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ORIGINAL ARTICLE

Physicians declining patient enrollment in a critical care trial: a case study in thromboprophylaxis

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Abstract *Purpose:* To analyze the frequency, rationale and determinants of attending physicians requesting that their eligible patients not be approached for participation in a thromboprophylaxis trial. *Methods:* Research personnel in 67 centers prospectively documented eligible non-randomized patients due to physicians declining to allow their patients to be approached. *Results:* In 67 centers, 3,764 patients were enrolled, but 1,460 eligible patients had no consent encounter. For 218 (14.9 %) of these, attending physicians requested that their patients not be approached. The most common reasons included a high risk of bleeding (31.2 %) related to fear of heparin bioaccumulation in renal failure, the presence of an epidural catheter, peri-operative status or other factors; specific preferences for thromboprophylaxis (12.4 %); morbid obesity (9.6 %); uncertain prognosis (6.4 %); general discomfort with research (3.7 %) and unclear reasons (17.0 %). Physicians were more likely to decline when approached by less experienced research personnel; considering those with >10 years of experience as the reference category, the odds ratios (OR) for physician refusals to personnel without trial experience was 10.47 [95 % confidence interval (CI) 2.19–50.02] and those with less than 10 years experience was 1.72 (95 % CI 0.61–4.84). Physicians in open rather than closed units were more likely to decline (OR 4.26; 95 % CI 1.27–14.34). Refusals decreased each year of enrollment compared to the pilot phase. *Conclusions:* Tracking, analyzing, interpreting and reporting the rates and reasons for physicians declining to allow their patients to be approached for enrollment provides insights into clinicians' concerns and attitudes to trials. This information can encourage physician communication and education, and potentially enhance efficient recruitment.

Keywords Critical care · Randomized trials · Eligible · Informed consent · Physician consent

Introduction

Numerous factors may influence physicians in their decision to endorse or decline patient enrollment in a clinical trial. These include general concerns such as an adverse impact on the doctor-patient relationship, difficulty with informed consent, dislike of discussions involving uncertainty and concerns about the specific trial (e.g., procedures or treatment alternatives) [1–3].

A broad taxonomy of plausible reasons explains why physicians decline to allow their patients to be approached for research. Their rationale may be (1) setting-specific (e.g., related to lack of trained research personnel, inaccessibility of trial interventions or insufficient infrastructure); (2) physician-specific (e.g., personal lack of interest in, or knowledge about, research methods, perceived lack of autonomy, concern about role conflict and inducing therapeutic misconception); (3) trial-specific (e.g., lack of equipoise about the question, perceptions about trial rigor, relevance, medico-legal risk or personal inconvenience) or (4) patient-specific (e.g., perceived balance of probable benefits, burdens and harms in a unique participant, or preference for a particular intervention).

The context for physician reluctance to enroll patients in research has largely focused on the patient-physician dyad in an outpatient setting. Our venue of interest was the intensive care unit (ICU), where patients are typically unable to make decisions. Although trials in critical care occasionally report physician decline rates [4, 5], reasons are seldom documented. Understanding why physicians decline to endorse approaching eligible patients for research participation can help to optimize study design, enhance recruitment efficiency and ensure the generalizability of trial results. The objective of this study was to analyze the frequency, rationale and determinants of physicians declining to allow their critically ill patients or families to be approached for enrollment in a thromboprophylaxis trial. Some of this work was presented in abstract form [6].

Methods

PROTECT (Prophylaxis for ThromboEmbolism in Critical Care Trial) was a concealed, randomized, blinded multicenter international trial (clinicaltrials.gov

NCT00182143) of thromboprophylaxis with dalteparin, a low-molecular-weight heparin (LMWH), versus unfractionated heparin (UFH) in ICU patients. Patients were considered for enrollment if they were ≥18 years of age, weighed ≥45 kg and were expected to remain in the ICU ≥72 h. Exclusion criteria were platelet count ≤75 × 10^9/l or serious coagulopathy (international normalized ratio or activated partial thromboplastin time ≥2 the upper limit of normal); major hemorrhage in the previous week; ischemic stroke or intracranial hemorrhage in the last 3 months; admission diagnosis of trauma, neurosurgery or orthopedic surgery; need for therapeutic anticoagulation; receipt of ≥72 h of any heparin dose; contraindication to heparin, blood products or pork products; pregnancy; limitation of life support; and prior enrollment in this or a related trial. The presence of an epidural catheter and morbid obesity were not exclusion criteria. As discussed in the protocol [7, 8], renal failure (creatinine clearance <30 ml/min) was an exclusion criterion in the pilot phase of the trial [9], but was removed from the principal phase after a study showing no bioaccumulation of dalteparin in such patients [10].

The primary outcome was proximal leg deep vein thrombosis (DVT). Secondary outcomes were pulmonary embolism (PE), venous thromboembolism (VTE) at any site, the composite of VTE or death, major bleeding, minor bleeding and heparin-induced thrombocytopenia. All other aspects of clinical management were at the discretion of the ICU team. The main trial was preceded by an internal pilot trial at 14 centers in Canada and 2 centers in Australia. The pilot and full trial methods and results were published previously [7–9].

Over 4 years of recruitment in 67 ICUs, research coordinators used screening forms to document all eligible non-randomized patients, including any reason for non-enrollment of eligible patients.

Research coordinators screened for eligible patients daily, asking attending physicians if they agreed that eligible patients or their families could be invited to participate. When physicians declined to permit eligible patients or families to be approached for enrollment, research coordinators enquired about the reason, recording this on a pilot-tested case report form with prespecified categories. Research coordinators sought written informed consent from substitute decision-makers (SDMs) or patients before enrollment. However, in 16 of 67 centers, it was predominantly physicians who attempted to procure consent. In these centers, the principal investigator or other physician not caring for the patient sought agreement from the attending physician, then approached the SDM or patient.

Regardless of who approached the attending physician prior to approaching the SDM or patient, we monitored the reasons for attending physicians declining enrollment throughout the trial to detect any reasons that the Methods Center should have considered as an exclusion criterion and to identify the need for enhanced communication and education. We considered each occasion when an attending physician declined to allow their patient to be approached as an opportunity to enhance our understanding of the perception of the trial in the community, share existing or new literature bearing on enrollment, and improve enrollment procedures. We did not collect identifying physician information.

Ethics

The protocol and a template informed consent form were provided to each participating center by the Methods Center. Each center's Research Ethics Board (REB) approved the trial. The study was performed in accordance with the ethical standards in the Declaration of Helsinki.

Analysis

We defined patients whose physicians allowed their enrollment in PROTECT as those patients who agreed themselves or by proxy (from SDMs) to be randomized to receive prophylactic dose LMWH or UFH in PROTECT, or those who themselves declined to consent. In other words, these patients or SDMs were approached for trial participation after agreement by their attending physician. We defined patients whose physicians declined to allow their enrollment as those who fulfilled inclusion criteria and had no exclusion criteria, but whose physicians requested that research personnel not invite trial participation. This was one of four reasons patients were classified as eligible non-randomized [8]. The primary outcome occurred when an eligible patient was not approached for consent because the attending physician declined to allow it.

We analyzed the frequency, rationale and determinants of physicians requesting that research personnel not approach their eligible patients or families for participation. We used descriptive statistics, reporting categorical data as proportions and continuous data as mean and standard deviation (SD) or median and interquartile range (IQR) if data were skewed. Considering all patients for whom consent was sought (i.e., patients randomized and patients who declined to consent) and all patients who were not approached because the physician declined, we performed a hierarchical logistic regression [11] to examine predictors of physician declining. In this multilevel model, we considered patients clustered within centers and entered center as a random effect in the model. Potential predictors considered in this multivariable analysis were research personnel years of experience,

center size, open versus closed unit, center affiliation with Trials Groups and year of the trial. We present factors associated with physicians declining using odds ratios (ORs) and 95 % confidence intervals (CIs). A p value of <0.05 was considered statistically significant. Analyses were performed using SAS version 9.2 (Cary, NC, USA).

Results

Among the 6,034 eligible patients, 1,460 had no consent encounter and were not randomized because an SDM could not be located (1,002, 68.6 %), the physician declined (218, 14.9 %), the patients were missed for administrative reasons (175, 12.0 %), or the patients were enrolled in a related trial (65, 4.5 %). Of the 4,574 patients whose physicians were approached for approval before patients were approached for consent, we enrolled 3,764 patients, and 810 patients or SDMs ultimately declined.

The 218 patients whose physicians declined were in 35 of 67 (52.2 %) participating centers. Among these 35 centers, the number of patients for whom physicians declined enrollment was a median of 4 (IQR 2–10). Centers in which physicians declined were no different from centers in which this did not occur. In Table 1 we present reasons for physicians declining. The most common was a perceived high risk of bleeding (68 patients, 31.2 %), which related to general concern about future bleeding, fear of heparin bioaccumulation in renal failure, epidural in place, concern about peri-operative bleeding or other factors. Unclear reasons constituted the second most common category (37 patients, 17.0 %). Preferences for specific thromboprophylaxis methods were the third most common reason (27 patients, 12.4 %), including the desire for exclusively UFH or exclusively LWMH, thrice daily UFH or concomitant mechanical prophylaxis. Other reasons included morbid obesity (21, 9.6 %) and uncertain patient prognosis (14, 6.4 %). Physicians' general discomfort with research was an uncommon reason for declining enrollment ($n = 8$, 3.7 %). We did not modify any of the exclusion criteria after the pilot phase on the basis of ongoing assessment of reasons for physicians declining to enroll patients.

Data comparing patients who were approached for consent to those not approached because physicians declined are presented in Table 2, according to center characteristics. The hierarchical multivariable analysis shows several factors significantly associated with propensity for physician declining (Table 3). Physicians were more likely to decline when approached by less experienced research personnel; considering those with more than 10 years of trial experience as the reference category, the OR for physicians' refusals to research personnel with no prior trial experience and to those with some but less than 10 years of prior experience were 10.47 (95 %CI 2.19–50.02) and 1.72 (95 %CI 0.61–4.84), respectively. Physicians in open units were more likely to decline than those in closed units (OR 4.26, 95 %CI 1.27–14.34). Physician refusals decreased over the course of the trial compared to the pilot phase. The ORs (95 %CIs) were for year 1: 0.67 (0.21–2.10), for year 2: 0.67 (0.22–2.06), for year 3: 0.32 (0.10–1.02) and for year 4: 0.42 (0.13–1.29). ICU size and affiliation with clinical trials groups were not associated with physician decline rates.

Table 1 Reasons for physician declining patient enrollment in PROTECT

Reason	Number	Percent
Bleeding risk	68	31.2
Perceived high risk of bleeding	29	13.3
Acute renal failure	8	3.7
Epidural catheter in situ	16	7.3
Surgeon declined (further details unavailable)	14	6.4
Anesthesiologist declined (concern unrelated to epidural, further details unavailable)	1	0.5
Specific prophylaxis preferred	27	12.4
Thrice daily unfractionated heparin dosing preferred	11	5.0
Unfractionated heparin preferred	4	1.8
Low-molecular-weight heparin preferred	5	2.3
Pneumatic compression devices preferred	5	2.3
Long-term paralysis; debating therapeutic anticoagulation	2	0.9
Morbid obesity	21	9.6
Uncertain prognosis	14	6.4
Possible venous thromboembolism not yet diagnosed; therapeutic anticoagulation needed in near future	13	6.0
Serious family stress	12	5.5
Malignancy	7	3.2
Suspected heparin-induced thrombocytopenia	2	0.9
Other specific reasons[a]	9	3.7
Physician generally uncomfortable with research	8	3.7
Unclear	37	17.0
Total	218	100.0

In this table, we present the 218 eligible critically ill patients whose physicians refused to allow the research personnel to approach them or their family for enrollment in a thromboprophylaxis trial. Reasons are mutually exclusive

[a] Nine other reasons not categorized into established reasons included: unsuitability for research for unspecified reasons (4), inability to follow patient because of research personnel leaving (2), patient too complex (2) and patient suffering from iatrogenic complications (1)

Discussion

In this trial of anticoagulant prophylaxis for critically ill patients, physician consent was sought prior to approaching eligible patients for participation. Physicians declining to allow a consent discussion for their eligible patients represented $\sim$15 % of reasons for non-randomization of eligible patients.

Table 2 Factors associated with physicians declining versus physicians allowing their patients to be approached for enrollment

	All patients $N = 4{,}792$	Physician allowed patients to be approached for consent $N = 4{,}574$	Physician declined $N = 218$
Years of ICU research experience of the lead consenting research personnel, *N* (%)			
0 years (e.g., new staff)	256 (5.3)	224 (4.9)	32 (14.7)
>0–10 years	3,538 (73.8)	3,376 (73.8)	162 (74.3)
>10 years	998 (20.8)	974 (21.3)	24 (11.0)
Center size, *N* (%)			
<15 beds	530 (11.1)	499 (10.9)	31 (14.2)
15–20 beds	2,118 (44.2)	2,028 (44.3)	90 (41.3)
21–25 beds	617 (12.9)	595 (13.0)	22 (10.1)
>25 beds	1,527 (31.9)	1,452 (31.7)	75 (34.4)
Unit type, *N* (%)			
Closed	4,335 (90.5)	4,148 (90.7)	187 (85.8)
Open	457 (9.5)	426 (9.3)	31 (14.2)
Formal trial group affiliation, *N* (%)			
Yes	4,186 (87.4)	3,982 (87.1)	204 (93.6)
No	606 (12.6)	592 (12.9)	14 (6.4)
Year of PROTECT, *N* (%)			
Pilot	157 (3.3)	147 (3.2)	10 (4.6)
Year 1	769 (16.0)	730 (16.0)	39 (17.9)
Year 2	1,105 (23.1)	1,042 (22.8)	63 (28.9)
Year 3	1,246 (26.0)	1,197 (26.2)	49 (22.5)
Year 4	1,515 (31.6)	1,458 (31.9)	57 (26.1)

In this table, we present features of the lead research personnel, participating center and phase of the trial and their relation to physicians declining enrollment. Column percentages are shown

This rate of non-enrollment due to physician refusal was similar to those in other recent large ICU trials [12–14], although reporting transparency and metrics vary. Prevailing community equipoise may explain this, since clinicians prescribed both dalteparin and UFH prior to the trial. Physicians may also have been interested in the study question because of their participation in or awareness of preparatory studies. This included surveys of stated practice [15, 16] and perceptions about clinically important thrombi [17], audits [18, 19], a multicenter retrospective study [20], a prospective observational study [21], a multicenter observational study in renal failure [10, 22], and a multicenter pilot randomized trial in Canada and Australia [9].

Among specific reasons for non-enrollment cited by physicians, perceived high bleeding risk was the most common. This may have reflected the desire to withhold pharmacologic thromboprophylaxis altogether, despite their patients lacking trial exclusion criteria related to a high risk of bleeding. Renal failure was an uncommon reason for physicians declining, perhaps related to the preparatory study of LMWH in ICU patients with a range of renal dysfunction [10] and the lack of a demonstrable high bleeding rate. Following trial completion, we identified the independent risk factors for major bleeding as prolonged activated partial thromboplastin time, thrombocytopenia, therapeutic UFH, antiplatelet agents, dialysis and recent surgery, but not thromboprophylaxis with either LMWH or UFH [23].

Another physician objection to enrollment was that the protocolized dose was considered unsuitable, as might have been the case for the 27 patients identified as well as the 21 otherwise eligible morbidly obese patients who were not approached at their physician's directive. Indeed, these physicians' concerns were astute; increased body mass index was subsequently found to be an

Table 3 Factors independently associated with physicians declining: hierarchical regression

	Odds ratio (95 % CI)	*p* value
Years of ICU research experience of the lead consenting research personnel		
0 years versus >10 years	10.47 (2.19, 50.02)	0.010
>0–10 years versus >10 years	1.72 (0.61, 4.84)	
Center size (beds screened for possible PROTECT patients)		
15–20 beds versus <15 beds	1.63 (0.51, 5.19)	0.162
21–25 beds versus <15 beds	2.26 (0.55, 9.27)	
>25 beds versus <15 beds	3.96 (1.07, 14.66)	
Unit type		
Open versus closed	4.26 (1.27, 14.34)	0.020
Formal trials group affiliation		
Yes versus no	3.35 (0.98, 11.41)	0.054
Year of PROTECT		
Year 1 versus pilot	0.67 (0.21, 2.10)	0.005
Year 2 versus pilot	0.67 (0.22, 2.06)	
Year 3 versus pilot	0.32 (0.10, 1.02)	
Year 4 versus pilot	0.42 (0.13, 1.29)	

In this table, we present factors independently associated with physicians declining to allow their eligible patients to be enrolled derived from hierarchical regression analysis whereby physician refusal is the outcome. Center was entered as a random effect. The *p* values refer to the overall variable and test the null hypothesis that the odds ratios of physician refusal are the same for all levels of the variable

independent predictor of leg DVT [24], PE [25] and VTE [26] in this large trial database. Importantly, physicians may refuse enrollment based on their knowledge of emerging literature, such that monitoring such physician rationale may sometimes prompt modification of trial exclusion criteria.

Other reasons for physicians declining enrollment may be modifiable. For example, in 11.5 % of cases, physicians preferred a specific thromboprophylaxis regimen, of which some consisted of one of the two options being evaluated in the trial. It is possible that additional physician education about the scientific rationale, existing research, objective, methods, community equipoise, peer-review funding and REB endorsement may mitigate this reason for declining enrollment. On the other hand, some physicians prefer to prescribe according to their habits or preference. Some such physicians may be implicitly indicating that they know what is best for that patient, or they believe that they know the answer to the trial question or that they don't wish to support the question. Others may be uncomfortable caring for patients in a research protocol, particularly if the trial is blinded, and this may not be modifiable. Physicians infrequently cited general discomfort with research as a reason for declining patient enrollment.

Patients were excluded from this thromboprophylaxis trial if therapeutic anticoagulation was indicated. There were 13 patients whose physicians disagreed with patient enrollment because they anticipated possible therapeutic anticoagulation in the near future; inclusion of these patients would have been undesirable if their study drug exposure was of very short duration.

We acknowledge the key role of trained professional research personnel who screen patients and obtain informed consent for participation. Hierarchical regression identified that physicians were less likely to agree to have their patients approached for research when interacting with less experienced research personnel. This may reflect more careful patient selection by seasoned personnel or may reflect an ICU environment with long-standing research participation. Physicians who declined were more likely to practice in open than closed units, perhaps because the most responsible physicians for ICU patients in open units are generally not intensivists, and may be uncomfortable with ICU protocols. Physicians declined less often as the trial continued compared to the pilot phase, perhaps reflecting increasing comfort or protocol familiarity annually.

Obtaining informed consent for the majority of patients eligible for a critical care trial is essential to the timely, efficient identification of interventions that are effective, as well as those that have no effect or induce harm. When a REB approves a trial, it acknowledges that on balance, there is insufficient clinical research evidence to select one trial intervention over the other. Following REB approval, trial conduct assumes institutional commitment to answering the research question and that discussions have occurred to engage physicians, ensure trial participation and endorse (or at least not prohibit) patient enrollment. Segelov and colleagues wonder whether physicians who choose to treat trial-eligible patients off protocol when an appropriate, approved trial is available should be interviewed to encourage accountability for their action in the same rigorous way that it is demanded of those entering patients in the trial [27]. Interviewing could be helpful to gain deeper insights about physician rationale; indeed, better understanding was the impetus for us to record reasons for physicians declining.

As others have noted, the ethics of not enrolling eligible patients into an established, ethically approved clinical trial is rarely discussed [27]. These reasons may reflect legitimate safety concerns, although a systematic review of 31,140 patients treated in randomized trials and 20,380 comparable patients receiving similar treatment outside trials found similar outcomes, suggesting, among, other conclusions, that trials have appropriate exclusion criteria [28]. Nevertheless, assuming valid trial inclusion and exclusion criteria, bias could be introduced when physicians decline enrollment of otherwise trial-eligible patients, potentially compromising the external validity of trial results. We believe that selection bias is unlikely in PROTECT because of the low proportion of patients not enrolled for this reason, relative to patients enrolled overall, and the diverse rationales offered rather than one dominant reason.

These data reflect the conduct of one trial as a prototype to approach this issue. This study is limited in that we did not conduct semi-structured interviews to explore physician discomfort. Reasons were those stated in real time by physicians and documented by research coordinators, and could be influenced by social desirability bias. The probability of physicians refusing would likely be greater in a trial enrolling high-risk populations, testing unfamiliar or high-risk interventions, and in centers without well-established research infrastructure. Non-primary physicians obtained consent in 24 % of centers in this trial; the probability of attending physicians declining might have been lower if all centers had approached patients by their non-primary physician (to avoid therapeutic misconception). The taxonomy of reasons for physicians declining might differ if less preparatory research is conducted, if community equipoise does not exist, if physician research experience is modest or if the trial tests different interventions.

Strengths of this study include the prospective design, extending prior work from retrospective self-reported physician surveys [29] and focus on this topic for which evidence is sparse, but beginning to emerge [14]. Data collection was longitudinal rather than cross sectional, nested within a recent clinical trial to obtain representative results over the duration of an internal pilot and 4 years of

Table 4 Author recommendations for preventing and responding to physicians who decline to enroll eligible patients into randomized trials

Trial phase	Recommendations
Before the trial begins	• Incorporate physician feedback into trial enrollment criteria • Consider pilot trials (for many reasons, one of which is to understand physician decline rates and reasons) • For pragmatic trials, maximize physician flexibility regarding usual care practices and co-interventions that are not integral to the study question • Document community equipoise through formal or informal surveys or observational studies • Thoroughly address safety concerns (e.g., handling of adverse events) and external oversight (e.g., Data Monitoring Committee) • Visit physicians in participating centers to (1) Highlight the importance of the trial question to their practice (2) Address questions and concerns (3) Educate about enrollment criteria, trial impact on other aspects of practice, community equipoise (4) Underscore safety issues and research oversight (5) Highlight ethical aspects of the decision to enroll patients in ongoing funded, peer-reviewed, research ethics board-approved trials • Train research personnel on optimal methods to approach bedside physicians (e.g., considering enrollment contraindications, patient prognosis, family stress) • Promote mentoring of junior research personnel by more experienced personnel before and throughout the trial
During recruitment: general strategies	• Seek new research that may modify the suitability of enrollment criteria • Communicate with each participating center about trial progress and changes to enrollment criteria • Listen and respond promptly to local physicians' concerns, ensuring that a site investigator and principal investigator are available • Disclose any emerging safety concerns with all site investigators and physicians • Provide ongoing feedback to research personnel on optimal methods to approach bedside physicians
During recruitment: responding to physicians who decline to enroll eligible patients	• Track and analyze the rates and reasons for physicians declining to allow patients to be approached • Each time a physician declines, review and decide on course of action (e.g., augment education, consider modifying enrollment criteria if appropriate, discuss concerns directly with physician, site investigator and research personnel) • At investigators' meetings, share scenarios when physicians decline, disclose physician decline rates in the context of eligible non-randomized rates and brainstorm solutions
After the trial is over	• Publish the rates and reasons for physicians declining to allow their patients to be enrolled to aid with interpreting the generalizability of trial results • Report this in the context of all eligible non-randomized patients • Share lessons learned with other trialists

In this table the authors make some recommendations about responding to physicians declining to allow their patients to be approached for enrollment. These are staged according to various phases of a trial. These strategies may represent a good return on investment for the effort and cost expended to minimize physician decline rates

multicenter recruitment. We conducted a multilevel analysis of possible predictors, including features of the lead research personnel, center and phase of the trial. Representation from a diverse group of 67 ICUs in six countries enhances the generalizability of the findings.

Although physicians are free to disagree with approaching eligible patients or family members for possible trial enrollment, we outline several recommendations that may decrease the probability of this occurrence (Table 4). These recommendations arose during initial discussion among three authors (DJC, YA, NKJA), with refinement by all authors and consensus. We believe that broad input into trial design should incorporate the views of front-line physicians regarding inclusion and exclusion criteria. For pragmatic trials [30], it may be helpful to maximize physician flexibility regarding usual co-interventions when suitable. We recommend widespread education before trials begin to educate clinicians about research informing the trial design. We recommend that during recruitment, the rates and reasons for physicians declining to allow their patients to be approached should be tracked, analyzed and acted upon as needed so that we can be responsive to bedside concerns, learn about patient prognosis, possible medical contraindications and unappreciated family stress, educate physicians about evidence bearing on enrollment, offer patients research opportunities where suitable, enlighten trialists about real and perceived trial safety issues, and enhance recruitment

efficiency. Finally, we recommend publishing these figures to aid interpretation of trial results.

Conclusions

In an international randomized thromboprophylaxis trial, we found that the rate of physicians declining to allow their patients or their families to be approached for consent by research personnel despite meeting all trial enrollment criteria was relatively low. Reasons for declining were variable but included concerns about bleeding or dose appropriateness for morbidly obese patients and preference for a specific thromboprophylaxis regimen. Trialists should prospectively collect data on such reasons during enrollment to refine enrollment criteria if appropriate, provide ongoing communication about eligibility and develop strategies to enhance recruitment efficiency.

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Conflicts of interest The investigators declare that they have no conflict of interest.

Ethics statement This study was approved by the Research Ethics Board in each center. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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