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Statistical analysis plan for the Diagnosing deep-vein Thrombosis early in critically ill patients (DETECT) trial: a study protocol for a randomized controlled trial

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Abstract

Background: The Diagnosing deep-vein Thrombosis early in critically ill patients (DETECT) trial aims to evaluate the effect of twice-weekly surveillance bilateral lower limb ultrasound compared to usual care on 90-day mortality of critically ill adults admitted to medical, surgical, and trauma ICUs.

Methods/Design: In this multicenter randomized trial, critically ill as will be randomized to twice-weekly surveillance bilateral lower limb ultrasound (surveillance group) or usual care group. The primary outcome is 90-day mortality. The trial has 80 % power to detect a 6% absolute risk reduction in 90-day mortality from 30 to 24 %. Secondary outcomes include lower limb proximal DVT, pulmonary embolism and clinically important bleeding.

Discussion: This statistical analysis plan for the DETECT Trial was developed following international guidelines. This plan specifies a priori the statistical methods for evaluating primary and secondary outcomes and defines covariables for adjusted analyses.

Trial registration: Clinicaltrials.gov NCT05112705 (registered on 2021-11-09).

Background

Deep vein thrombosis (DVT) in critically ill patients is often undetected and could lead to pulmonary embolism (PE) and subsequent morbidity and mortality.[1] Several studies have shown that surveillance using ultrasound detects many DVTs that would otherwise go unnoticed.[2-5] Ultrasound surveillance for DVT may facilitate early detection and treatment of DVTs in high-risk medical-surgical ICU patients and thus may improve patient outcomes. Still, it may also increase the risk of unnecessary treatment of silent DVTs and increase the risk of bleeding. The DETECT trial (Diagnosing deep-vein thrombosis early in critically ill patients) evaluates the effect of twice-weekly bilateral lower limb ultrasound compared to usual care on 90-day mortality of critically ill adult patients admitted to medical, surgical, and trauma ICUs.

This manuscript describes the DETECT statistical analysis plan (SAP). The statistical analysis plan complies with the “Statistical principles for clinical trials E9” and “Structure and content of clinical study reports E3”. [6, 7] This statistical analysis plan outlines the procedures to be applied to the primary and secondary analyses for the entire trial cohort once trial data validation is complete. All analyses were prospectively defined as the SAP was finalized during trial implementation. The SAP was written by the Principal Investigator and members of the Steering committee, who will remain blinded to the study results until all patients have been recruited and the database has been locked. Patient recruitment is expected to be completed in December 2026. The final study report will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting randomized controlled trials.[8-10]

Methods

Study Design

The DETECT trial is an international, parallel-group, open-label, randomized trial expected to enroll 1800 critically ill patients from hospitals in Saudi Arabia and Kuwait. The study has been approved by the Institutional Review Board (IRB) of Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia (IRB/0215/23) and all other participating sites' IRBs. The trial is registered in clinicaltrials.gov: (NCT05112705). The study is sponsored by King Abdullah International Medical Research Center (Grant no: RC20/257/R), Riyadh, Saudi Arabia. The sponsor has no role in the study design, management or analysis.

All patients admitted to the ICU will be assessed for eligibility within the first 48 hours of ICU admission. The eligibility criteria has been described in the previously published protocol. [11] Those meeting the inclusion criteria will be consented and randomized using a secure, password-protected web-based platform employing a computer-generated, variable block randomization sequence. Randomization will be stratified by study site and admission category (trauma, surgical, or medical). Patients will be assigned in a 1:1 ratio to either the surveillance group or the usual care group.

Patients in the surveillance group will undergo bilateral lower limb compression ultrasonography twice weekly, beginning within three calendar days of ICU admission and continuing for up to 28 days or until ICU discharge. Clinical management, including decisions regarding pharmacologic or mechanical thromboprophylaxis, will remain at the discretion of the treating team. The results of surveillance imaging will be shared with the clinical team, and they will make any decisions regarding anticoagulation therapy. In the usual care group, lower limb ultrasonography may be performed if clinically indicated, as determined by the treating clinicians.

Study Population

Patient progression through the trial will be reported using a CONSORT diagram (Figure 1). This will include the number of patients screened, excluded (with reasons), deemed eligible but not enrolled, and those randomized to each group. We will also report the number of patients who received the assigned intervention and those with available data for the primary outcome.

The **intention-to-treat (ITT) population** will comprise all randomized patients and serve as the basis for the primary analysis. All enrolled individuals will be included in this analysis regardless of adherence to the assigned intervention. Post-randomization exclusions from the ITT population will be limited to patients or their substitute decision-makers (SDMs) who explicitly withdraw consent for data usage. However, if consent for continued data collection is granted despite withdrawal from the trial, such patients will remain in the ITT analysis. Patients randomized in error and discovered post-randomization not meeting eligibility criteria will also be excluded.[12].

The **per-protocol population** will include all randomized patients who receive their assigned intervention. In the surveillance group, protocol adherence requires the completion of at least one lower limb

ultrasound. However, in some cases, no ultrasound may be performed—such as in early death, ICU discharge within 72 hours, or scheduling constraints (e.g., weekends). These cases will be documented, and protocol deviations will be considered.

Sample size calculation:

The assumptions underlying the sample size calculation are detailed in the published study protocol.[11] Briefly, assuming a baseline 90-day mortality of 30% and an absolute risk reduction of 6% (from 30% to 24%), with 80% power and a two-sided alpha of 0.05, a total sample size of 1,716 patients is required. To account for an anticipated 5% loss to follow-up, the target enrollment for the trial was increased to 1,800 patients.

Analysis Plan:

Baseline Characteristics

Baseline characteristics of patients in the intention-to-treat population will be presented and compared between the two study groups (Supplement Table 1). Demographic variables such as age, sex, weight, height, and body mass index (BMI) will be summarized. We will also report and compare the source of ICU admission, APACHE IV scores,[13] admission categories (non-operative non-trauma, post-operative non-trauma, trauma), and pre-existing chronic conditions defined per the APACHE IV classification system.[13]

A predefined list of venous thromboembolism (VTE) risk factors that are present before ICU admission will be analyzed. These include a personal or family history of VTE, known inherited or acquired thrombophilias (e.g., protein C or S deficiency, antithrombin deficiency, activated protein C resistance, Factor V Leiden, prothrombin gene mutation, antiphospholipid syndrome, hyperhomocysteinemia), recent postpartum state (within 3 months), estrogen use (oral contraceptives or hormone replacement therapy), current or recent malignancy (active treatment or palliative care within 6 months), history of malignancy, immobility due to stroke or trauma, recent hospital admission (within 3 months), recent surgery (within 48 hours), acute stroke, trauma, or current smoking status.

We will assess and compare VTE risk prediction using the Caprini model.[14]. We will use other scoring systems for secondary analyses, including the ICU-Venous Thromboembolism (ICU-VTE) score, [15] Kucher,[16] Padua Prediction score,[17] International Medical Prevention Registry on Venous Thromboembolism (IMPROVE),[18] and the Intermountain[19] models as we reported earlier. [20] Additional baseline laboratory values will be compared, including platelet count, international normalized ratio (INR), activated partial thromboplastin time (aPTT), hemoglobin, and creatinine levels. Furthermore, we will evaluate ICU interventions at the time of enrollment—mechanical ventilation,

vasopressor support, renal replacement therapy, and the presence of femoral central venous catheters or dialysis catheters. Time from ICU admission to study enrollment will also be recorded and compared. The coronavirus disease 2019 (COVID-19) status at enrollment will be documented.

Intervention Data

We will compare both groups with respect to the number of patients who underwent at least one lower limb ultrasound, the time to first ultrasound post-randomization, and the total number of ultrasounds per patient during the intervention period (Supplement Tables 2 and 3).

Co-interventions

Thromboprophylaxis:
Details on pharmacologic thromboprophylaxis (e.g., unfractionated heparin [UFH], low-molecular-weight heparin [LMWH]) and mechanical prophylaxis (intermittent pneumatic compression [IPC], graduated compression stockings [GCS]) will be reported at baseline and throughout the intervention period in both groups.

Anticoagulation and Antiplatelet Therapy:
Therapeutic anticoagulation during the intervention period will be documented, including the type of agent used and clinical indication. Thrombolytic agents and antiplatelet medications (e.g., aspirin, clopidogrel, ticlopidine, glycoprotein IIb/IIIa inhibitors) will also be compared.

Catheter Use:
Central venous or dialysis catheters in the femoral veins will be reported and compared across groups.

Organ Support:
The use of mechanical ventilation, vasopressor agents, and renal replacement therapy during the intervention period will be evaluated.

Mobility Assessment:
Patient mobility will be assessed daily using a predefined ordinal scale ranging from 0 (no activity) to 7 (walking), with scores reflecting increasing levels of mobilization.[21] The highest level of mobility achieved each day and throughout the intervention period will be compared between groups.

Primary Outcome

The primary outcome is 90-day all-cause mortality. This outcome tests the hypothesis that routine twice-weekly lower limb surveillance ultrasonography reduces mortality by day 90 (Supplemental Table S4).

Secondary Outcomes

A detailed list of secondary outcomes and their definitions has been published and summarized in Supplemental Table S5. These include:

1. Proximal lower extremity deep vein thrombosis (DVT).
2. Pulmonary embolism.
3. Clinically significant bleeding.
4. Ventilator-free days.
5. Vasopressor-free days.
6. Number of days alive and out of hospital by day 90.

Statistical Analysis

Descriptive statistics will be used to summarize study variables. Categorical data will be expressed as counts and percentages, and comparisons between groups will be performed using the appropriate Chi-square test or Fisher's exact test. Depending on the distribution, continuous variables will be reported as mean with standard deviation (SD) or median with interquartile range (IQR, Q1–Q3). Group comparisons for continuous variables will be made using either the Student's *t*-test or the Wilcoxon–Mann–Whitney U test based on the assessment of normality.

Changes over time and between-group differences will be analyzed for repeated measurements. Missing values will not be imputed for descriptive or repeated measures analyses. To adjust for multiple testing for secondary outcomes and subgroup analyses, we will use the False Discovery Rate (FDR) as described by Benjamini and Hochberg.[22] Unless otherwise stated, all statistical tests will be two-sided with a significance threshold of $p < 0.05$. Analyses will be performed using SAS software (version 9.1.3 or later; SAS Institute Inc., Cary, NC, USA).

A. Primary Outcome Analysis

The primary outcome will be assessed in the intention-to-treat population using a generalized linear mixed-effects model (GLMM), adjusted for stratification variables, with the study site included as a random effect unless issues of model convergence arise [20,21]. This adjustment is recommended to preserve statistical power and precision. The results will be reported as risk differences (RD) and relative risks (RR) with corresponding 95% confidence intervals (CI) derived via maximum likelihood estimation (Table 1). A secondary, unadjusted analysis will also be conducted.

A sensitivity analysis will be performed using multiple imputations to account for missing data on the primary outcome. This will involve 100 imputations using the fully conditional specification, with imputations based on age, sex, trial site, admission category, and APACHE IV score.

In addition, Cox proportional hazard models (adjusted and unadjusted) will be used to evaluate time-to-event data, with results expressed as hazard ratios (HR) and 95% CIs. Time-to-death will be visualized using Kaplan–Meier survival curves and compared between groups using the log-rank test. A corresponding per-protocol analysis will also be conducted. An overview of planned statistical methods for primary and secondary endpoints is provided in Table 1.

B. Secondary Outcome Analysis

The occurrence of deep vein thrombosis (DVT) will be analyzed using a Cox proportional hazards model, adjusting for stratification variables. Patients without DVT will be censored at ICU discharge, death, or day 28—whichever occurs first. Time-to-event outcomes such as pulmonary embolism will be evaluated similarly, using Kaplan–Meier curves and the log-rank test for between-group comparisons.

C. Subgroup Analyses

Predefined subgroup analyses for the primary outcome will be conducted within the intention-to-treat population using the same modeling approach as the primary analysis. Adjusted RRs and 95% CIs will be reported, and interaction effects will be tested using multivariable logistic regression. Subgroups include:

1. Admission category (medical, surgical, trauma)
2. Use of pharmacologic thromboprophylaxis (yes vs. no)
3. Presence of femoral central venous catheter at baseline
4. Coagulopathy vs no coagulopathy (defined as INR>1.5 or platelets<100,000/mm^3
5. BMI <30 Kg/m^2 vs. BMI ≥30 Kg/m^2
6. Use of mechanical ventilation versus none
7. Use of vasopressor therapy versus none
8. APACHE IV score (dichotomized at median)
9. Caprini risk assessment score <5 vs ≥5

Each subgroup is selected based on its potential relevance to thrombosis risk and clinical outcome variability in accordance with the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) criteria[23] (Table 2 and Supplemental Table S6). The heterogeneity of treatment effect will be examined by testing for interaction.

D. Interim Analyses

Interim monitoring will be overseen by an independent Data Safety Monitoring Board (DSMB). Two formal interim analyses are planned, occurring after 33% and 67% of the target sample size enrollment. The primary outcome of 90-day mortality will be the basis for assessing safety and efficacy. The trial may be halted for safety concerns ($p < 0.01$) or for overwhelming efficacy ($p < 0.001$), but not for futility.

The O'Brien–Fleming alpha-spending function will be used to adjust for multiple looks at the data, with a final significance level set at $p < 0.048$.

E. Deviations, violations and Serious adverse events

We will report descriptive data on study deviations, violations and serious adverse events (Supplemental Table 7).

Discussion

The DETECT trial investigates the impact of conducting twice-weekly bilateral lower limb ultrasound surveillance compared to standard care on 90-day mortality among critically ill adult patients admitted to medical, surgical, and trauma intensive care units (ICUs).

A comprehensive account of the trial's strengths and limitations has been published.[11] This statistical analysis plan (SAP) presents the predefined methods for data analysis before the trial's completion.

This SAP adheres to established guidelines for reporting statistical plans in clinical trials.[24] Key strengths include adherence to the intention-to-treat (ITT) principle, a robust multicenter design, and a large sample size. We will report the false discovery rate to account for multiple secondary analyses. Prespecified subgroup and sensitivity analyses are also incorporated into the analysis framework.

The findings from the DETECT trial are expected to provide valuable insights into the role of ultrasound surveillance in critically ill adult patients and support the development of future clinical practice guidelines and patient safety measures.

Trial Status

The first patient was enrolled in March, 2023. As of December, 2025 a total of 1348 patients have been recruited from 15 centers across Saudi Arabia and Kuwait. The first interim

analysis was conducted on May 2025. Recruitment of the target 1800 patients is anticipated to conclude by December 2026.

Abbreviations

Abbreviation	Term
CI	Confidence Interval
DVT	Deep vein thrombosis
GCS	Graduated Compression Stocking
HR	Hazard Ratio

ICU	Intensive Care Unit
INR	International normalized ratio
IPC	Intermittent Pneumatic Compression
IQR	Interquartile Range
LMWH	Low Molecular Weight Heparin
PE	Pulmonary Embolism
RR	Relative Risk
SAP	Statistical Analysis Plan
UFH	Unfractionated heparin
VTE	Venous Thromboembolism

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YA is the Chief Investigator responsible for the conception, design and development of the protocol, analytical plan, drafting and critical revision of the manuscript for important and intellectual content.

FA, FH, HA, AK, WA, MAS, HG, KM, JC, AM, RQ, AA, WM, AF, SB, FH, MB, GA, AA,MA, MS, AT, AH, MQ, and AD contributed to the development of the protocol and critical revision of the manuscript for important intellectual content. HAR, JJ provided the statistical expertise for the statistical plan. All authors read and approved the final manuscript

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Ethics approval and consent to participate

The study has been approved by the Institutional Review Board (IRB) of the Ministry of National Guard Health Affairs (MNGHA) and the other centers' respective Institutional Review Boards.

Competing interests

The authors declare that they have no competing interests

Consent for publication

Not applicable

Provenance and peer review

Not commissioned; externally peer-reviewed.

Availability of data and materials

The data supporting this study's findings are available from the corresponding author upon reasonable request as per the regulations of King Abdullah International Medical Research Center (KAIMRC).

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Tables

Table 1: Summary of analysis plan for the intention-to-treat cohort. The primary outcome will also be analyzed for the per protocol cohort.

Variables	Tests
Baseline characteristics	No statistical comparisons
Intervention and co-interventions	Chi-square, Fisher's exact Test, Mann Whitney U test, t-test as applicable.
Primary outcome	Primary analysis: Generalized linear mixed model (GLMM), adjusted for stratification variables and incorporating center/site as a random effect. Report as adjusted relative risk. If a significant difference is detected, relative risk reduction, absolute risk reduction and number needed to treat (or harm) will be reported. Secondary analyses: Chi-square or Fisher’s exact test Sensitivity analyses using generalized mixed effects model with adjustment to stratification variables and multiple imputations Crude Cox proportional analysis Adjusted Cox proportional analysis Kaplan Meier curves with log rank test
Secondary outcomes	Categorical variables: Cox proportional analysis with adjustment to stratification variables. Report adjusted hazard ratio. Continuous variables: linear regression model and van Elteren test as appropriate. The results will be reported as median and mean differences and beta coefficients with 95% CI. Multiplicity adjustment by False Discovery Rate (FDR)
Subgroup analyses	Generalized mixed effects model with adjustment to stratification variables. Report risk difference and relative risk, and tests of interaction and FDR.
Repeated measures	Generalized linear mixed model (GLMM)

Table 2: Predefined subgroups

Subgroups	Hypothesis
Non-operative non-trauma vs. post-operative non-trauma vs. trauma	DVT surveillance is more likely to reduce mortality in medical (non-operative patients), probably because of the higher underlying mortality risk[1]
Pharmacologic thromboprophylaxis vs. no pharmacologic thromboprophylaxis	DVT surveillance is more likely to reduce mortality in patients on no pharmacologic prophylaxis, probably because of the higher underlying DVT risk[2]
Femoral central venous catheter vs. no femoral central venous catheter	DVT surveillance is more likely to reduce mortality in patients with femoral central venous catheters, probably because of the higher underlying DVT risk[3]
Coagulopathy vs no coagulopathy	DVT surveillance is more likely to reduce mortality in patients with coagulopathy, probably because of the higher underlying DVT risk[3]
BMI <30 vs. BMI ≥30	DVT surveillance is more likely to reduce mortality in patients with high BMI, probably because of the higher underlying DVT risk [4]
Mechanical ventilation vs. no mechanical ventilation	DVT surveillance is more likely to reduce mortality in patients on mechanical ventilation, probably because of the higher underlying DVT risk[3]
Vasopressors vs. no vasopressors	DVT surveillance is more likely to reduce mortality in patients on vasopressors, probably because of the higher underlying DVT risk[4]
APACHE IV score <median vs. APACHE IV score ≥median	DVT surveillance is more likely to reduce mortality in patients with high APACHE IV scores, probably because of the higher underlying mortality risk[1]
Caprini risk assessment score<5 vs. Caprini risk assessment score≥5	DVT surveillance is more likely to reduce mortality in patients with high Caprini scores, probably because of the higher underlying DVT risk[3]

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Figures

Figure 1: CONSORT flow chart for the DETECT trial

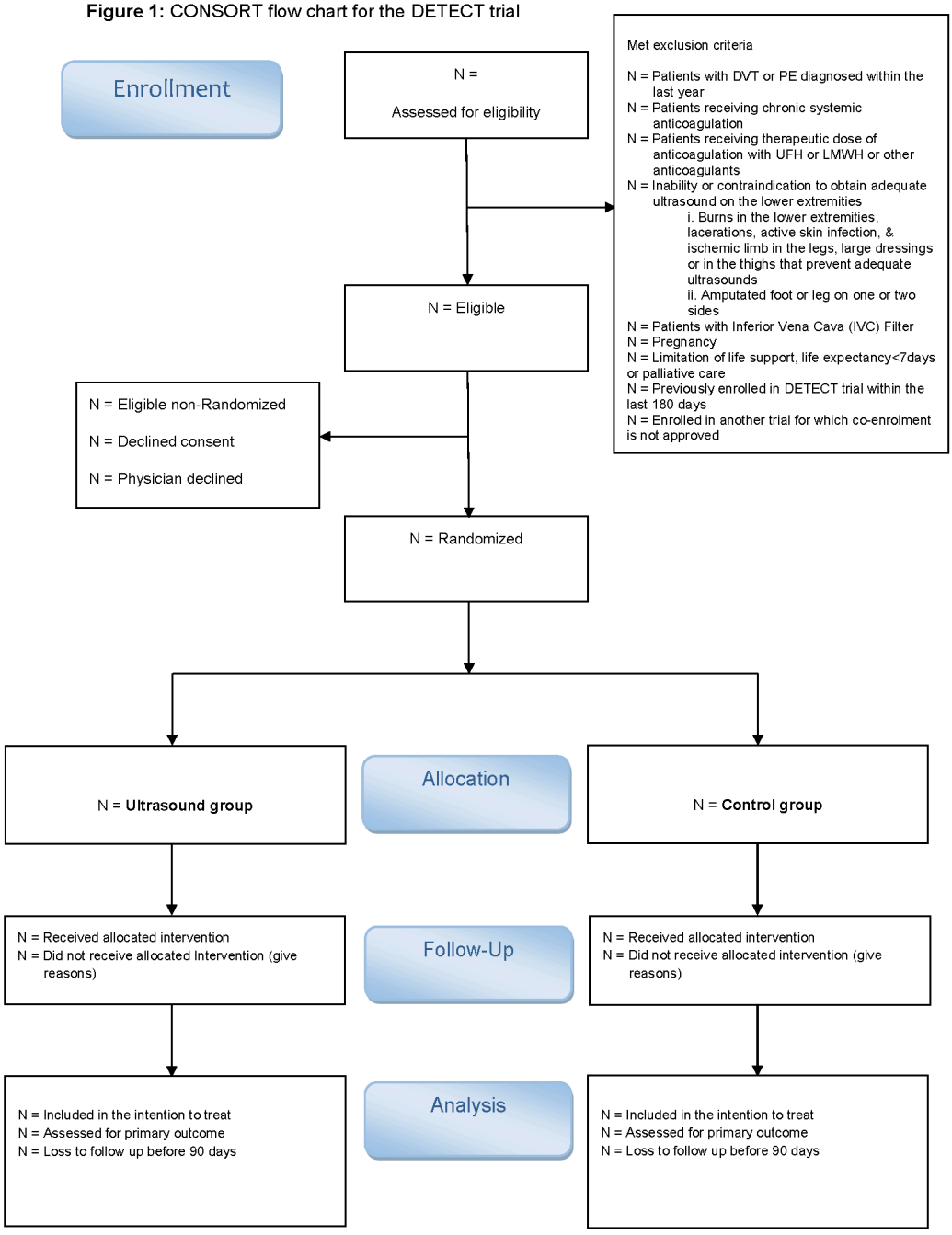


Figure 1

See image above for figure legend

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