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Detailed assessment of benefits and risks of retrievable inferior vena cava filters on patients with complicated injuries: the da Vinci multicentre randomised controlled trial study protocol

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ABSTRACT

Introduction Retrievable inferior vena cava (IVC) filters have been increasingly used in patients with major trauma who have contraindications to anticoagulant prophylaxis as a primary prophylactic measure against venous thromboembolism (VTE). The benefits, risks and cost-effectiveness of such strategy are uncertain.

Methods and analysis Patients with major trauma, defined by an estimated Injury Severity Score >15, who have contraindications to anticoagulant VTE prophylaxis within 72 hours of hospitalisation to the study centre will be eligible for this randomised multicentre controlled trial. After obtaining consent from patients, or the persons responsible for the patients, study patients are randomly allocated to either control or IVC filter, within 72 hours of trauma admission, in a 1:1 ratio by permuted blocks stratified by study centre. The primary outcomes are (1) the composite endpoint of (A) pulmonary embolism (PE) as demonstrated by CT pulmonary angiography, high probability ventilation/perfusion scan, transoesophageal echocardiography (by showing clots within pulmonary arterial trunk), pulmonary angiography or postmortem examination during the same hospitalisation or 90-day after trauma whichever is earlier and (B) hospital mortality; and (2) the total cost of treatment including the costs of an IVC filter, total number of CT and ultrasound scans required, length of intensive care unit and hospital stay, procedures and drugs required to treat PE or complications related to the IVC filters. The study started in June 2015 and the final enrolment target is 240 patients. No interim analysis is planned; incidence of fatal PE is used as safety stopping rule for the trial.

Ethics and dissemination Ethics approval was obtained in all four participating centres in Australia. Results of the main trial and each of the secondary endpoints will be submitted for publication in a peer-reviewed journal.

Trial registration number ACTRN12614000963628; Pre-results.

Strengths and limitations of this study

► This study is conducted as a phase IIb multicentre randomised controlled trial (RCT) concerning the benefits and risks of early use of inferior vena cava (IVC) filters in patients with major trauma who have contraindications to anticoagulant prophylaxis against venous thromboembolism (VTE). It will provide the much needed important information to clinicians about the best strategy to reduce the burden of VTE in patients with major trauma.

► In addition to clinical effectiveness, this study will also examine the (A) mechanical complications of IVC filters, (B) bleeding complications, (C) cost-effectiveness and (D) long-term health outcomes after using IVC filters as a primary VTE prophylactic measure in patients with major trauma.

► Blinding of the treating clinicians to treatment allocation is deemed to be impossible; centralised web-based randomisation to ensure adequate allocation concealment, and strict guidelines on when and how often a CT pulmonary angiography (CTPA) should be performed to detect mild or early pulmonary embolism for the study patients. This study design will (A) reduce outcome detection bias, (B) avoid unnecessary radiation from routine CTPA for asymptomatic study patients and (C) ensure the clinical safety of the patient allocated to the control group.

► The study is not powered to detect a small to moderate difference in 90-day mortality (<9%); but the results of this study will inform us whether a phase III RCT is necessary to confirm the role of IVC filters—as a primary VTE prophylactic device—for patients with major trauma.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary

embolism (PE), is one of the most preventable causes of death and morbidity in hospitalised patients.[1 2] VTE accounted for over 14 000 hospitalisations (or 70 per 100 000) and 5000 deaths in Australia in 2008[3]; and according to the New South Wales Clinical Excellence Commission, a large number of hospital-associated VTE (n=2229) including fatal PE were identified in 2012 and 2013. The total cost of VTE per person per annum, including loss in productivity, was estimated to be over US$1.47 million and the total cost of VTE for Australia in 2008 was $A3.9 billion.[3] The total burden of VTE in the European Union countries exceeded 1.6 million events, comprising 0.7 million cases of DVT, 0.4 million cases of non-fatal PE and 0.5 million VTE-related deaths.[4] The majority of patients with VTE-related deaths were untreated with VTE prophylaxis and VTE was not diagnosed before postmortem; only 7% of deaths occurred in those on prophylaxis or therapy.[5] Studies of routine screening of hospital patients for asymptomatic DVT have shown that VTE is common but clinically silent in a high proportion. As such, VTE prophylaxis is of paramount importance in reducing mortality and morbidity of VTE. Although underutilisation of VTE prophylaxis in many situations has improved with education and use of electronic prescription alert systems, recent studies show that a significant proportion of hospitalised patients, at high risk for VTE, including those who are critically ill or injured, do not receive VTE prophylaxis.[6 7]

The incidence of asymptomatic VTE, including PE, in critically ill or injured patients is very high despite anticoagulant prophylaxis.[8] In one cohort study, up to 10% of the patients already had unsuspected DVT at the time of intensive care unit (ICU) admission.[9] The American College of Chest Physicians guidelines recommend that all ICU patients should be assessed for their risk of VTE, and that most should receive VTE prophylaxis on admission to the ICU.[10] Both the National Quality Forum and The Joint Commission (the organisation that accredits American hospitals) also recommend that the proportion of patients who receive VTE prophylaxis or have documentation about why VTE prophylaxis is not given within 24 hours of ICU admission, should be used as a performance indicator.[2 11] However, many clinicians perceive the risk of bleeding as more important than the risk of VTE, leading to a delay or even omission of VTE prophylaxis in a high proportion of patients.[12–14] Observational studies have suggested that a delay of more than 1–3 days in initiating VTE prophylaxis is associated with a threefold increased risk of VTE and possibly also mortality in critically ill and injured patients.[15–18] Early initiation of VTE prophylaxis using a multimodal approach, including the use of mechanical VTE prophylaxis for many critically ill and injured patients, may be the most effective way to reduce the disease burden of VTE in the critically ill and injured patients.[19 20]

Injury is a leading cause of death among young people and was responsible for two-thirds of deaths of young Australians in 2005 despite the injury death rate falling by 50% between 1986 and 2005.[21] Guidelines from the American College of Chest Physicians have suggested that subcutaneous low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (UFH) should be used for thromboprophylaxis in patients at high risk of VTE including patients with major trauma.[22] Although LMWH may be more efficacious than UFH, and there was no difference in major bleeding in patients without obvious contraindications to anticoagulants,[23] the clinical concern about excessive haemorrhage persists especially for patients who have significant risk of bleeding after trauma. The incidence of asymptomatic PE between 3 and 7 days after moderate to major trauma is extremely high (24%), despite LMWH or UFH prophylaxis,[8] and use of pneumatic lower limb compression devices or UFH prophylaxis alone may not be completely effective in preventing VTE.[8 22 24] Indeed, fatal PE is the third leading cause of death in patients who survive the first 24 hours after major trauma.[25] As such, retrievable inferior vena cava (IVC) filters have been increasingly used in many patients with trauma.[26 27]

PRELIMINARY EVIDENCE TO SUPPORT THE ROLE OF IVC FILTERS IN MAJOR TRAUMA

IVC filters are, however, expensive ($A>3000 per filter without considering radiology costs), invasive and associated with significant complications, including erosion of the IVC, inducing thrombosis either above or below the filter, migration of the filter to the right atrium, and tilting or malpositioning of the filter resulting in ineffective filtering of emboli and fatal PE.[28–30] Despite the risk of having significant complications and evidence to support its cost-effectiveness from randomised controlled trials (RCTs) or meta-analyses is sparse,[31–35] IVC filters are increasingly used in many trauma centres worldwide.[36] In 2007, the US market for IVC filters was valued at under $200 million, with expected growth to top $300 million in 2012.[37] The most appropriate patients who will benefit from an IVC filter and the optimal time to insert and remove a retrievable IVC filter in patients after major trauma remains uncertain.[38–40] Confounding these issues further, some retrievable IVC filters are not removed (>10% for many centres) which may induce long-term venous thromboembolic or mechanical complications especially if the filter is left in situ for longer than 60–90 days.[41 42]

Currently the use of different strategies in preventing VTE after major trauma remains very controversial,[22 43–50] and the practice of thromboprophylaxis, especially in patients who have significant risk of bleeding within the first week of trauma, varies considerably between different trauma centres.[25] The optimal method of thromboprophylaxis in patients after major trauma at risk of bleeding remains highly uncertain.

Fatal PE is an important patient-centred outcome after major trauma.[51] It has been reported to occur at a frequency between 0.4% and 4.2% after major trauma.[24 52 53] It has

been argued that thromboprophylaxis may not be cost-effective in trauma patients,[35] because fatal PE occurs more often in patients who have more severe traumatic injuries and some of these patients may die with PE, instead of from PE. Our recent study did, however, suggest that fatal PE is a preventable disease, with an attributable mortality of 50% (95% CI 36% to 62%), and it accounts for about 12% of all deaths after major trauma.[54 55] Furthermore, our recent multicentre observational studies showed that acute PE is a major cause of morbidity and mortality in critically ill patients,[56] and omission of early VTE prophylaxis in critically ill patients, in particular after multiple trauma, either without clinical reasons (relative risk of 1.66, 95% CI 1.22 to 2.25; absolute increase in risk 3.9%, 95% CI 2.2 to 5.6) or due to contraindications from increased bleeding risk, is associated with a substantial increased risk of mortality.[18]

Retrievable IVC filters have been used in our patients with trauma in Western Australia (WA) since 2007, and in the years 2007 and 2008, 7.4% of all patients with trauma received a retrievable IVC filter. During these 2 years, the incidence of radiological or postmortem examination confirmed symptomatic PE occurred at 3% of all hospitalised patients with trauma, and this risk increased substantially to about 10% if only patients with trauma who had an Injury Severity Score (ISS) >15 (see online supplementary appendix 1) were considered. Since we noted that fatal PE is likely preventable with an IVC filter, retrievable IVC filters have been increasingly used as a primary thromboprophylaxis for our patients with trauma who have contraindications to pharmacological thromboprophylaxis (>70–100 per annum in WA), very similar to many trauma centres.[26] The preliminary findings from our most recent observational study showed that retrievable IVC filters appeared to be very effective in reducing fatal PE (none observed for all 223 patients who received an IVC filter). The use of IVC filters was still associated with substantial risks of lower or upper limb VTE (16%) and mechanical complications (12%) including adherent filter (5%) and IVC filter occlusion due to thrombus (4%), despite a high filter retrieval rate (87%) through a centralised protocol and process.[42] Evidence suggested that if IVC filters are applied to all patients with major trauma, the estimated number of IVC filters needed to prevent one fatal PE is relatively large (mean 125, 95% CI 100 to 167)[54] and may not be cost-effective.

Because retrievable IVC filters are relatively expensive and invasive as a preventive strategy, it is more likely to be cost-effective if it is reserved for patients who have a very high risk of PE and, at the same time, the injuries are still compatible with survival when use of pharmacological thromboprophylaxis is contraindicated.[54] According to the Trauma Embolic Scoring System (TESS) (see online supplementary appendix 2),[57 58] the TESS score for this type of patients would be likely greater than 10 with an estimate risk of symptomatic VTE between 10% and 20% even when a proactive approach to detect VTE is not adopted. Even though many patients with major trauma will have deranged coagulation profiles which are considered as contraindicated to receive anticoagulant prophylaxis, their propensity to develop VTE does not appear to be different from those without such acquired coagulopathy.[59–61] This group of patients with trauma will serve as the best candidates to assess the cost-effectiveness of IVC filters and will form the study population of this planned RCT in which we will adopt a proactive approach to detect VTE in our study patients (for details see below).

Primary aims of the study

1. To assess whether the early use of IVC filters as primary VTE prophylaxis can reduce the incidence of symptomatic PE in patients who are at high risk of developing DVT and PE after major trauma who also have contraindications to anticoagulant VTE prophylaxis.
2. To assess the cost-effectiveness of IVC filters in preventing PE after major trauma in this cohort of patients.

Secondary aims of the study

1. To assess whether IVC filters are effective in reducing symptomatic PE in patients who do not receive pharmacological DVT prophylaxis within the first 7 days of major trauma.
2. To assess the incidence of complications of IVC filters in patients with major trauma, including whether IVC filter will increase the risk of symptomatic and asymptomatic DVT in the lower limbs.
3. To assess the risk factors associated with DVT and PE after an IVC filter placement.

METHODS AND ANALYSIS

Protocol version 1.1 Feb 2015, no protocol amendment since initiation of the trial.

Randomisation process

This is a pragmatic four-centre population-based phase IIb randomised controlled parallel-design study comparing the benefits, harms and cost-effectiveness of IVC filters in patients with major trauma at high risk of developing DVT and PE but with contraindications to pharmacological VTE prophylaxis (see figure 1).

Written informed consent will be obtained either from each patient or their next of kin (or person responsible for the patient) for participation in the trial including use of long-term health outcome data through the data linkage unit; and for those who are allocated to the IVC filter group, separate clinical consents for IVC filter insertion and removal will be obtained. Randomisation will be conducted by a random number generator, in permuted blocks stratified by centre, and allocation concealment will be maintained by a web-page randomisation and allocation portal (http://davinci.statisticalrevelations.com.au/). Blinding of the patients and attending clinicians is not intended or possible, but the data analyst will be
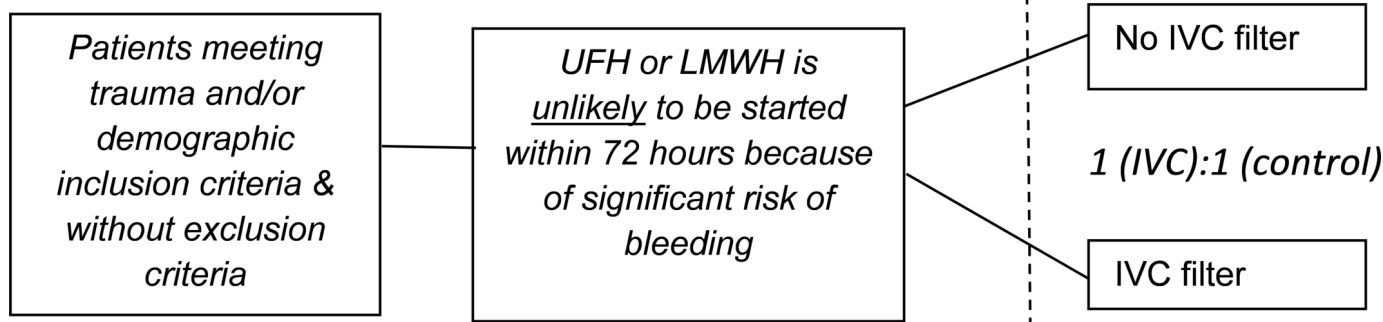
Figure 1 Flow chart showing inclusion and equal allocation of participants to receive an IVC filter or no IVC filter for thromboembolic prophylaxis. IVC, inferior vena cava; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

blinded to the study allocation. All VTE outcomes will be adjudicated by radiologists independent of the trial to reduce detection bias. Deidentified data will be entered into the password-protected web portal of the trial (http://davinci.statisticalrevelations.com.au/); and only the chief investigators and members of the data monitoring and safety committee (DMSC) would have access to outcome data of the participants. As in May 2017, the trial has reached >80% enrolment target.

Inclusion criteria

Patients will be eligible for the trial (1) if they are considered to have contraindications to pharmacological thromboprophylaxis within 72 hours of hospital admission by their attending intensivist, trauma or spinal surgeon or neurosurgeon; and (2) ISS >15 (see online supplementary appendix 1). A list of contraindications to pharmacological VTE prophylaxis is described in the case record form (CRF) and web data portal.

Exclusion criteria

1. severe head or systemic injury where death within 48–72 hours is expected;
2. attending clinicians judge that patients are at low risk of bleeding, without contraindications to pharmacological VTE prophylaxis (as listed in the CRF) and can receive pharmacological thromboprophylaxis within 3 days after major trauma;
3. patients who have CT evidence of PE on admission to the hospital after trauma;
4. patients who have been treated with full systemic anticoagulation by warfarin, UFH or LMWH for pre-existing medical disease (eg, patients with chronic atrial fibrillation requiring systemic anticoagulation) until admission due to trauma;
5. pregnancy;
6. aged <18 years old;
7. the IVC filter cannot be inserted within 72 hours of trauma admission.

Study intervention and follow-up

In this study, the types of retrievable IVC filters used will be determined by the usual standard practice of the study centres, and will be inserted by a trained interventional radiologist either in the X-ray department or ICU. Dates of insertion and removal of the IVC filter will be recorded. All IVC filters will be removed before hospital discharge or 90 days after the trauma, unless the clinicians believe that the IVC filter should be left for longer than this predefined period due to a strong clinical indication. The reasons for leaving the IVC filters will be recorded for those that are left in situ for >90 days. Currently, there is a WA statewide standardised protocol to ensure all retrievable IVC filters are removed by the Department of Radiology within 60–90 days. All complications related to IVC filters will be recorded (eg, migration/displacement, caval occlusion) and managed according to the best clinical practice available. Mechanical complications related to the IVC filters are considered as severe adverse events (SAEs). All retrieved filters will be examined by the Department of Medical Engineering and Physics at Royal Perth Hospital for filter fractures, clot loads and mechanical properties (spring load of the 'legs', hardness of the alloy, chemical composition) as a substudy. All trauma deaths including those included in this study will be referred to the Coroner's office for postmortem examination to exclude fatal PE. Clinical follow-up will be maintained up to day 90 after the injury (or hospital discharge whichever is longer) and subsequent further long-term follow-up will be achieved using data linkage of WA statewide health data for patients recruited in WA.

We adopt a proactive approach to detect asymptomatic DVT and symptomatic PE events in this study. Routine compression ultrasonography of the thighs and calf of all patients will be performed at 2 weeks after study enrolment, or later if it is not possible at that time (eg, external fixation of lower limb fractures). Although routine lower limbs ultrasonography screening may reduce the risk of PE in seriously injured patients,[62] it may not be cost-effective and is currently not used in the study centres nor most trauma centres in Australia.[63]

Imaging techniques used to diagnose PE and when this will be performed is at the discretion of the attending clinicians according to their clinical suspicion for PE. However, CT pulmonary angiography (CTPA) is considered mandatory if one or more of the following conditions

or situations occur unless a prior CTPA has already been performed within the last 3 days:

1. hypotension with systolic blood pressure <90 mm Hg for longer than 30 min;
2. unexplained chest pain;
3. hypoxia requiring ≥6 L/min of oxygen or 50% inspired oxygen to maintain arterial oxygen saturation >94%.

Routine imaging to screen for asymptomatic PE is not used in this study. Routine lower limb venography will not be used. D-dimers also will not be used to screen for DVT or PE in this study because of its very low specificity and positive predictive value in trauma patients.

Concurrent treatments

The study is not blinded and attending clinicians should initiate pharmacological VTE prophylaxis as appropriate or as soon as possible. The trial recommends initiation of pharmacological VTE prophylaxis within 7 days of injury regardless of whether the patients have received an IVC filter. Because this is a pragmatic study, the decisions about when to initiate UFH or LMWH and the doses needed after study enrolment are at the discretion of the attending clinicians and the data will be recorded. Intravenous low-dose heparin (<800 units/hour) as an anticoagulant for continuous renal replacement therapy is not contraindicated in the study, but patients who require full systemic anticoagulation by either UFH or LMWH before randomisation are not eligible for the study (eg, patients with atrial fibrillation requiring systemic anticoagulation). Antiplatelet agents for new or pre-existing medical conditions (eg, coronary artery disease, stroke, vertebral artery dissection) are permissible.

All patients will receive mechanical DVT prophylaxis, in the form of lower limb compression devices, to the leg that is not injured. There is no restriction on attending clinicians to insert an IVC filter for VTE prophylaxis for patients randomised to the control group if there is a well-established indication to do so (eg, development of VTE with absolute contraindications to initiate systemic anticoagulation according to the treating clinicians) but these data will be recorded.

Primary endpoints

1. The composite endpoint of (A) PE as demonstrated by CTPA, high probability ventilation/perfusion scan, transoesophageal echocardiography (by showing clots within pulmonary arterial trunk), pulmonary angiography or postmortem examination during the same hospitalisation or 90-day after trauma whichever is earlier; and (B) hospital mortality.
2. The total cost of treatment including the costs of an IVC filter, total number of CT and ultrasound scans required, length of ICU and hospital stay, procedures and drugs required to treat PE or complications related to the IVC filter.

Secondary endpoints

1. All complications related to an IVC filter, including displacement of the filter, erosion of IVC, inducing lower limb DVT and failure to remove the IVC filter in the recommended period.
2. Risk of fatal PE and non-fatal PE in patients who do not receive any pharmacological VTE prophylaxis within 7 days of major trauma.
3. Hospital mortality or 90-day mortality whichever is earlier.
4. Risk of bleeding after study enrolment

   A. Major bleeding—contributing to death, at a critical site (eg, intracranial, spinal, epidural, airway haemorrhage), requiring transfusion (of either red blood cells, platelets or fresh frozen plasma) or a reduced haemoglobin >2 g/dL within 24 hours.
   B. Non-major but clinically relevant bleeding—requiring new medical interventions (eg, gastrointestinal endoscopy, local or systemic drugs to control bleeding).
   C. Minor bleeding—not requiring new medical intervention (eg, mild haematuria, coffee-ground nasogastric aspirate, skin bruises).

Participant withdrawal criteria and management

A. side effects of an IVC filter are detected and removal of the filter is deemed to confer more benefits than harms by the attending clinicians, but all complications related to the IVC filter and reasons for removal of the filter will be recorded and all patients will be followed up for at least 90 days after enrolment (or hospital discharge whichever is longer) and further follow-up on health outcomes is achieved by data linkage;
B. no participants withdrawing from the trial will be replaced and the proposed sample size has allowed for 20% dropout or crossover between the two treatment arms.

Data collection (table 1)

The following data will also be obtained for all patients enrolled in the study and these characteristics will be used to generate a TESS to ensure that the randomisation is balanced, in terms of VTE risk, between the two groups (see online supplementary appendix 2).

1. demographics;
2. previous history of DVT/PE (see online supplementary appendix 3);
3. comorbidity including the history of smoking and drug use before the injury;
4. injury pattern and severity including ISS (see online supplementary appendix 1);
5. neurological signs and CT findings on admission for patients with head injury;
6. body mass index;

Table 1 Baseline and clinical data collected until day 90 after enrolment for patients included in the trial

Baseline characteristics	Concurrent interventions and investigations	Bleeding and transfusion outcomes	VTE and other important clinical outcomes
Demographic factors	Total number of CTPA or echocardiography, V/Q perfusion scan	Major bleeding—contributing to death, at a critical site (eg, intracranial, spinal, epidural, airway haemorrhage), requiring transfusion (of either red blood cells, platelets, or fresh frozen plasma) or a reduced haemoglobin >2g/dL within 24hours	Occurrence of symptomatic PE or DVT and duration between hospital admission and occurrence of VTE, including fatal PE in the postmortem examination
Comorbidities including previous history of VTE and body mass index	The duration between hospital admission and the first attempt to diagnose PE by any form of imaging modality	Non-major but clinically relevant bleeding—requiring new medical interventions (eg, gastrointestinal endoscopy, local or systemic drugs to control bleeding)	Occurrence of asymptomatic DVT on lower limb screening ultrasound within 14 days of study enrolment
Relevant medication history including antiplatelet agents, hormonal replacement therapy or oral contraceptive pills for female patients	Duration between hospital admission and the time to start the first dose of antithrombotic prophylaxis	Minor bleeding—not requiring new medical intervention (eg, mild haematuria, coffee-ground nasogastric aspirate, skin bruises)	ICU, hospital and 90-day mortality (if length of hospital stay is >90days)
Pattern of injuries, ISS and CT brain findings including Marshall CT brain grading	Whether full anticoagulation is used, the indications for such therapy and the duration between hospital admission and full systemic anticoagulation	Total amount of allogeneic blood products needed within 90days after enrolment	Length of ICU and hospital stay. For patients with ICU readmission, the reasons for ICU readmission will be noted and the total number of ICU days of all ICU admission during the same hospitalisation will be calculated
The type of the IVC filter used for the study patients	Whether UFH or LMWH is used for DVT/PE prophylaxis, the dose used, and duration between hospital admission and initiation of anticoagulant prophylaxis		Occurrence of acute kidney injury requiring renal replacement therapy
	Whether sequential lower limb compression device is used and the duration between hospital admission and the time this device is commenced and the total time of use of this type of device		Total length of mechanical ventilation, including invasive and non-invasive ventilation
	Use of femoral vein as an access for central venous catheter and dialysis catheter		Use of all forms of vasopressor/inotropic support and the total days of requiring such support after study enrolment
	Use of intracranial pressure monitor		Duration of filter left in situ and all complications related to IVC filters (eg, migration/displacement, caval occlusion, filter thrombosis)

Continued

Table 1 Continued		
Baseline characteristics	**Concurrent interventions and investigations**	**Bleeding and transfusion outcomes**
		VTE and other important clinical outcomes
		The total number of operations required after study enrolment, and reasons for the operations and the operative diagnoses
		Long-term VTE and complications related to the use of IVC filters beyond day 90 (up to 5 years) using data linkage techniques

CTPA, CT pulmonary angiography; DVT, deep vein thrombosis; ICU, intensive care unit; ISS, Injury Severity Score; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; V/Q, ventilation/perfusion; VTE, venous thromboembolic events.

7. medications before and after the injury: antiplatelet agents, hormonal replacement therapy or oral cntraceptive (OC) pills for female patients;

8. the duration between injury and hospital admission;

9. the duration between hospital admission and IVC filter insertion for patients who are randomised into IVC group and also for patients who require IVC filter in the control group due to clinical reason (ie, crossed over for clinical reason such as DVT but with active contraindication for anticoagulation);

10. total number of CTPA or other imaging modalities used (eg, echocardiography, ventilation / perfusion (V/Q) or perfusion scan, and so on);

11. the duration between hospital admission and the first attempt to diagnose PE by any form of imaging modality;

12. duration between hospital admission and the time to start the first dose of antithrombotic prophylaxis;

13. whether full anticoagulation is used, the indications for such therapy and the duration between hospital admission and full systemic anticoagulation;

14. whether UFH or LMWH is used for DVT/PE prophylaxis, the dose used, and duration between hospital admission and initiation of pharmacological thromboprophylaxis;

15. whether sequential lower limb compression device is used and the duration between hospital admission and the time this device is commenced and the total time of use of this type of device;

16. occurrence of DVT or PE and duration between hospital admission and occurrence of DVT/PE;

17. occurrence of acute kidney injury requiring renal replacement therapy;

18. use of femoral vein as an access for central venous catheter and dialysis catheter;

19. bleeding complications and interventions required for all bleeding complications after study enrolment as defined in the secondary endpoints;

20. ICU, hospital and 90-day mortality (if length of hospital stay is >90 days);

21. length of ICU and hospital stay: for patients with ICU readmission, the reasons for ICU readmission will be noted and the total number of ICU days of all ICU admission during the same hospitalisation will be calculated;

22. total length of mechanical ventilation, including invasive and non-invasive ventilation;

23. use of all forms of vasopressor/inotropic support and the total days of requiring such support after study enrolment;

24. use of intracranial pressure monitor;

25. the total number of operations required after study enrolment, reasons for the operations and the operative diagnoses; in addition, the number of surgical procedures that require cessation of heparin and the duration of withholding DVT prophylaxis each time will be recorded;

26. the type of the IVC filter used for the study patients and dates of insertion and removal of the IVC filter; for IVC filters that are left in situ for >90 days, the reasons for leaving the IVC filters will be recorded;

27. proportion of IVC filters found to have clots after being retrieved;

28. all complications related to IVC filters (eg, migration/displacement, caval occlusion); mechanical complications related to the IVC filters are considered as SAEs;

29. we will also use the unique data linkage unit in WA to evaluate hospital readmissions due to all causes, VTE, complications related to the IVC filters and long-term survival at about 3–5 years after study enrolment as a substudy of this randomised controlled study.

Sample size calculation

Although IVC filters are increasingly used for thromboprophylaxis in many patients with trauma, their clinical effectiveness has never been well documented. They are invasive, expensive and have significant complications some of which are life threatening. It is important to demonstrate clinical superiority before they are widely used in patients who are already at risk of mortality and, hence, a superiority trial rather than a non-inferiority trial is preferred. We are planning a study of independent treatment cases and placebo controls with one control per case. The incidence of asymptomatic PE between 3 and 7 days after moderate to major trauma is extremely high (24%) despite LMWH or UFH prophylaxis. Prior data indicate that the PE rate among patients who are at high risk of VTE without thromboprophylaxis (similar to our control patients) is >0.09 (or 9%). The relatively high incidence of PE is expected because (A) we use a proactive approach to detect mildly symptomatic PE, and (B)

we have chosen the group of patients with trauma who are at extreme risk of VTE and, at the same time, cannot receive pharmacological thromboprophylaxis. The TESS score of these patients is expected to be >10. Evidence suggested that IVC filters are highly effective in reducing PE. If the PE rate of the intervention group is close to 0.5%, we will need to study 97 experimental subjects and 97 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8 (or 0.9 if the baseline risk of PE is 10%). We assume there will be a small proportion of patients who will have study intervention crossed over between the two groups. Therefore, the total sample size of this study is 240 (120 per group), allowing up to 20% of the study subject crossed over between the control and intervention groups without affecting the power of the study (see figure 2). If an IVC is associated with an increased risk of lower limb DVT, this sample size will also have >80% power to detect an increased risk of DVT due to the IVC filter from 10% to 25%.

Data analysis plan

An interim analysis is not planned because this will compromise the power of the proposed study. However, fatal PE and SAEs will be reported to the ethics committee and monitored by an independent DMSC comprising two members who have experience in conducting clinical trials related to trauma and critical illness. Statistically, at least four fatal PEs all occurring only in the control group of 100–120 patients are needed to conclude that without IVC (or control group) would lead to an increased risk of fatal PE in the study population and this will terminate the entire trial before the completion of the study with the proposed sample size (n=240). Any significant side effects experienced by participants of the trial will be addressed according to the standard clinical management
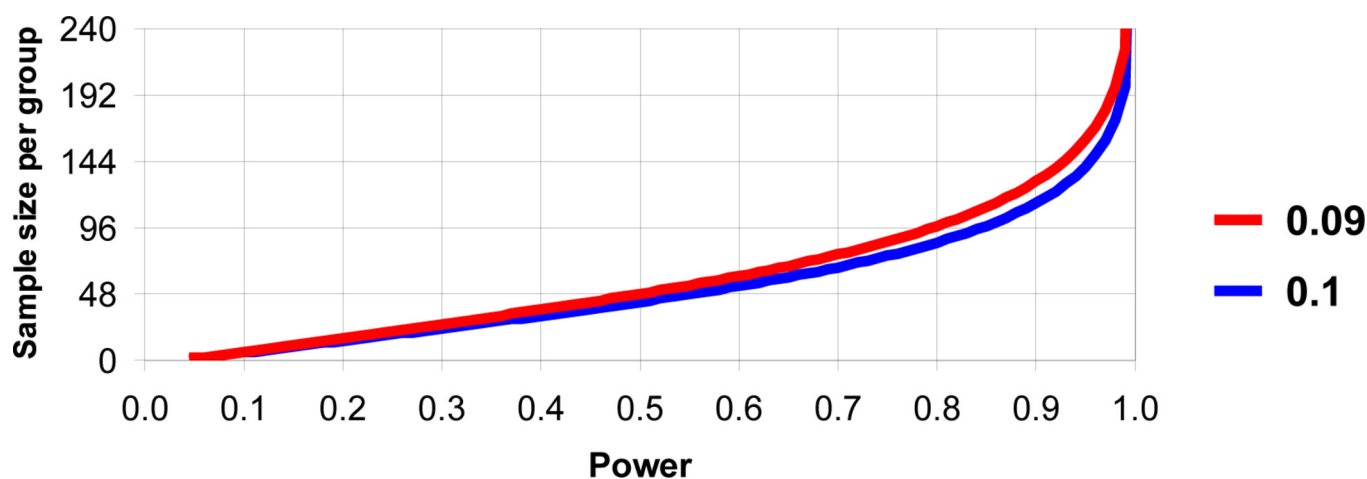
Lines define the risk of PE in the control group

Figure 2 Graph showing the power of the study in relation to the sample size in each study group and incidence of PE in the control group. PE, pulmonary embolism.

procedures that this may include early removal of the IVC filter. The primary and secondary outcomes will be analysed by an intention-to-treat principle, and as such, any patients that cross over into the other group will be analysed as the group they are originally allocated to.

Categorical and continuous baseline variables and outcomes with skewed distributions will be compared by χ^2 test and Mann-Whitney U test, respectively. Kaplan-Meier survival analysis will be used to assess whether early use of retrievable IVC filters will affect the time for the patients to experience the first composite endpoint event (eg, PE or death) within 90 days of randomisation. A predefined restricted or subgroup analysis on risk of fatal PE and non-fatal PE in patients who do not receive any pharmacological VTE prophylaxis within 7 days of major trauma is planned.

As for the economic analysis, it will comprise (A) the net resource cost of IVC compared with the status quo without IVC (cost analysis) and (B) comparison of net resource use with net health benefits (cost-effectiveness).

A. Cost analysis

The total cost of treatment using an IVC filter includes the device itself, the consumables required for insertion and removal, the costs of personnel required for the procedure and costs of complications. Cost components for both arms of the trial which require analysis include length of index hospital stay including number of days in ICU, readmission days including ICU, pharmaceuticals required to treat PE, DVT prophylaxis, associated investigations including all X-rays, CTPA, ultrasonography and any other associated procedures. Follow-up will extend to 90 days postprocedure in the first instance; furthermore, long-term outcomes including survival and venous thromboembolic complications and the cost-effectiveness in preventing these complications beyond day 90 will be assessed through use of linked health data. Costs will be drawn from hospital finance data where possible, but all resources will be collected in standard units and otherwise quantified using standard Australian resource data such as the Medicare Benefits Schedule (MBS) for medical procedures and the Pharmaceutical Benefits Scheme (PBS) for pharmaceuticals. Costs will be standardised to 2015 Australian dollars. The cost analysis will take the perspective of the Australian health system. Because different institutions may have ways of managing patients with trauma and hence also the costs needed, we will also analyse the cost outcomes using the funding provided to each recruited patient according to the Australian Activity-Based Funding model.

Current cost data estimates

It is estimated that the total cost of the procedure using IVF filters is approximately $A6000, comprising: $3000—IVF filter, $3000—consumables for insertion + labour costs for insertion and removal.[64] Given the significant number needed to treat (estimated to be 10), net savings are unlikely to accrue unless additional individual

benefits are evident such as survival and venous insufficiency after VTE. Given estimates of 20% expected DVT and 9%–10% expected PE in the study cohort, the device will only be cost saving if PE costs on average, more than $A60 000. However, if there is a difference in life saved after the use of IVC filters—that is a reduction in fatal PE as suggested by existing observational studies[35]—this will contribute enormously to cost-effectiveness (as distinct from cost savings).

B. Cost-effectiveness

Costs of the procedure will be compared with health outcomes as determined from the trial. The cost analysis as described above will indicate whether IVC filters provide a net saving to the healthcare system. A net saving in costs combined with a net health benefit suggests a dominant health intervention strategy. In the event that the IVC filters demonstrate health benefits at some cost, formal cost-effectiveness analysis can provide information around the relative health benefits for a given cost, compared with alternative resource demands, such as comparable procedures.

Using mortality outcomes, both at 90 days after admission and long term after hospital discharge obtained by linked health data, cost per life year gained can be estimated. Long-term outcomes can also be estimated using Markov decision analysis based on probabilities from the literature. Sensitivity analysis will be undertaken to test robustness of the parameters, to identify cost drivers and to estimate conditions under which the procedure is cost-effective. Cost-effectiveness ratios can be compared with similar procedures to estimate potential acceptability for wider policy.

ETHICS AND DISSEMINATION

This study has been approved by the ethics committees of the Coroner's Court of Western Australia (EC03-14), Royal Perth Hospital (14-139; consent forms in online supplementary appendix 4), Sir Charles Gairdner Hospital (2014-161), Fiona Stanley Hospital (14-139) and Royal Brisbane and Women's Hospital (15/QRBW/437). Informed consent information forms can be obtained by contacting the corresponding author of this manuscript (KMH). This study has been registered with the Australian and New Zealand Clinical Trial Register (ACTRN12614000963628). A manuscript with the results of the primary clinical outcome and secondary outcomes will be published in a peer-reviewed journal. Separate manuscripts will be written on cost-effective analyses, determinants of the mechanical complications of the IVC filters and long-term outcomes after use of retrievable IVC filters, and these will also be submitted for publication in peer-reviewed journals. Chief investigators listed in this study protocol and those who contribute to the completion of the trial including drafting and critical revising of the final manuscripts will be the authors of the published manuscripts. Patient-level raw data of this study

can be obtained from the corresponding author and the full data set may also be deposited in open clinical data registry if funding is available on completion of all substudies.

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