

1 **SUPPLEMENT 2. Statistical Analysis Plan for “Effect of aspirin vs enoxaparin on**
2 **symptomatic venous thromboembolism in patients undergoing hip or knee arthroplasty:**
3 **the CRISTAL randomized trial”**

4

5

6

7 This trial statistical analysis plan has been provided to give readers additional information
8 about the authors’ work.

9

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18 ii. Final Statistical Analysis Plan Pages 27 – 51

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22

23 **STATISTICAL ANALYSIS PLAN (INITIAL): 14 May 2021**

24

25 **TITLE PAGE**

26

27 **Study Title**

28 CRISTAL (A cluster-randomised, crossover, non-inferiority trial of aspirin compared to low
29 molecular weight heparin for venous thromboembolism prophylaxis in hip or knee
30 arthroplasty, a registry nested study): statistical analysis plan

31

32

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87

88 **ABSTRACT**

89

90 **Background:**

91 This *a priori* statistical analysis plan describes the analysis for CRISTAL .

92

93 **Methods:**

94 CRISTAL (cluster-randomised, crossover, non-inferiority trial of aspirin compared to low
95 molecular weight heparin for venous thromboembolism prophylaxis in hip or knee
96 arthroplasty, a registry nested study) aims to determine whether aspirin is non-inferior to
97 low molecular weight heparin (LMWH) in preventing symptomatic venous
98 thromboembolism (VTE) following hip arthroplasty (HA) or knee arthroplasty (KA). The study
99 is nested within the Australian Orthopaedic Association National Joint Replacement
100 Registry. The trial was commenced in April 2019 and after an unplanned interim analysis,
101 recruitment was stopped (December 2020), as the stopping rule was met for the primary
102 outcome.

103

104 The clusters comprised hospitals performing > 250 HA and/or KA procedures per annum,
105 whereby all adults (> 18 years) undergoing HA or KA were recruited. Each hospital was
106 randomised to commence with aspirin, orally, 85-150mg daily or LMWH (enoxaparin),
107 40mg, subcutaneously, daily within 24 hours postoperatively, for 35 days after HA and 14
108 days after KA. Crossover was planned once the registration target was met for the first arm.

109

110 The primary end point is symptomatic VTE within 90 days. Secondary outcomes include
111 readmission, reoperation, major bleeding and death within 90 days, and reoperation and
112 patient-reported pain, function and health status at 6 months.

113

114 The main analyses will focus on the primary and secondary outcomes for patients
115 undergoing elective primary total HA and KA for osteoarthritis. The analysis will use an
116 intention-to-treat approach with cluster summary methods to compare treatment arms. As
117 the trial stopped early, analyses will account for incomplete cluster crossover and unequal
118 cluster sizes.

119

120 **Conclusions:**

121 This paper provides a detailed statistical analysis plan for CRISTAL.

122

123 **Trial registration:** Australian and New Zealand Clinical Trials Registry, ID:
124 ACTRN12618001879257. Registered on 19/11/2018.

125

126

127 **Key Words**

128 Venous Thromboembolism, Hip Arthroplasty, Knee Arthroplasty, Aspirin, Low Molecular
129 Weight Heparin, Statistical Analysis Plan

130

131 **MANUSCRIPT**

132

133 **Background**

134 Despite the increasing use of aspirin as a sole chemotherapeutic agent for symptomatic
135 venous thromboembolic event (VTE) prophylaxis following hip arthroplasty (HA) and knee
136 arthroplasty (KA) [1], there remains limited high quality comparative evidence for its safety
137 and efficacy. The majority of studies supporting the safety and efficacy of aspirin compared
138 to other agents, including low molecular weight heparin (LMWH), have been retrospective
139 or non-randomised [2-11]. The only randomised trials have been underpowered or have
140 used an alternative form of prophylaxis (e.g., LMWH or a novel oral anticoagulant (NOAC))
141 for the immediate postoperative period following HA or KA prior to changing to aspirin for
142 extended prophylaxis, which does not reflect the way aspirin is used in Australia [12, 13].
143 CRISTAL is a pragmatic, multicentre cluster-randomised, crossover trial that aims to
144 determine if aspirin is non-inferior to LMWH in the prevention of symptomatic VTE
145 following HA and KA. It is nested within the Australian Orthopaedic Association National
146 Joint Replacement Registry (AOANJRR).

147

148 The trial commenced in April 2019 and the estimated timeline for completion of patient
149 registration was 24 months. However, after an unplanned interim analysis in which the trial
150 stopping rule was met, patient registration was ceased in December 2020, resulting in
151 incomplete crossover. This statistical analysis plan details the planned analyses for CRISTAL
152 to facilitate transparency of data analysis. The trial protocol has previously been published
153 [14].

154

155 **STUDY OVERVIEW**

156

157 **Ethics**

158 Ethics approval was granted from all relevant central, lead ethics committees involved and
159 all participating hospitals, as outlined in the published trial protocol [14]. The trial is
160 registered with the Australian New Zealand Clinical Trials Registry
161 (ACTRN12618001879257p) and is endorsed by the Australia and New Zealand
162 Musculoskeletal (ANZMUSC) Clinical Trials Network.

163

164 **Participating Hospitals and Patient Registration**

165 The clusters in CRISTAL comprise 31 consenting hospitals that perform greater than 250 HA
166 and/or KA procedures per annum.

167

168 Each recruited hospital was responsible for registering patients and complying with the trial
169 protocol. The AOANJRR routinely collects data pertaining to the procedure, patient age, sex,
170 American Society of Anaesthesiologists (ASA) class and body mass index (BMI) and death on
171 all patients undergoing HA and KA procedures. Patient-reported outcomes are collected
172 through the electronic Clinical Trials Platform, which requires pre-operative registration of
173 the patient onto the electronic system. All adult (age 18 and older) patients undergoing HA
174 or KA were eligible for registration into the study and eligible to receive the allocated study
175 drug, except for those who were already on long-term anticoagulation (specifically a NOAC,
176 warfarin or dual antiplatelet therapy (DAPT)) and those with a medical contraindication to

177 either drug, e.g., an allergy or a medical comorbidity such as thrombophilia that precluded
178 treatment with the study drug.

179

180 Patients who were not registered in the electronic Clinical Trials Platform will be included in
181 secondary analyses, as procedure information, demographics and mortality were still
182 recorded even though the primary outcome and other patient-reported outcomes were not
183 recorded.

184

185 **Intervention**

186 Each hospital (cluster) was allocated to consecutive periods of a standard protocol of LMWH
187 and a standard protocol of aspirin as VTE prophylaxis, with the order being randomised.

188 Patients in the aspirin group received aspirin at 85-150mg once daily, orally for 35 days post
189 HA and for 14 days post KA, commencing within 24 hours of surgery. Patients in the LMWH
190 group received enoxaparin at 40mg once daily, subcutaneously for the same time periods,
191 with this dose reduced to 20mg for patients who weigh less than 50kg and for patients with
192 an estimated glomerular filtration rate (eGFR) of less than 30mL/min who are not on
193 dialysis. Other interventions that were standard across all sites were the intra- and post-
194 operative use of intermittent pneumatic compression (IPC) calf devices until patients are
195 mobile, the use of compression stockings, and mobilisation offered on day 0 or day 1
196 postoperatively.

197

198 **Randomisation and allocation**

199 Study investigators have remained blinded to group allocation. Hospitals were randomised
200 to commence with either LMWH or aspirin, in randomly permuted blocks of size four by
201 statisticians from the South Australian Health and Medical Research Institute (SAHMRI),
202 independent of study investigators. The randomisation sequence was generated using an
203 online application [15] and this was provided to an unblinded data manager from SAHMRI.
204 The hospital was then allocated to a treatment sequence by SAHMRI staff and this
205 information was provided to the AOANJRR (independent of study investigators), with the
206 site being informed of their allocated treatment arm the week prior to commencing initial
207 patient registration. Hospitals were advised to crossover to the alternate treatment once
208 the sample size for the first treatment arm was met.

209

210 For clusters who did not reach the sample size for the first arm within 18 months of
211 commencement, crossover occurred prior to reaching the sample size so that an equal
212 number of patients could be registered in each arm within the study timeframe.

213

214 **Evaluation of adherence to the study protocol and protocol deviations**

215 At a hospital level, during the course of the trial each hospital was audited within the first
216 month of each treatment arm to ensure they were complying with the trial protocol. The
217 audit consisted of the first 20 patients of each treatment arm. If a site had a compliance of
218 less than 80%, the site was educated on methods of improving protocol compliance and
219 subsequently re-audited until compliance to the protocol was above 80%.

220

221 Hospitals were also advised to inform trial co-ordinators of patients not receiving the
222 correct study drug or those patients who had the study drug withheld for greater than 48

223 hours due to side effects (e.g. allergy, excessive wound drainage or bleeding events). These
224 protocol deviations were recorded using the Clinical Trials Platform.

225
226

227 **Outcome variables**

228 The primary outcome of the study is symptomatic VTE within 90 days of surgery. Secondary
229 outcomes are:

- 230 • Deep vein thrombosis (DVT) only (total, below-knee and above-knee) within 90 days
- 231 • Pulmonary embolism (PE) only within 90 days
- 232 • Readmission related to the original surgery or associated treatment (including
233 bleeding and VTE-related) within 90 days
- 234 • Reoperation on the same joint within 90 days and within 6 months of surgery
- 235 • Major bleeding events within 90 days defined as bleeding events resulting in
236 readmission, reoperation or death
- 237 • Death within 90 days
- 238 • Change in patient-reported pain, function and health status measures as measured
239 by the Oxford Hip Score (OHS), Oxford Knee Score (OKS), EQ-5D score and the EQ-
240 VAS from baseline to 6 months postoperatively

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242

243 Outcome and demographic data were collected preoperatively (demographics, patient
244 reported pain, function and health status) and at 90 days and 6 months postoperatively.
245 Data for all primary and secondary outcomes are patient-reported (except for death). All
246 patients who responded 'yes' to having experienced a VTE or a secondary operation within
247 6 months had this result verified by AOANJRR staff through contact with treating doctors
248 and hospitals. A random audit of 200 patients who did not report a VTE event was
249 undertaken to detect the false negative reporting rate. All data collected for registered
250 patients specific to CRISTAL have been outlined in the published protocol [14]. Mortality
251 data were collected through linkage between the AOANJRR and the National Death Index.

252

253 In the published protocol [14], mortality was to be measured at 90 days and 6 months. Due
254 to the lack of sensitivity in measuring VTE-related mortality at 6 months, and due to the lag
255 in data availability for mortality, we will only analyse mortality at 90 days [16].

256
257

258 **Power and sample size**

259 For the sample size calculation in CRISTAL, we used an estimated overall event rate of 2%
260 (based on the current available literature) [17, 18], a non-inferiority margin of 1% (based on
261 clinician opinion and a recent randomised controlled trial) [12], i.e., an event rate of 2.5%
262 for aspirin and 1.5% for LMWH, a power of 90% and a one-sided significance level of 0.025.
263 For an individual randomised trial, this yields a sample size of 4,117 per treatment group or
264 a total of 8,234 patients. For a cluster-randomised crossover trial with an intracluster
265 correlation of 0.01, an interperiod correlation of 0.008 and 31 clusters, the required sample
266 size is 11,160 patients [19, 20]. From each cluster and from each arm, we aimed to register
267 251 patients eligible for the primary objective of the study [14]. This provided a total of
268 15,562 patients and allows for a 27% loss to follow-up.

269 **STATISTICAL ANALYSIS PLAN**

270 **Patient Populations and Subgroups for Analyses**

271 The total patient population for CRISTAL comprises all patients undergoing HA or KA at
272 participating institutions over the duration of the study, regardless of whether these
273 patients were registered or eligible to receive the study drug (defined as population 5, see
274 Figure 1).

275

276 Within this total population, the following populations will be used to form the basis of the
277 analyses:

- 278 • Registered patients undergoing any form of HA or KA (including partial or revision
279 surgery, for any indication) regardless of eligibility to receive the study drug
280 (population 4)
- 281 • Registered patients undergoing any form of HA or KA (including partial or revision
282 surgery, for any indication) who were eligible to receive the study drug (population
283 3)
- 284 • Registered patients undergoing elective primary THA or TKA (for any indication) who
285 were eligible to receive the study drug (population 2)
- 286 • All registered patients undergoing elective primary THA or TKA for a recorded
287 diagnosis of osteoarthritis (OA) who were eligible to receive the study drug
288 (population 1)

289

290 These populations are represented diagrammatically in Figure 1.

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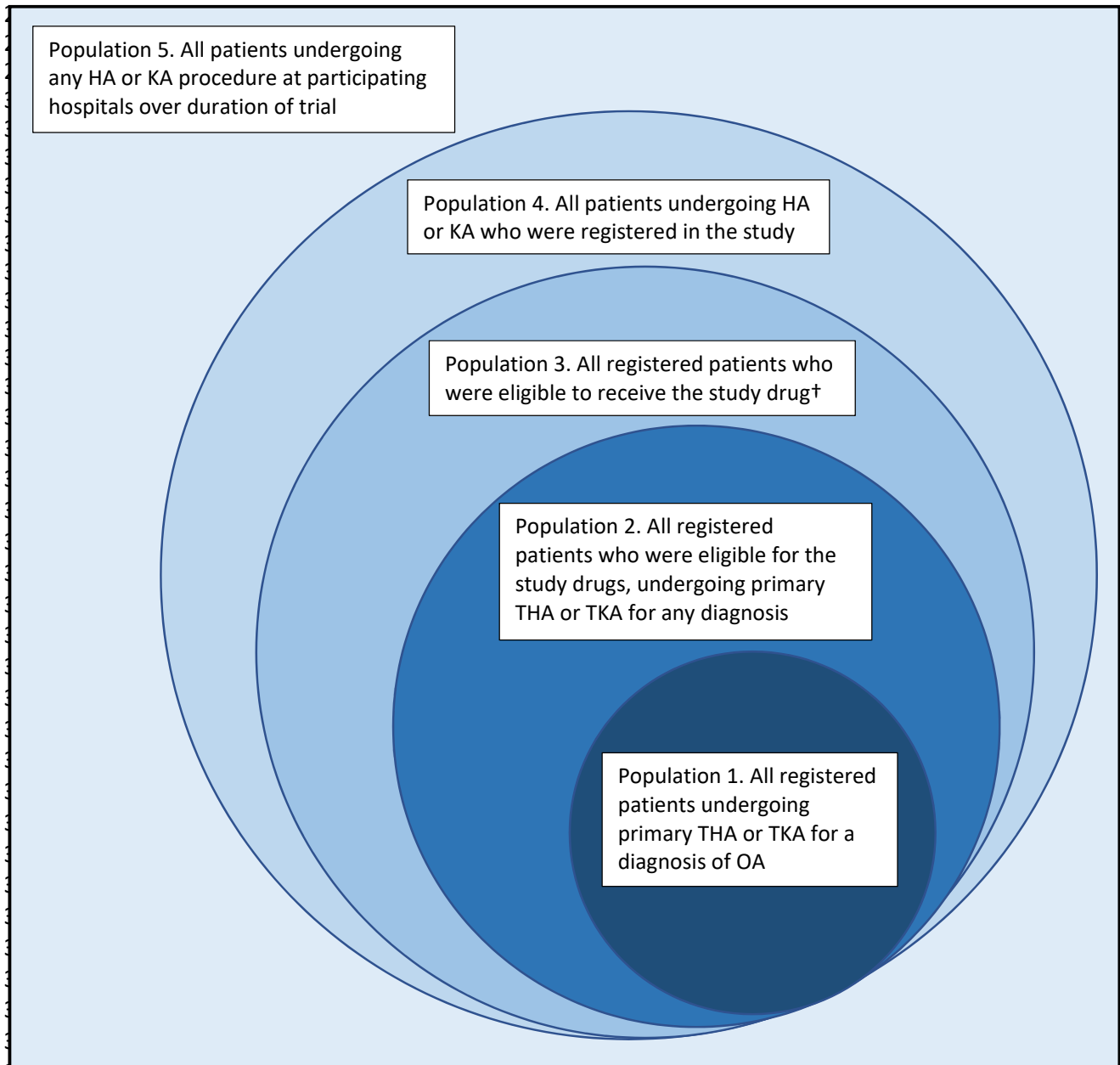
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294 **Figure 1.** Patient populations within CRISTAL

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336 **Legend:**

337 Abbreviations: *HA* hip arthroplasty, *KA* knee arthroplasty, *THA* total hip arthroplasty, *TKA* total knee arthroplasty, *OA*

338 osteoarthritis

339 † Study drug excluded for patients who already on long-term anticoagulation (specifically a novel oral anticoagulant –

340 NOAC, warfarin or dual antiplatelet therapy – DAPT) and those who have a medical contraindication

341

342 Each outcome (primary and secondary) will be assessed for populations 1, 2, 3 and 4 listed
343 in Figure 1. Mortality will be assessed for all populations (including population 5). The
344 primary objective of the study as outlined in the published protocol [14], was the analysis of
345 population 1 only (registered patients undergoing primary THA or TKA for a diagnosis of OA
346 who are eligible to receive the study drug), as this was the focus of the sample size
347 calculation. This population will remain the focus of the main analyses.

348

349 Population 1 was chosen as the focus of the main analysis as these patients represent the
350 majority of patients undergoing HA or KA procedures and there are known differences in
351 outcomes and co-morbidities with other diagnoses (e.g., fracture, tumour), which could
352 confound the primary outcome [21].

353

354 For the primary end point of VTE, the following subgroup analyses will be conducted within
355 the corresponding populations listed:

356

- Type of joint replacement: primary THA compared to primary TKA – population 1
- Bilateral arthroplasty: patients undergoing simultaneous bilateral arthroplasty compared to those who are not – population 1
- Revision arthroplasty: patients undergoing revision hip or knee arthroplasty compared to those undergoing primary arthroplasty – population 3
- Prior history of VTE: patients with a prior history of VTE compared to those without – population 1

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Analysis principles

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Interim analysis

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An interim analysis was not initially planned, as both treatments are considered standard practice for VTE prophylaxis in Australia and the trial is investigating an adverse event as the primary outcome. However, due to concerns of an increased adverse event rate (symptomatic VTE and death) in one of the prophylaxis groups, a Data Safety Monitoring

388 Board (DSMB) was convened one year into patient recruitment. The DSMB consisted of an
389 orthopaedic surgeon, a haematologist and a statistician, all independent of the trial.

390

391 The DSMB were advised by the Trial Management Committee (TMC) to conduct an interim
392 analysis. In conjunction with the DSMB (prior to the interim analysis), the TMC applied the
393 Haybittle-Peto stopping rule of a two-sided significance of 0.001 for the primary outcome in
394 the population 1 [22, 23]. This stopping rule was chosen as it does not require adjustment of
395 the significance threshold for the final analysis and allows further interim analyses using the
396 same threshold (if required).

397

398 After the first interim analysis (in September 2020), the DSMB recommended continuing the
399 trial and performing a second interim analysis in November 2020. After reviewing the
400 second interim analysis, the DSMB recommended ceasing patient recruitment as the
401 stopping rule had been met. The study ceased recruiting patients in December 2020 and
402 sites reverted to their usual VTE prophylaxis pathways.

403

404 ***Methods used for Interim Analyses***

405 Interim analyses were conducted for VTE and mortality within 90 days for population 1. To
406 account for unequal cluster sizes, incomplete crossover or clusters which had not yet
407 crossed over, a composite analysis was designed. For clusters which had crossed over,
408 including with partial completion of the second period, the cluster weighted estimator
409 intended for the primary outcome was used. Clusters which had not crossed over were
410 analysed using the cluster period summaries, weighted by cluster size, in a parallel design
411 approach. Estimates for the two approaches were combined using inverse variance weights
412 to provide a final estimate. Confidence intervals were constructed using the Haybittle-Peto
413 boundary of 0.001.

414

415 **Data integrity**

416 Integrity of data will be checked prior to conducting the final analysis. The data set will be
417 checked for errors, omissions and double data entry. These will be resolved prior to
418 commencing the analysis in consultation with the data management plan [14].

419

420 **Blinding**

421 The DSMB were blinded to treatment allocation (groups in the interim analyses were
422 labelled A and B). All researchers involved in the preparation of this analysis plan will have
423 no access to trial data broken down by treatment allocation for the final statistical analysis.
424 Once data integrity checks have been conducted, a blind review to quantify missing data of
425 the entire dataset will be conducted and any final amendments to the statistical analysis
426 plan will be made before the database is locked. During analysis and interpretation, group
427 allocation will be masked by dummy group names and the true allocation will be unmasked
428 only after the final statistical report has been completed and interpretation has been agreed
429 to by the writing group and minuted.

430

431 **Methods for handling missing data**

432 Multiple imputation using chained equations will be used to account for missing data, using
433 auxiliary variables gathered from routine AOANJRR data (including age, sex, baseline health,
434 pain and function, diagnosis and surgical factors). If there is any possibility of bias due to

435 perfect prediction of rare outcomes such as VTE [24] or imputing values out of range for
436 bounded variables such as pain scores or EQ5D [25], imputation will not be performed.
437 Since the most likely reason for loss to follow-up is difficulty in contacting patients
438 postoperatively (rather than association with treatment assignment or outcome), missing
439 data will be assumed to be missing at random.

440

441

442 **Trial profile and baseline characteristics**

443 The flow of participating hospitals through the study and participating patients will be
444 reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement
445 (Figures 2 and 3).

446

447 The number of patients registered for population 1 (the population used for the sample size
448 calculation) by each participating hospital and the overall registration rate of each hospital
449 will be presented as outlined in Table 1. The overall registration rate describes the number
450 of registered patients undergoing any HA or KA procedure (population 4) divided by the
451 number of patients who underwent any HA or KA procedure over the duration of the trial at
452 participating hospitals (regardless of whether they were registered – population 5). Hospital
453 names will remain anonymous.

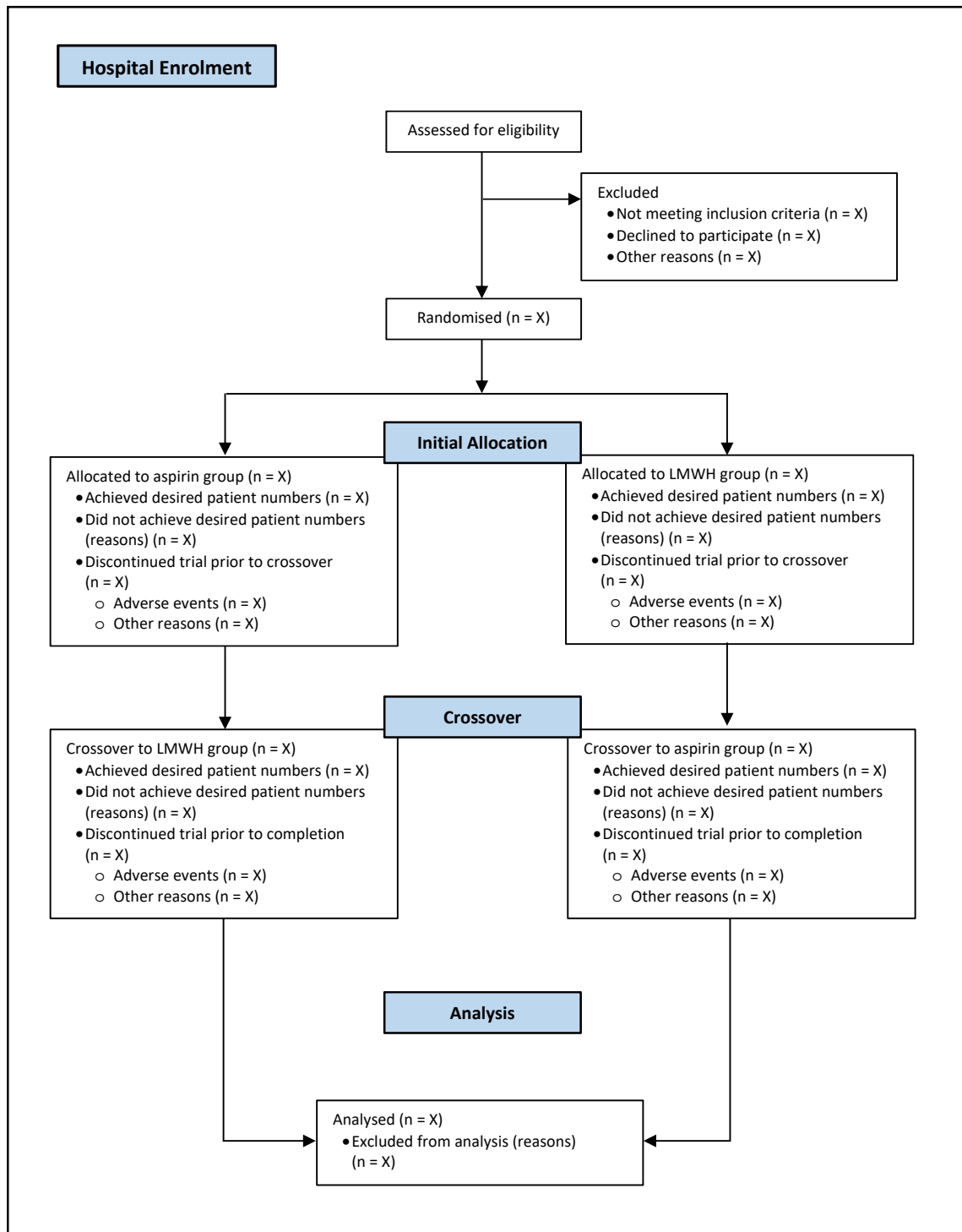
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455 Descriptive statistics of baseline patient characteristics for all registered patients eligible to
456 receive the study drug (population 3) will be presented by prophylaxis group (Table 2).

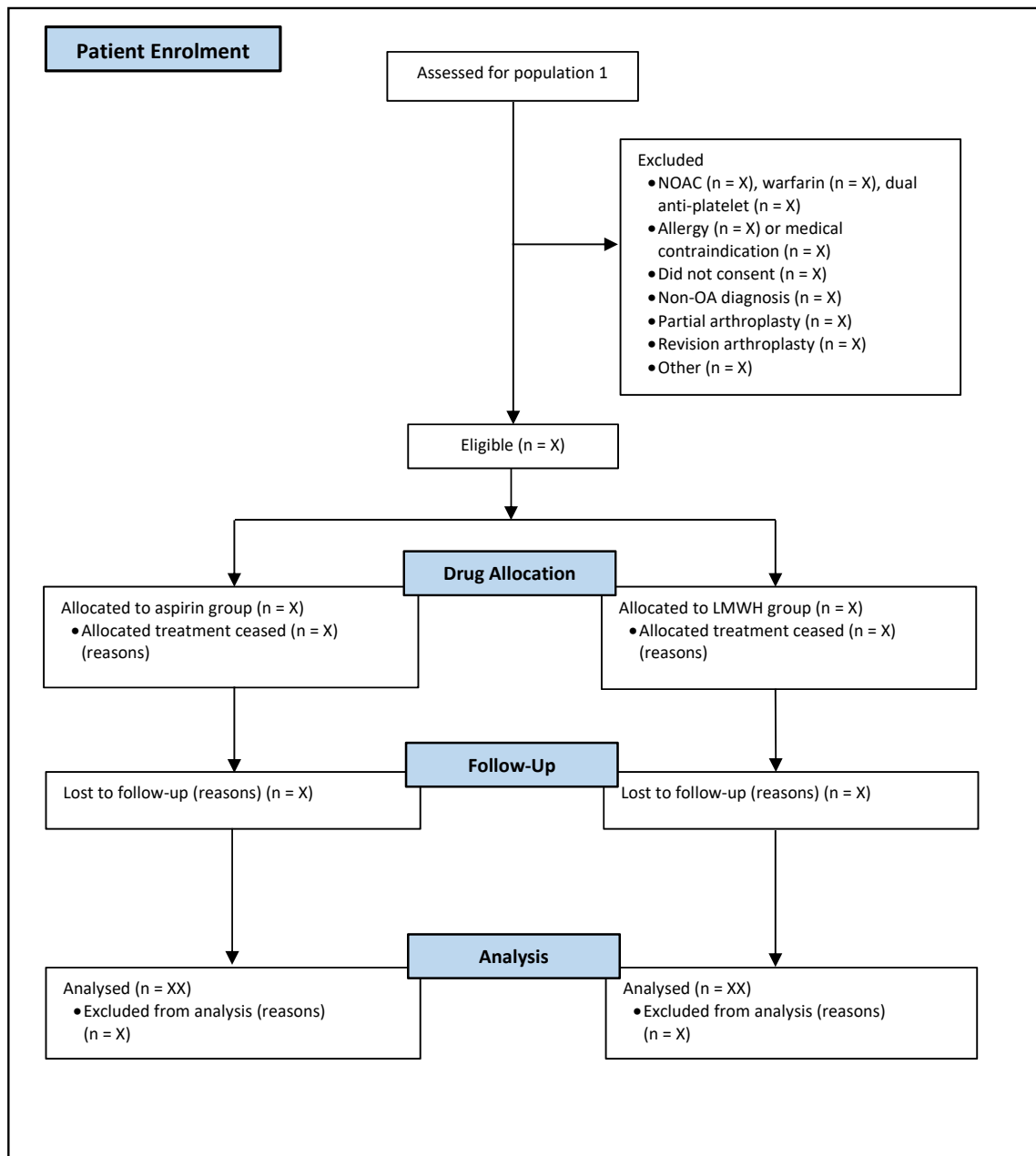
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Figure 2. Flowsheet of participating hospitals



462 **Figure 3.** Flowsheet of patients within population 1[†]



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502 [†] Population 1 refers to registered patients undergoing primary THA or TKA for a diagnosis of OA, who are eligible to receive the study
503 drug

508 **Table 1.** Number of registered patients for population 1[†] by treatment group and overall
 509 registration rate for each participating hospital
 510

Hospital	Sequence Allocation?	LMWH Group (Population 1)	Aspirin Group (Population 1)	Overall Registration Rate (combined for both groups)
1		n	n	%
2		n	n	%
3		n	n	%
4		n	n	%
5		n	n	%
6		n	n	%
7		n	n	%
8		n	n	%
9		n	n	%
10		n	n	%
11		n	n	%
12		n	n	%
13		n	n	%
14		n	n	%
15		n	n	%
16		n	n	%
17		n	n	%
18		n	n	%
19		n	n	%
20		n	n	%
21		n	n	%
22		n	n	%
23		n	n	%
24		n	n	%
25		n	n	%
26		n	n	%
27		n	n	%
28		n	n	%
29		n	n	%
30		n	n	%
31		n	n	%
Total		n	n	%

511
 512 [†] Population 1 refers to registered patients undergoing primary THA or TKA for a diagnosis of OA, who are eligible to receive the study
 513 drug
 514
 515
 516

517 **Table 2.** Baseline patient characteristics for all registered patients eligible to receive study
 518 drug (population 3), according to treatment allocation
 519

	LMWH (n = X)	Aspirin (n = X)
Age (years)	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
BMI (kg/m ²)	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
Male sex	n (%)	n (%)
ASA Grading		
1	n (%)	n (%)
2	n (%)	n (%)
3	n (%)	n (%)
4	n (%)	n (%)
5	n (%)	n (%)
Previous venous thromboembolism	n (%)	n (%)
Long term anticoagulant use		
Aspirin	n (%)	n (%)
Other single antiplatelet	n (%)	n (%)
Joint replacement		
THA	n (%)	n (%)
TKA	n (%)	n (%)
Other HA	n (%)	n (%)
Other KA	n (%)	n (%)
Bilateral	n (%)	n (%)
Type of surgery		
Primary total	n (%)	n (%)
Primary partial	n (%)	n (%)
Primary resurfacing	n (%)	n (%)
Revision	n (%)	n (%)
Other	n (%)	n (%)
Indication		
Osteoarthritis	n (%)	n (%)
Inflammatory	n (%)	n (%)
Avascular Necrosis	n (%)	n (%)
Fracture	n (%)	n (%)
Other	n (%)	n (%)
Prosthesis		
Cemented	n (%)	n (%)
Hybrid	n (%)	n (%)
Uncemented	n (%)	n (%)
Pain and Function		
Oxford Hip Score	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
Oxford Knee Score	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
EQ-5D	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
EQ-VAS	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n

Abbreviations: *BMI* body mass index, *ASA* American society of anaesthesiologists

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525 **MAIN ANALYSES**

526

527 The main analyses will include the primary and secondary outcomes for registered patients
528 eligible to receive the study drug undergoing THA or TKA for a diagnosis of OA (population
529 1). In addition, the primary and secondary outcomes will be analysed for populations 2, 3
530 and 4. Mortality will also be analysed for population 5 (see “Additional analyses” below).

531

532 For the primary outcome, the analysis will test the between-group difference of cases
533 developing a symptomatic VTE within 90 days for non-inferiority of aspirin at a margin of
534 1%. Cluster summary methods will be used to estimate the treatment effect using cluster
535 level differences. These have been shown to be appropriate for cluster-randomised
536 crossover trials with rare outcomes, and the intracluster and interperiod correlation
537 coefficients expected in this trial. The crossover difference per cluster is the mean outcome
538 for the intervention period minus the mean outcome for the control period. In a linear
539 regression of cluster differences on treatment sequence, the treatment effect estimate is
540 the intercept. To account for potential unequal cluster sizes, a cluster size weighted
541 estimator will be used with harmonic mean weights of the number of patients in the two
542 periods [26, 27]. Treatment effects will be presented as absolute risk differences and 95%
543 confidence intervals will be examined to determine whether the non-inferiority margin has
544 been met and whether superiority of one drug can be concluded. The primary outcome will
545 be presented in Table 3 and Figure 4 will be used to demonstrate whether the non-
546 inferiority margin has been met for the population 1 [28].

547

548 The secondary outcomes will investigate non-VTE complications (death, re-operation,
549 readmission and major bleeding events) within 90 days, and reoperation and patient-related
550 pain and function at 6 months (OHS, OKS, EQ-5D and EQ-VAS). Cluster summary methods
551 will be used within an intention-to treat approach. For binary outcomes, the cluster mean
552 per period will be the proportion of patients who had the outcome, while for continuous
553 outcomes such as pain score, the cluster mean will be the mean outcome. Treatment
554 effects will be presented as absolute risk differences and 95% confidence intervals to
555 determine if one treatment is superior to the alternative. Results for the secondary
556 outcomes in population 1 will be presented in tabular form (Table 3) and results for the
557 primary and secondary outcomes in populations 2, 3 and 4 in Table 4.

558

559 Due to the early stopping of the trial, final analyses of the primary and secondary outcomes
560 will use the composite method for the interim analyses with appropriate confidence
561 intervals.

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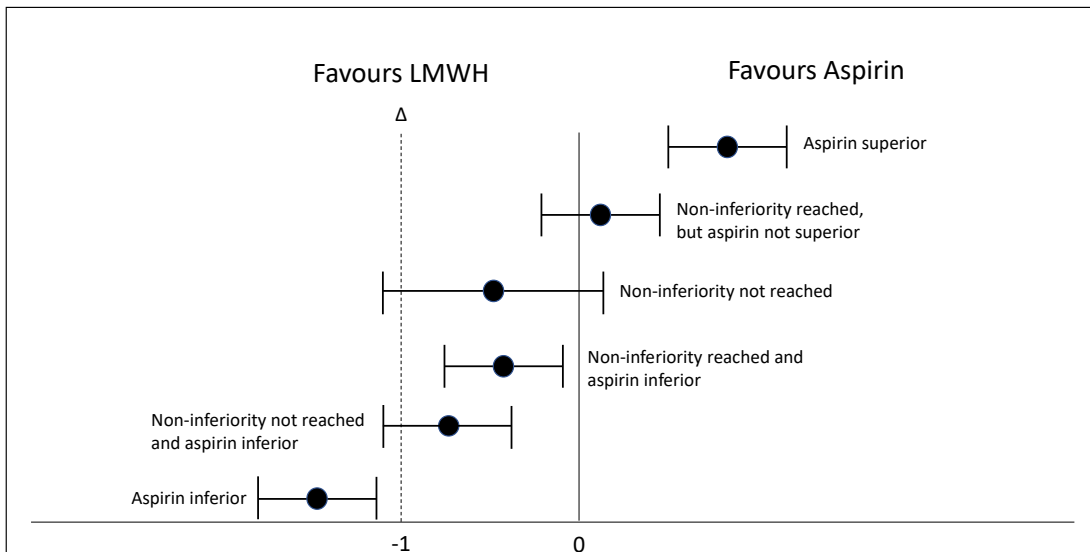
563 **Table 3.** Outcomes for population 1

Outcome	LMWH Allocation (n = X)	Aspirin Allocation (n = X)	Absolute Risk Difference	95% Confidence Interval	p-value
Any Venous thromboembolism	n (%)	n (%)	X	X - X	
Type of Venous thromboembolism					
Pulmonary embolism	n (%)	n (%)	X	X - X	
Deep venous thrombosis	n (%)	n (%)	X	X - X	
Both Pulmonary embolism and deep venous thrombosis	n (%)	n (%)	X	X - X	
Above knee deep venous thrombosis	n (%)	n (%)	X	X - X	
Below knee deep venous thrombosis	n (%)	n (%)	X	X - X	
Death	n (%)	n (%)	X	X - X	
Re-operation (90d)	n (%)	n (%)	X	X - X	
Reoperation (6 months)	n (%)	n (%)	X	X - X	
Re-admission	n (%)	n (%)	X	X - X	
Major Bleeding	n (%)	n (%)	X	X - X	
Pain and Function (median and IQR) [†]			X	X - X	
Oxford Hip Score	X (X - X)	X (X - X)	X	X - X	
Oxford Knee Score	X (X - X)	X (X - X)	X	X - X	
EQ-5D	X (X - X)	X (X - X)	X	X - X	
EQ-VAS	X (X - X)	X (X - X)	X	X - X	

564
565 [†] at 6 months

566
567
568 **Figure 4.** Between group change in overall 90-day symptomatic VTE rate and non-inferiority margin. The dotted line represents the non-inferiority margin

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575 **Table 4.** Outcomes for populations 2, 3 and 4

Population	Outcome	LMWH Allocation (n = X)	Aspirin Allocation (n = X)	Absolute Risk Difference	95% Confidence Interval	p-value
All primary THA/TKA for any diagnosis eligible to receive study drug (population 2)	Any Venous thromboembolism	n (%)	n (%)	X	X – X	
	Type of Venous thromboembolism					
	Pulmonary embolism	n (%)	n (%)	X	X – X	
	Deep venous thrombosis	n (%)	n (%)	X	X – X	
	Both Pulmonary embolism and deep venous thrombosis	n (%)	n (%)	X	X – X	
	Above knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Below knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Death	n (%)	n (%)	X	X – X	
	Re-operation (90d)	n (%)	n (%)	X	X – X	
	Reoperation (6 months)	n (%)	n (%)	X	X – X	
	Re-admission	n (%)	n (%)	X	X – X	
	Major Bleeding	n (%)	n (%)	X	X – X	
	Pain and Function (median and IQR) [†]					
Oxford Hip Score			X	X – X		
Oxford Knee Score	X (X – X)	X (X – X)	X	X – X		
EQ-5D	X (X – X)	X (X – X)	X	X – X		
EQ-VAS	X (X – X)	X (X – X)	X	X – X		
X (X – X)	X (X – X)	X (X – X)				
All HA/KA eligible to receive study drug (population 3)	Any Venous thromboembolism	n (%)	n (%)	X	X – X	
	Type of Venous thromboembolism					
	Pulmonary embolism	n (%)	n (%)	X	X – X	
	Deep venous thrombosis	n (%)	n (%)	X	X – X	
	Both Pulmonary embolism and deep venous thrombosis	n (%)	n (%)	X	X – X	
	Above knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Below knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Death	n (%)	n (%)	X	X – X	
	Re-operation (90d)	n (%)	n (%)	X	X – X	
	Reoperation (6 months)	n (%)	n (%)	X	X – X	
	Re-admission	n (%)	n (%)	X	X – X	
	Major Bleeding	n (%)	n (%)	X	X – X	
	Pain and Function (median and IQR) [†]					
Oxford Hip Score			X	X – X		
Oxford Knee Score	X (X – X)	X (X – X)	X	X – X		
EQ-5D	X (X – X)	X (X – X)	X	X – X		
EQ-VAS	X (X – X)	X (X – X)	X	X – X		
X (X – X)	X (X – X)	X (X – X)				
All HA/KA including study drug exclusion (population 4)	Any Venous thromboembolism	n (%)	n (%)	X	X – X	
	Type of Venous thromboembolism					
	Pulmonary embolism	n (%)	n (%)	X	X – X	
	Deep venous thrombosis	n (%)	n (%)	X	X – X	
	Both Pulmonary embolism and deep venous thrombosis	n (%)	n (%)	X	X – X	
	Above knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Below knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Death	n (%)	n (%)	X	X – X	
	Re-operation (90d)	n (%)	n (%)	X	X – X	
	Reoperation (6 months)	n (%)	n (%)	X	X – X	
	Re-admission	n (%)	n (%)	X	X – X	
	Major Bleeding	n (%)	n (%)	X	X – X	
	Pain and Function (median and IQR) [†]					
Oxford Hip Score			X	X – X		
Oxford Knee Score	X (X – X)	X (X – X)	X	X – X		
EQ-5D	X (X – X)	X (X – X)	X	X – X		
EQ-VAS	X (X – X)	X (X – X)	X	X – X		
X (X – X)	X (X – X)	X (X – X)				

576

577 [†] at 6 months

578

579

580 **Subgroup Analyses**

581 Subgroup analyses for the primary outcome will include THA or TKA, bilateral or unilateral
582 procedures and a prior history of VTE or not for population 1, and primary arthroplasty or
583 revision arthroplasty for population 3.

584
585 To assess treatment effects for each subgroup separately, cluster summaries will be
586 produced for each subgroup. An interaction term between treatment group and subgroup
587 (e.g., THA/TKA, bilateral/unilateral) will be added to the model for the primary outcome.
588 The treatment differences for each subgroup will be assessed for non-inferiority. Since the
589 trial was stopped early, the same composite method for the primary outcome will be used.

590

591

592 **Sensitivity analyses**

593 Sensitivity analyses will be performed to determine: (a) the effect of high-volume
594 arthroplasty sites; (b) sites with high and low overall registration rates; (c) sites that
595 required multiple compliance audits; and (d) the effect of patients who take long-term
596 aspirin therapy on the results of the analyses for the primary outcome in population 1.

597

598 **Order of planned analyses**

599 Analyses will be performed in the following order:

- 600
- 601 • Interim analyses of population 1
 - 602 • Primary and secondary outcomes for population 1
 - 603 • Subgroup analyses for population 1
 - 604 • Primary and secondary outcomes for populations 2, 3 and 4
 - 605 • Subgroup analyses of population 3
 - 606 • Sensitivity analyses in population 1

607

608 **ADDITIONAL ANALYSES**

609

610 **Mortality Analysis**

611 In addition to analysing between-group mortality for populations 1, 2, 3 and 4, the between-
612 group 90-day mortality will be analysed for two further populations:

- 613 1. All patients undergoing HA or KA over the duration of the study at participating
614 hospitals, regardless of whether they were registered (total population described
615 above, population 5)
- 616 2. All patients undergoing elective THA or TKA over the duration of the study at
617 participating hospitals regardless of whether they were registered (a subset of
618 population 5)

619

620 Analysing these additional populations will assess the effect of implementing the VTE
621 prophylaxis protocol on mortality at an institutional/departmental level (the unit of
622 randomisation), on an intention-to-treat basis.

623

624 **Sub-Studies**

625 Data from this trial will be used to form the basis of sub-studies. These will include a sub-
626 study comparing rates of persistent wound drainage between LMWH and aspirin groups at
627 two participating sites and a sub-study investigating rates of post-hospital discharge
628 compliance to either study drug.

629

630

631

632 **Conclusions**

633 CRISTAL aims to provide much needed definitive evidence about the effectiveness and
634 safety of aspirin compared to LMWH in preventing symptomatic VTE following HA or KA.
635 This statistical analysis plan details the study's planned analyses, including modifications to
636 intended analyses to account for early stopping of the trial.

637

638

639 **DECLARATIONS**

640

641 **Ethics Approval**

642 Ethics approval was granted by the Sydney Local Health District (Royal Prince Alfred Zone)
643 Human Research and Ethics Committee, which is a lead ethics committee in Australia
644 (approval number X18-0424) prior to study commencement. Site-specific approvals for each
645 participating hospital were granted from the following ethics committees prior to study
646 commencement: Calvary John James Memorial Hospital Australian Capital Territory (3-2019
647 CRISTAL), Mid-North Coast Local Health District New South Wales (NSW – SSA/19/NCC/41),
648 South Western Sydney Local Health District (NSW, SSA/10/LPOOL/22), Sydney Local Health
649 District (NSW, SSA/19/RPAH/12, SSA/18/RPAH/762), Ramsay Hospital Research Foundation
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653 Hospital and Health Service (Queensland, HREC/18/RPAH/603), University of South Australia
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660 Launceston General Hospital Tasmania (H0017903).

661

662 **Consent for publication**

663 Not applicable.

664 **Availability of data and materials**

665 The datasets during and/or analysed during the current study will be made available from
666 the corresponding author on reasonable request

667 **Competing interests**

668 The authors declare that they have no competing interests

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675 **Authors' contributions**

676 All authors listed have contributed to this protocol and the ICMJE guidelines were consulted
677 for determining authorship. VS, IAH, RB, SG, SA, JMN, RdS, NP, INA, ML, DB, KC and TLK
678 were responsible for the planning of the trial, protocol development and writing, TLK and

679 NP were responsible for the description of the statistical analyses used. All authors
680 reviewed the final version of this manuscript prior to submission.

681

682

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685

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778 **STATISTICAL ANALYSIS PLAN (FINAL): 20 July 2021**

779

780 **TITLE PAGE**

781 **Study Title**

782 CRISTAL (A cluster-randomised, crossover, non-inferiority trial of aspirin compared to low
783 molecular weight heparin for venous thromboembolism prophylaxis in hip or knee
784 arthroplasty, a registry nested study): statistical analysis plan

785

786

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841

842 **ABSTRACT**

843

844 **Background:**

845 This *a priori* statistical analysis plan describes the analysis for CRISTAL.

846

847 **Methods:**

848 CRISTAL (cluster-randomised, crossover, non-inferiority trial of aspirin compared to low
849 molecular weight heparin for venous thromboembolism prophylaxis in hip or knee
850 arthroplasty, a registry nested study) aims to determine whether aspirin is non-inferior to
851 low molecular weight heparin (LMWH) in preventing symptomatic venous
852 thromboembolism (VTE) following hip arthroplasty (HA) or knee arthroplasty (KA). The study
853 is nested within the Australian Orthopaedic Association National Joint Replacement
854 Registry. The trial was commenced in April 2019 and after an unplanned interim analysis,
855 recruitment was stopped (December 2020), as the stopping rule was met for the primary
856 outcome.

857

858 The clusters comprised hospitals performing > 250 HA and/or KA procedures per annum,
859 whereby all adults (> 18 years) undergoing HA or KA were recruited. Each hospital was
860 randomised to commence with aspirin, orally, 85-150mg daily or LMWH (enoxaparin),
861 40mg, subcutaneously, daily within 24 hours postoperatively, for 35 days after HA and 14
862 days after KA. Crossover was planned once the registration target was met for the first arm.

863

864 The primary end point is symptomatic VTE within 90 days. Secondary outcomes include
865 readmission, reoperation, major bleeding and death within 90 days, and reoperation and
866 patient-reported pain, function and health status at 6 months.

867

868 The main analyses will focus on the primary and secondary outcomes for patients
869 undergoing elective primary total HA and KA for osteoarthritis. The analysis will use an
870 intention-to-treat approach with cluster summary methods to compare treatment arms. As
871 the trial stopped early, analyses will account for incomplete cluster crossover and unequal
872 cluster sizes.

873

874 **Conclusions:**

875 This paper provides a detailed statistical analysis plan for CRISTAL.

876

877 **Trial registration:** Australian and New Zealand Clinical Trials Registry, ID:
878 ACTRN12618001879257. Registered on 19/11/2018.

879

880

881 **Key Words**

882 Venous Thromboembolism, Hip Arthroplasty, Knee Arthroplasty, Aspirin, Low Molecular
883 Weight Heparin, Statistical Analysis Plan

884

885 **MANUSCRIPT**

886

887 **Background**

888 Despite the increasing use of aspirin as a sole chemotherapeutic agent for symptomatic
889 venous thromboembolic event (VTE) prophylaxis following hip arthroplasty (HA) and knee
890 arthroplasty (KA) [1], there remains limited high quality comparative evidence for its safety
891 and efficacy. The majority of studies supporting the safety and efficacy of aspirin compared
892 to other agents, including low molecular weight heparin (LMWH), have been retrospective
893 or non-randomised [2-11]. The only randomised trials have been underpowered or have
894 used an alternative form of prophylaxis (e.g., LMWH or a novel oral anticoagulant (NOAC))
895 for the immediate postoperative period following HA or KA prior to changing to aspirin for
896 extended prophylaxis, which does not reflect the way aspirin is used in Australia [12, 13].
897 CRISTAL is a pragmatic, multicentre cluster-randomised, two period cross-sectional
898 crossover trial that aims to determine if aspirin is non-inferior to LMWH in the prevention of
899 symptomatic VTE following HA and KA. It is nested within the Australian Orthopaedic
900 Association National Joint Replacement Registry (AOANJRR).

901

902 The trial commenced in April 2019 and the estimated timeline for completion of patient
903 registration was 24 months. However, after an unplanned interim analysis in which the trial
904 stopping rule was met, patient registration was ceased in December 2020, resulting in
905 incomplete crossover. This statistical analysis plan details the planned analyses for CRISTAL
906 to facilitate transparency of data analysis. The CONSORT statement for cluster randomised
907 trials was referred to in preparation of this document [14]. The trial protocol has previously
908 been published [15].

909 **STUDY OVERVIEW**

910

911 **Ethics**

912 Ethics approval was granted from all relevant central, lead ethics committees involved and
913 all participating hospitals, as outlined in the published trial protocol [15]. The trial is
914 registered with the Australian New Zealand Clinical Trials Registry
915 (ACTRN12618001879257p) and is endorsed by the Australia and New Zealand
916 Musculoskeletal (ANZMUSC) Clinical Trials Network.

917

918 **Participating Hospitals and Patient Registration**

919 The clusters in CRISTAL were defined as hospitals where hip and knee arthroplasty
920 procedures were performed. Hospitals were eligible for recruitment provided they agreed
921 to follow the trial protocol and if they performed greater than 250 HA and/or KA procedures
922 per annum. There were 31 hospitals (clusters) that were recruited.

923

924 Each recruited hospital was responsible for registering patients and complying with the trial
925 protocol. The AOANJRR routinely collects data pertaining to the procedure, patient age, sex,
926 American Society of Anaesthesiologists (ASA) class and body mass index (BMI) and death on
927 all patients undergoing HA and KA procedures. Patient-reported outcomes are collected
928 through the electronic Clinical Trials Platform, which requires pre-operative registration of
929 the patient onto the electronic system. All adult (age 18 and older) patients undergoing HA
930 or KA were eligible for registration into the study and eligible to receive the allocated study
931 drug, except for those who were already on long-term anticoagulation (specifically a NOAC,

932 warfarin or dual antiplatelet therapy (DAPT)) and those with a medical contraindication to
933 either drug, e.g., an allergy or a medical comorbidity such as thrombophilia that precluded
934 treatment with the study drug.

935

936 Patients who were not registered in the electronic Clinical Trials Platform will be included in
937 secondary analyses, as procedure information, demographics and mortality were still
938 recorded even though the primary outcome and other patient-reported outcomes were not
939 recorded.

940

941 **Intervention**

942 Each hospital (cluster) was allocated to consecutive periods of a standard protocol of LMWH
943 and a standard protocol of aspirin as VTE prophylaxis, with the order being randomised.

944 Patients in the aspirin group received aspirin at 85-150mg once daily, orally for 35 days post
945 HA and for 14 days post KA, commencing within 24 hours of surgery. Patients in the LMWH
946 group received enoxaparin at 40mg once daily, subcutaneously for the same time periods,
947 with this dose reduced to 20mg for patients who weigh less than 50kg and for patients with
948 an estimated glomerular filtration rate (eGFR) of less than 30mL/min who are not on
949 dialysis. Other interventions that were standard across all sites were the intra- and post-
950 operative use of intermittent pneumatic compression (IPC) calf devices until patients are
951 mobile, the use of compression stockings, and mobilisation offered on day 0 or day 1
952 postoperatively.

953

954

955 **Randomisation and allocation**

956 Study investigators have remained blinded to group allocation. All 31 participating hospitals
957 were randomised to commence with either LMWH or aspirin, in randomly permuted blocks
958 of size four by statisticians from the South Australian Health and Medical Research Institute
959 (SAHMRI), independent of study investigators. The randomisation sequence was generated
960 using an online application [16] and this was provided to an unblinded data manager from
961 SAHMRI. The hospital was then allocated to a treatment sequence by SAHMRI staff and this
962 information was provided to the AOANJRR (independent of study investigators), with the
963 site being informed of their allocated treatment arm the week prior to commencing initial
964 patient registration. Hospitals followed the designed protocol for patients for their allocated
965 treatment arm and were advised to crossover to the alternate treatment once the sample
966 size for the first treatment arm was met.

967

968 For clusters who did not reach the sample size for the first arm within 18 months of
969 commencement, crossover occurred prior to reaching the sample size so that an equal
970 number of patients could be registered in each arm within the study timeframe.

971

972 **Evaluation of adherence to the study protocol and protocol deviations**

973 At a hospital level, during the course of the trial each hospital was audited within the first
974 month of each treatment arm to ensure they were complying with the trial protocol and to
975 ensure each cluster received the intended allocated treatment. The audit consisted of the
976 first 20 patients of each treatment arm. If a site had a compliance of less than 80%, the site
977 was educated on methods of improving protocol compliance and subsequently re-audited
978 until compliance to the protocol was above 80%.

979

980 Hospitals were also advised to inform trial co-ordinators of patients not receiving the
981 correct study drug or those patients who had the study drug withheld for greater than 48
982 hours due to side effects (e.g. allergy, excessive wound drainage or bleeding events). These
983 protocol deviations were recorded using the Clinical Trials Platform.

984

985

986 **Outcome variables**

987 The primary outcome of the study is symptomatic VTE within 90 days of surgery. Secondary
988 outcomes are:

- 989 • Deep vein thrombosis (DVT) only (total, below-knee and above-knee) within 90 days
- 990 • Pulmonary embolism (PE) only within 90 days
- 991 • Readmission related to the original surgery or associated treatment (including
992 bleeding and VTE-related) within 90 days
- 993 • Reoperation on the same joint within 90 days and within 6 months of surgery
- 994 • Major bleeding events within 90 days defined as bleeding events resulting in
995 readmission, reoperation or death
- 996 • Death within 90 days
- 997 • Change in patient-reported pain, function and health status measures as measured
998 by the Oxford Hip Score (OHS), Oxford Knee Score (OKS), EQ-5D score and the EQ-
999 VAS from baseline to 6 months postoperatively

1000

1001

1002 Outcome and demographic data were collected preoperatively (demographics, patient
1003 reported pain, function and health status) and at 90 days and 6 months postoperatively.
1004 Data for all primary and secondary outcomes are patient-reported (except for death). All
1005 patients who responded 'yes' to having experienced a VTE or a secondary operation within
1006 6 months had this result verified by AOANJRR staff through contact with treating doctors
1007 and hospitals. A random audit of 200 patients who did not report a VTE event was
1008 undertaken to detect the false negative reporting rate. All data collected for registered
1009 patients specific to CRISTAL have been outlined in the published protocol [15]. Mortality
1010 data were collected through linkage between the AOANJRR and the National Death Index.

1011

1012 In the published protocol [15], mortality was to be measured at 90 days and 6 months. Due
1013 to the lack of sensitivity in measuring VTE-related mortality at 6 months, and due to the lag
1014 in data availability for mortality, we will only analyse mortality at 90 days [17].

1015

1016

1017 **Power and sample size**

1018 For the sample size calculation in CRISTAL, we used an estimated overall event rate of 2%
1019 (based on the current available literature) [18, 19], a non-inferiority margin of 1% (based on
1020 clinician opinion and a recent randomised controlled trial) [12], i.e., an event rate of 2.5%
1021 for aspirin and 1.5% for LMWH, a power of 90% and a one-sided significance level of 0.025.
1022 For an individual randomised trial, this yields a sample size of 4,117 per treatment group or
1023 a total of 8,234 patients. For a cluster-randomised crossover trial with an intracluster
1024 correlation of 0.01, an interperiod correlation of 0.008 and 31 clusters, the required sample

1025 size is 11,160 patients, or 180 patients per arm for each cluster [20, 21]. However, due to
1026 the uncertainty surrounding the event rate and intracluster and interperiod correlations,
1027 loss to follow-up, uneven recruitment rates leading to unequal cluster sizes or clusters
1028 dropping out of the study, we aimed to register 251 patients eligible for the primary
1029 objective of the study, providing a total of 15,562 patients. This figure allowed for a
1030 maximum 27% reduction in the above sample size calculation [15], however, actual loss to
1031 follow-up was expected to be less than this.
1032
1033

1034 **STATISTICAL ANALYSIS PLAN**

1035 **Patient Populations and Subgroups for Analyses**

1036 The total patient population for CRISTAL comprises all patients undergoing HA or KA at
1037 participating institutions over the duration of the study, regardless of whether these
1038 patients were registered or eligible to receive the study drug (defined as population 5, see
1039 Figure 1).

1040

1041 Within this total population, the following populations will be used to form the basis of the
1042 analyses:

- 1043 • Registered patients undergoing any form of HA or KA (including partial or revision
1044 surgery, for any indication) regardless of eligibility to receive the study drug
1045 (population 4)
- 1046 • Registered patients undergoing any form of HA or KA (including partial or revision
1047 surgery, for any indication) who were eligible to receive the study drug (population
1048 3)
- 1049 • Registered patients undergoing elective primary THA or TKA (for any indication) who
1050 were eligible to receive the study drug (population 2)
- 1051 • All registered patients undergoing elective primary THA or TKA for a recorded
1052 diagnosis of osteoarthritis (OA) who were eligible to receive the study drug
1053 (population 1)

1054

1055 These populations are represented diagrammatically in Figure 1.

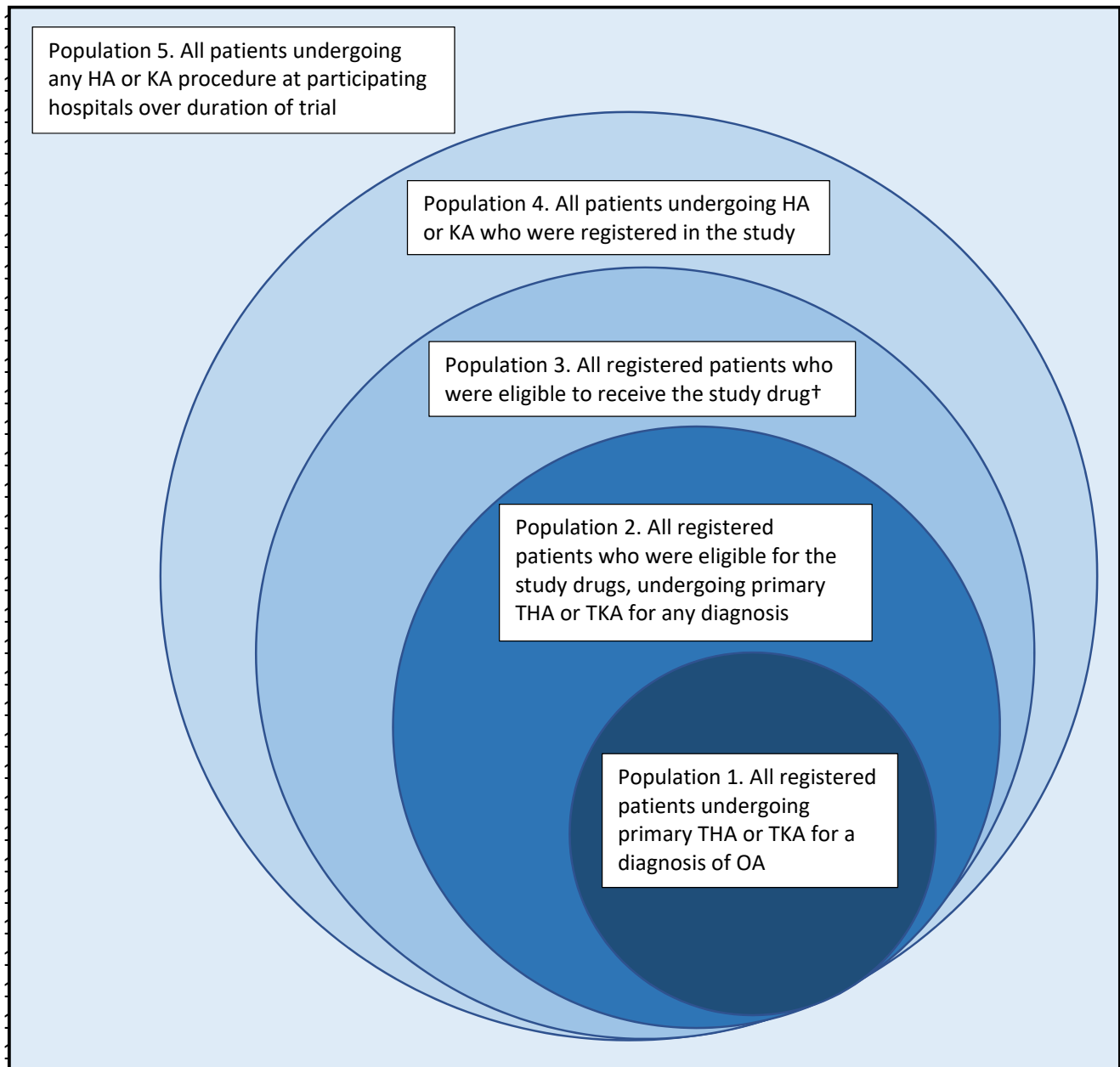
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1057

1058

1059 **Figure 1.** Patient populations within CRISTAL

1060



1095

1096

1097 **Legend:**

1098 Abbreviations: *HA* hip arthroplasty, *KA* knee arthroplasty, *THA* total hip arthroplasty, *TKA* total knee arthroplasty, *OA*

1099 osteoarthritis

1100 † Study drug excluded for patients who already on long-term anticoagulation (specifically a novel oral anticoagulant –

1101 NOAC, warfarin or dual antiplatelet therapy – DAPT) and those who have a medical contraindication

1102

1103 Each outcome (primary and secondary) will be assessed for populations 1, 2, 3 and 4 listed
1104 in Figure 1. Mortality will be assessed for all populations (including population 5). The
1105 primary objective of the study as outlined in the published protocol [15], was the analysis of
1106 population 1 only (registered patients undergoing primary THA or TKA for a diagnosis of OA
1107 who are eligible to receive the study drug), as this was the focus of the sample size
1108 calculation. This population will remain the focus of the main analyses.

1109

1110 Population 1 was chosen as the focus of the main analysis as these patients represent the
1111 majority of patients undergoing HA or KA procedures and there are known differences in
1112 outcomes and co-morbidities with other diagnoses (e.g., fracture, tumour), which could
1113 confound the primary outcome [22].

1114

1115 For the primary end point of VTE, the following subgroup analyses will be conducted within
1116 the corresponding populations listed:

1117

- Type of joint replacement: primary THA compared to primary TKA – population 1

1118

- Bilateral arthroplasty: patients undergoing simultaneous bilateral arthroplasty
1119 compared to those who are not – population 1

1120

- Revision arthroplasty: patients undergoing revision hip or knee arthroplasty
1121 compared to those undergoing primary arthroplasty – population 3

1122

- Prior history of VTE: patients with a prior history of VTE compared to those without –
1123 population 1

1124

1125

1126 **Analysis principles**

1127

1128 Data will be analysed according to the intention-to-treat principle with clusters analysed
1129 according to assigned group allocation. Although hospital and patient protocol deviations
1130 will be recorded, no as-treated analyses will be performed, as there are no verified data
1131 available to determine whether individual patients received the assigned study drug for the
1132 full period, given the pragmatic nature of the trial. The timing of analyses will be stratified
1133 by follow-up time of the outcomes measured (90 days and 6 months). The difference in
1134 absolute risk for symptomatic VTE between each group and 95% confidence intervals (upper
1135 and lower) will be examined to determine if the non-inferiority margin is met.

1135

1136

1137 Continuous variables will be summarised using standard measures of central tendency and
1138 dispersion, using either mean and standard deviation or median and interquartile range.

1138

1139 Categorical variables will be summarised by frequencies and percentages.

1139

1140

1141 Analyses will be performed using SAS version 9.4 (SAS Institute, Cary USA) and R (R

1141

1142 Foundation for Statistical Computing Platform) version 4.0.2 or higher.

1142

1143

1144 **Interim analysis**

1145

1146 An interim analysis was not initially planned, as both treatments are considered standard
1147 practice for VTE prophylaxis in Australia and the trial is investigating an adverse event as the
1148 primary outcome. However, due to concerns of an increased adverse event rate
(symptomatic VTE and death) in one of the prophylaxis groups, a Data Safety Monitoring

1149 Board (DSMB) was convened one year into patient recruitment. The DSMB consisted of an
1150 orthopaedic surgeon, a haematologist and a statistician, all independent of the trial.

1151

1152 The DSMB were advised by the Trial Management Committee (TMC) to conduct an interim
1153 analysis. In conjunction with the DSMB (prior to the interim analysis), the TMC applied the
1154 Haybittle-Peto stopping rule of a two-sided significance of 0.001 for the primary outcome in
1155 the population 1 [23, 24]. This stopping rule was chosen as it does not require adjustment of
1156 the significance threshold for the final analysis and allows further interim analyses using the
1157 same threshold (if required).

1158

1159 After the first interim analysis (in September 2020), the DSMB recommended continuing the
1160 trial and performing a second interim analysis in November 2020. After reviewing the
1161 second interim analysis, the DSMB recommended ceasing patient recruitment as the
1162 stopping rule had been met. The study ceased recruiting patients in December 2020 and
1163 sites reverted to their usual VTE prophylaxis pathways.

1164

1165 ***Methods used for Interim Analyses***

1166 Interim analyses were conducted for VTE and mortality within 90 days for population 1. To
1167 account for unequal cluster sizes, incomplete crossover or clusters which had not yet
1168 crossed over, a composite analysis was designed. For clusters which had crossed over,
1169 including with partial completion of the second period, the cluster weighted estimator
1170 intended for the primary outcome was used. Harmonic mean weighting when there are
1171 unequal cluster sizes has been shown to improve precision and 95% confidence interval
1172 coverage compared with unweighted or inverse variance estimates [25, 26]. Clusters which
1173 had not crossed over were analysed using the cluster period summaries, weighted by cluster
1174 size, in a parallel design approach, i.e., as if it were a cluster randomised trial without
1175 crossover. Estimates for the two approaches were combined using inverse variance weights
1176 to provide a final estimate. Confidence intervals were constructed using the Haybittle-Peto
1177 boundary of 0.001.

1178

1179 **Data integrity**

1180 Integrity of data will be checked prior to conducting the final analysis. The data set will be
1181 checked for errors, omissions and double data entry. These will be resolved prior to
1182 commencing the analysis in consultation with the data management plan [15].

1183

1184 **Blinding**

1185 The DSMB were blinded to treatment allocation (groups in the interim analyses were
1186 labelled A and B). All researchers involved in the preparation of this analysis plan will have
1187 no access to trial data broken down by treatment allocation for the final statistical analysis.
1188 Once data integrity checks have been conducted, a blind review to quantify missing data of
1189 the entire dataset will be conducted and any final amendments to the statistical analysis
1190 plan will be made before the database is locked. During analysis and interpretation, group
1191 allocation will be masked by dummy group names and the true allocation will be unmasked
1192 only after the final statistical report has been completed and interpretation has been agreed
1193 to by the writing group and minuted.

1194

1195

1196 **Methods for handling missing data**

1197 Multiple imputation using chained equations will be used to account for missing data. The
1198 imputation model will use auxiliary variables gathered from routine AOANJRR data
1199 (including age, sex, baseline health, pain and function, diagnosis and surgical factors), as
1200 well as cluster and period effects. One hundred datasets will be imputed at the patient level,
1201 then each dataset will be analysed using the main analysis method with cluster summaries
1202 and combined using Rubin’s rules. If there is any possibility of bias due to perfect prediction
1203 of rare outcomes such as VTE [27] or imputing values out of range for bounded variables
1204 such as pain scores or EQ5D [28], multiple imputation using chained equations will not be
1205 performed. Since the most likely reason for loss to follow-up is difficulty in contacting
1206 patients postoperatively (rather than association with treatment assignment or outcome),
1207 missing data will be assumed to be missing at random.

1208
1209 As a further sensitivity analysis for the primary outcome only, inverse probability weighting,
1210 where the complete cases are weighted by the inverse probability of being complete case
1211 will also be used to account for missing data. Inverse probability weighting has an advantage
1212 over multiple imputation when there are large blocks of missing data with either observed
1213 values for all variables or missing values for the majority of the variables, for example, pre-
1214 operative pain and function scores [29]. The inverse probability weights will be used to
1215 produce weighted cluster summaries, which will be analysed using the main analysis
1216 method, with cluster sizes calculated as the sum of the inverse probability weights.

1217

1218

1219 **Trial profile and baseline characteristics**

1220 The flow of participating hospitals (including losses and exclusions) through the study and
1221 participating patients will be reported in line with the Consolidated Standards of Reporting
1222 Trials (CONSORT) statement (Figures 2 and 3).

1223

1224 Baseline characteristics of participating clusters, including number of annual HA and KA
1225 procedures performed in the year prior to trial commencement, hospital type (public or
1226 private hospital), initial treatment allocation and whether the hospital achieved crossover
1227 are shown in Table 1. This table also shows the number of patients registered for population
1228 1 (the population used for the sample size calculation) by each participating hospital and the
1229 overall registration rate of each hospital will be presented as outlined. The overall
1230 registration rate describes the number of registered patients undergoing any HA or KA
1231 procedure (population 4) divided by the number of patients who underwent any HA or KA
1232 procedure over the duration of the trial at participating hospitals (regardless of whether
1233 they were registered – population 5). Hospital names will remain anonymous.

1234

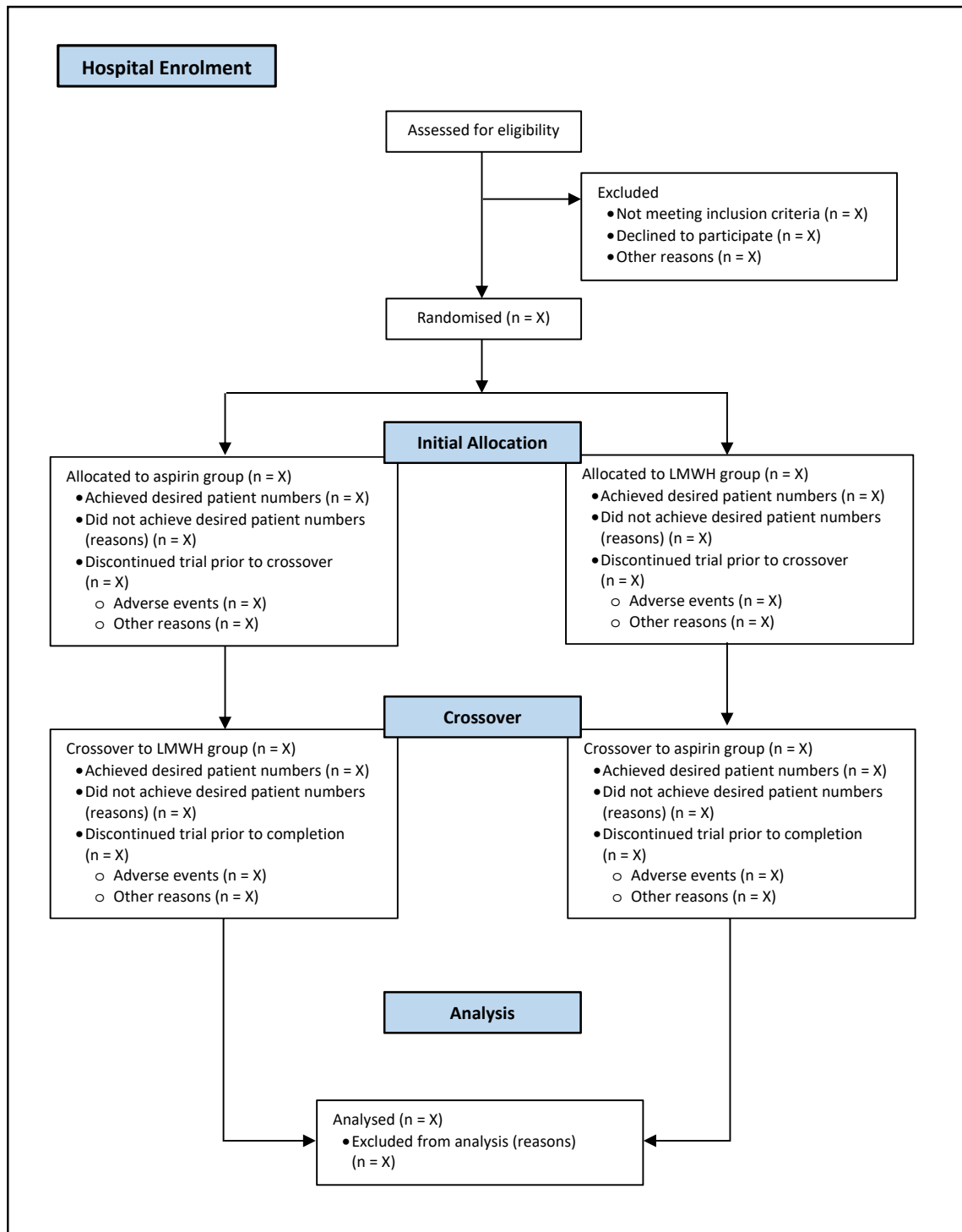
1235 Descriptive statistics of baseline patient characteristics for all registered patients eligible to
1236 receive the study drug (population 3) will be presented by prophylaxis group (Table 2).

1237

1238

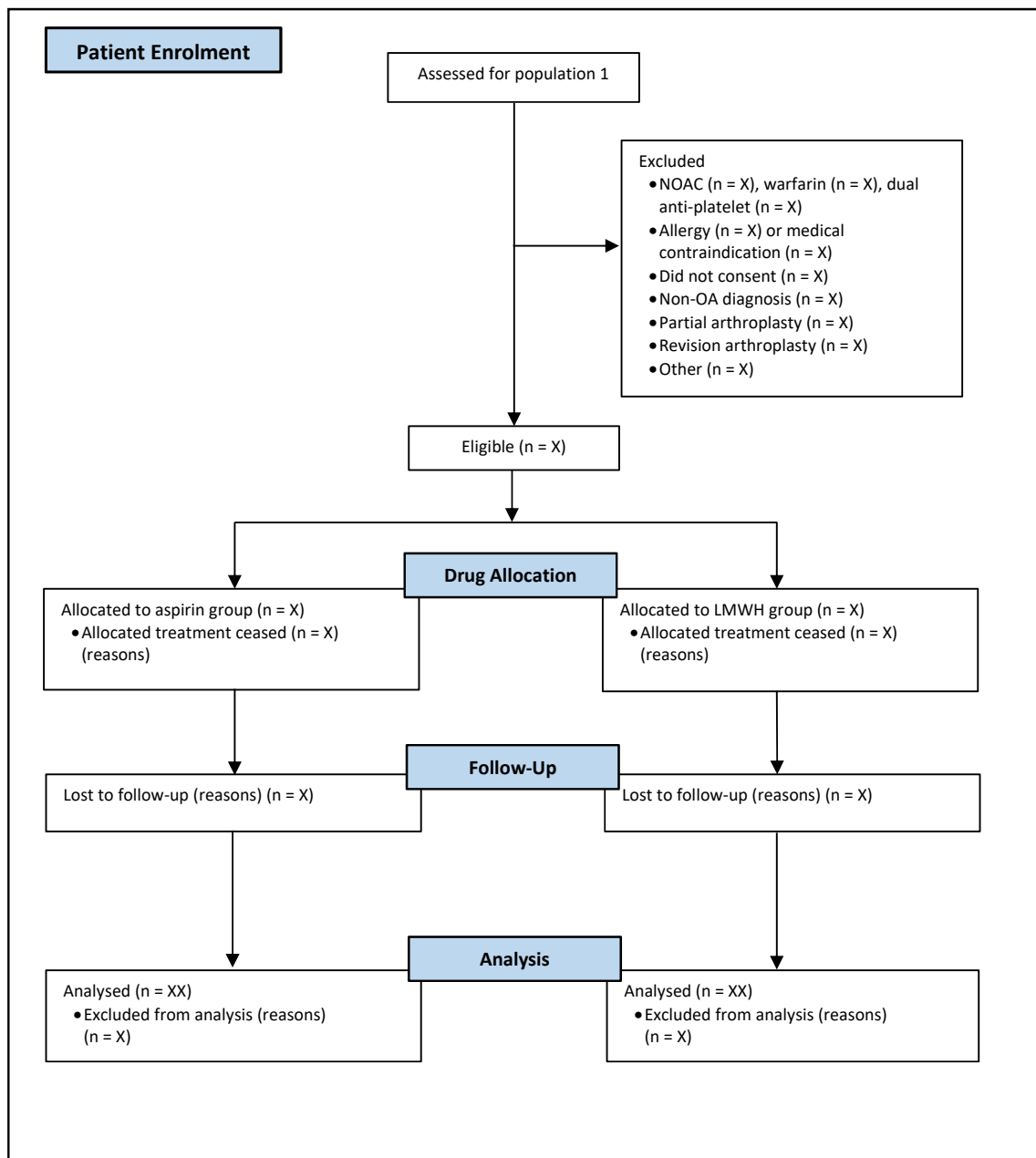
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Figure 2. Flowsheet of participating hospitals



1245 **Figure 3.** Flowsheet of patients within population 1[†]

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[†] Population 1 refers to registered patients undergoing primary THA or TKA for a diagnosis of OA, who are eligible to receive the study drug

1289 **Table 1.** Number of registered patients for population 1[†] by treatment group and overall
 1290 registration rate for each participating hospital
 1291

Hospital	Number of HA and KA Procedures performed (2018)	Insurance Status	Initial Treatment Allocation	Crossover Achieved	LMWH Group (Population 1)	Aspirin Group (Population 1)	Overall Registration Rate (combined for both groups)
1					n	n	%
2					n	n	%
3					n	n	%
4					n	n	%
5					n	n	%
6					n	n	%
7					n	n	%
8					n	n	%
9					n	n	%
10					n	n	%
11					n	n	%
12					n	n	%
13					n	n	%
14					n	n	%
15					n	n	%
16					n	n	%
17					n	n	%
18					n	n	%
19					n	n	%
20					n	n	%
21					n	n	%
22					n	n	%
23					n	n	%
24					n	n	%
25					n	n	%
26					n	n	%
27					n	n	%
28					n	n	%
29					n	n	%
30					n	n	%
31					n	n	%
Total					n	n	%

1292
 1293 [†] Population 1 refers to registered patients undergoing primary THA or TKA for a diagnosis of OA, who are eligible to receive the study
 1294 drug
 1295
 1296
 1297

1298 **Table 2.** Baseline patient characteristics for all registered patients eligible to receive study
 1299 drug (population 3), according to treatment allocation
 1300

	LMWH (n = X)	Aspirin (n = X)
Age (years)	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
BMI (kg/m ²)	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
Male sex	n (%)	n (%)
ASA Grading		
1	n (%)	n (%)
2	n (%)	n (%)
3	n (%)	n (%)
4	n (%)	n (%)
5	n (%)	n (%)
Previous venous thromboembolism	n (%)	n (%)
Long term anticoagulant use		
Aspirin	n (%)	n (%)
Other single antiplatelet	n (%)	n (%)
Joint replacement		
THA	n (%)	n (%)
TKA	n (%)	n (%)
Other HA	n (%)	n (%)
Other KA	n (%)	n (%)
Bilateral	n (%)	n (%)
Type of surgery		
Primary total	n (%)	n (%)
Primary partial	n (%)	n (%)
Primary resurfacing	n (%)	n (%)
Revision	n (%)	n (%)
Other	n (%)	n (%)
Indication		
Osteoarthritis	n (%)	n (%)
Inflammatory	n (%)	n (%)
Avascular Necrosis	n (%)	n (%)
Fracture	n (%)	n (%)
Other	n (%)	n (%)
Prosthesis		
Cemented	n (%)	n (%)
Hybrid	n (%)	n (%)
Uncemented	n (%)	n (%)
Pain and Function		
Oxford Hip Score	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
Oxford Knee Score	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
EQ-5D	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n
EQ-VAS	xx.x (xx.x – xx.x), n	xx.x (xx.x – xx.x), n

Abbreviations: *BMI* body mass index, *ASA* American society of anaesthesiologists

1301
 1302
 1303
 1304

1305 **MAIN ANALYSES**

1306

1307 The main analyses will include the primary and secondary outcomes for registered patients
1308 eligible to receive the study drug undergoing THA or TKA for a diagnosis of OA (population
1309 1). In addition, the primary and secondary outcomes will be analysed for populations 2, 3
1310 and 4. Mortality will also be analysed for population 5 (see “Additional analyses” below).

1311

1312 For the primary outcome, the analysis will test the between-group difference of cases
1313 developing a symptomatic VTE within 90 days for non-inferiority of aspirin at a margin of
1314 1%. Cluster summary methods will be used to estimate the treatment effect using cluster
1315 level differences. These have been shown to be appropriate for cluster-randomised
1316 crossover trials with rare outcomes, and the intracluster and interperiod correlation
1317 coefficients expected in this trial. The crossover difference per cluster is the mean outcome
1318 for the intervention period minus the mean outcome for the control period. In a linear
1319 regression of cluster differences on treatment sequence, the treatment effect estimate is
1320 the intercept. To account for potential unequal cluster sizes, a cluster size weighted
1321 estimator will be used with harmonic mean weights of the number of patients in the two
1322 periods, which was the same method used in the interim analyses for incomplete crossover
1323 [25, 26]. Treatment effects will be presented as absolute risk differences and 95%
1324 confidence intervals will be examined to determine whether the non-inferiority margin has
1325 been met and whether superiority of one drug can be concluded. The primary outcome will
1326 be presented in Table 3 and Figure 4 will be used to demonstrate whether the non-
1327 inferiority margin has been met for the population 1 [30].

1328

1329

1330 The secondary outcomes will investigate non-VTE complications (death, re-operation,
1331 readmission and major bleeding events) within 90 days, and reoperation and patient-related
1332 pain and function at 6 months (OHS, OKS, EQ-5D and EQ-VAS). Cluster summary methods
1333 will be used within an intention-to treat approach. For binary outcomes, the cluster mean
1334 per period will be the proportion of patients who had the outcome, while for continuous
1335 outcomes such as pain score, the cluster mean will be the mean outcome. Treatment
1336 effects will be presented as absolute risk differences and 95% confidence intervals to
1337 determine if one treatment is superior to the alternative. Results for the secondary
1338 outcomes in population 1 will be presented in tabular form (Table 3) and results for the
1339 primary and secondary outcomes in populations 2, 3 and 4 in Table 4.

1340

1341 Due to the early stopping of the trial, final analyses of the primary and secondary outcomes
1342 will use the same composite method as the interim analyses which accounts for clusters
1343 with incomplete as well as no crossover, with 95% confidence intervals. No bias is expected
1344 from early stopping if the patients included in the trial are not systematically different from
1345 later patients who would have been included after the trial was stopped. Our composite
1346 analysis method accounts for clusters which either had incomplete crossover and or did not
1347 crossover. However, the lower sample size and unequal cluster sizes decreases the precision
1348 of the outcome estimates. Since we used cluster weighted estimates to account for unequal
1349 cluster sizes and increased the initial sample size by 27% above the minimum required, the
1350 loss of precision will be mitigated. The trial was stopped based on the Haybittle-Peto

1351 boundary of 0.001, so we anticipate the final analysis using 95% confidence intervals will
 1352 have sufficient power.

1353

1354

1355 **Table 3.** Outcomes for population 1

Outcome	LMWH Allocation (n = X)	Aspirin Allocation (n = X)	Absolute Risk Difference	95% Confidence Interval	p-value
Any Venous thromboembolism	n (%)	n (%)	X	X - X	
Type of Venous thromboembolism					
Pulmonary embolism	n (%)	n (%)	X	X - X	
Deep venous thrombosis	n (%)	n (%)	X	X - X	
Both Pulmonary embolism and deep venous thrombosis	n (%)	n (%)	X	X - X	
Above knee deep venous thrombosis	n (%)	n (%)	X	X - X	
Below knee deep venous thrombosis	n (%)	n (%)	X	X - X	
Death	n (%)	n (%)	X	X - X	
Re-operation (90d)	n (%)	n (%)	X	X - X	
Reoperation (6 months)	n (%)	n (%)	X	X - X	
Re-admission	n (%)	n (%)	X	X - X	
Major Bleeding	n (%)	n (%)	X	X - X	
Pain and Function (median and IQR) [†]			X	X - X	
Oxford Hip Score	X (X - X)	X (X - X)	X	X - X	
Oxford Knee Score	X (X - X)	X (X - X)	X	X - X	
EQ-5D	X (X - X)	X (X - X)	X	X - X	
EQ-VAS	X (X - X)	X (X - X)	X	X - X	

1356

1357 [†] at 6 months

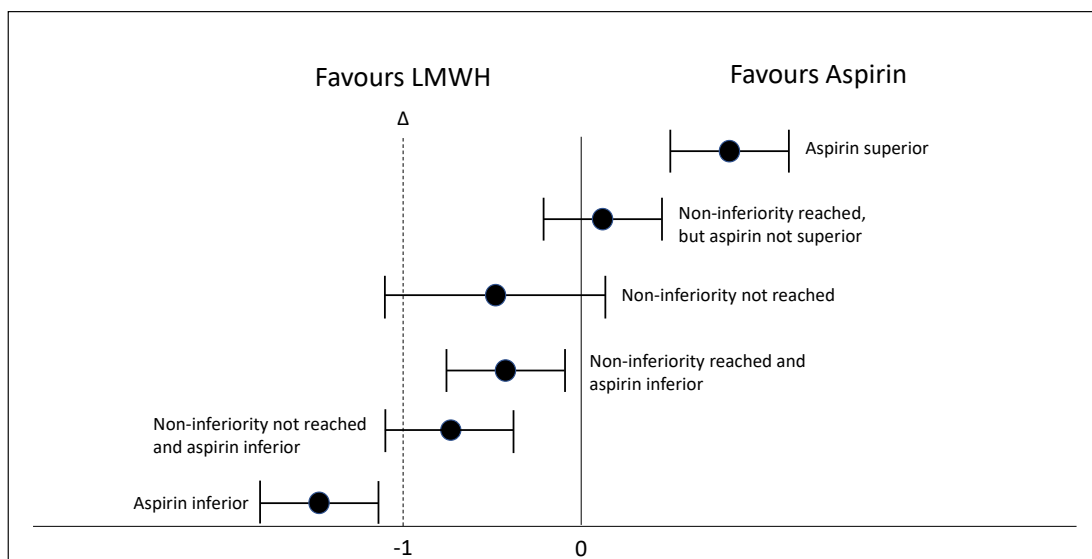
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1359

1360 **Figure 4.** Between group change in overall 90-day symptomatic VTE rate and non-inferiority margin. The dotted line represents the non-inferiority margin

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1362



1363

1364

1365 **Table 4. Outcomes for populations 2, 3 and 4**

Population	Outcome	LMWH Allocation (n = X)	Aspirin Allocation (n = X)	Absolute Risk Difference	95% Confidence Interval	p-value
All primary THA/TKA for any diagnosis eligible to receive study drug (population 2)	Any Venous thromboembolism	n (%)	n (%)	X	X – X	
	Type of Venous thromboembolism					
	Pulmonary embolism	n (%)	n (%)	X	X – X	
	Deep venous thrombosis	n (%)	n (%)	X	X – X	
	Both Pulmonary embolism and deep venous thrombosis	n (%)	n (%)	X	X – X	
	Above knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Below knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Death	n (%)	n (%)	X	X – X	
	Re-operation (90d)	n (%)	n (%)	X	X – X	
	Reoperation (6 months)	n (%)	n (%)	X	X – X	
	Re-admission	n (%)	n (%)	X	X – X	
	Major Bleeding	n (%)	n (%)	X	X – X	
	Pain and Function (median and IQR) [†]					
Oxford Hip Score			X	X – X		
Oxford Knee Score	X (X – X)	X (X – X)	X	X – X		
EQ-5D	X (X – X)	X (X – X)	X	X – X		
EQ-VAS	X (X – X)	X (X – X)	X	X – X		
X (X – X)	X (X – X)	X (X – X)				
All HA/KA eligible to receive study drug (population 3)	Any Venous thromboembolism	n (%)	n (%)	X	X – X	
	Type of Venous thromboembolism					
	Pulmonary embolism	n (%)	n (%)	X	X – X	
	Deep venous thrombosis	n (%)	n (%)	X	X – X	
	Both Pulmonary embolism and deep venous thrombosis	n (%)	n (%)	X	X – X	
	Above knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Below knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Death	n (%)	n (%)	X	X – X	
	Re-operation (90d)	n (%)	n (%)	X	X – X	
	Reoperation (6 months)	n (%)	n (%)	X	X – X	
	Re-admission	n (%)	n (%)	X	X – X	
	Major Bleeding	n (%)	n (%)	X	X – X	
	Pain and Function (median and IQR) [†]					
Oxford Hip Score			X	X – X		
Oxford Knee Score	X (X – X)	X (X – X)	X	X – X		
EQ-5D	X (X – X)	X (X – X)	X	X – X		
EQ-VAS	X (X – X)	X (X – X)	X	X – X		
X (X – X)	X (X – X)	X (X – X)				
All HA/KA including study drug exclusion (population 4)	Any Venous thromboembolism	n (%)	n (%)	X	X – X	
	Type of Venous thromboembolism					
	Pulmonary embolism	n (%)	n (%)	X	X – X	
	Deep venous thrombosis	n (%)	n (%)	X	X – X	
	Both Pulmonary embolism and deep venous thrombosis	n (%)	n (%)	X	X – X	
	Above knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Below knee deep venous thrombosis	n (%)	n (%)	X	X – X	
	Death	n (%)	n (%)	X	X – X	
	Re-operation (90d)	n (%)	n (%)	X	X – X	
	Reoperation (6 months)	n (%)	n (%)	X	X – X	
	Re-admission	n (%)	n (%)	X	X – X	
	Major Bleeding	n (%)	n (%)	X	X – X	
	Pain and Function (median and IQR) [†]					
Oxford Hip Score			X	X – X		
Oxford Knee Score	X (X – X)	X (X – X)	X	X – X		
EQ-5D	X (X – X)	X (X – X)	X	X – X		
EQ-VAS	X (X – X)	X (X – X)	X	X – X		
X (X – X)	X (X – X)	X (X – X)				

1366

1367 [†] at 6 months

1368

1369

1370 **Subgroup Analyses**

1371 Subgroup analyses for the primary outcome (treatment group differences by subgroup) will
1372 include THA or TKA, bilateral or unilateral procedures, a prior history of VTE or not for
1373 population 1, and primary arthroplasty or revision arthroplasty for population 3.

1374

1375 To assess treatment effects for each subgroup separately, cluster summaries will be
1376 produced for each subgroup. An interaction term between treatment group and subgroup
1377 (e.g., THA/TKA, bilateral/unilateral) will be added to the model for the primary outcome.
1378 The treatment differences for each subgroup will be assessed for non-inferiority. Since the
1379 trial was stopped early, the same composite method for the primary outcome and interim
1380 analyses will be used.

1381

1382 **Sensitivity analyses**

1383 Sensitivity analyses will be performed to determine: (a) the effect of high-volume
1384 arthroplasty sites; (b) sites with high and low overall registration rates; (c) sites that
1385 required multiple compliance audits; and (d) the effect of patients who take long-term
1386 aspirin therapy on the results of the analyses for the primary outcome in population 1. The
1387 same methods for the main analyses will be used.

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1389 **Order of planned analyses**

1390 Analyses will be performed in the following order:

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- Interim analyses of population 1
- Primary and secondary outcomes for population 1
- Subgroup analyses for population 1
- Primary and secondary outcomes for populations 2, 3 and 4
- Subgroup analyses of population 3
- Sensitivity analyses in population 1

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1399 **ADDITIONAL ANALYSES**

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1401 **Mortality Analysis**

1402 In addition to analysing between-group mortality for populations 1, 2, 3 and 4, the between-
1403 group 90-day mortality will be analysed for two further populations:

- 1404 3. All patients undergoing HA or KA over the duration of the study at participating
1405 hospitals, regardless of whether they were registered (total population described
1406 above, population 5)
- 1407 4. All patients undergoing elective THA or TKA over the duration of the study at
1408 participating hospitals regardless of whether they were registered (a subset of
1409 population 5)

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1411 Analysing these additional populations will assess the effect of implementing the VTE
1412 prophylaxis protocol on mortality at an institutional/departmental level (the unit of
1413 randomisation), on an intention-to-treat basis.

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1415 **Sub-Studies**

1416 Data from this trial will be used to form the basis of sub-studies. These will include a sub-
1417 study comparing rates of persistent wound drainage between LMWH and aspirin groups at
1418 two participating sites and a sub-study investigating rates of post-hospital discharge
1419 compliance to either study drug.

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1423 **Conclusions**

1424 CRISTAL aims to provide much needed definitive evidence about the effectiveness and

1425 safety of aspirin compared to LMWH in preventing symptomatic VTE following HA or KA.

1426 This statistical analysis plan details the study's planned analyses, including modifications to
1427 intended analyses to account for early stopping of the trial.

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1431 **DECLARATIONS**

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1433 **Ethics Approval**

1434 Ethics approval was granted by the Sydney Local Health District (Royal Prince Alfred Zone)
1435 Human Research and Ethics Committee, which is a lead ethics committee in Australia
1436 (approval number X18-0424) prior to study commencement. Site-specific approvals for each
1437 participating hospital were granted from the following ethics committees prior to study
1438 commencement: Calvary John James Memorial Hospital Australian Capital Territory (3-2019
1439 CRISTAL), Mid-North Coast Local Health District New South Wales (NSW – SSA/19/NCC/41),
1440 South Western Sydney Local Health District (NSW, SSA/10/LPOOL/22), Sydney Local Health
1441 District (NSW, SSA/19/RPAH/12, SSA/18/RPAH/762), Ramsay Hospital Research Foundation
1442 (NSW, HREC/18/RPAH/603), South Eastern Sydney Local Health District (NSW, 19/G/028,
1443 18/G/338), Nepean Blue Mountains Local Health District (NSW, SSA/19/NEPAN/11),
1444 Northern Sydney Local Health District (NSW, RESP/19/027, RESP/19/028), Metro North
1445 Hospital and Health Service (Queensland, HREC/18/RPAH/603), University of South Australia
1446 (SA – 201215), Calvary Health Care Adelaide (SA, 19-CHREC-F001), Southern Adelaide Local
1447 Health Network (SA, HREC/18/RPAH/603), Bendigo Health Victoria (SSA/48255/BHCG-2019),
1448 Barwon Health (18/246), Peninsula Health Victoria (SSA/48255/PH-2019), Western Health
1449 Victoria (48255), St John of God Health Care Victoria (1540), South Metropolitan Health
1450 Western Australia (WA – Western Australia, RGS0000001358), North Metropolitan Health
1451 (WA – RGS0000001358), Sir Charles Gardiner Hospital (WA – RGS0000001358) and
1452 Launceston General Hospital Tasmania (H0017903).

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1454 **Consent for publication**

1455 Not applicable.

1456 **Availability of data and materials**

1457 The datasets during and/or analysed during the current study will be made available from
1458 the corresponding author on reasonable request

1459 **Competing interests**

1460 The authors declare that they have no competing interests

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1464 MRFF has no authority over the design of the study or collection, management, analysis or
1465 interpretation of data or the writing of manuscripts for submission. No industry funding or
1466 other sources of funding are being used for this trial.

1467 **Authors' contributions**

1468 All authors listed have contributed to this protocol and the ICMJE guidelines were consulted
1469 for determining authorship. VS, IAH, RB, SG, SA, JMN, RdS, NP, INA, ML, DB, KC and TLK
1470 were responsible for the planning of the trial, protocol development and writing, TLK and

1471 NP were responsible for the description of the statistical analyses used. All authors
1472 reviewed the final version of this manuscript prior to submission.

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1476 Not applicable.

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1571 **CRISTAL: Aspirin or LMWH for VTE Prophylaxis After Hip or Knee Arthroplasty**

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1574 **Historical Summary of Amendments for Statistical Analysis Plan**

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1577 **Previous Statistical Analysis (In Protocol): 29 October 2020**

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1579 **Updated in Initial Statistical Analysis Plan: 14 May 2021**

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1581 **AMENDMENT 1 – Changes from Protocol to Initial Statistical Analysis Plan**

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1583

1584 1. **ITEM: STUDY OVERVIEW – Outcome Variables.** Change in time point for secondary
1585 outcome of mortality as written in protocol

1586 **CHANGE:** Mortality to be measured at 90 days only, not at 90 days and 6 months

1587 **RATIONALE:** Due to the lack of sensitivity in measuring VTE-related mortality at 6
1588 months and due to the lag in data availability for mortality, we changed the analysis
1589 to measure mortality at 90 days only

1590 2. **ITEM: MAIN ANALYSES**

1591 **CHANGE:** Inclusion of composite analysis method to account for incomplete
1592 crossover

1593 **RATIONALE:** After the interim analyses demonstrated that the stopping rule had
1594 been met, a composite analysis method was required given that a number of sites
1595 had not completed crossover

1596 3. **ITEM: MAIN ANALYSES – Subgroup Analyses.**

1597 **CHANGE:** Addition of patients with a prior history of VTE or not and of patients on
1598 long-term single antiplatelet therapy as subgroup analyses (not previously in study
1599 protocol)

1600 **RATIONALE:** Given this data was collected preoperatively, the senior author (IAH),
1601 corresponding author (VS), lead statistician (TLK) and senior statistician (NP) decided
1602 to add these subgroup analyses

1603 4. **ITEM: MAIN ANALYSES – Subgroup Analyses.**

1604 **CHANGE:** Clarification of the method used for subgroup analyses (using summaries
1605 by cluster and subgroup and an interaction term)

1606 **RATIONALE:** Methods used for subgroup analyses added to initial version of
1607 statistical analysis plan

1608 5. **ITEM: MAIN ANALYSES – Sensitivity Analyses.**

1609 **CHANGE:** Addition of sensitivity analyses to determine: (a) the effect of high-volume
1610 arthroplasty sites; (b) sites with high and low overall registration rates; (c) sites that
1611 required multiple compliance audits and method used for sensitivity analyses
1612 provided (same as subgroup analyses)

1613 **RATIONALE:** To determine if the results for the primary outcome were consistent
1614 amongst sites despite variations in the above parameters. Addition of methods used
1615 for sensitivity analyses

1616 6. **ITEM:** MAIN ANALYSES – Order of Analyses

1617 **CHANGE:** Order of planned analyses changed to include interim analyses and
1618 specification of the Haybittle-Peto threshold

1619 **RATIONALE:** The initial statistical analyses in the protocol did not include the interim
1620 analysis and this was included in the initial version of the statistical analysis plan

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Previous Statistical Analysis Plan (Initial): 14 May 2021

Updated in Statistical Analysis Plan (Final): 20 July 2021

AMENDMENT 2 – Changes from Initial Statistical Analysis Plan to Final Statistical Analysis Plan

1. **ITEM:** STATISTICAL ANALYSIS PLAN – Methods used for Interim Analyses
CHANGE: Addition of using harmonic mean weighting as a method to account for unequal cluster sizes
RATIONALE: Given early trial cessation and unequal cluster sizes, further information provided on how unequal cluster sizes were analysed
2. **ITEM:** STATISTICAL ANALYSIS PLAN – Methods for handling missing data
CHANGE: Addition of methods used for multiple imputation, “The imputation model will use auxiliary variables gathered from routine AOANJRR data (including age, sex, baseline health, pain and function, diagnosis and surgical factors), as well as cluster and period effects. One hundred datasets will be imputed at the patient level, then each dataset will be analysed using the main analysis method with cluster summaries and combined using Rubin’s rules.”
RATIONALE: More in-depth description provided to account for clustering
3. **ITEM:** STATISTICAL ANALYSIS PLAN – Methods for handling missing data
CHANGE: Addition of the use of inverse probability weighting as a sensitivity analysis for the primary outcome to handle missing data
RATIONALE: An additional method (to that of multiple imputation) to account for missing data
4. **ITEM:** STATISTICAL ANALYSIS PLAN – Trial and baseline characteristics
CHANGE: Addition of demographic information to Table 1 for participating hospitals (clusters) – number of joint replacements performed in year preceding trial, insurance status
RATIONALE: Prior to this, there was no demographic description of participating clusters, only numbers registered by each hospital
5. **ITEM:** MAIN ANALYSES: Analyses of primary and secondary outcomes
CHANGE: Description of composite methods used (cluster weighted estimates) for primary and secondary outcomes
RATIONALE: To explain methods used to mitigate bias and any possible loss of precision from sites that had incomplete crossover or did not crossover