PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	CRISTAL: Protocol for a cluster randomised, crossover, non-inferiority trial of aspirin compared to low molecular weight heparin for venous thromboembolism prophylaxis in hip or knee arthroplasty, a registry nested study.
AUTHORS	Sidhu, Verinder; Graves, Steven; Buchbinder, Rachelle; Naylor, Justine; Pratt, Nicole; de Steiger, Richard; Chong, Beng; Ackerman, Ilana; Adie, Sam; Harris, Anthony; Hansen, Amber; Cripps, Maggie; Lorimer, Michelle; Webb, Steve; Clavisi, Ornella; Griffith, Elizabeth; Anandan, Durga; O'Donohue, Grace; Kelly, Lan; Harris, Ian A.

VERSION 1 – REVIEW

REVIEWER	Charles Marc Samama Professor of Anaesthesiology Department of Anaesthesia and Intensive Care Medicine Cochin University Hospital 27 rue du Faubourg St Jacques 75014 Paris, France
REVIEW RETURNED	23-Jun-2019

GENERAL COMMENTS	Very nice and pragmatic study. More than useful! One major concern: it may happen that aspirin is responsible for less major bleeding or less clinically significant non-major bleeding: there's nothing in the protocol to assess this point Two minor criticisms: - "The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001879257p)" This sentence can be found in the abstract, but I didn't find it in the body of the manuscript. To be added. - The recent (2018) ESA guidelines on VTE prophylaxis should be added in the reference list and especially the section dedicated to aspirin! (Jenny J-Y, Pabinger I, Samama CM, ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis: Aspirin. Eur J Anaesthesiol. 2018 Feb;35(2):123–9.) and Samama CM, Afshari A, ESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis. Eur J Anaesthesiol. 2018 Feb;35(2):73–6.

REVIEWER	Patrick BLIN University of Bordeaux, France
REVIEW RETURNED	26-Jul-2019

GENERAL COMMENTS	Nice protocol and original design to assess the effectiveness of aspirin versus LMWH for VTE prophylaxis after jip or knee arthroplasty. The protocol is well presented with clear objectives and criteria. The study started to include first patients in April 2019. I just wonder that the sample size estimation was a little optimistic, with an event rate of symptomatic VTE event of 1.5% from one of their own study (not published). In a recent meta-analysis of recent randomized controlled trials, the symptomatic DVT, fatal and non-fatal pulmonary embolism event rate was 1.8% in one trial, between 1.2-1.4% in three trials, 0.9% in one trial, and between 0.4 and 0.5% in 5 trials with an global mean of 0.9% (Cimminiello Intern Emerg Med 2017) ; I wonder also with outcome multiple imputation for missing outcome which is rare event (from age, sex, baseline health, pain and function, diagnosis and surgical factors), that are not major prognostic factors, and an estimation of 10% of lost to follow-up, with a risk a regression to the mean in favour of no difference between aspen and LMWH.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

One major concern: it may happen that aspirin is responsible for less major bleeding or less clinically significant non-major bleeding: there's nothing in the protocol to assess this point

We apologise for not making this clearer in the original manuscript, however, we will be assessing major bleeding events as a secondary outcome, defined as bleeding resulting in readmission, reoperation or death. We are collecting data on bleeding events via the electronic patient questionnaire at 90 days (self-reported, Appendix 2). Patients reporting bleeding events at 90 days will have these verified by staff from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), via contact with the treating surgeon. Bleeding events will then be classified as "major" according the above definition. We will not be including bleeding events that fail to meet these criteria ("non-major" bleeding) as a secondary outcome. This has been updated in the protocol in the "Secondary objectives" section on page 11, the "Secondary outcomes" section on page 20 and the "Statistical analysis" section on page 23:

To compare safety outcomes (death, readmission, major bleeding events and re-operation within 90 days and 6 months) between LMWH and aspirin groups.

"The trial is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12618001879257p)". This sentence can be found in the abstract, but I don't find it in the body of the manuscript. To be added.

The trial registration number from the Australian and New Zealand Clinical Trials Registry (ANZCTR) has been added under the "Ethics and dissemination" section, on page 26 of the main manuscript.

The trial was prospectively registered on the Australian and New Zealand Clinical Trials Registry (ANZCTR, registration number ACTRN12618001879257) on 13 November 2018, and was updated on 19 September 2019.

The recent (2018) ESA guidelines on VTE prophylaxis should be added in the reference list and especially the section dedicated to aspirin.

The suggested reference has been added as reference number 7, under the “Introduction” section of the manuscript, on page.

Guideline recommendations for VTE (venous thromboembolism) prophylaxis vary due to a lack of evidence regarding the comparative safety and effectiveness of these two common chemoprophylaxis agents.[4-7]

Response to Reviewer 2

I just wonder that the sample size estimation was a little optimistic, with an event rate of symptomatic VTE event of 1.5% from one of their own study (not published). In a recent meta-analysis of recent randomized controlled trials, the symptomatic DVT, fatal and non-fatal pulmonary embolism event rate was 1.8% in one trial, between 1.2-1.4% in three trials, 0.9% in one trial, and between 0.4 and 0.5% in 5 trials with an global mean of 0.9% (Cimminiello Intern Emerg Med 2017)

With 31 clusters now recruited (the final number of clusters recruited), we have repeated the sample size calculations using a range of VTE rates that reflect the reviewer’s concerns and we have included a sample size table (Table 2), which demonstrates that the study will be powered using a non-inferiority margin of 1%, with an overall event rate up to 3% at 80% power, and with an overall event rate up to 2% at 90% power (provided that loss to follow-up of less than 17%). As a secondary measure, we will obtain preliminary symptomatic VTE and loss to follow-up rates from the first 1,000 patients completing 90-day follow-up (without performing any comparative statistical analyses and maintaining blinding) to determine whether the estimates for the primary event rate (2%) and loss to follow-up rate (27%) are adequate. We will adjust the sample size accordingly if the primary event rate from this is greater than 3%, whilst accounting for loss to follow-up. This has been updated in “Sample size” section on page 21 of the manuscript and we have included the suggested reference (Cimminiello C, et al) as reference 37.

A recent large cohort study of 1900 THA and TKA patients from 19 institutions across Australia showed an incidence of symptomatic VTE within 90 days of THA and TKA of 2.6% (manuscript under preparation). A recent randomised trial of aspirin versus rivaroxaban used a minimum clinically important difference of 1%, based on a survey of thromboembolism experts and orthopaedic surgeons.[21 22]

For the sample size calculation in the CRISTAL study, we used an estimated overall event rate of 2% (a conservative estimate based on the recent Australian cohort study and the current available literature)[33 34], the same non-inferiority margin of 1% from the recent randomised controlled trial[22] (an event rate of 2.5% for aspirin and 1.5% for LMWH), a power of 90% and a one-sided significance level of 0.025. For an individual randomised trial, this yields a sample size of 4,117 per treatment group or a total of 8,234 patients. For a cluster randomised crossover trial, the sample size must account for correlations within clusters during the same time period (intracluster correlation) and between study periods in the same cluster (interperiod correlation).[35 36] Assuming an intracluster correlation of 0.01, an interperiod correlation of 0.008 and 31 clusters, the sample size required increases to 11,160 patients. From each cluster, we will aim to recruit 251 registered patients from each group (a total of 15,562 patients), which will allow a 27% loss to follow-up.

Due to uncertainty around the exact event rate[19 21 22 24 25 37] and to allow for a smaller non-inferiority margin, we have constructed a sample-size table (Table 2) to demonstrate that the trial will be adequately powered using a non-inferiority margin of 1%, for an event rate up to 3% at 80% power and for an event rate up to 2% at 90% power, provided that loss to follow-up is less than 17%. As a secondary measure, after 1,000 patients have completed the 90-day follow-up, we will obtain a preliminary symptomatic VTE rate for the whole sample and a loss to follow-up rate (without performing any comparative statistical analyses and maintaining blinding) to determine whether the estimates for the primary event rate (2%) and loss to follow-up rate (27%) are accurate and adjust the sample size accordingly if the primary event rate is greater than 3%, whilst accounting for loss to follow-up.

We therefore aim to recruit 251 patients from each arm, from each of the 31 clusters (502 in total from each cluster and allowing for loss to follow-up, a total sample size of 15,562 patients for the primary analysis) and these figures have been updated throughout the manuscript. Table 2, the sample size table has been included as an additional file and is included here:

Table 2 – Sample Size Table for the CRISTAL Trial † ‡

Event rate in experimental	Event rate in control	Overall event rate	Non inferiority margin	N in each arm (individual)	Cluster size (for 31 clusters)	N total (cluster randomised)
Power = 0.8						
0.015	0.005	0.01	0.01	1553	56	3472
0.02	0.01	0.015	0.01	2319	88	5456
0.025	0.015	0.02	0.01	3076	123	7626
0.03	0.02	0.025	0.01	3826	163	10106
0.035	0.025	0.03	0.01	4567	207	12834
0.04	0.03	0.035	0.01	5301	258	15996
0.0125	0.005	0.00875	0.0075	2420	92	5704
0.015	0.0075	0.01125	0.0075	3104	124	7688
0.0175	0.01	0.01375	0.0075	3784	160	9920
0.02	0.0125	0.01625	0.0075	4461	201	12462
0.0225	0.015	0.01875	0.0075	5134	246	15252
Power = 0.9						
0.015	0.005	0.01	0.01	2079	77	4774
0.02	0.01	0.015	0.01	3103	124	7688
0.025	0.015	0.02	0.01	4117	180	11160
0.03	0.02	0.025	0.01	5121	245	15190
0.015	0.0075	0.01125	0.0075	4154	182	11284
0.0175	0.01	0.01375	0.0075	5065	241	14942

† A one sided α = 0.025 is required for a 95% CI. The number of clusters is assumed to 31, the ICC = 0.01 and the IPC=0.008.
‡ Table does not account for an estimation of loss to follow-up

I wonder also with outcome multiple imputation for missing outcome which is rare event (from age, sex, baseline health, pain and function, diagnosis and surgical factors), that are not major prognostic factors, and an estimation of 10% of lost to follow-up, with a risk a regression to the mean in favour of no difference between aspen and LMWH.

We thank the reviewer for pointing out that imputation of a rare binary event may produce biased results. Therefore, we have added extra text in the manuscript which states that imputation will be investigated, but if we encounter problems with predicting the outcome with the auxiliary variables available to us, then no imputation will be performed. An extra reference has been added (reference number 40). The expected missing data mechanism is Missing Completely at Random as it will be due to difficulty in contacting patients postoperatively (rather than being dependent on the outcome or treatment assignment), so complete case analysis should not produce biased estimates. This extra text and reference (number 40) is under the “Statistical analysis” section of the manuscript on page 22.

Multiple imputation to account for missing outcome data will be investigated, using auxiliary variables gathered from routine AOANJRR data (including age, sex, baseline health, pain and function, diagnosis and surgical factors). Since VTE is rare, if prediction in the imputation models using these auxiliary variables is a problem, no imputation will be performed due to the possibility of bias.[40] Since the most likely reason for loss to follow-up is difficulty in contacting patients postoperatively (rather than any association with treatment assignment or outcome), missing outcome data is expected to be missing completely at random, which will not cause bias in the estimates.

VERSION 2 – REVIEW

REVIEWER	Charles Marc Samama Professor of Anaesthesiology Chair, Department of Anaesthesia, Intensive Care and Perioperative Medicine Same type of study in project with a national funding but not yet accepted
REVIEW RETURNED	19-Sep-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Patrick BLIN Bordeaux PharmacoEPI, CIC Bordeaux CIC1401, France
REVIEW RETURNED	01-Oct-2019

GENERAL COMMENTS	The authors provided a detailed response to my remarks on sample size and multiple imputation with rare events.

Correction: *CRISTAL: protocol for a cluster randomised, crossover, non-inferiority trial of aspirin compared to low molecular weight heparin for venous thromboembolism prophylaxis in hip or knee arthroplasty, a registry nested study*

Sidhu VS, Graves SE, Buchbinder R, *et al*. CRISTAL: protocol for a cluster randomised, crossover, non-inferiority trial of aspirin compared to low molecular weight heparin for venous thromboembolism prophylaxis in hip or knee arthroplasty, a registry nested study. *BMJ Open* 2019;9:e031657. doi: 10.1136/bmjopen-2019-031657

This article was previously published with an error.

The second paragraph under the 'Study Governance' section on the eighth page has been updated from:
The AOANJRR has overall responsibility for the study. The AOANJRR is owned by the Australian Orthopaedic Association (AOA) and is funded by the Australian Federal Government. The AOA holds General Liability insurance cover and compensation will be provided to any patient who suffers harm from trial participation. Proof of insurance cover has been submitted to all ethics committees approving the trial.
to:
The Trial is sponsored by the University of New South Wales (UNSW) and any participant claims will be responded to under UNSW's Clinical Trials insurance.

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