 0.999	0.00241	0.00001	0.0175	0	0.0166	0.0191	0.779	0.00002	0.774	0.00001	0	0	0.0206	0.999	0
Pr(no arm superior)	0.00075 to 0.993	0.993	0.266	0.965	0.00101	0.967	0.962	0.221	0.222	0.226	0.261	0.00075	0.216	0.96	0.00094	0.00094
Pr(erroneous superiority)	0 to 0.0401	0.00742	0.00001	0.0348	0	0.033	0.0378	0	0.00002	0.00001	0.00001	0	0	0.0401	0	0
RMSE (superiority only)	0.273 to 0.653	0.653	0.298	0.52	0.358	0.538	0.535	0.299	0.328	0.298	0.273	0.368	0.289	0.591	0.365	0.323
MAE (superiority only)	0.152 to 0.562	0.562	0.161	0.421	0.238	0.445	0.418	0.171	0.183	0.172	0.152	0.251	0.169	0.485	0.248	0.22
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.242 to 0.368	0.242	0.296	0.252	0.359	0.264	0.252	0.317	0.333	0.319	0.28	0.368	0.306	0.276	0.366	0.323
MAE (select best)	0.162 to 0.251	0.169	0.171	0.163	0.238	0.175	0.162	0.192	0.199	0.193	0.167	0.251	0.188	0.181	0.248	0.22
IDP (select best)	98.1 to 100	-	98.1	99.9	100	100	99.9	98.4	98.6	98.8	98.2	100	98.6	100	100	100

Calibrated stopping threshold for superiority: 0.995 (re-used from the final, primary design).
Abbreviations: 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 final primary *INCEPT-Thromboprophylaxis* domain design with higher mean number of days in those with >0 days

Metric	Range	ND	B +1 C 0	B -1 C 0	B +2 C 0	B -2 C 0	B +1 C +1	B -1 C +1	B +2 C +1	B -2 C +1	B -1 C -1	B +2 C -1	B -2 C -1	B +2 C +2	B -2 C +2	B -2 C -2
Mean number of days (arm A)	12.6 to 12.7	12.7	12.7	12.7	12.7	12.7	12.6	12.7	12.6	12.7	12.6	12.7	12.7	12.7	12.7	12.7
Mean number of days (arm B)	10.7 to 14.5	12.7	13.6	11.7	14.5	10.7	13.6	11.7	14.5	10.7	11.7	14.5	10.7	14.5	10.7	10.7
Mean number of days (arm C)	10.7 to 14.5	12.7	12.7	12.7	12.7	12.7	13.6	13.6	13.6	13.6	11.7	11.7	11.7	14.5	14.5	10.7
Sample size - mean	2638.6 to 6287.7	6287.7	6234.6	5010	3214.1	3951.2	5592.3	4685.3	5177.4	4516.4	5633.9	2804.4	4262.3	4640.8	2786	2638.6
Sample size - SD	781.7 to 2291.1	1678.7	2291.1	1751.3	1160.5	1144	1945.9	1860.7	2062.3	1818.5	2114.4	943.2	1637.8	1392.4	938.5	781.7
Sample size - median	2450 to 5950	5950	5950	4450	2950	3450	4950	4450	4950	3950	5450	2450	3950	3950	2450	2450
Sample size - P25	1950 to 4950	4950	4450	3450	2450	2950	3950	3450	3450	2950	3950	1950	2950	3450	1950	1950
Sample size - P75	2950 to 7950	7450	7950	5950	3950	4450	6950	5950	6450	5450	6950	3450	5450	5450	3450	2950
Sample size - minimum	1950 to 1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950	1950
Sample size - maximum	8450 to 10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	8950	10000	10000	8950	8450
Total DAOH - mean	30267.5 to 81697	79596.9	81697	62290.1	43251.7	48680.8	74905.8	60704.2	71990.6	57997.5	68355.1	37023	51036.2	66041.5	36164.4	30267.5
Total DAOH - SD	9204.1 to 30101.5	21283.1	30101.5	21744.1	15861.4	14489.5	26007.3	24571.2	29132.9	24107.2	25743.7	12963.4	20065.4	20190.1	12923.5	9204.1
Total DAOH - median	28016 to 78988.5	75710	78988.5	56160.5	39853	43018	67725	57153.5	68036	51514	66269	32580	47294	58126.5	31871	28016
Total DAOH - P25	22320 to 63441	63441	58109	43538	32013	36873.8	53052	43602	48217	38084.8	47945.8	25566	35114	50112	24883	22320
Total DAOH - P75	34416 to 105008	93735	105008	74720	53051	54958	92623.2	77221	90805	72353.2	85967.5	45369	65020	75638.2	44695	34416
Total DAOH - minimum	20066 to 24986	23376	23438	22673	23757	21723	24557	22296	24367	21537	21403	23120	20791	24986	22366	20066
Total DAOH - maximum	97883 to 148605	130784	135773	130666	136129	127786	138985	134411	144855	133481	125275	122091	123198	148605	121810	97883
Mean DAOH - mean	11.4 to 14.2	12.7	13.1	12.4	13.4	12.3	13.4	12.9	13.9	12.8	12.1	13.2	11.9	14.2	12.9	11.4

Mean DAOH - SD	0.161 to 0.342	0.161	0.182	0.191	0.254	0.22	0.194	0.236	0.236	0.281	0.18	0.299	0.234	0.227	0.342	0.244
Mean DAOH - median	11.5 to 14.2	12.7	13.1	12.4	13.4	12.3	13.4	12.9	13.9	12.8	12.1	13.2	12	14.2	12.9	11.5
Mean DAOH - P25	11.3 to 14.1	12.6	13	12.3	13.3	12.2	13.3	12.8	13.7	12.6	12	13	11.8	14.1	12.7	11.3
Mean DAOH - P75	11.6 to 14.4	12.8	13.2	12.6	13.6	12.5	13.5	13.1	14	13	12.2	13.4	12.1	14.4	13.2	11.6
Mean DAOH - minimum	10.3 to 12.8	11.9	12	11.6	12.2	11.1	12.5	11.4	12.5	11	11	11.9	10.7	12.8	11.5	10.3
Mean DAOH - maximum	12.6 to 15.2	13.6	13.9	13.4	14.4	13.3	14.3	13.8	14.8	13.7	12.9	14.2	12.8	15.2	14	12.6
Pr(conclusive)	0.95 to 1	0.982	0.95	0.996	1	1	0.98	0.999	0.992	1	0.986	1	1	0.998	1	1
Pr(superiority)	0.0108 to 0.999	0.0108	0.643	0.049	0.997	0.0453	0.0504	0.73	0.688	0.726	0.69	0.997	0.759	0.0508	0.997	0.999
Pr(equivalence)	0.00123 to 0.971	0.971	0.307	0.947	0.00331	0.955	0.929	0.269	0.304	0.274	0.296	0.00257	0.241	0.947	0.00295	0.00123
Pr(maximum)	0 to 0.0505	0.0178	0.0505	0.0041	0.00001	0	0.0202	0.00082	0.00802	0.00024	0.0137	0	0	0.00203	0	0
Pr(arm A superior)	0 to 0.999	0.00373	0.00005	0.0244	0	0.0227	0	0.00009	0	0.00014	0.69	0	0.759	0	0	0.999
Pr(arm B superior)	0 to 0.997	0.00338	0.643	0	0.997	0	0.0258	0	0.687	0	0.00007	0.997	0	0.0256	0	0
Pr(arm C superior)	0 to 0.997	0.00368	0.00004	0.0246	0	0.0226	0.0247	0.73	0.00032	0.726	0	0	0.00011	0.0252	0.997	0
Pr(no arm superior)	0.00123 to 0.989	0.989	0.357	0.951	0.00332	0.955	0.95	0.27	0.312	0.274	0.31	0.00257	0.241	0.949	0.00295	0.00123
Pr(erroneous superiority)	0 to 0.0508	0.0108	0.00009	0.049	0	0.0453	0.0504	0.00009	0.00032	0.00014	0.00007	0	0.00011	0.0508	0	0
RMSE (superiority only)	0.34 to 0.809	0.809	0.34	0.619	0.429	0.663	0.631	0.362	0.382	0.377	0.343	0.437	0.351	0.699	0.442	0.401
MAE (superiority only)	0.168 to 0.649	0.649	0.168	0.463	0.255	0.507	0.471	0.187	0.194	0.194	0.175	0.273	0.186	0.531	0.274	0.257
IDP (superiority only)	100 to 100	-	100	100	100	100	100	100	100	100	100	100	100	100	100	100
RMSE (select best)	0.259 to 0.443	0.259	0.328	0.28	0.43	0.29	0.284	0.366	0.374	0.377	0.329	0.438	0.358	0.3	0.443	0.401
MAE (select best)	0.175 to 0.275	0.175	0.181	0.175	0.256	0.185	0.175	0.21	0.212	0.215	0.181	0.274	0.208	0.188	0.275	0.258
IDP (select best)	97.1 to 100	-	97.1	99.8	100	100	99.8	98.1	97.9	98.5	97.5	100	98.3	100	100	100

Calibrated stopping threshold for superiority: 0.995 (re-used from the final, primary design).

Abbreviations: IDP: ideal design percentage; MAE: median absolute error; P25: 25th percentile; P75: 75th percentile; Pr: probability; RMSE: root mean squared error; SD: standard deviation.

14.2 | Appendix 2: completed reporting checklists

Completed *SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2025* [43] and *CONSORT-ACE (Consolidated Standards Of Reporting Trials [CONSORT], Adaptive designs CONSORT [ACE] extension to the CONSORT 2010 statement)* [44] checklists for the *INCEPT-Thromboprophylaxis* 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. Of note, for both checklists we report section numbers instead of page numbers to facilitate protocol navigation and future updating.

SPIRIT 2025 checklist of items to address in a randomized trial protocol (adapted to report section numbers instead of page numbers)

Section / Topic	No	SPIRIT 2025 checklist item description	Reported in section no.
Administrative information			
Title and structured summary	1a	Title stating the trial design, population, and interventions, with identification as a protocol	Front page, 1
	1b	Structured summary of trial design and methods, including items from the World Health Organization Trial Registration Data Set	Front page, 1-2
Protocol version	2	Version date and identifier	Front page
Roles and responsibilities	3a	Names, affiliations, and roles of protocol contributors	2.2
	3b	Name and contact information for the trial sponsor	2.1
	3c	Role of trial sponsor and funders in design, conduct, analysis, and reporting of trial; including any authority over these activities	11.2
	3d	Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable	2.2
Open science			
Trial registration	4	Name of trial registry, identifying number (with URL), and date of registration. If not yet registered, name of intended registry	Front page
Protocol and statistical analysis plan	5	Where the trial protocol and statistical analysis plan can be accessed	Front page, 2.1
Data sharing	6	Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials will be accessible	8.2, core protocol
	7a	Sources of funding and other support (e.g., supply of drugs)	11.2

Funding and conflicts of interest	7b	Financial and other conflicts of interest for principal investigators and steering committee members	11.1
Dissemination policy	8	Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., reporting in trial registry, plain language summary, publication)	11.4, core protocol
Introduction			
Background and rationale	9a	Scientific background and rationale, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5
	9b	Explanation for choice of comparator	5
Objectives	10	Specific objectives related to benefits and harms	4.1
Methods: Patient and public involvement, trial design			
Patient and public involvement	11	Details of, or plans for, patient or public involvement in the design, conduct, and reporting of the trial	9.2
Trial design	12	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	6.1
Methods: Participants, interventions, and outcomes			
Trial setting	13	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial will be conducted	Core protocol
Eligibility criteria	14a	Eligibility criteria for participants	6.2
	14b	If applicable, eligibility criteria for sites and for individuals who will deliver the interventions (e.g., surgeons, physiotherapists)	Core protocol
Intervention and comparator	15a	Intervention and comparator with sufficient details to allow replication including how, when, and by whom they will be administered. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	6.3
	15b	Criteria for discontinuing or modifying allocated intervention/comparator for a trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	6.7
	15c	Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (e.g., drug tablet return, sessions attended)	6.9
	15d	Concomitant care that is permitted or prohibited during the trial	6.3
Outcomes	16	Primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	6.6-6.7

Harms	17	How harms are defined and will be assessed (e.g., systematically, non-systematically)	6.7
Participant timeline	18	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6.3, core protocol
Sample size	19	How sample size was determined, including all assumptions supporting the sample size calculation	7.10, 14.1
Recruitment	20	Strategies for achieving adequate participant enrollment to reach target sample size	Core protocol
Methods: Assignment of interventions			
Randomization:			
Sequence generation	21a	Who will generate the random allocation sequence and the method used	Core protocol
	21b	Type of randomization (simple or restricted) and details of any factors for stratification. To reduce predictability of a random sequence, other details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	6.4, 7.4, core protocol
Allocation concealment mechanism	22	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions are assigned	Core protocol
Implementation	23	Whether the personnel who will enroll and those who will assign participants to the interventions will have access to the random allocation sequence	Core protocol
Blinding	24a	Who will be blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	6.5, core protocol
	24b	If blinded, how blinding will be achieved and description of the similarity of interventions	Not applicable
	24c	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	25a	Plans for assessment and collection of trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of trial instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be accessed, if not in the protocol	Core protocol
	25b	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	6.9, core protocol

Data management	26	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be accessed, if not in the protocol	Core protocol
Statistical methods	27a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	7.1-7.9, core protocol
	27b	Definition of who will be included in each analysis (e.g., all randomized participants), and in which group	7.2
	27c	How missing data will be handled in the analysis	7.8, core protocol
	27d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses)	7.6, 7.9
Methods: Monitoring			
Data monitoring committee	28a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and funder; conflicts of interest 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	10, core protocol
	28b	Explanation 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	7.3, 10.2, core protocol
Trial monitoring	29	Frequency and procedures for monitoring trial conduct. If there is no monitoring, give explanation	10.2, core protocol
Ethics			
Research ethics approval	30	Plans for seeking research ethics committee/institutional review board approval	Core protocol
Protocol amendments	31	Plans for communicating important protocol modifications to relevant parties	Core protocol
Consent or assent	32a	Who will obtain informed consent or assent from potential trial participants or authorized proxies, and how	Core protocol
	32b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	33	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
Ancillary and post-trial care	34	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Core protocol

*We strongly recommend reading this checklist in conjunction with the SPIRIT 2025 Explanation and Elaboration and the SPIRIT 2025 Expanded Checklist for important clarifications on all the items. We also recommend reading relevant SPIRIT extensions. See www.consort-spirit.org. © 2025 Chan A-W et al. This is an Open Access

article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Abbreviations: NA: not applicable

Consolidated Standards of Reporting Trials (CONSORT) - Adaptive designs CONSORT Extension (ACE) Checklist (adapted to report section numbers instead of page numbers)

Section/Topic	Item no	Checklist item	Section no
Title and abstract	1a	Identification as a randomised trial in the title	Front page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see ACE checklist for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	4.1
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b« ǂ	Type of adaptive design used, with details of the pre-planned trial adaptations and the statistical information informing the adaptations	7.3-7.5
	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	Core protocol
Participants	4a	Eligibility criteria for participants	6.2
	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	6.3
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	6.6-6.7
	6b ‡	Any unplanned changes to trial outcomes after the trial commenced, with reasons	NA
Sample size and operating characteristics	7a ‡	How sample size and operating characteristics were determined	7.10, 14.5
	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	7.3-7.5
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	6.4, 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	6.5, core protocol
	11b	If relevant, description of the similarity of interventions	NA
	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	7.1-7.5
	12b« ǂ	For the implemented adaptive design features, statistical methods used to estimate treatment effects for key endpoints and to make inferences	7.1-7.5
	12c«2b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7.6
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	14.4
	13b	For each group, losses and exclusions after randomisation, together with reasons	14.4
Recruitment and adaptations	14a ‡	Dates defining the periods of recruitment and follow-up, for each group	NA
	14b †	Why the trial ended or was stopped	NA
	14c ǂ	Specify what trial adaptation decisions were made in light of the pre-planned decision-making criteria and observed accrued data	NA
Baseline data	15a«15 †	A table showing baseline demographic and clinical characteristics for each group	14.7
	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	14.4 & 14.7
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)	14.7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14.7
	17c ǂ	Report interim results used to inform interim decision-making	14.7
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	14.7
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) [1]	14.7
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	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	Front page
Protocol	24a«24	Where the full trial protocol can be accessed	Front page
SAP and other relevant trial documents	24b ǂ	Where the full statistical analysis plan and other relevant trial documents can be accessed	Front page, 2.1, core protocol
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	11.2

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.

Abbreviations: NA: not applicable

14.3 | Appendix 3: variable definitions

This appendix includes definitions of all domain-specific variables (i.e., all variables not defined in the core protocol), except domain-specific outcomes (section 6.6), domain-specific serious adverse reactions (SARs, section 6.7), and domain-specific feasibility outcomes (section 6.9).

Site-specific variables:

- Site-preferred LMWH: enoxaparin / dalteparin / tinzaparin / nadroparin, may be changed during conduct of the domain, in which case this will be registered with the date of change, see section 6.3. The use of biosimilar LMWHs subject to stricter monitoring per the European Medicines Agency "List of medicines under additional monitoring" [49] is not allowed.

Screening variables

- All interventions in this domain are considered clinically appropriate: yes/no, a patient may not fulfil this inclusion criterion if, for example, the treating clinician judges that the patient has a condition that is associated with increased risk of bleeding or thromboembolism, and that is not compatible with the dosing of LMWH in one or more of the *INCEPT-Thromboprophylaxis* domain arms.
- Decision by the treating clinician to start thromboprophylaxis with LMWH, or to continue LMWH prophylaxis: yes/no, the previously used LMWH dose is not important.
- More than one prophylactic dose of anticoagulation administered during current ICU stay, including ICU days in other hospitals: yes/no, administration of more than one prophylactic dose of LMWH, unfractionated heparin, pentasaccharides, or direct oral anticoagulants during current ICU stay. This includes ICU days in another ICU and/or hospital.
- Known or suspected previous adverse reaction to any type of heparin, including allergy and HIT: yes/no, documented allergic reaction to heparin (including type I reactions [i.e., angioedema, bronchospasm, generalised urticaria, and anaphylaxis], type III reactions [i.e. injection site edema, inflammation and induration] and type IV reactions [i.e. plaques and pruritic eczemas at the injection site]) and/or documented history of HIT.
- Known pregnancy: yes/no, women with known pregnancy based on clinical examination, medical history, or human chorionic gonadotropin (hCG). We do not demand negative hCG-status in all eligible fertile women, because 1) screening for enrolment has to be done within some time constraint (waiting for the hCG result will delay screening and result in fewer fertile women included), 2) pregnancy is very rare among acutely admitted ICU patients and 3) domain participation is very unlikely to endanger the woman or the fetus since LMWHs do not cross the placenta and are the preferred anticoagulant for use during pregnancy (39). The same procedure was recently approved in the *INCEPT-Albumin* domain [53].

- Mechanical circulatory support: yes/no, current application of central or peripheral extracorporeal membrane oxygenation devices (including veno-venous).
- Solid organ transplant during current hospital admission: yes/no, solid organ transplant during current hospital admission.
- Weight <40 kg: yes/no, measured or estimated body weight <40 kg at the time of screening.
- Inclusion in another interventional trial or *INCEPT* domain where co-enrolment with the *INCEPT-Thromboprophylaxis* domain is not permitted: yes/no, documented inclusion in a trial/domain where it is known that co-enrolment in *INCEPT-Thromboprophylaxis* is not permitted (after a formal evaluation).

Baseline variables:

- History of VTE: yes/no, documented medical history of pulmonary embolism and/or lower or upper extremity deep vein thrombosis.
- Lowest platelet count in the 24 hours prior to randomisation: 10^9/L, the lowest platelet count from any blood sample in the 24 hours preceding randomisation.
- Presence of a central venous catheter: yes/no, presence of a central venous catheter or peripherally inserted central venous catheter at the time of randomisation.
- Suspected sepsis: yes/no, suspected sepsis according to the Sepsis 3 criteria at the time of randomisation.
- Use of antiplatelet medication: yes/no, use of acetylsalicylic acid, dipyridamole, clopidogrel, prasugrel, and/or ticagrelor in the 24 hours preceding randomisation.

Variables collected daily until 90 days after domain inclusion:

- Severe anaphylactic reaction to LMWH (in participating ICUs): yes/no, defined in section 6.7.
- HIT (in participating ICUs): yes/no, as defined in section 6.7.
- VTE (in hospital): yes/no, as defined in section 6.6.
- Major bleeding (in hospital): yes/no, as defined in section 6.6.
- Administration of the site-preferred LMWH in the allocated dose (in participating ICUs: yes/no.

If *Administration of the site-preferred LMWH in the allocated dose* = ‘no’:

- Administered LMWH: enoxaparin/dalteparin/tinzaparin/nadroparin/none.

If *Administered LMWH* = ‘enoxaparin’ OR ‘dalteparin’ OR ‘tinzaparin’ OR ‘nadroparin’:

- Deviation from the allocated dose: yes/no, applies to the LMWH that was administered on this day (See table Table 2 in section 6.3).

If *Deviation from the allocated dose* = 'yes' AND *Administered LMWH* = 'enoxaparin':

- Administered dose in mg

If *Deviation from the allocated dose* = yes AND *Administered LMWH* = 'dalteparin' OR 'tinzaparin' OR 'nadroparin':

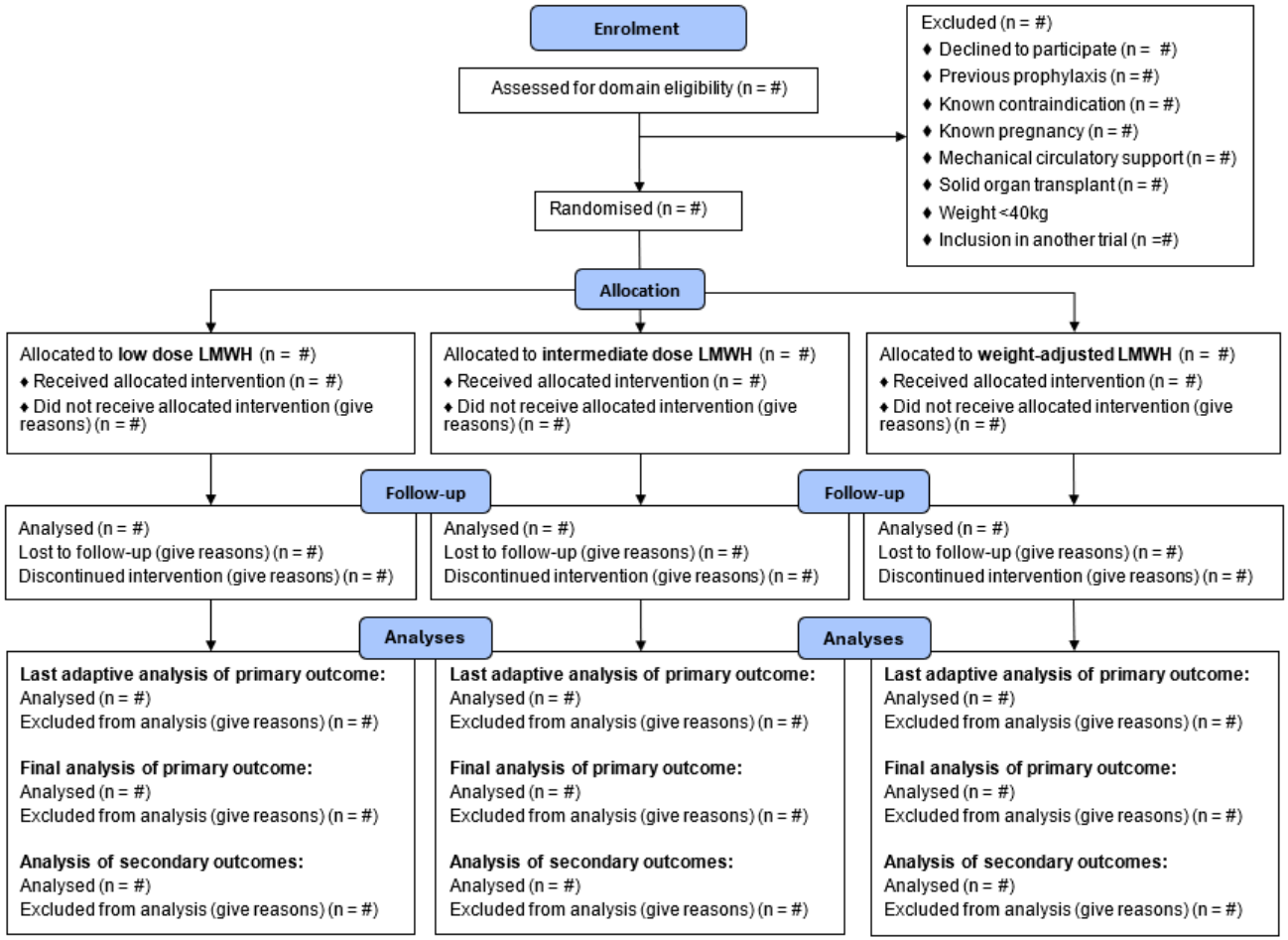
- Administered dose in IU.

If *Deviation from the allocated dose* = 'yes' OR *Administered LMWH* = 'none':

- Reason for deviation, one or more of the following:
  - Acute or chronic kidney injury: yes/no, as judged by treating clinician.
  - Renal replacement therapy: yes/no, as defined in core protocol.
  - Invasive procedure: yes/no, as judged by treating clinician.
  - Thrombocytopenia: yes/no, as judged by treating clinician.
  - Use of thrombolysis: yes/no, as judged by treating clinician.
  - Active bleeding: yes/no, active bleeding as judged by treating clinician.
  - Start of therapeutic anticoagulation, e.g. for VTE or atrial fibrillation: yes/no, start of anticoagulation treatment, e.g. for treatment of VTE or atrial fibrillation.
  - Serious adverse reaction: yes/no, severe anaphylactic reaction or HIT, as defined in section 6.7.
  - Dose adjustment (or temporary withholding of dose) for another reason: yes/no, this constitutes a protocol violation.

14.4 | Appendix 4: domain inclusion flowchart

Figure S2. Domain inclusion flowchart



Mock domain inclusion flowchart, as will be used for each domain, adapted from the *CONSORT 2010* flowchart [91]. The total number of participants included in the platform trial while the domain has been active will be presented in the figure legend.

14.5 | Appendix 5: prophylactic to therapeutic dose ratios

Figure S3. Prophylaxis to therapeutic dose ratio, sorted by drug

		Patient weights (kg)								
		45	55	65	75	85	95	105	115	125
Study arm	**Drug**	%	%	%	%	%	%	%	%	%
low	*Enoxaparin*	44	36	31	27	24	21	19	17	16
int	*Enoxaparin*	67	55	46	40	35	32	29	26	24
weight	*Enoxaparin*	44	36	31	40	35	42	38	35	40
low	*Tinzaparin*	32	26	22	19	17	15	14	12	11
int	*Tinzaparin*	57	47	40	34	30	27	24	22	21
weight	*Tinzaparin*	32	26	40	34	30	42	38	40	37
low	*Dalteparin*	28	23	19	17	15	13	12	11	10
int	*Dalteparin*	56	45	38	33	29	26	24	22	20
weight	*Dalteparin*	28	23	38	33	29	39	36	33	40
low	*Nadroparin*	37	30	25	22	19	17	16	14	13
int	*Nadroparin*	74	60	51	44	39	35	32	29	27
weight	*Nadroparin*	37	40	34	29	39	35	42	38	35

Legend

- 10 to 20%
- 20 to 30%
- 30 to 40%
- 40 to 50%
- > 50%

All ratios were calculated under the following assumptions: the unrounded recommended therapeutic enoxaparin dose is 1mg/kg twice daily (we did not use the 1.5 mg/kg/day dose); the unrounded recommended therapeutic tinzaparin dose is 175 IU/kg once daily; the unrounded recommended therapeutic dalteparin dose is 200 IU/kg once daily (we did not cap the dose at 18.000 IU); and the unrounded recommended therapeutic nadroparin dose is 86 IU/kg twice daily.

Abbreviations: int: fixed intermediate dose LMWH; LMWH: low-molecular-weight heparin; low: fixed low dose LMWH; weight: weight-adjusted dose LMWH.

Figure S4. Prophylaxis to therapeutic dose ratio, sorted by arm

		Patient weights (kg)								
		45	55	65	75	85	95	105	115	125
Study arm	Drug	%	%	%	%	%	%	%	%	%
low	*Enoxaparin*	44	36	31	27	24	21	19	17	16
low	*Tinzaparin*	32	26	22	19	17	15	14	12	11
low	*Dalteparin*	28	23	19	17	15	13	12	11	10
low	*Nadroparin*	37	30	25	22	19	17	16	14	13
int	*Enoxaparin*	67	55	46	40	35	32	29	26	24
int	*Tinzaparin*	57	47	40	34	30	27	24	22	21
int	*Dalteparin*	56	45	38	33	29	26	24	22	20
int	*Nadroparin*	74	60	51	44	39	35	32	29	27
weight	*Enoxaparin*	44	36	31	40	35	42	38	35	40
weight	*Tinzaparin*	32	26	40	34	30	42	38	40	37
weight	*Dalteparin*	28	23	38	33	29	39	36	33	40
weight	*Nadroparin*	37	40	34	29	39	35	42	38	35

Legend

10 to 20%
20 to 30%
30 to 40%
40 to 50%
> 50%

All ratios were calculated under the following assumptions: the unrounded recommended therapeutic enoxaparin dose is 1mg/kg twice daily (we did not use the 1.5 mg/kg/day dose); the unrounded recommended therapeutic tinzaparin dose is 175 IU/kg once daily; the unrounded recommended therapeutic dalteparin dose is 200 IU/kg once daily (we did not cap the dose at 18.000 IU); and the unrounded recommended therapeutic nadroparin dose is 86 IU/kg twice daily.
Abbreviations: int: fixed intermediate dose LMWH; LMWH: low-molecular-weight heparin; low: fixed low dose LMWH; weight: weight-adjusted dose LMWH.

14.6 | Appendix 6: suggested dose adjustment strategies

Table S13. Suggested dose adjustment strategies

Clinical scenario	LMWH	Study arm	Course of action
Acute or chronic kidney injury with an estimated glomerular filtration rate < 20 ml/min and no renal replacement therapy	Enoxaparin	Low	Suggestion to lower the dose to 20 mg[1,2]
		Intermediate	Suggestion to lower the dose to 40 mg[1,2]
		Weight-adjusted	Suggestion to lower to 50% of the weight-adjusted dose (round down to nearest available syringe size) [1,2]
	Tinzaparin	Low	Suggestion to make no adjustments[1,3]
		Intermediate	Suggestion to make no adjustments[1,3]
		Weight-adjusted	Weight <90 kg: suggestion to make no adjustments[1,3] Weight ≥90 kg: suggestion to administer 4500 IU[1,3]
	Dalteparin	Low	Suggestion to make no adjustments[1,4]
		Intermediate	Suggestion to make no adjustments[1,4]
		Weight-adjusted	Weight <90 kg: suggestion to make no adjustments[1,4] Weight ≥90 kg: suggestion to administer 5000 IU[1,4]
	Nadroparin	Low	Suggestion to make no adjustments[1,5]
		Intermediate	Suggestion to make no adjustments[1,5]
		Weight-adjusted	Weight <100 kg: suggestion to make no adjustments[1,5] Weight ≥100 kg: suggestion to administer 5700 IU[1,5]
Renal replacement therapy	All LMWHs	All arms	Suggestion to make no adjustments[1]
Thrombocytopenia with platelet count < 30x10^9/L	All LMWHs	All arms	Suggestion to temporarily halt intervention until recovery of platelet count > 30x10^9/L[1]
Invasive procedures[6]	All LMWHs	All arms	At discretion of treating clinician[1]
Use of thrombolysis	All LMWHs	All arms	Suggestion to temporarily halt intervention. Restart allocated dose at discretion of treating clinician[1]
Active bleeding	All LMWHs	All arms	Suggestion to temporarily halt intervention. Restart, either in allocated or adjusted dose, at discretion of the treating clinician[1]
Start of therapeutic anticoagulation, e.g. for VTE or atrial fibrillation	All LMWHs	All arms	**Permanently stop intervention**
Serious adverse reaction (severe allergy and HIT, see section 6.7)	All LMWHs	All arms	**Permanently stop intervention**

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; ICU: Intensive Care Unit; IU: international unit; L: liter, mg: milligram; ml: millilitre; min: minute; LMWH: low-molecular-weight heparin; n: number; SmPCs: summary of medical product characteristics.

[1] Suggestions are based either on evidence or on the clinical practice of the domain management committee. In general, the evidence for these suggestions is limited and dose adjustments may be subject to national or local guidelines. Therefore, deviations from the provided suggestions are allowed, both with respect to using other triggers for dose adjustment (for example using an estimated glomerular filtration rate (eGFR) cut-off of 30 instead of 20 ml/min), and to using alternative dose adjustments.

[2] Several studies have documented the occurrence of bioaccumulation of enoxaparin [92]. US and Australian SmPCs recommend dose lowering to respectively 30 and 20 mg whereas most European SmPCs recommends to avoid in case of eGFR <15ml/min [22–27,47,48].

[3] Limited evidence regarding the safety of tinzaparin exists in the form of two small studies (n = 27 and 28) that used tinzaparin at doses of 4,500 IU and 3,500 IU daily (2,500 for patients weighing <40 kg and 4,500 for those with a BMI ≥30 kg/m2) in patients with renal failure (mean creatinine clearance of 35 and 20 ml/min), reporting no bioaccumulation and no major bleedings [93,94]. Additionally, tinzaparin has the highest molecular weight of all LMWHs, which in theory decreases its dependency on renal elimination [92].

[4] A prospective cohort study (n = 156) of repeated anti-Xa measurements in ICU patients with severe renal insufficiency found no evidence for bioaccumulation of dalteparin 5000 IU [95]. Based on these findings, the dalteparin dose was not adjusted for renal insufficiency in the *PROTECT* trial [5].

[5] A prospective cohort study (n = 108) evaluated nadroparin (5,700 IU once daily) in ICU patients with COVID-19 and varying degrees of acute renal failure and observed no bioaccumulation [96]. This was in line with results from a small trial on low dose nadroparin (2,850 IU) during continuous veno-venous hemofiltration and another cohort study on intermediate dose nadroparin (5,700 IU) in patients with moderate renal insufficiency, so that both studies found no evidence for accumulation [97,98].

[6] Includes mechanical circulatory support.

14.7 | Appendix 7: mock baseline and outcome tables

Table S14. Domain baseline data

Characteristic	**Fixed low dose LMWH (N = #)**	**Fixed intermediate dose LMWH (N = #)**	**Weight-adjusted dose LMWH (N = #)**
Country of enrolment			
- *[Each participating country listed separately in the domain report(s)]*	n (#.#%)	n (#.#%)	n (#.#%)
Age, median (IQR), years	## (## to ##)	## (## to ##)	## (## to ##)
Sex			
- Female	n (#.#%)	n (#.#%)	n (#.#%)
- Male	n (#.#%)	n (#.#%)	n (#.#%)
Weight, median (IQR), kg	## (## to ##)	## (## to ##)	## (## to ##)
Height, median (IQR), m	#.## (#.## to #.##)	#.## (#.## to #.##)	#.## (#.## to #.##)
Use of invasive mechanical ventilation	n (#.#%)	n (#.#%)	n (#.#%)
Use of vasopressors/inotropes	n (#.#%)	n (#.#%)	n (#.#%)
Use of renal replacement therapy	n (#.#%)	n (#.#%)	n (#.#%)
Presence of a central venous catheter	n (#.#%)	n (#.#%)	n (#.#%)
Limitations of care	n (#.#%)	n (#.#%)	n (#.#%)
Co-existing conditions			
- Active haematological malignancy or metastatic cancer	n (#.#%)	n (#.#%)	n (#.#%)
- History of ischaemic heart disease or heart failure	n (#.#%)	n (#.#%)	n (#.#%)
- Diabetes mellitus	n (#.#%)	n (#.#%)	n (#.#%)
- Chronic pulmonary disease	n (#.#%)	n (#.#%)	n (#.#%)
- Chronic liver disease	n (#.#%)	n (#.#%)	n (#.#%)
- Known use of immunosuppressive therapy within the last 3 months	n (#.#%)	n (#.#%)	n (#.#%)
- Previous organ transplantation	n (#.#%)	n (#.#%)	n (#.#%)
- Chronic dialysis	n (#.#%)	n (#.#%)	n (#.#%)
- Treatment with antipsychotics at hospital admission	n (#.#%)	n (#.#%)	n (#.#%)
- History of VTE	n (#.#%)	n (#.#%)	n (#.#%)
Suspected sepsis at ICU admission	n (#.#%)	n (#.#%)	n (#.#%)
Acute surgery within 7 days prior to randomisation	n (#.#%)	n (#.#%)	n (#.#%)
SMS-ICU			
- Score, median (IQR)	## (## to ##)	## (## to ##)	## (## to ##)
- Predicted 90-day mortality[1], median (IQR), %	##% (## to ##)	##% (## to ##)	##% (## to ##)
Predicted in-hospital VTE risk[2], median (IQR), %	##% (## to ##)	##% (## to ##)	##% (## to ##)
Clinical Frailty Scale, median (IQR)	## (## to ##)	## (## to ##)	## (## to ##)
Lowest systolic blood pressure in the 24 hours preceding randomisation, median (IQR), mmHg	## (## to ##)	## (## to ##)	## (## to ##)
Highest plasma lactate in the 24 hours prior to randomisation, median (IQR), mmol/L	## (## to ##)	## (## to ##)	## (## to ##)
Highest plasma creatinine in the 24 hours prior to randomisation, median (IQR), µmol/L	## (## to ##)	## (## to ##)	## (## to ##)
Lowest platelet count in the 24 hours prior to randomisation, median (IQR), 10^9/L	## (## to ##)	## (## to ##)	## (## to ##)

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 3, section 14.3. 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).

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* [70], µmol/L: micromoles per litre, VTE: venous thromboembolism.

[1] The predicted 90-day mortality will be calculated using the SMS-ICU score [70], with the scores ranging from 0-42 points with corresponding predicted 90-day mortality of 3.3 to 91.0%.

[2] The predicted in-hospital VTE incidence will be calculated using the PROVE-IT score (section 7.6).

Table S15. 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 Absolute difference [RD/MD, 95% CrI] *Relative difference [RR/RoM, 95% CrI]*			Probabilities of each intervention being best[2]		
Outcome	**Low (N = #)**	**Int (N = #)**	**Weight-adj (N = #)**	**Int vs low**	**Weight-adj vs low**	**Weight-adj vs int**	**Low**	**Int**	**Weight - adj**
Days alive out of hospital at day 30 (primary and guiding outcome)	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
Days alive without life support at day 30	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
Days free of delirium at day 30	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
All-cause 30-day mortality	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
Days alive without life support at day 90	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
Days alive out of hospital at day 90	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
All-cause 90-day mortality	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
All-cause 180-day mortality	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
EQ-5D-5L index values at day 180	#.## (#.## to #.##) *#.## (#.## to #.##)*	#.## (#.## to #.##) *#.## (#.## to #.##)*	#.## (#.## to #.##) *#.## (#.## to #.##)*	MD: #.## (#.## to #.##) *RoM: #.## (#.## to #.##)*	MD: #.## (#.## to #.##) *RoM: #.## (#.## to #.##)*	MD: #.## (#.## to #.##) *RoM: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
EQ VAS at day 180	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
Cognitive function at day 180	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	MD: #.# (#.# to #.#) *RoM: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
Venous thromboembolism during hospital stay at day 30	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
Venous thromboembolism during hospital stay at day 90	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
Major bleeding during hospital stay at day 30	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#)	RD: #.#%-points (#.# to #.#)	RD: #.#%-points (#.# to #.#)	#.##%	#.##%	#.##%

				RR: #.## (#.## to #.##)	*RR: #.## (#.## to #.##)*	*RR: #.## (#.## to #.##)*			
Major bleeding during hospital stay at day 90	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
One or more domain-specific safety outcomes at day 30	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	#.##%	#.##%	#.##%
One or more domain-specific safety outcomes at day 90	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	n/N (#.#%) *#.#% (#.# to #.#)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	RD: #.#%-points (#.# to #.#) *RR: #.## (#.## to #.##)*	#.##%	#.##%	#.##%

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

Abbreviations (in alphabetical order): CrI: credible interval; Int: intermediate dose low-molecular-weight heparin; Low: low dose low-molecular-weight heparin; 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; Weight-adj: weight-adjusted dose low-molecular-weight heparin.

[1] For all 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 in each domain, with descriptive data and model estimates based on multiply imputed data unless complete.

[2] The probabilities of each arm being the best will be presented; secondarily, the probabilities of each arm being superior compared to the other arms will be presented. Probabilities of practical equivalence between all arms and for all pairwise comparisons will also be presented (along with the probabilities of intervention effects larger than the practical equivalence threshold(s) in both directions for the pairwise comparisons). 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.

Table S16. Results from successive adaptive analyses

Adaptive analysis	**Analysed/ randomised**			**Outcome data per intervention**[1] descriptive data [median (IQR)] *model estimate [probability or mean with (95% CrI)]*			**Probabilities of superiority**[2]			**Probability of practical equivalence for all active arms**	**Subsequent allocation profile**		
Number, last inclusion date, analysis date, implementation date	**Low**	**Int**	**Weight-adj**	**Low**	**Int**	**Weight-adj**	**Low**	**Int**	**Weight-adj**		**Low**	**Int**	**Weight -adj**
#1, YYYY-MM-DD, YYYY-MM-DD, YYYY-MM-DD	n/N (#.#%) [complete: n/N (#.#%)]	n/N (#.#%) [complete: n/N (#.#%)]	n/N (#.#%) [complete: n/N (#.#%)]	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.# (#.# to #.#) *#.# (#.# to #.#)*	#.##%	#.##%	#.##%	#.##%	#.##%	#.##%	#.##%
#2, …													

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

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

[1] For each intervention, descriptive outcome data (medians with interquartile ranges) and sample-average estimates from the primary models (mean values with 95% CrIs) are presented. All descriptive data and model estimates in this table will be based on multiply imputed data unless complete.

[2] The probabilities of superiority of each active arm will be presented. The probability of practical equivalence of all active arms will be included where relevant (this will be the same probability for all active arms). Where relevant (e.g., where arm(s) are dropped and analyses are repeated without inclusion of more participants), results from all analyses conducted during each adaptive analysis round will be included.

14.8 | Appendix 8: PROVE-IT score

The PROVE-IT score is a prognostic model developed to predict the risk of in-hospital venous thromboembolism (VTE) in critically ill patients. The model was developed using multiple logistic regression on data from 26,218 patients in the MIMIC-IV database and externally validated in 1,983 patients from Dutch ICU cohorts [99]. The final model includes 14 predictors selected based on a systematic literature review. As the development cohort lacked a single sepsis variable, the individual components of the Sepsis-2 definition were incorporated (serum lactate concentration, leukocyte count, heart rate, mean arterial pressure, body temperature, and respiratory rate) [100]. Additionally, a simplified, modified version of the model was developed where these variables were replaced with a single dichotomous sepsis variable (which in the development cohort was defined as SIRS + lactate >2 mmol/L). The manuscript has been submitted for publication and is currently under peer review.

Given that continuous physiological variables are unavailable in INCEPT, we will utilise the simplified version of the PROVE-IT score for the analyses of heterogeneous intervention effects. The simplified model demonstrated slightly lower performance than the full model (C-statistic: 0.654 versus 0.681 at internal validation and 0.607 versus 0.629 at external validation), but calibration was preserved (integrated calibration index: 0.00664, E50 0.000585, and E90 0.00223 at external validation) [101].

The fitted logistic regression model for the association between VTE risk (p) and the predictors is given by:

*logit(p) = -5.9636205 + 0.0360970*CVC + 0.2810256*VTE history + 0.4017655*malignancy + 0.6537808*sepsis + 0.1147804*surgery + 0.0388813*vasopressors + 0.8118268*mechanical ventilation + 0.1427952*thromboprophylaxis + 0.1045694*(weight/10)*

Where CVC = central venous catheter; VTE = venous thromboembolism. All binary variables are dichotomous (yes/no) and will be defined according to the core protocol and section 8.1. For the purpose of the HTE analyses, thromboprophylaxis will be assigned a value of 1 for all participants.

This can be converted to a predicted in-hospital VTE risk:

Predicted probability of in-hospital VTE = exp(logit(p))/(1+exp(logit(p)))

14.9 | Appendix 9: priors

Prior probability distributions used for all analyses of the clinical outcomes in the *INCEPT-Thromboprophylaxis* domain are described in this section, which is based on a corresponding section in the *EMPRESS* trial protocol [71] and the domain-specific appendix for *INCEPT-Albumin* [53]. 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 + age + age squared + sex + 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 + history of VTE + use of antiplatelet medication.

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 low-dose arm will initially be the reference category for the intervention effect in the analyses; if this arm is dropped, the reference arm will be the intermediate dose arm.

Primary priors for the linear regression models
All continuous/count outcomes will be analysed using linear regression models with the following priors, specified on the natural scales.

- 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 domain (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 [56,102]. 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 effects: *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 out of hospital at day 30 (maximum possible value 29 days), 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 out of hospital at day 30 (maximum possible value 89 days), 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 domain (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 effects: *N(0, 1)*, corresponding to a distribution on the odds ratio scale centred at 1.00 (no difference) and with 95% probability mass between 0.14 and 7.1. This prior corresponds to approximately 12 participants randomised to each arm in a 2-arm comparison in a trial with fixed, equal allocation and identical event probabilities of 22.3% in both arms (based on the 30-day mortality observed in the *AFIB-ICU* cohort [76], as

discussed in section 7.10) analysed using a conventional, frequentist logistic regression model [103,104].

- 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 out of hospital 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 514 participants randomised to each arm in a two-arm trial with fixed, equal allocation and identical event rates of 22.3% 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 out of hospital 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, 2.5)* 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 <2 participants randomised to each arm in a two-arm trial with fixed, equal allocation and identical event rates of 22.3% 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. These sensitivity analyses will only be conducted for the outcomes and comparisons where sufficient, relevant external evidence is available, and none of these sensitivity analyses will be conducted if no or very limited external evidence (e.g., evidence so weak that the sensitivity analyses are not expected to provide any additional insights due to similarity with the other planned analyses and priors). At the time of writing, the external evidence is too insufficient for the specification of such analyses to be sensible, as described in section 7.7.

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 the PROVE-IT score, plasma creatinine, and platelet counts). 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 out of hospital 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.