

The Intensive Care Platform Trial (INCEPT)

INCEPT-Thromboprophylaxis

Synopsis

Domain-specific appendix version and date
Version 1.1, 2025-08-20

Corresponding core protocol version and date
Version 1.4, 2025-08-20

Applicable core protocol registration numbers
European Union Clinical Trials Information System (CTIS) EUCT number: 2024-516208-41-00.
ClinicalTrials.gov identifier: NCT06667999.
Universal Trial Number: U1111-1313-8171.

Websites
www.incept.dk

www.incept.dk/thromboprophylaxis

Synopsis

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) 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

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