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Coenrolment of critically ill patients into multiple studies: patterns, predictors and consequences

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Abstract

Introduction: Research on coenrolment practices and its impact are limited in the ICU setting. The objectives of this study were: 1) to describe patterns and predictors of coenrolment of patients in a thromboprophylaxis trial, and 2) to examine the consequences of coenrolment on clinical and trial outcomes.

Methods: In an observational analysis of an international thromboprophylaxis trial in 67 ICUs, we examined the coenrolment of critically ill medical-surgical patients into more than one study, and examined the clinical and trial outcomes among coenrolled and non-coenrolled patients.

Results: Among 3746 patients enrolled in the Prophylaxis for ThromboEmbolism in Critical Care Trial, 713 (19.0%) were coenrolled in at least one other study (53.6% in a randomized trial, 37.0% in an observational study, and 9.4% in both). Six factors independently associated with coenrolment (all p<0.001) were illness severity (odds ratio [OR] 1.35, 95% confidence interval [CI] 1.19-1.53 for each 10 point APACHE II score increase), substitute decision-makers providing consent, rather than patients (OR 3.31, 2.03-5.41), experience of persons inviting consent (OR 2.67, 1.74-4.11 for persons with >10 years experience compared to persons with none), center size (all ORs >10 for ICUs with >15 beds), affiliation with trials groups (OR 5.59, 3.49-8.95), and main trial rather than pilot phase (all ORs >8 for recruitment year beyond the pilot). Coenrolment did not influence clinical or trial outcomes or risk of adverse events.

Conclusions: Coenrolment was strongly associated with features of the patients, research personnel, setting and study. Coenrolment had no impact on trial results, and appeared safe, acceptable and feasible. Transparent reporting, scholarly discourse, ethical analysis, and further research are needed on the complex topic of coenrolment during critical illness.
Introduction

Clinical trials are essential to improve care and reduce morbidity and mortality in the intensive care unit (ICU). Some critically ill patients are eligible for more than one study. Restricting enrolment to only one study when patients are eligible for more than one is a potentially modifiable barrier to recruitment [1]. Testing 2 interventions concurrently can be achieved with a factorial design as used successfully by the Acute Respiratory Distress Syndrome Network. In other circumstances, when trials are initiated by different investigators at different times, with different inclusion and exclusion criteria, coenrolment can facilitate either sequential or simultaneous recruitment (Figure 1).

Coenrolment in multiple trials, often driven by patient demand, occurs in persons with human immunodeficiency virus (HIV) [2], and was documented among 23% of persons with HIV in 6 ongoing studies [3]. In this population, coenrolment is actively encouraged by some research programs [3] but not others [2]. In pre-hospital resuscitation trials, coenrolment occurs either in series or in parallel [4]. Half of the members of two critical care research consortia reported coenrolment of a patient in more than 1 study in the last year [5]. In a parental survey, 74% endorsed enrolment of their premature babies in 2 or more studies, 50% would consent to 3 or more studies, and 10% were willing to join more than 10 studies [6].

Some Institutional Review Boards restrict the practice of coenrolment, while concerned about patient safety, decisional burden or scientific integrity. Given the dearth of evidence on these issues, trialists have called for consideration of coenrolment on a case-by-base basis, and reporting on its impact [7]. The primary objective of this study was to document the patterns and predictors of patient coenrolment in an international heparin thromboprophylaxis trial. The secondary objective was to examine the consequences of coenrolment on clinical and trial outcomes.
Materials and methods

PROTECT (Prophylaxis for ThromboEmbolism in Critical Care Trial) (clinicaltrials.gov NCT00182143) was a randomized blinded clinical trial comparing unfractionated heparin to dalteparin for thromboprophylaxis [8]. Patients considered eligible were ≥18 years old, weighed >45 kilograms, and were expected to remain in ICU >72 hours. Exclusion criteria were admission diagnosis of trauma, neurosurgery or orthopedic surgery, need for therapeutic anticoagulation, receipt of >72 hours of heparin, contraindication to heparin, blood or pork products, pregnancy, life support limitation, and prior enrolment in this or a related trial. The primary outcome was proximal leg deep vein thrombosis (DVT). Other outcomes were pulmonary embolism, venous thromboembolism, bleeding, heparin-induced thrombocytopenia, duration of mechanical ventilation, ICU and hospital stay, and ICU and hospital mortality.

PROTECT was conducted over 4 years from May 2006 to June 2010 in 67 ICUs in Canada, United States, United Kingdom, Australia, Brazil and Saudi Arabia, as published previously [9].

Ethical approval was obtained from each participating Institutional Research Board (listed at the end of the manuscript under PROTECT Collaborators). In-person informed consent was required prior to randomization. Deferred consent was not permitted. For substitute decision-makers not in hospital, initial telephone consent, followed by in-person consent when possible, was approved in 16 of the 67 (23.9%) of centers.

Beginning and throughout the trial, the PROTECT Steering Committee reviewed each multicenter protocol to decide whether coenrolment was admissible, using Canadian Critical Care Trials Group guidelines [10]. These guidelines outline important scientific (e.g., interacting interventions), psychosocial (e.g., family stress) and logistic (e.g., research coordinator workload) factors to consider. The general approach to coenrolment was that all reasonable
efforts should be made to minimize the exclusion of patients coenrolled in another trial if they would likely represent those patients to whom trial results would possibly be applied in practice, as long as biologic interaction of the interventions being tested in the 2 trials seemed highly implausible. Dialogue between the principal investigator and steering committees of each multicenter study determined whether coenrolment would impact the scientific integrity of either study. When relevant, this was reasoned at the Canadian Critical Care Trials Group or the Australian and New Zealand Intensive Care Society Clinical Trials Group meetings for refutation or ratification. If coenrolment was endorsed, each participating center handled the relevant study governed by formal or informal coenrolment policies of their ICU or hospital Institutional Review Board. Local policies could deny coenrolment approved centrally. Local, single-center study coenrolment could also be approved after agreement with the PROTECT Steering Committee and the relevant consortium. Decisions were revisited if emerging evidence required reconsideration (Figure 2). All other studies into which patients were enrolled before, concurrent with, or subsequent to, PROTECT were documented on case report forms.

One example was coenrolment into the Age of Blood Evaluation Study (ABLE, ISRCTN44878718). ABLE is randomized trial evaluating mortality following transfusion of red blood cells stored up to one week versus stored up to 42 days [11]. Both PROTECT and ABLE investigators initially endorsed coenrolment. Months later, an observational trauma study suggested that among a subgroup of patients transfused more than 5 units, when patients received blood stored less than, versus more than 28 days, DVT rates (16.7% versus 34.5%, p=0.006), and mortality rates (13.9% versus 26.7% p=0.02) were lower [12]. If prolonged blood storage is thrombophilic in trauma, this could similarly increase DVT risk in critically ill medical-surgical patients. In reconsidering PROTECT and ABLE coenrolment, we sought additional evidence.
Using an existing prospective observational study database of 261 medical-surgical ICU patients screened for DVT [13] we evaluated age of transfused blood as an additional DVT risk factor. We also examined red blood cell transfusion as a possible risk factor in this population because in 349 trauma patients, transfusions increased DVT risk [14]. We found that 126 (48.3%) patients had at least 1 transfusion, and patients had a median 4 (IQR 2, 8) units. Multivariable analyses documented that neither red blood cell transfusion nor storage age predicted DVT in medical-surgical patients. Trends were counter to findings in trauma (e.g., red blood cells stored for <7 days had a higher associated DVT risk compared to >7 days [hazard ratio 5.3; 95%CI 1.3-22.1]) [15]. Based on inconclusive research evidence, the PROTECT and ABLE Steering Committees affirmed coenrolment into these trials. Given the PROTECT sample size, we anticipated similar transfusion rates and similar age of red blood cells transfused in the 2 arms. The ABLE trial now includes venous thromboembolism as a tertiary outcome.

**Statistical analysis**

We reported proportions with 95% confidence intervals (CI), and mean and standard deviation (SD) or median and interquartile range (IQR). We compared groups using Chi square, t-test and Fisher’s Exact test. We examined univariate associations between coenrolment rates (the dependent variable) and other factors (independent variables) related to characteristics of the patient, research coordinator, center and trial. A p value of <0.01 was considered statistically significant.

We conducted multivariable logistic regression analyses. To avoid incorporation of highly correlated independent variables into the model, we selected 1 of 4 measures of research coordinator experience, 1 of 3 measures of research infrastructure, and research consortium affiliation rather than country. The following independent factors were analyzed: patient factors (age, sex, Acute Physiology and Chronic Health Evaluation Score [APACHE] II score, medical
versus surgical status); individual consenting (substitute decision-maker or patient); research coordinator factors (years of experience obtaining consent for studies in the ICU when PROTECT began); center factors (number of ICU beds; number of full time research staff; national research consortium affiliation (Canadian Critical Care Trials Group or the Australian or New Zealand Intensive Care Society Clinical Trials Group); and year (pilot trial or year 1, 2, 3 and 4 of the full trial). Results are summarized using odds ratios (OR) with 95% CI. A p value of <0.01 was considered statistically significant.

We calculated the proportion of patients in each arm of the PROTECT trial who were coenrolled. To evaluate whether coenrolment affected patient safety, we re-analyzed the proportion of patients in each arm who had serious adverse events. To evaluate whether trial results would be any different without coenrolled patients, we re-analyzed overall results excluding these patients.

Results

In 67 participating ICUs, 3746 patients were enrolled in PROTECT. Consent was declined for 810 patients. Patients who were not enrolled in PROTECT due to enrolment in another study represented 65 of 2288 patients (2.8%) who were eligible but not randomized. Those 65 patients were enrolled in 71 other studies, 41 (63.1%) of which were industry-funded.

Among the 3746 patients in PROTECT, 713 (19.0%) were coenrolled in at least one other study (53.6% in a randomized trial, 37.0% in an observational study, and 9.4% in both types of studies). Coenrolment rates across participating centers ranged from 0 to 53.9% and across participating countries from 1.1 to 26.0%. No coenrolment occurred in 30 of 67 (44.8%) centers.
Factors associated with coenrolment in univariate analysis are presented in Table 1. Patients with higher illness severity and medical conditions were more likely to be coenrolled than patients who were less ill and surgical. Substitute decision-makers were more likely to agree to coenrolment than patients. Research coordinators with more ICU experience, and those with more experience obtaining consent in the ICU, were more likely to coenrol patients than those with less experience. Centers with more ICU beds and centers affiliated with national research consortia were more likely to coenrol than others. A higher proportion of patients were coenrolled in Canada, the United States and Australia than in the Brazil, Saudi Arabia and the United Kingdom. Coenrolment was less common in the pilot phase of the trial than the main trial.

In Table 2, we present the 6 factors independently associated with coenrolment in the multivariable analysis. In order of decreasing strength of association, these were: phase of the trial (all ORs >8 for recruitment beyond the pilot phase); center affiliation with a research consortium (OR 5.59, 3.49-8.95); center size (all ORs >10 for ICUs with >15 beds); substitute decision-makers providing consent rather than patients (OR 3.31, 2.03-5.41); experience of research coordinator (OR 2.67, 1.74-4.11 for >10 years of experience compared to persons whose first trial was PROTECT); and patient illness severity (odds ratio [OR], 95%CI 1.35 (1.19-1.53 for each 10 point increase in APACHE II Score).

Table 3 summarizes characteristics of the studies into which PROTECT patients were coenrolled. The majority were coenrolled into another academic investigator-initiated study (97.5%). Of 713 patients, 592 (83.0%) were coenrolled in 1 other study, 93 (13.0%) were coenrolled in 2 studies, and 28 (3.9%) were coenrolled in 3 or more studies.

Of 865 coenrolments involving 713 patients, the most common other international trials tested pharmaconutrition, intensive glucose control, sedation interruption, and high frequency
oscillation (Table 1). Observational studies were both quantitative (e.g., registries, audits, quality improvement studies, diagnostcs, translational biology or long-term follow up studies), and qualitative (e.g., interviews, focus groups).

The proportion of patients coenrolled in any study was similar between the dalteparin group and the unfractionated heparin group (352 (18.8%) versus 361 (19.3%), p=0.74). There were no differences between groups in patients enrolled in any randomized trial (209 (11.2%) versus 239 (12.8%), p=0.14), or the proportion in each group enrolled in any of the 5 most common coenrolment studies (197 (10.5%) versus 223 (11.9%), p=0.20). Twenty PROTECT patients were coenrolled in ABLE (9 of 1873 (0.5%) in the dalteparin group and 11 of 1873 (0.6%) in the unfractionated heparin group), p=0.82.

Among patients coenrolled in other randomized trials, rates of serious adverse events were similar between the dalteparin (2 of 209, 1.0%) and unfractionated heparin (0 of 239, 0.0%) groups, p=0.14, as per the main trial findings (7 of 1873, 0.4%) versus 6 of 1873, 0.3%), respectively, p=0.74. Protocol violations were also similar (data not shown). In Table 4, we show that the overall PROTECT results excluding patients coenrolled in other randomized trials, which were no different than the results of all patients randomized [9]. That is, pulmonary embolism rates were lower in patients receiving dalteparin compared to those receiving unfractionated heparin; rates of DVT, venous thrombosis, and major bleeding were similar. No patients were withdrawn or lost to follow-up whether coenrolled or not.

Discussion

In this international heparin thromboprophylaxis trial, one fifth of patients were coenrolled in at least one other study. Half of the coenrolments were in randomized trials, although a variety of
study designs were involved. Coenrolment was limited to 1 or 2 additional studies in 83% and 13% of patients, respectively. These findings are consistent with membership surveys of research consortia indicating that 2 was the median number of randomized trials into which 1 patient was enrolled [5].

Multivariate analysis showed that consent encounters with substitute decision-makers were more likely to involve coenrolment than those with patients. This suggests that more seriously ill patients are frequently eligible for several studies, yet too sick to make decisions themselves, congruent with the finding that patients who were coenrolled were more seriously ill than those who were not. Substitute decision-makers may seek several research opportunities while helping to advance science, so-called conditional altruism [16].

Research coordinators with greater consent experience were more likely to coenrol than others, suggesting that professional maturity may foster sound judgment about approaching persons for coenrolment; whether training enhances comfort and success with coenrolment is unclear. Coenrolment occurred more often in larger ICUs, and in centers affiliated with a national consortium, perhaps reflecting group norms. More frequent during the full trial than the pilot phase, facility with coenrolment may have increased over time.

Participation in another study was the reason why 65 eligible patients were not enrolled in PROTECT; 63% of these studies were industry-initiated. Only 2% of PROTECT patients were coenrolled in industry studies. Generally, industry-funded trials, compared to other trials, are more likely to exclude individuals due to age, comorbidities and concomitant medications, raising concerns about their generalizability [17]. However, if industry trials prohibit coenrolment in academic studies, selection bias in academic trials may result, as well as slower completion, thereby delaying answers to publicly motivated research questions. Certainly, coenrolment in trials of investigational drugs or devices is imprudent due to difficulty monitoring safety and
interpreting harm. Since patients in the investigator-informed, industry-funded trial comparing drotrecogin alfa to placebo in patients with persistent septic shock (PROWESS-SHOCK, NCT00604214) [18] would typically receive heparin thromboprophylaxis in the absence of contraindications, PROTECT coenrolment was permitted. We identified 3 patients who were eligible for PROTECT but not recruited because of enrolment in PROWESS-SHOCK, and no PROTECT patients who were coenrolled in PROWESS-SHOCK.

One major focus regarding permissible coenrolment in 2 academic trials is the biologic plausibility of the 2 interventions having a potentiating or attenuating effect on each other. Having identical primary outcomes in 2 academic trials would not be a sole criterion for prohibiting coenrolment, especially when treatment effects are expected to be modest, which is common in critical care. For example, if 2 trials had the same primary outcome of mortality (e.g., a trial comparing starch resuscitation vs normal saline in septic shock and intensive insulin therapy vs liberal glucose management in heterogeneous ICU patients), the 2 interventions would likely be considered unrelated, and coenrolment would be permitted, because starch and antioxidants would not be known to mediate their effect on mortality through related mechanisms. Several additional scientific issues need careful consideration regarding coenrolment, such as projected impact on statistical power, outcome ascertainment bias, increased risk of adverse events, and the ultimate interpretation of study results. We recommend widespread consultation about the merits and demerits of various coenrolment pairs before and during conduct of a trial.

Furthermore, specific approaches to data collection and analysis can be established a priori if concerns exist about coenrolment. Shared definitions and case report forms for use across studies could help [3], as we used for PROTECT and ABLE. New research influencing previous coenrolment decisions should prompt revisiting previous decisions as studies unfold. Documenting consecutive and concurrent coenrolment eligibility and consent rates throughout a
trial, and transparent reporting of coenrolment upon completion, including effect modification and risk of harm, will help to disseminate coenrolment patterns, and provide data to examine its actual rather than perceived impact. If concerns exist and trialists are willing to exchange randomization codes, unadjusted and adjusted analyses can be conducted to evaluate the impact not just of substantial coenrolment of patients in one trial on the results of the other trial, and vice versa, but also the impact of each specific allocation arm.

Although an understanding of all available treatment options is important for informed consent for medical therapy, there is no similar perception that patients should be informed of all available studies for which they are eligible. Indeed, most human subjects research discourse deals with protection from harm rather than opportunity for participation [1], which is particularly germane to coenrolment. More open discussion will help to elucidate key ethical issues, since the vulnerability of critically ill patients [19] raises concern about adverse effects from coenrolment. We found that PROTECT patients coenrolled in randomized trials were not more likely to have serious adverse events or protocol violations compared to patients who were not coenrolled. Post hoc analyses of PROTECT omitting patients coenrolled in randomized trials yielded the same overall results as the main analysis. Finally, no PROTECT patients were lost to follow-up, thus, no coenrolled patients were withdrawn.

In 2007, a tri-national survey showed that only 11% of respondents indicated that their local Institutional Review Board had a coenrolment policy, whereas 35% reported a local ICU guideline [5]. Coenrolment guidelines exist for adult resuscitation studies [4], pediatric [20] and adult [10] critical care. Public health mandates to answer research questions quickly during pandemics have encouraged coenrolment of patients in treatment and observational studies [21]. Professional position statements about whether, when, why and how to coenrol will raise awareness and facilitate stakeholder dialogue.
Limitations of this study include our inability to explore the decisional burden on substitute decision-makers, patients and research coordinators. However, in another 4-month single center study, we found consent rates similar for any single enrolment (84%) and coenrolment (79%) opportunity [22]. We could not document rates or reasons for no coenrolment, or which person declined (e.g., patient, substitute decision-maker, physician, surgeon, anesthesiologist). Examining the choice of which study to pursue if a patient was eligible for more than one was beyond the scope of this project. However, investigators report that when approaching persons for coenrolment in a randomized trial, they consider trial rigour and relevance, potential for benefit or harm, consortium affiliation and remuneration [5].

Strengths of this study include comprehensive documentation of coenrolment throughout a multicenter trial. Investigators used a prospective, transparent framework for coenrolment decisions, independently examining each pair of studies, guided by independent Institutional Review Boards, and research consortia. Using multivariate analysis, significant predictors of coenrolment were identified, adjusting for confounding. We examined the impact on patient and trial outcomes. Representation from diverse ICUs and countries enhances the generalizability of these findings, which may apply to other academic trials testing currently available interventions.

Conclusions

Coenrolment was common in this thromboprophylaxis trial, and was strongly associated with specific features of the patients, research personnel, setting and study. Coenrolment was an effective, feasible method to enhance recruitment, provided that the patients or substitute decision-maker, clinicians, principal investigators, steering committees, research consortium and local Institutional Review Boards agreed. Coenrolment did not influence overall trial results, patient safety or adverse events. Further scientific debate, ethical analysis, and research are
needed on the complex topic of coenrolment for critically ill patients.

**Key messages**

- In this international heparin thromboprophylaxis trial of 3746 patients, one fifth of patients were coenrolled in at least one other study. Half of the coenrolments were in randomized trials, although a variety of study designs were involved, and almost all coenrolments were in academic investigator-initiated studies.

- In decreasing strength of association, 6 factors were independently associated with coenrolment: later phase of the trial compared to the pilot phase, center affiliation with a research consortium, larger center size, substitute decision-makers providing consent rather than patients, greater research coordinator experience, and higher patient illness severity.

- Coenrolment did not influence overall trial results, patient safety or adverse events.

- Before and during a trial, we suggest widespread consultation among investigators, clinicians, trial steering committees, research consortia and local Institutional Review Boards about the scientific, psychosocial and logistic effects of various coenrolment pairs.

- Transparent reporting, scholarly discourse, ethical analysis, and further research are needed on the complex topic of coenrolment during critical illness.

**Abbreviations**

ABLE, Age of Blood Evaluation; APACHE, acute physiology and chronic health evaluation; CI, confidence interval; DVT, deep vein thrombosis; HIV, human immunodeficiency virus; ICU,
intensive care unit; IQR, interquartile range; OR, odds ratio; PROTECT, Prophylaxis for ThromboEmbolism in Critical Care Trial; SD, standard deviation.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

DC, EM, FC, and NZ conceived of the study. DC, EM, FC, NZ, IW, TM, AM, FC, and MCF designed the study. NZ and SV coordinated the study. DC obtained funding. EM, OS, NZ, IW, TM, AM, FC, SV and MCF collected data. DC, RF, NA, JM and MM consulted on methods. DHA performed the analyses. YA, NA, RF and DC designed the figure. DHA, DC, SF, TC, RF, YA, CW, NO, RH, NA, JM and MM interpreted the data. DC, EM, OS, DHA and MM wrote the draft. All authors read and approved the final manuscript for publication.

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Data Monitoring Committee: Drs Robin Roberts (Chair), Christian Brun-Buisson and Victor Montori

References


10) The Canadian Critical Care Trials Group [www.ccctg.ca].


Figure 1. Factorial and coenrolment designs. In this figure, we present a schematic for a factorial design randomized trial, sequential coenrolment in 2 randomized trials and simultaneous coenrolment in 2 randomized trials.

Figure 2. Coenrolment Schema. In this figure, we outline steps taken to consider coenrolment of 1 patient into 1 or more additional studies. ABLE Trial, Age of Blood Evaluation Trial; ANZICS, Australian and New Zealand Intensive Care Society Clinical Trials Group; CCCTG, Canadian Critical Care Trials Group; Fonda, fondaparinux; REB, Research Ethics Board; UFH, unfractionated heparin.
<table>
<thead>
<tr>
<th>Table 1. Characteristics of factors associated and not associated with coenrolment.</th>
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<tbody>
<tr>
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<tr>
<td><strong>Patient Characteristics</strong></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
</tr>
<tr>
<td>Female, N (%)</td>
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<tr>
<td>APACHE II score, mean (SD)**</td>
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<tr>
<td>Medical admission type, N (%)</td>
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<tr>
<td><strong>Person Consenting, N (%)</strong>*</td>
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<tr>
<td>Patient</td>
</tr>
<tr>
<td>Substitute decision-maker</td>
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<tr>
<td><strong>Research Coordinator Characteristics</strong></td>
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<tr>
<td>Years of Non-research ICU Experience, N (%)</td>
</tr>
<tr>
<td>0 years</td>
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<tr>
<td>&gt;0 to 10 years</td>
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<tr>
<td>&gt;10 years</td>
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<tr>
<td>Years of procuring consent for clinical studies <em>in ICU</em>, N (%)</td>
</tr>
<tr>
<td>0 years</td>
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<tr>
<td>&gt;0 to 10 years</td>
</tr>
<tr>
<td>&gt;10 years</td>
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<tr>
<td><strong>Center Characteristics</strong></td>
</tr>
<tr>
<td>Number of ICU beds screened, N (%)</td>
</tr>
<tr>
<td>&lt;15 beds</td>
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<tr>
<td>15-20 beds</td>
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<tr>
<td>&gt;20 beds</td>
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<tr>
<td>Characteristic</td>
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<td>----------------</td>
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<tr>
<td>Full time ICU research staff, N (%)</td>
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<tr>
<td>&lt;1 FTE</td>
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<tr>
<td>1 FTE</td>
</tr>
<tr>
<td>&gt;1 FTE</td>
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<tr>
<td>Formal Trials Group Affiliation, N (%)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
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<tr>
<td>Country, N (%)</td>
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<tr>
<td>Canada</td>
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<td>Australia</td>
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<td>Brazil</td>
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<td>Saudi Arabia</td>
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<td>United States</td>
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<td>United Kingdom</td>
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<tr>
<td>Characteristic of Enrolment Phase, N (%)</td>
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<tr>
<td>Pilot trial</td>
</tr>
<tr>
<td>Year 1</td>
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<tr>
<td>Year 2</td>
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<tr>
<td>Year 3</td>
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<tr>
<td>Year 4</td>
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</tbody>
</table>

In this table, we compare patients, person consenting, approaches to consent, and research environment associated with coenrolment versus no coenrolment. Formal trials group affiliation refers to a center associated with either the Canadian Critical Care Trials Group or the Australian and New Zealand Intensive Care Society Clinical Trials Group. P values refer to results of univariate analyses. APACHE II score, Acute physiology and chronic health evaluation
score; ICU, intensive care unit; SD, standard deviation.
| Table 2. Factors independently associated with coenrolment in multivariate analysis. |
|---------------------------------|---------------------------------|-----------------|
|                                 | Odds Ratio (95% CI)              | P value         |
| **Patient demographics**        |                                 |                 |
| Age (10 year increase)          | 0.96 (0.91, 1.02)               | 0.155           |
| Female                          | 0.92 (0.77, 1.11)               | 0.403           |
| APACHE II score (10 point increase) | 1.35 (1.19, 1.53)               | <0.001          |
| Medical versus surgical         | 1.26 (1.01, 1.57)               | 0.041           |
| **Individual consenting**       |                                 |                 |
| Substitute decision-maker versus patient | 3.31 (2.03, 5.41)               | <0.001          |
| **Years of procuring consent for clinical studies in ICU** | | |
| >0 to 10 years versus 0 years   | 0.83 (0.55, 1.25)               | <0.001          |
| >10 years versus 0 years        | 2.67 (1.74, 4.11)               |                 |
| **Center size (beds screened for PROTECT patients)** | | |
| 15-20 beds versus <15 beds      | 20.06 (7.56, 53.25)             | <0.001          |
| >20 beds versus < 15 beds       | 13.76 (5.15, 36.80)             |                 |
| **Full time ICU research staff**|                                 |                 |
| 1 FTE versus <1 FTE             | 1.13 (0.41, 3.11)               | 0.966           |
| >1 versus <1 FTE                | 1.10 (0.40, 3.03)               |                 |
| **Formal Trials Group Affiliation** |                                 |                 |
| Yes versus no                   | 5.59 (3.49, 8.95)               | <0.001          |
| **Year of PROTECT**             |                                 |                 |
| Year 1 versus Pilot             | 8.22 (1.95, 34.61)              | <0.001          |
| Year 2 versus Pilot             | 32.89 (7.95, 135.98)            |                 |
| Year 3 versus Pilot             | 38.15 (9.24, 157.51)            |                 |
In this table, we present the independent factors associated with coenrolment of 1 patient into 2 or more studies identified by multivariate regression analysis, presented using odds ratios (OR) and 95% confidence intervals (95% CI). P values refer to results of multivariate analyses. ANZICS, Australian and New Zealand Intensive Care Society Clinical Trials Group; APACHE II score, Acute physiology and chronic health evaluation score; CCCTG, Canadian Critical Care Trials Group; FTE, full time equivalent; ICU, intensive care unit.
Table 3. Coenrolment study characteristics.

<table>
<thead>
<tr>
<th>N (% of 713 Patients)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of other study</strong></td>
<td></td>
</tr>
<tr>
<td>Randomized trial</td>
<td>380 (53.3)</td>
</tr>
<tr>
<td>Observational study</td>
<td>265 (37.2)</td>
</tr>
<tr>
<td>Both</td>
<td>68 (9.5)</td>
</tr>
</tbody>
</table>

| **Genesis of other study** |                   |
| Investigator-initiated | 695 (97.5)       |
| Industry-initiated     | 15 (2.1)         |
| Both                  | 3 (0.4)          |

| **CCCTG or ANZICS affiliated study** |                   |
| Yes | 451 (63.3) |
| No  | 181 (25.4) |
| Both| 81 (11.4)  |

| **Number of studies into which patients were coenrolled** |                   |
| 1 | 591 (82.9) |
| 2 | 94 (13.2)  |
| 3 | 25 (3.5)   |
| 4*| 3 (0.4)    |

In this table, among 713 patients who were coenrolled in another study, we present the coenrolment study type (randomized trial, observational study), study genesis (investigator-initiated versus industry-initiated), affiliation with a research consortia, and the number of studies into which PROTECT patients were coenrolled. The bottom half of the table outlines, of the 865 coenrolments, which studies were involved. ANZICS, Australian and New Zealand Intensive Care Society Clinical Trials Group; CCCTG, Canadian Critical Care Trials Group.
Table 4. PROTECT results excluding patients coenrolled in another randomized trial.

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Dalteparin (N=1873)</th>
<th>UFH (N=1873)</th>
<th>Hazard Ratio (95%CI)</th>
<th>Dalteparin (N=1664)</th>
<th>UFH (N=1633)</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>All patients</td>
<td></td>
<td>Not Coenrolled in RCT</td>
<td>Not Coenrolled in RCT</td>
<td></td>
</tr>
<tr>
<td>Primary outcome: proximal leg deep vein thrombosis</td>
<td>94 (5.1)</td>
<td>108 (5.9)</td>
<td>0.91 (0.68, 1.23)</td>
<td>83 (5.0)</td>
<td>93 (5.7)</td>
<td>0.87 (0.63, 1.21)</td>
</tr>
<tr>
<td>Any pulmonary embolism</td>
<td>22 (1.2)</td>
<td>42 (2.3)</td>
<td>0.48 (0.27, 0.84)</td>
<td>19 (1.1)</td>
<td>35 (2.1)</td>
<td>0.48 (0.26, 0.89)</td>
</tr>
<tr>
<td>Any venous thromboembolism</td>
<td>150 (8.2)</td>
<td>184 (10.0)</td>
<td>0.87 (0.69, 1.10)</td>
<td>133 (8.0)</td>
<td>161 (9.9)</td>
<td>0.83 (0.64, 1.07)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>100 (5.5)</td>
<td>105 (5.7)</td>
<td>0.98 (0.73, 1.31)</td>
<td>88 (5.3)</td>
<td>93 (5.7)</td>
<td>0.94 (0.69, 1.28)</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>5 (0.3)</td>
<td>12 (0.7)</td>
<td>0.47 (0.16, 1.37)</td>
<td>5 (0.3)</td>
<td>10 (0.6)</td>
<td>0.56 (0.18, 1.67)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>395 (21.7)</td>
<td>444 (24.3)</td>
<td>0.91 (0.79, 1.05)</td>
<td>372 (22.4)</td>
<td>391 (23.9)</td>
<td>0.95 (0.82, 1.10)</td>
</tr>
</tbody>
</table>

In this table we report main results of the original trial including all patients, and results including only those patients (209 in the dalteparin group and 239 in the unfractionated heparin group) who were not coenrolled in another randomized trial (1664 in the dalteparin arm and 1633 in the unfractionated heparin arm). CI, confidence interval; RCT, randomized clinical trial; UFH, unfractionated heparin.
Figure 1

Factorial Design (single RCT)

Sequential Coenrolment In 2 RCTs

Simultaneous Coenrolment In 2 RCTs

Time
START: Discuss potential study for coenrolment with respective PIs and Steering Committees

New evidence bearing on previous coenrolment decision (e.g., ABLE)

Consider biological interaction

Yes, likely

No coenrolment

Discuss with research consortia if relevant

Not likely; consider coenrolment

Notify all relevant participating centers

Local site considers coenrolment of centrally approved study or local study

Consider local REB guideline (e.g., approved, annual report)

Yes, continue

No coenrolment

Consider local ICU guideline (e.g., 2 study maximum)

Yes, continue

No coenrolment

Consider logistic issues (e.g., no additional central access)

Yes, continue

No coenrolment

Consider psycho-social issues (e.g., family dynamics)

Yes, continue

No coenrolment

Consider coenrolment

Obtain consent

Coenrol

Questions and coenrolment reporting to Methods Centers

Public reporting of coenrolment

Figure 2