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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 major trauma patients 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 Major trauma patients, defined by an estimated injury severity score >15, who have contraindications to anticoagulant VTE prophylaxis within 72hrs 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 72hrs of trauma admission, in a 1:1 ratio by permuted blocks stratified by study centre. The primary outcomes are (i) the composite end-point of (a) pulmonary embolism (PE) as demonstrated by CT pulmonary angiography (CTPA), high probability ventilation / perfusion scan, trans-oesophageal echocardiography (by showing clots within pulmonary arterial trunk), pulmonary angiography or post-mortem examination during the same hospitalisation or 90-day after trauma whichever is earlier and (b) hospital mortality; and (ii) the total cost of treatment including the costs of an IVC filter, total number of CT & ultrasound scans required, length of ICU 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 4 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; prospectively registered and 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 major trauma patients 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 major trauma patients.

- The secondary outcomes include mechanical complications of IVC filters, bleeding complications, and long-term health outcomes after using IVC filters as a primary VTE prophylactic measure in major trauma patients.

- The results of this study will inform whether a phase III RCT is necessary to confirm the role of IVC filters for major trauma patients.

- Blinding of the treating clinicians to treatment allocation is deemed to be impossible; centralised web-based randomisation and strict guidelines on when, and how often, a CT pulmonary angiogram should be performed for the study patients are used to overcome selection and detection biases in the study design, respectively.

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 (NSW) 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 AU$3.9 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 post-mortem; 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 under-utilisation 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 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 24hrs 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 to 3 days in initiating VTE prophylaxis is associated with a 3-fold 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 pulmonary embolism is the third leading cause of death in patients who survive the first 24 hours after major trauma.[25] As such, retrievable IVC filters have been increasingly used in many trauma patients.[26,27]

Preliminary evidence to support the role of IVC filters in major trauma

IVC filters are, however, expensive (>AU$3000 per filter without considering radiology costs), invasive, and associated with significant complications, including erosion of the inferior vena cava, inducing thrombosis either above or below the filter, migration of the filter to the right atrium, and tilting or mal-positioning 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 randomized controlled trials (RCTs) or meta-analyses is sparse,[31-35] IVC filters are increasingly used in many trauma centres worldwide.[36] In 2007, the United States 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,[22,43-48] 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.[49] It has been reported to occur at a frequency between 0.4% and 4.2% after major trauma.[24,50,51] 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% confidence interval [CI]: 36-62%), and it accounts for about 12% of all deaths after major trauma.[52,53] Furthermore, our recent multicentre observational studies showed that acute PE is a major cause of morbidity and mortality in critically ill patients,[54] 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: 1.22-2.25; absolute increase in risk 3.9%, 95% CI: 2.2-5.6) 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 trauma patients in Western Australia since 2007, and in the years 2007 and 2008, 7.4%of all trauma patients received a retrievable IVC

filter. During these two years, the incidence of radiological or post-mortem examination confirmed symptomatic PE occurred at 3% of all hospitalized trauma patients, and this risk increased substantially to about 10% if only trauma patients who had an Injury Severity Score (ISS) >15 (**Appendix 1**) were considered. Since we noted that fatal PE after likely preventable with an IVC filter, retrievable IVC filters have been increasing used as a primary thromboprophylaxis for our trauma patients who have contraindications to pharmacologic thromboprophylaxis (>70-100 per annum in Western Australia), 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), but the use of IVC filters was 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%).[42] Evidence suggested that if IVC filters are applied to all major trauma patients, the estimated number of IVC filters needed to prevent one fatal PE is relatively large (mean 125, 95%CI: 100-167)[52] 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 pharmacologic thromboprophylaxis is contraindicated.[52] According to the Trauma Embolic Scoring System (TESS)(**Appendix 2**),[55,56] the TESS score for this type of patients would be likely greater than 10 with an estimate risk of symptomatic VTE between 10% -20% even when a proactive approach to detect VTE is not adopted. This group of trauma patients 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 (details see below).

The primary aims of this study are:

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.

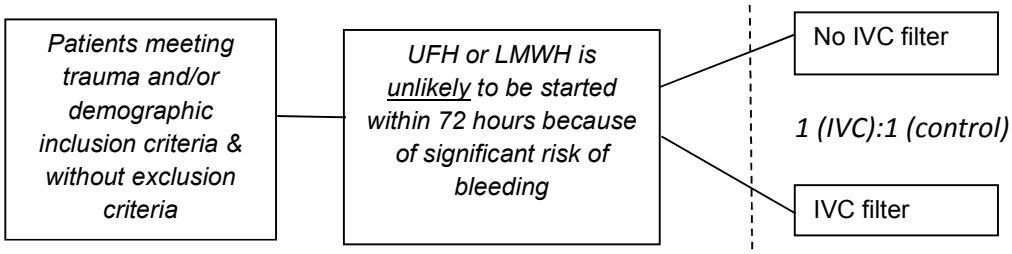
The secondary aims of this study are:

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

Randomisation process:

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



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 blinded to the study allocation. All VTE outcomes will be adjudicated by radiologists independent of the trial to reduce detection bias.

Inclusion criteria:

Patients will be eligible for the trial (1) if they are considered to have contraindications to pharmacologic thromboprophylaxis within 72 hours of hospital admission by their attending intensivist, trauma or spinal surgeon or neurosurgeons AND (2) Injury Severity Score >15 (**Appendix 1**). A list of contraindications to pharmacologic VTE prophylaxis is described in the case record form (CRF) and web data portal.

***E*xclusion criteria:**

1. severe head or systemic injury where death within 48 to 72hrs is expected,
2. attending clinicians judge that patients are at low-risk of bleeding, without contraindications to pharmacologic VTE prophylaxis (as listed in the CRF) and can receive pharmacologic thromboprophylaxis within 3 days after major trauma,
3. patients who have CT evidence of pulmonary embolism 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 (e.g. patients with chronic atrial fibrillation requiring systemic anticoagulation) until admission due to trauma,
5. pregnancy,
6. age <18 years old, or
7. the IVC filter cannot be inserted within 72hrs 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 a longer than this pre-defined period if they believe there is 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 Western Australia (WA) state wide 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 (e.g. migration / displacement, caval occlusion). 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 sub-study. All trauma deaths including those included in this study will be referred to the Coroner's office for post-mortem 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 state wide 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 (e.g. external fixation of lower limb fractures). 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, CTPA is considered mandatory if one or more of the following conditions or situations occurs unless a prior CTPA has already been performed within the last 3 days.

(1) Hypotension with systolic blood pressure <90mmHg for longer than 30 minutes, or

(2) Unexplained chest pain, or

(3) Hypoxia requiring ≥ 6 litres per 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 pharmacologic 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 of needed after study enrolment are at the discretion of the attending clinicians and the data will be recorded. Intravenous low-dose heparin (<800unit/hr) 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 randomization are not eligible for the study (e.g. patients with atrial fibrillation requiring systemic anticoagulation). Anti-platelet agents for new or pre-

existing medical conditions (e.g. 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 (e.g. development of VTE with absolute contraindications to initiate systemic anticoagulation according to the treating clinicians) but this data will be recorded.

Primary end-points:

1. The composite end-point of (a) PE as demonstrated by CT pulmonary angiography (CTPA), high probability ventilation / perfusion scan, trans-oesophageal echocardiography (by showing clots within pulmonary arterial trunk), pulmonary angiography or post-mortem examination during the same hospitalization 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 & ultrasound scans required, length of ICU and hospital stay, procedures and drugs required to treat PE or complications related to the IVC filter.

Secondary end-points:

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 (e.g. intracranial, spinal, epidural, airway haemorrhage), requiring transfusion (of either red blood cells, platelets, or fresh frozen plasma) or a reduction haemoglobin >2g/dL within 24 hours.
   (b) Non-major but clinically relevant bleeding - requiring new medical interventions (e.g. gastrointestinal endoscopy, local or systemic drugs to control bleeding).
   (c) Minor bleeding - not requiring new medical intervention (e.g. 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, and

(b) no participants withdrawing from the trial will be replaced and the proposed sample size has allowed for 20% drop out or cross over between the two treatment arms.

Data collection:

The following data will also be obtained for all patients enrolled in the study and these characteristics will be used to generate a Trauma Embolic Scoring System (TESS) to ensure that the randomization is balanced, in terms of VTE risk, between the two groups (**Appendix 2**).

1. Demographics
2. Previous history of DVT / PE
3. Co-morbidity (**Appendix 3**) including the history of smoking and drug use before the injury
4. Injury pattern and severity including Injury Severity Score (**Appendix 1**)
5. Neurological signs and CT findings on admission for patients with head injury
6. Body mass index
7. Medications before and after the injury: anti-platelet agents, hormonal replacement therapy or 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 randomized into IVC group and also for patients who require IVC filter in the control group due to clinical reason (i.e. crossed-over for clinical reason such as DVT but with active contraindication for anticoagulation)
10. Total number of CTPA or other imaging modalities used (e.g. echocardiography, V/Q or perfusion scan, etc.)
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 anti-thrombotic 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 end-points
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 hospitalization 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 there are found to have clots after retrieved
28. All complications related to IVC filters (e.g. migration / displacement, caval occlusion) Mechanical complications related to the IVC filters are considered as severe adverse events (SAEs)
29. We will also use the unique Data linkage Unit in Western Australia 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 sub-study of this randomized controlled study

Sample size calculation:

Although IVC filters are increasingly used for thromboprophylaxis in many trauma patients, 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 1 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 trauma patients who are at extreme risk of VTE and, at the same time, cannot receive pharmacologic 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 below). 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 severe adverse events (SAEs) will be reported to the ethics committee and monitored by an independent data monitoring and safety committee (DMSC) comprising of two members who have experience in conducting clinical trials

related to trauma and critical illness. Statistically, at least 4 fatal PE 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 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.

Categorical and continuous baseline variables and outcomes with skewed distributions will be compared by Chi-square and Mann-Whitney tests, 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 end-point event (e.g. PE or death) within 90 days of randomisation. A pre-defined 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 of (a) the net resource cost of IVC compared to 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 removable, 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, CT pulmonary angiography, ultrasonography and any other associated procedures. Follow-up will extend to 90 days post procedure in the first instance; furthermore, long-term outcomes including survival and venous thromboembolic complications & 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 MBS for medical procedures and the PBS for pharmaceuticals. Costs will be standardized to 2015 Australian dollars. The cost analysis will take the perspective of the Australian Health system.

Current cost data estimates:

It is estimated that the total cost of the procedure using IVF filters is approximately AU$6,000, comprising: $3000 - IVF filter, $3000 - consumables for insertion + labour costs for insertion and removal.[57] 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 AU$60,000. 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 to health outcomes as determined from the trial. The cost analysis as described above will indicate whether IVC filters provide a net saving to the health care 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 to 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 LYG (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), 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. Raw data of this study may also be deposited in open clinical data registry.

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KMH, SR, SH, RZ, AK, JL, BW, AH, and EG were all involved in conception and trial design. All authors were involved in drafting of the article and critical revision of the article for important intellectual content. All the authors were involved in final approval of the article. KMH provided statistical expertise and EG provided expertise on economic analysis of the study. Preparing study design, collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication is the responsibility of KMH.

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Appendix 1: Injury Severity Score

Injury Severity Score (ISS) is an anatomical scoring system that has been used as a measure of severity of traumatic injuries for a few decades in many trauma centres.

Each of six body regions (head, face, chest, abdomen, extremities including pelvis, external) is assigned an Abbreviated Injury Scale (AIS) between 0 and 6, and the ISS is equal to the sum of the squares of the highest three AIS scores. If there is a non-survivable injury to one region the AIS equals 6 and the ISS score is automatically assigned the maximum of 75.

Appendix 2: Trauma Embolic Scoring System (TESS)

Age: <30 years old =0, 30-64=1, 65 or older=2
ISS score: 1-9=0, 10-16=3, 17-25=3, >25=5
Obesity (body mass index >30): yes= 1
Ventilator use =/> 1 days: yes = 4
Lower extremity trauma: yes=2

Appendix 3: Charlson co-morbidity index component and its weighting

Co-morbidity	Weight
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes mellitus	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end-organ damage	2
Any tumour	2
Leukaemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumour	6
AIDS	6

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME	Page 1	
1.	Provide the name or a phrase that describes the intervention.		_____
	WHY	Pages 4-6	
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.		_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Pages 6-7	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Pages 6-7	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Page 7	_____
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Page 7	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Page 7	_____

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Page 7	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	Pages 8-9	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	Pages 8-9	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Page 9	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Page 9	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

TIDieR checklist

BMJ Open

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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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 major trauma patients 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 Major trauma patients, defined by an estimated injury severity score >15, who have contraindications to anticoagulant VTE prophylaxis within 72hrs 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 72hrs of trauma admission, in a 1:1 ratio by permuted blocks stratified by study centre. The primary outcomes are (i) the composite end-point of (a) pulmonary embolism (PE) as demonstrated by CT pulmonary angiography (CTPA), high probability ventilation / perfusion scan, trans-oesophageal echocardiography (by showing clots within pulmonary arterial trunk), pulmonary angiography or post-mortem examination during the same hospitalisation or 90-day after trauma whichever is earlier and (b) hospital mortality; and (ii) the total cost of treatment including the costs of an IVC filter, total number of CT & ultrasound scans required, length of ICU 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 4 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; prospectively registered and 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 major trauma patients 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 major trauma patients.

- 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 major trauma patients.

- 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 angiogram (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 major trauma patients.

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 (NSW) 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 AU$3.9 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 post-mortem; 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 under-utilisation 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 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 24hrs 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 to 3 days in initiating VTE prophylaxis is associated with a 3-fold 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 pulmonary embolism is the third leading cause of death in patients who survive the first 24 hours after major trauma.[25] As such, retrievable IVC filters have been increasingly used in many trauma patients.[26,27]

Preliminary evidence to support the role of IVC filters in major trauma

IVC filters are, however, expensive (>AU$3000 per filter without considering radiology costs), invasive, and associated with significant complications, including erosion of the inferior vena cava, inducing thrombosis either above or below the filter, migration of the filter to the right atrium, and tilting or mal-positioning 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 randomized controlled trials (RCTs) or meta-analyses is sparse,[31-35] IVC filters are increasingly used in many trauma centres worldwide.[36] In 2007, the United States 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% confidence interval [CI]: 36-62%), 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: 1.22-2.25; absolute increase in risk 3.9%, 95% CI: 2.2-5.6) 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 trauma patients in Western Australia since 2007, and in the years 2007 and 2008, 7.4%of all trauma patients received a retrievable IVC

filter. During these two years, the incidence of radiological or post-mortem examination confirmed symptomatic PE occurred at 3% of all hospitalised trauma patients, and this risk increased substantially to about 10% if only trauma patients who had an Injury Severity Score (ISS) >15 (**Appendix 1**) were considered. Since we noted that fatal PE after likely preventable with an IVC filter, retrievable IVC filters have been increasing used as a primary thromboprophylaxis for our trauma patients who have contraindications to pharmacologic thromboprophylaxis (>70-100 per annum in Western Australia), 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 major trauma patients, the estimated number of IVC filters needed to prevent one fatal PE is relatively large (mean 125, 95%CI: 100-167)[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 pharmacologic thromboprophylaxis is contraindicated.[54] According to the Trauma Embolic Scoring System (TESS)(**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% -20% even when a proactive approach to detect VTE is not adopted. Even though many major trauma patients 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 trauma patients 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 (details see below).

The primary aims of this study are:

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.

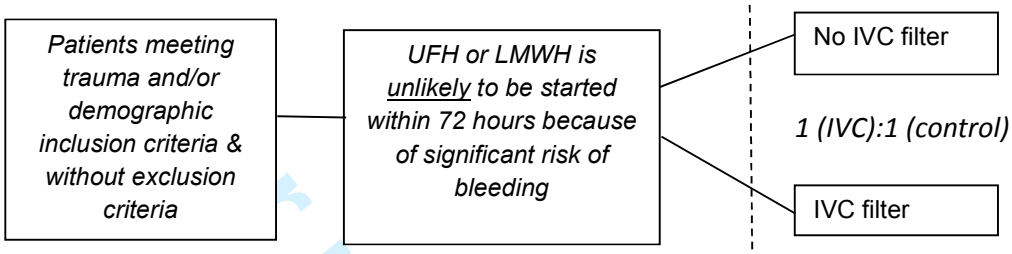
The secondary aims of this study are:

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 randomized controlled parallel-design study comparing the benefits, harms and cost-effectiveness of IVC filters in major trauma patients at high-risk of developing DVT and PE but with contraindications to pharmacologic VTE prophylaxis.



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 blinded to the study allocation. All VTE outcomes will be adjudicated by radiologists independent of the trial to reduce detection bias. De-identified 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 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 pharmacologic thromboprophylaxis within 72 hours of hospital admission by their attending intensivist, trauma or spinal surgeon or neurosurgeons AND (2) Injury Severity Score >15 (**Appendix 1**). A list of contraindications to pharmacologic VTE prophylaxis is described in the case record form (CRF) and web data portal.

***E*xclusion criteria:**

1. severe head or systemic injury where death within 48 to 72hrs is expected,
2. attending clinicians judge that patients are at low-risk of bleeding, without contraindications to pharmacologic VTE prophylaxis (as listed in the CRF) and can receive pharmacologic thromboprophylaxis within 3 days after major trauma,
3. patients who have CT evidence of pulmonary embolism 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 (e.g. patients with chronic atrial fibrillation requiring systemic anticoagulation) until admission due to trauma,
5. pregnancy,
6. age <18 years old, or
7. the IVC filter cannot be inserted within 72hrs 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 a longer than this pre-defined period if they believe there is 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 Western Australia (WA) state wide 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 (e.g. 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 sub-study. All trauma deaths including those included in this study will be referred to the Coroner's office for post-mortem 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 state wide 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 (e.g. 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, CTPA is considered mandatory if one or more of the following conditions or situations occurs unless a prior CTPA has already been performed within the last 3 days.

(1) Hypotension with systolic blood pressure <90mmHg for longer than 30 minutes, or

(2) Unexplained chest pain, or
(3) Hypoxia requiring ≥ 6 litres per 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 pharmacologic 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 of needed after study enrolment are at the discretion of the attending clinicians and the data will be recorded. Intravenous low-dose heparin (<800unit/hr) 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 (e.g. patients with atrial fibrillation requiring systemic anticoagulation). Anti-platelet agents for new or pre-existing medical conditions (e.g. 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 (e.g. development of VTE with absolute contraindications to initiate systemic anticoagulation according to the treating clinicians) but this data will be recorded.

Primary end-points:

1. The composite end-point of (a) PE as demonstrated by CT pulmonary angiography (CTPA), high probability ventilation / perfusion scan, trans-oesophageal echocardiography (by showing clots within pulmonary arterial trunk), pulmonary angiography or post-mortem examination during the same hospitalization 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 & ultrasound scans required, length of ICU and hospital stay, procedures and drugs required to treat PE or complications related to the IVC filter.

Secondary end-points:

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 (e.g. intracranial, spinal, epidural, airway haemorrhage), requiring transfusion (of either red blood cells, platelets, or fresh frozen plasma) or a reduction haemoglobin >2g/dL within 24 hours.
   (b) Non-major but clinically relevant bleeding - requiring new medical interventions (e.g. gastrointestinal endoscopy, local or systemic drugs to control bleeding).
   (c) Minor bleeding - not requiring new medical intervention (e.g. 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, and

(b) no participants withdrawing from the trial will be replaced and the proposed sample size has allowed for 20% drop out or cross over 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 Trauma Embolic Scoring System (TESS) to ensure that the randomization is balanced, in terms of VTE risk, between the two groups (**Appendix 2**).

1. Demographics
2. Previous history of DVT / PE
3. Co-morbidity (**Appendix 3**) including the history of smoking and drug use before the injury
4. Injury pattern and severity including Injury Severity Score (**Appendix 1**)
5. Neurological signs and CT findings on admission for patients with head injury
6. Body mass index
7. Medications before and after the injury: anti-platelet agents, hormonal replacement therapy or 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 (i.e. crossed-over for clinical reason such as DVT but with active contraindication for anticoagulation)
10. Total number of CTPA or other imaging modalities used (e.g. echocardiography, V/Q or perfusion scan, etc.)
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 anti-thrombotic 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 end-points
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 there are found to have clots after retrieved
28. All complications related to IVC filters (e.g. migration / displacement, caval occlusion) Mechanical complications related to the IVC filters are considered as severe adverse events (SAEs)
29. We will also use the unique Data linkage Unit in Western Australia 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 sub-study of this randomised controlled study

Sample size calculation:

Although IVC filters are increasingly used for thromboprophylaxis in many trauma patients, 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 1 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 trauma patients who are at extreme risk of VTE and, at the same time, cannot receive pharmacologic 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 below). 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 severe adverse events (SAEs) will be reported to the ethics committee and monitored by an independent data monitoring and safety committee (DMSC) comprising of two members who have experience in conducting clinical trials related to trauma and critical illness. Statistically, at least 4 fatal PE 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 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 Chi-square and Mann-Whitney tests, 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 end-point event (e.g. PE or death) within 90 days of randomisation. A pre-defined 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 of (a) the net resource cost of IVC compared to 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 removable, 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, CT pulmonary angiography, ultrasonography and any other associated procedures. Follow-up will extend to 90 days post procedure in the first instance; furthermore, long-term outcomes including survival and venous thromboembolic complications & 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 MBS for medical procedures and the 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 trauma patients 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 (ABF) model.

Current cost data estimates:

It is estimated that the total cost of the procedure using IVF filters is approximately AU$6,000, 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 AU$60,000. 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 to health outcomes as determined from the trial. The cost analysis as described above will indicate whether IVC filters provide a net saving to the health care 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 to 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 LYG (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 **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 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 dataset may also be deposited in open clinical data registry if funding is available upon completion of all sub-studies.

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Contributors:
KMH, SR, SH, RZ, AK, JL, BW, AH, EG, and TC were all involved in conception and trial design. All authors were involved in drafting of the article and critical revision of the article for important intellectual content. All the authors were involved in final approval of the article. KMH provided statistical expertise and EG provided expertise on economic analysis of the study. Preparing study design, collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication is the responsibility of KMH. Drs Fred Rogers (a trauma surgeon in US) and Michael Corkeron (an intensivist in Australia) are the members of the data monitoring and safety committee members for this trial.

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Competing interests:
None declared.

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	Venous thromboembolic events (VTE) and other important clinical outcomes
Demographic factors	Total number of CT pulmonary angiography (CTPA) or echocardiography, V/Q perfusion scan	Major bleeding - contributing to death, at a critical site (e.g. intracranial, spinal, epidural, airway haemorrhage), requiring transfusion (of either red blood cells, platelets, or fresh frozen plasma) or a reduction haemoglobin >2g/dL within 24 hours	Occurrence of symptomatic PE or deep vein thrombosis (DVT) and duration between hospital admission and occurrence of VTE, including fata PE in the post-mortem examination
Comorbidities including previous history of VTE and body mass index	The duration between hospital admission and the first attempt to diagnose pulmonary embolism (PE) by any form of imaging modality	Non-major but clinically relevant bleeding - requiring new medical interventions (e.g. 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 anti-platelet agents, hormonal replacement therapy or oral contraceptive pills for female patients	Duration between hospital admission and the time to start the first dose of anti-thrombotic prophylaxis	Minor bleeding - not requiring new medical intervention (e.g. mild haematuria, coffee ground nasogastric aspirate, skin bruises).	ICU, hospital and 90-day mortality (if length of hospital stay is >90 days)

Pattern of injuries, Injury Severity Score (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 90 days 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 inferior vena cava (IVC) filter used for the study patients	Whether unfractionated heparin (UFH) or low-molecular-weight-heparin (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 (e.g. migration / displacement, caval occlusion, filter thrombosis)
			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

Appendix 1: Injury Severity Score

Injury Severity Score (ISS) is an anatomical scoring system that has been used as a measure of severity of traumatic injuries for a few decades in many trauma centres.

Each of six body regions (head, face, chest, abdomen, extremities including pelvis, external) is assigned an Abbreviated Injury Scale (AIS) between 0 and 6, and the ISS is equal to the sum of the squares of the highest three AIS scores. If there is a non-survivable injury to one region the AIS equals 6 and the ISS score is automatically assigned the maximum of 75.

Appendix 2: Trauma Embolic Scoring System (TESS)

Age: <30 years old =0, 30-64=1, 65 or older=2
ISS score: 1-9=0, 10-16=3, 17-25=3, >25=5
Obesity (body mass index >30): yes= 1
Ventilator use =/> 1 days: yes = 4
Lower extremity trauma: yes=2

Appendix 3: Charlson co-morbidity index component and its weighting

Co-morbidity	Weight
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes mellitus	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end-organ damage	2
Any tumour	2
Leukaemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumour	6
AIDS	6

Appendix 4

Patient Label

Royal Perth Hospital

Patient Information Sheet

Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the Da Vinci Trial)

Principal Investigator: Clin. A/Prof Kwok M. Ho, Intensive Care Unit RPH

You are being invited to participate in a research trial because you have been admitted to the RPH Intensive Care Unit or the State Major Trauma Unit following a major trauma. This information sheet explains the trial and describes what will be involved should you decide to participate. Please read the information carefully and ask any questions you might have. You may also wish to discuss the trial with a relative or friend.

Background and aim of the trial

Venous thromboembolism (VTE) is a significant health problem especially in hospitalised patients. Patients who have suffered major trauma and those that undergo surgery are at the greatest risk. For most patients, the standard of care is to use blood-thinning medications (prophylactic anticoagulation i.e. heparin) and intermittent pneumatic compression pumps to both lower limbs. However, there is a group of patients who are at very high risk of VTE but blood-thinning medications cannot be used, due to risk of bleeding from blood thinning medications (such as severe brain injury). In these patients, the options are to use no / minimal intervention or to place a filter in the big vein inside the abdomen (also called inferior vena cava [IVC]) to block the migration of clots from the legs to the lung circulation to prevent pulmonary embolism (PE) that can be life-threatening in severe cases. The current filters that are placed inside the IVC are retrievable when they are no longer needed and are usually called Inferior Vena Cava filters (IVCF). Although IVCFs have been widely used for over two decades as a mechanical means to prevent pulmonary embolism in patients who have contraindications to conventional VTE prophylactic measures, their effectiveness in this situation has not been established. Despite the uncertainty about its effectiveness, IVCFs are used for about 50-100 trauma patients who cannot receive blood-thinning drugs to prevent pulmonary embolism every year in Western Australia.

The aim of this trial is to assess the clinical effectiveness, benefits and harms, and also the cost-effectiveness of the early use of IVCF for trauma patients who have contraindications to pharmacological VTE prophylaxis and they are at high risk of having PE (e.g. complicated fractures of the pelvis, severe brain injury or spinal injury).

What participation in the trial will involve

Patients who participate in this trial will be randomly separated into two groups (50% of the participants in each group). The first group of patients will be managed using a traditional

way of preventing VTE. For patients who can receive mechanical deep vein thrombosis (DVT) prophylaxis in the form of lower limb compression devices, they will receive this means of DVT prevention to the leg that is non-injured. Blood thinning drugs, such as heparin, that are commonly used to prevent DVT will be started at the discretion of the attending clinicians. Because this trial only considers patients who have contraindications to blood thinning drugs in the initial phase after their injuries, we expect the attending clinicians will not start the blood thinning drugs within the first three days, and in some cases, this delay could be up to 7 days or even longer.

The second group of patients, who have similar injuries as the first group, will receive an IVCF within the first 72 hours of injury as a means to prevent pulmonary embolism. The other treatments will be exactly the same as the first group of patients. All IVCFs will be removed before the patient is discharged from hospital or 90 days after the trauma, unless the treating doctor believes the IVCF should be left in for longer. All patients who have received an IVCF will have an abdominal x-ray before being discharged from hospital to make sure that either the IVCF has been removed entirely or, if it has not been removed, to ensure that it has not been displaced or migrated.

If you choose to participate you will receive the same medical treatment that you would if you were not participating, with the exception that intensive surveillance of VTE will not occur for patients who are not enrolled in the study.

1 Possible benefits and risks.

All participants who are enrolled in this trial will receive an intensive surveillance for VTE, in the form of an ultrasound scan to their lower limbs at 2 weeks after injury, and a proactive approach to detect pulmonary embolism. The standard methods to detect pulmonary embolism include a CT pulmonary angiography, high probability ventilation/ perfusion scan or trans-oesophageal echocardiogram – which are commonly used in hospitalised patients who are suspected to have pulmonary embolism. We expect this trial will detect all forms of VTE at a much earlier stage than in the usual clinical situation for patients who are not enrolled in the trial due to the proactive approach to detect pulmonary embolism according to the trial protocol. Early detection of VTE will benefit patients in the trial because appropriate therapy can be initiated earlier to prevent the progression of the disease.

For participants who are randomized to receive an IVCF, it is possible that they may experience a lower incidence of symptomatic pulmonary embolism as an additional benefit of being in the trial if they are not in the trial when an IVCF is not used.

IVCF is not an experimental treatment and is currently used on a regular basis in many patients worldwide. Although an IVCF may have benefits, it always has some potential risks. Complications of an IVCF include, but are not limited to, erosion of the inferior vena cava, developing a thrombus (blood clot) above or below the IVCF, migration of the filter to the right atrium of the heart, tilting or mal-positioning of the filter resulting in ineffective filtering of emboli, adherent IVCF, fracture of the filter, and risk of bleeding. Any significant side effects experienced by participants of the trial will be addressed according to the standard clinical management procedures, including early removal of the IVCF, similar to when an IVCF is used for patients not enrolled in the trial. For participants with IVCFs not removed due to mechanical complications (i.e. adherent filters), they will be followed up every 6 months until the end of the study or longer if clinically indicated. All participants will also be followed up for all medical problems, which may or may not be related to an IVCF, until January 2018 by linkage of their health data to the WA Department of Health Data Linkage Unit databases.

For patients who are randomized to the traditional way of preventing VTE, they will not experience the potential complications of an IVCF, unless the attending clinicians decide that an IVF is still clinically indicated at a later stage. It is possible that those participants that don't receive an IVC filter may experience a higher risk of pulmonary embolism if IVCFs are proved to be effective in reducing PE. All participants will also be followed up for all medical problems, which may or may not be related to an IVCF, until January 2018 by linkage of their health data to the WA Department of Health Data Linkage Unit databases.

Whether or not you participate in this trial you will not affect the way you are managed in the Intensive Care Unit or the State Major Trauma Unit and you have the right to withdraw from the trial at any time after enrolment into the trial. If you are enrolled in the trial to receive an IVCF, a separate informed clinical consent for this procedure will be obtained and you have the right to not consent for this procedure even though you have consented to be enrolled in this trial.

What if something goes wrong?

In the event that you suffer an adverse event or a medical accident during this trial that arises from your participation in the trial, you will be offered all full and necessary treatment by RPH. The Ethics Committee has approved this trial on the basis (amongst others) that the reported risk of such an event is either small or acceptable in terms of the risk you face as a result of your current injuries or the benefit that is possible with the new treatment being tested. No provisions have been made in this trial to offer trial subjects who suffer an adverse reaction monetary compensation, but the absence of such a provision does not remove your rights to seek compensation under common law.

2 Confidentiality and privacy

The information gathered about you by the Investigators or obtained during the trial will be held by the investigators in strict confidence. Clinical information will be stored securely on-site at Royal Perth Hospital in a locked filing cabinet inside a locked office or on computer where access is password protected. Only research personnel associated with the trial or members of the Ethics Committee who wish to review trial procedures will have access to this information. Your trial records **without your name attached** will be made available to the trial management committees and through them may be made available to government regulatory bodies in Australia and overseas. All the people who handle your information will adhere to traditional standards of confidentiality and will also comply with all relevant privacy legislation. In Australia this is the Privacy Act 1988. The Ethics Committee has obtained assurances from the research team that the 'Information Privacy Principles' laid down in the Act will be met, and will oblige the Investigator and other hospital staff to meet strict privacy standards. If the results of the trial are published in a medical journal, as is intended, no reader will be able to identify individual patients.

Voluntary participation

You do not have to participate in this trial. Participation in this trial is entirely voluntary and if you agree to participate you may withdraw from the trial at any time without it affecting your medical treatment. Your participation in this trial may be ended without your consent by the doctor if the doctor that is treating you decides to end the trial for other reasons.

Contacts for questions or further information

Further information may be obtained from the Principal Investigator Dr K.M. Ho, ICU, on (08) 9224 2601

This trial has been approved by the Royal Perth Hospital Ethics Committee. If you have any concerns about the conduct of the trial or your rights as a research participant, please contact Prof Frank van Bockxmeer, Chairman of the RPH Ethics Committee, via (08) 9224 2292 or rph.hrec@health.wa.gov.au and quote the ethics approval number (ECXXX).

Patient Label

Royal Perth Hospital

Consent Form

Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the Da Vinci Trial)

Principal Investigator: Clin. A/Prof Kwok M. Ho, Intensive Care Unit RPH

By signing the following consent form, you authorise as described above the recording, review, information storage and data transfer of information collected during the trial pertaining to you, including long-term follow-up of your health conditions through the WA Department of Health Data Linkage Unit. Your signature indicates you have read and that you understand the above information, that you have discussed this trial with the person obtaining consent, and that you have consented to participate based in the information provided. A signed and dated copy of this form will be given to you.

If you are enrolled in the trial to receive an IVCF, a separate informed clinical consent for this procedure will be obtained and you have the right to not consent for this procedure even though you have consented to be enrolled in this trial.

Signature of Participant Date Time

_____

Printed Name of Participant _____

Signature of Investigator Obtaining Consent Date Time

_____

Printed Name of Investigator: _____

One copy to be given to participant, one copy filed in the participant's medical record

Patient Label

Royal Perth Hospital

Next-of-Kin Information Sheet

Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the Da Vinci Trial)

Principal Investigator: Clin. A/Prof Kwok M. Ho, Intensive Care Unit RPH

The RPH Intensive Care Unit (ICU) and the State Major Trauma Unit is conducting a **research trial** that involves patients who experience a major trauma. Patients who are admitted following a major trauma are critically ill and may require other life support treatment rendering them unable to provide consent for this trial.

The RPH Ethics Committee has approved this trial and allowed the Next-of-Kin of the patients to acknowledge that they believe their family member (or the patient) would have consented for enrolment in this study should they be competent to do so. The Ethics Committee has done this because (i) it considers this research is asking a clinically important question that has no evidence to guide clinical practice and (ii) many patients under the study condition of this trial would not be able to give their consent directly and (iii) if your Next-of-Kin are enrolled in the trial to receive an IVCF, a separate informed clinical consent will be obtained from you and you have the right to not consent on behalf of your Next-of-Kin for this procedure even though you have acknowledged for your Next-of-Kin to be enrolled in this trial, after knowing the fact that IVCF is often used in this situation and the potential benefits and risks of this procedure.

Your Next-of-Kin is eligible to participate in the trial.

As part of approving the trial with a 'waiver of consent', the Ethics Committee requires that the patient's Next-of-Kin is informed of the trial and acknowledges that they know of no reason why their family member would have objected to participation in the trial had they been asked.

When your Next-of-Kin is well again, we will discuss the trial with them and ask if they agree to continue to participate. The following information is provided to assist you to understand the trial and provide you with an opportunity to tell the Trial Investigator if you know of a reason/s why your family member would have objected to participating in this trial. If you do know of a reason or reasons why they would have objected to participation, they will not be enrolled in the trial.

Why is this trial being done?

Venous thromboembolism (VTE) is a significant health problem especially in hospitalised patients. Patients who have suffered major trauma and those that undergo surgery are at the

greatest risk. For most patients, the standard of care is to use blood-thinning medication (prophylactic anticoagulation i.e. heparin) and intermittent pneumatic compression pumps to both lower limbs. However, there is a group of patients who are at very high risk of VTE but blood-thinning medications cannot be used due to risk of bleeding from the blood thinning medications (such as severe brain injury). In these patients, the options are to use no / minimal intervention or to place a filter in the big vein inside the abdomen (also called inferior vena cava) to block the migration of clots from the legs to the lung circulation to prevent pulmonary embolism that can be life-threatening. The current filters that are placed inside the IVC are retrievable when they are no longer needed and are usually called Inferior Vena Cava filters (IVCF). Although IVCFs are widely used for over two decades as a mechanical means to prevent pulmonary embolism in patients who have contraindications to conventional VTE prophylactic measures, their effectiveness in this situation has not been established. Despite the uncertainty about its effectiveness, IVCFs are used for about 50-100 trauma patients who cannot receive blood-thinning drugs to prevent pulmonary embolism every year in Western Australia.

The aim of this trial is to assess the clinical effectiveness, benefits and harms, and also the cost-effectiveness of the early use of IVCF for trauma patients who have contraindications to conventional VTE prophylactic measures (pharmacological VTE prophylaxis and lower limb intermittent pneumatic compression) or such measures are judged to be inadequate to prevent pulmonary embolism (e.g. complicated fractures of the pelvis).

Why do we think your Next-of-Kin is suitable for this trial?

Your Next-of-Kin has suffered a major trauma and has been identified as having a significant risk of developing a venous thromboembolism which may result in pulmonary embolism (PE) that can be life-threatening. This is the type of patient we wish to enroll in this trial.

What will participation in the trial involve?

Patients who participate in this trial will be randomly separated into two groups (50% of the participants in each group). The first group of patients will be managed using a traditional way of preventing VTE. For patients who can receive mechanical DVT prophylaxis in the form of lower limb compression devices, they will receive this means of DVT prevention to the leg that is not injured. Blood thinning drugs, such as heparin, that are commonly used to prevent DVT will be started at the discretion of the attending clinicians. The trial recommends blood-thinning medications, such as heparin, within 7 days of injury. Because this trial only considers patients who have contraindications to blood thinning drugs in the initial phase after their injuries, we expect the attending clinicians will not start the blood thinning drugs within the first three days, and in some cases, could be much later.

The second group of patients, who have similar injuries as the first group, will receive an IVCF within the first 72 hours of injury as a means to prevent pulmonary embolism. The other treatments will be exactly the same as the first group of patients. All IVCFs will be removed before the patient is discharged from hospital or 90 days after the trauma, unless the treating doctor believes the IVC filter should be left in for longer. All patients who have received an IVCF will have an abdominal x-ray before being discharged from hospital to make sure that either the IVCF has been removed entirely or, if it has not been removed, to ensure that it has not been displaced or migrated.

If you choose to allow your Next-of-Kin to participate, he/she will receive the same medical treatment that they would if they were not participating, with the exception that intensive surveillance of VTE will not occur for patients who are not enrolled in the study.

What information will be collected about my Next-of-Kin?
Information collected during the trial about your Next of Kin will include:

- Personal information will include age, gender, and race
- Severity and location of injuries
- Previous medical history & other chronic health conditions (e.g. diabetes mellitus)
- Medications prior to injury
- Interventions and investigations conducted during the entire hospital stay
- Surgical interventions
- Any complications up to 12 months after study enrolment by linkage to WA Department of Health databases

Information for the trial about your Next-of-Kin will entered into an electronic Case Report Form (eCRF) on a computer.

Who will see my Next-of-Kin's medical and personal information?
The information gathered about your Next-of-Kin during the trial by the study team, will be held in strict confidence. To protect your Next-of-Kin's privacy, their records will be identified with a code. Any information that identifies your Next-of-Kin, such as their name, that links them to these records will be known only to the Investigator, Dr KM Ho and the information will be stored in a secure password protected computer. All the people who handle your Next-of-Kin's information will adhere to all relevant privacy legislation. In Australia this is the Privacy Act 1988. If the results of the trial are published in a medical journal, as may be intended, no reader will be able to identify individual patients.

What are the potential benefits and risks to my Next-of-Kin if they participate in this trial?

All participants who are enrolled in this trial will receive an intensive surveillance for VTE, in the form of an ultrasound scan to their lower limbs at 2 weeks after the injury, and a proactive approach to detect pulmonary embolism. The standard methods to detect pulmonary embolism include a CT pulmonary angiography, high probability ventilation/ perfusion scan or trans-oesophageal echocardiogram – which are commonly used in hospitalised patients who are suspected to have pulmonary embolism. We expect this trial will detect all forms of VTE at a much earlier stage than in the usual clinical situation for patients who are not enrolled in the trial. Early detection of VTE will benefit patients in the trial because appropriate therapy can be initiated earlier to prevent the progression of the disease.

For participants who are randomized to receive an IVCF, it is possible that they may experience a lower incidence of symptomatic pulmonary embolism as an additional benefit of being in the trial if they are not in the trial when an IVCF is not used.

IVCF is not an experimental treatment and is currently used on a regular basis in many patients worldwide. Although an IVCF may have benefits, it always has some potential risks. Complications of an IVCF include, but are not limited to, erosion of the inferior vena cava, developing a thrombus (blood clot) above or below the IVCF, migration of the filter to the right atrium of the heart, tilting or mal-positioning of the filter resulting in ineffective filtering of emboli, adherent IVCF, fracture of the filter, and risk of bleeding. Any significant side effects

experienced by participants of the trial will be addressed according to the standard clinical management procedures, including early removal of the IVCF, similar to when an IVCF is used for patients not enrolled in the trial. For participants with an IVC filter that is not removed due to mechanical complications (i.e. adherent filters), they will be followed up every 6 months until the end of the study, or longer if clinically indicated. All participants will also be followed up for all medical problems, which may or may not be related to an IVCF, until January 2018 by linkage of their health data to the WA Department of Health Data Linkage Unit databases.

For patients who are randomized to the traditional way of preventing VTE, they will not experience the potential complications of an IVCF, unless the attending clinicians decide that an IVF is still clinically indicated at a later stage. It is possible that those participants that don't receive an IVCF may experience a higher risk of pulmonary embolism if IVCFs are proved to be effective in reducing PE. All participants will also be followed up for all medical problems, which may or may not be related to an IVCF, until January 2018 by linkage of their health data to the WA Department of Health Data Linkage Unit databases.

Whether or not your Next-of-Kin participate in this trial it will not affect the way your Next-of-Kin are managed in the Intensive Care Unit or the State Major Trauma Unit and you have the right to withdraw your Next-of-Kin from the trial at any time after enrolment into the trial. If your Next-of-Kin is enrolled in the trial to receive an IVCF, a separate informed clinical consent for this procedure will be obtained from you and you have the right to not consent for this procedure even though you have acknowledged allowing him/her to be enrolled in this trial.

Your Next-of-Kin's participation

In the event that your family member's health improves and they regain the capacity to provide consent we will approach them for consent to confirm their participation in the trial. Whatever you decide, your Next-of-Kin will continue to receive the best medical care currently available to which they are entitled.

Contacts for questions or further information

Further information may be obtained from the Principal Investigator Dr K.M. Ho, ICU, on (08) 9224 2601

This trial has been approved by the Royal Perth Hospital Ethics Committee. If you have any concerns about the conduct of the trial or the rights of your Next of Kin, please contact Prof Frank van Bockxmeer, Chairman of the RPH Ethics Committee, via (08) 9224 2292 or rph.hrec@health.wa.gov.au and quote the ethics approval number (ECXXX).

Patient Label

Royal Perth Hospital

Next-of-Kin Acknowledgement Form

Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the Da Vinci Trial)

Principal Investigator: Clin. A/Prof Kwok M. Ho, Intensive Care Unit RPH

Participant's Full Name (please print): _____

Name of Next-of-Kin: _____

Relationship to Participant: _____

By signing this form, I acknowledge all of the following:

- I have read the Next-of-Kin Information Sheet and had the trial explained to me regarding what will be done and what I am being asked to do. I have had the opportunity to ask questions, and I understand that I may ask additional questions about this trial at any time.
- I understand that the RPH Ethics Committee has approved this trial and that, as such, I am not being asked to consent to my family member's participation, but to acknowledge that I know of no reason my family member would have objected to participating in the trial. If my Next-of-Kin is enrolled in the trial to receive an IVCF, a separate informed clinical consent for this procedure will be obtained from me and I have the right to not consent for this procedure even though I have acknowledged allowing him/her to be enrolled in this trial.
- I am not aware of any reason/s why my family member would have objected to participation in this trial.
- I understand that in the event of my family member regaining the capacity to consent that they will be fully informed of the trial and will then be asked to provide consent for continued participation.
- I understand I will be given a copy of the Next-of-Kin Information Sheet and this signed Acknowledgment Form to keep for my and my Next-of-Kin's reference.
- I acknowledge that my Next-of-Kin's confidential and personal information held by the Investigator and Study Team at RPH, will be made available for review by any health authorities, institutions, or governmental agencies assigned this task in this country or, if applicable, the Ethics Committee.

_____

Signature of Next-of-Kin **Print Name** **Date** **Time**

Statement of Investigator or person designated to obtain Informed acknowledgment:

I have explained the nature and purpose of this trial, and the potential benefits and reasonably foreseeable risks associated with participation, to the Next-of-Kin on the date noted I have answered any questions that were raised, and have witnessed the above signature

_____

Signature of Investigator **Print Name** **Date** **Time**

Patient Label

Royal Perth Hospital

Consent Form - For Continued Participation

Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the Da Vinci Trial)

Principal Investigator: Clin. A/Prof Kwok M. Ho, Intensive Care Unit RPH

Participant Name: ..... **Study Number:** .....

You have been enrolled in the above trial granted by the RPH Ethics Committee and with the acknowledgement of your Next-of-Kin. This occurred when you were not able to make your own decision due to your injuries. Now you are better, we are inviting you to continue to be in this trial.

As explained in the Participant Information Sheet, this is a research trial that involves patients who have experienced a major trauma and are at significant risk for developing venous thromboembolism (VTE). The decision is up to you. You may wish to discuss this with your family.

The research team from the Intensive Care Unit and State Major Trauma Unit are available to answer any questions about any part of this trial that is not clear to you.

- I understand the information in the Participant Information Sheet.
- I understand that my decision to continue participation or not, WILL NOT jeopardize any treatment or my relationship with Royal Perth Hospital.
- Please indicate your decision by checking (ticking) one of the two boxes below:
  □ **I agree to continue being in the trial**, specifically for the data collected from my involvement in the trial to be used by the Investigator.

□ **I do not agree to continue in the trial**

- I give my consent to be followed up by the research team up until January 2018.
- I understand I will be given a copy of the Participant Information Sheet and this document to keep.

Signature of Patient	Please PRINT name	Date	Time

Signature of Investigator	Please PRINT name	Date	Time

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Page	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2	Trial identifier and registry name.
Protocol version	7	Date and version identifier
Funding	19	Sources and types of financial, material, and other support
Roles and responsibilities	1	Names, affiliations, and roles of protocol contributors
	1	Name and contact information for the trial sponsor
	19	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	19	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	4-6	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6	Explanation for choice of comparators
Objectives	6	Specific objectives or hypotheses
Trial design	7	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework
Methods: Participants, interventions, and outcomes		

Study setting	7	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	7	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	7-8	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	8	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	8	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	9	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	9	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	10	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	11	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	7	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	7	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	7	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	7	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	7	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	7	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	8-11	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	10	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	12	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	12	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	12	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	12	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	12, 19	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	12	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	12	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	12	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	14	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	7	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	7	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	7	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	7	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	19	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	7	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	8	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	19	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	19	Authorship eligibility guidelines and any intended use of professional writers
	14	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	24-36	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	NA	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME	Page 1	
1.	Provide the name or a phrase that describes the intervention.		_____
	WHY	Pages 4-6	
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.		_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Pages 6-7	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Pages 6-7	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Page 7	_____
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Page 7	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Page 7	_____

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Page 7	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	Pages 8-9	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	Pages 8-9	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Page 9	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Page 9	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

TIDieR checklist