

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

4

5

6 This trial protocol has been provided to give readers additional information about the
7 authors’ work.

8

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21

22 **INITIAL PROTOCOL: 28 September 2018**

23

24

STUDY PROTOCOL

25 **CRISTAL: A cluster randomised, crossover, non-inferiority trial of aspirin compared to low**

26 **molecular weight heparin for venous thromboembolism prophylaxis and safety in hip or**

27 **knee arthroplasty, a registry nested study**

28

29

30 **Study Protocol**

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

34 **1. Administrative information**

35 **1.1. Registration**

36 CRISTAL will be registered with the Australian and New Zealand Clinical Trials Registry
37 (anzctr.org.au).

38

39 **1.2. Funding**

40 This study is fully and solely funded by a 4-year Medical Research Futures Fund Lifting
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43 any role during its execution, analyses, interpretation of the data, dissemination or decision
44 to publish.

45

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118 Investigators on the MRFF grant. NP is the primary statistician. AH is the primary health
119 economist. All contributors participated in protocol development.

120 **1.4. Sponsor**

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124 **1.5. Study Coordination**

125

126 Committees

Committee	Members	Responsibilities
Writing Committee	IAH, SG, RB, NP, SA, VS	Protocol development and publication Preparation of principal publications (primary and secondary outcomes)
Steering committee	All investigators listed above (contributors)	Final protocol approval Study oversight Principal publication approval
Trial management committee	IAH, SEG, VS, SA, RdS, Project Coordinator, AOANJRR Registry Manager, AOANJRR PROMs project manager, SAHMRI rep (LG), RdS, SAHMRI IT, SAHMRI Data Management, SAHMRI Statistician	Integration with AOANJRR PROMs program Ethics approval Site liaison (recruitment and maintenance)
Data Quality Committee	IAH, Project Manager, ML, RdS	Data management Data quality audits
Outcome Verification Committee	ACORN Manager, JN, IA, BHC	Validating imaging verification of DVT and PE reported during patient follow up

127

128 Coordinating Centre

129 The day to day management of the trial will be the responsibility of the Australian
130 Orthopaedic Association National Joint Replacement Registry (AOANJRR) and South
131 Australian Health & Medical Research Institute (SAHMRI).

132

133 Other expert subgroups may be established throughout the project to advise on specific
134 elements and make recommendations should the need arise.

135

136 **1.6. Abbreviations**

137	AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
138	AAOS	American Academy of Orthopaedic Surgeons
139	ACORN	Arthroplasty Clinical Outcomes Registry
140	DVT	Deep Venous Thrombosis
141	ICJME	International Committee of Medical Journal Editors
142	LMWH	Low Molecular Weight Heparin
143	NICE	National Institute of Health and Care Excellence
144	NOAC	Novel Oral Anticoagulant
145	PE	Pulmonary Embolus
146	PROMs	Patient Reported Outcome Measures
147	THA	Total Hip Arthroplasty
148	TKA	Total Knee Arthroplasty
149	HA	Hip Arthroplasty
150	KA	Knee Arthroplasty
151	VTE	Venous Thromboembolism
152		

153 **2. Introduction**

154

155 **2.1. Background**

156 Over 100,000 total hip and total knee arthroplasty (THA, TKA) procedures are performed
157 each year in Australia.¹ Venous thromboembolism (VTE) comprises deep venous thrombosis
158 (DVT) and pulmonary embolus (PE) and is a recognised serious complication of hip and knee
159 arthroplasty surgery. Patients undergoing THA and TKA receive chemoprophylaxis for VTE
160 prevention, with most patients in Australia receiving either low molecular weight heparin
161 (LMWH) or aspirin (manuscript in preparation).

162

163 Guideline recommendations and surgeon preference for VTE prophylaxis vary due to a lack
164 of evidence regarding the comparative safety and effectiveness of these two common
165 chemoprophylaxis agents. Aspirin is a low cost, over-the-counter, safe medication that is
166 easy to take (one oral tablet daily). LMWH requires daily injection (often requiring
167 professional or family support), is more expensive and requires prescription, but has a larger
168 body of evidence of effectiveness. Previous studies comparing LMWH and aspirin have been
169 underpowered for effectiveness and for safety.

170

171 Currently, practice guidelines provide conflicting recommendations for VTE prophylaxis. The
172 National Institute of Health and Care Excellence (NICE) guidelines (United Kingdom) now
173 (2018) recommend using LMWH, aspirin or Novel Oral Anticoagulants (NOACs) for VTE
174 prophylaxis in TKA (aspirin is not recommended for THA) whereas aspirin was not
175 recommended in the previous version.² In the US, two main guidelines are used: those
176 recommended by the American College of Chest Physicians (ACCP)³ and those produced by
177 the American Association of Orthopaedic Surgeons (AAOS).⁴ Both recommend the use of
178 LMWH, NOACs or aspirin. Previously, the ACCP guidelines recommended against aspirin
179 whereas the AAOS guidelines recommended its use. As of 2012, both guidelines now allow
180 the use of aspirin for VTE prophylaxis, and as a result the prevalence of aspirin prescription
181 has increased.⁵ The Australian National Health and Medical Research Council guidelines
182 (2011) did not recommend aspirin, however these guidelines were rescinded in 2016 as they
183 were considered outdated.⁶

184

185 A number of systematic reviews (including data from up to 22 trials) have summarised the
186 evidence for VTE prophylaxis in joint arthroplasty, but most do not assess aspirin, despite
187 being commonly used and recommended by some practice guidelines.^{3-4, 7-13}

188

189 Two small systematic reviews were found, including data from six pharmacological trials
190 that had aspirin as a comparator.^{14,15} In both reviews, the evidence was dominated by one
191 trial of 778 patients comparing aspirin to LMWH in THA.¹⁶ This trial was stopped early due to
192 poor recruitment. Furthermore, all patients in the trial received LMWH for the first 10 days
193 before random allocation to aspirin or continued LMWH. This does not reflect the way that
194 aspirin is commonly used in Australia as aspirin is commenced during the acute care period.
195 Another five trials were also described, including a total of 936 patients, but these trials
196 were small, measured different outcomes, and were subject to bias.¹⁴ Both reviews
197 concluded that there is insufficient evidence to support recommendations on the use of

198 aspirin, and suggest larger trials are needed.^{14,15} A recent large trial compared aspirin to
199 rivaroxaban (a NOAC) for VTE prophylaxis in TKA and THA. A total of 3424 patients were
200 recruited in this cluster-randomised trial, however both groups were treated with
201 rivaroxaban for the first 5 days before being randomised to aspirin or rivaroxaban for the
202 following 2-4 weeks.¹⁷

203
204 While studies using administrative datasets should be interpreted with caution due to risk of
205 coding errors, incomplete data and difficulty fully adjusting for possible confounding, two
206 studies of aspirin using large administrative datasets have been reported. The first, from the
207 US, used data from 93,804 patients undergoing elective total knee replacement surgery.¹⁸
208 The study compared early (30 day) mortality and VTE between patients given warfarin,
209 LMWH and aspirin, adjusted for patient factors (age, sex, race, VTE risk, comorbidities),
210 institution factors (size, urban/rural) and a separate propensity score. No difference was
211 found in the mortality rates or rates of post-operative bleeding complications between the
212 three groups, and there was no difference in the rate of VTE comparing LMWH to aspirin.
213 A study using data from the National Joint Registry for England, Wales, Northern Ireland and
214 the Isle of Man analysed data from 108,584 patients undergoing THA comparing LMWH to
215 aspirin for VTE prophylaxis using multivariable modelling and propensity score matching.¹⁹
216 The adjusted analysis showed no significant difference in mortality up to 90 days post-
217 operatively but this difference became significant (favouring LMWH) on propensity score
218 matching. There was no difference in VTE complications or re-operations (up to 90 days)
219 between groups. The reported rates of VTE were very low, possibly due to under-detection.

220
221 The existing uncertainty regarding the relative safety and effectiveness of these different
222 medications to prevent VTE following arthroplasty and inconsistencies in available clinical
223 practice guidelines likely contribute to widespread clinical practice variation in Australia. A
224 national survey²⁰ and recent large cohort study involving 1,900 patients from 19 institutions
225 across Australia (manuscript under preparation) show that nearly all surgeons use some
226 form of chemoprophylaxis, with approximately 80% using LMWH and nearly half using
227 aspirin (approximately 40% of patients had more than one drug). The survey indicated that
228 those using LMWH were more likely to do so for fear of litigation.²⁰ Aspirin does not require
229 a prescription, is easier for patients to take (tablet rather than injection), is safe and is
230 inexpensive. Therefore, establishing non-inferiority would provide patients with a preferred,
231 effective, safe, cheaper and simpler method of VTE prophylaxis compared to LMWH.

232
233 The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) was
234 established in 1999 and reports on revision surgery and mortality after joint arthroplasty in
235 Australia, with close to complete national coverage. The AOANJRR has established a system
236 to directly capture data entered by patients pre- and post-operatively; this system is a
237 platform for the conduct of clinical trials and is incorporated as part of the AOANJRR (not a
238 standalone project). The proposed CRISTAL trial will be embedded within the Clinical Trials
239 Platform of the AOANJRR.

240 241 **2.2. Choice of comparators**

242 Wide practice variation is evident for VTE chemoprophylaxis in Australia due to both
243 surgeon uncertainty in the evidence for effect, and differences in surgeon preference.
244 Aspirin and LMWH are the two most frequently used drugs for VTE prophylaxis in THA and

245 TKR in Australia. Alternatives, such as warfarin and unfractionated heparin are not
246 commonly used in Australia and are not reflected in practice guidelines in this country.
247 NOACs are an alternative to LMWH and aspirin but are not commonly used in Australia.
248 Given aspirin's popularity, ease of use, safety profile and low cost but lack of evidence of
249 comparative effectiveness against the most commonly recommended drug (LMWH), we
250 considered aspirin to be the most suitable comparator to LMWH for this trial.

251

252 **2.3. Study hypothesis**

253 Aspirin is non-inferior to LMWH for prevention of VTE after THA and TKA surgery.

254

255 **2.4. Primary aim**

256 To compare the effectiveness and safety of aspirin to LMWH in preventing symptomatic VTE
257 after primary elective TKA and THA for osteoarthritis.

258

259 **2.5. Secondary aims**

- 260 • To compare the effectiveness and safety of aspirin to LMWH in preventing
261 symptomatic VTE after TKA and THA (elective *primary and revision*, for any reason)
- 262 • To compare the effectiveness and safety of aspirin to LMWH in preventing
263 symptomatic VTE after *revision* TKA and THA
- 264 • To compare the cost effectiveness of aspirin to LMWH for VTE prophylaxis after
265 primary elective TKA and THA for osteoarthritis
- 266 • Compare the safety (proportion of non-VTE complications) between groups
- 267 • An extension of the primary analysis for: THA and TKA separately; unilateral and
268 bilateral separately; below-knee DVT, above-knee DVT and PE separately

269

270 **2.6. Trial design**

271 A pragmatic multicentre, cluster-randomised, crossover, non-inferiority study with a
272 primary endpoint of patient-reported VTE at 90 days.

273

274 **3. Methods**

275

276 **3.1. Setting**

277 Eligible hospitals (public and private) performing HA and KA in Australia. The study will be
278 nested within the AOANJRR Clinical Trials Platform, an electronic platform for recruitment
279 and data collection for patients undergoing joint replacement surgery.

280

281 **3.2. Eligibility**

282 Hospital level

- 283 • Departmental (or surgeon group) agreement to participate in the study and adhere
284 to study protocols
- 285 • Use of intermittent calf compression device intra-operatively and post-operatively
286 until mobile
- 287 • Offer mobilisation day 1 post-operatively or earlier
- 288 • No change in other practices or protocols relevant to VTE over the course of the
289 study (e.g. tourniquet use, anaesthetic type).

290 Patient level

- 291 • Adults (age 18 and older)
- 292 • Receiving elective primary or revision KA or HA for any reason

293

294 Exclusion criteria

295 As a pragmatic study, all patients undergoing elective revision and primary arthroplasty for
296 any reason during the study period will be included. The only exclusion for a department is if
297 the volume of primary elective THA and TKA for osteoarthritis is less than 222 joints per year
298 (as this renders the site unable to recruit the required sample size required for the primary
299 analysis within the prespecified study timeframe). For the primary analysis, the following
300 exclusions will apply (at a patient level):

- 301 • Partial joint replacement
- 302 • Revision surgery
- 303 • Non-osteoarthritis diagnosis
- 304 • Use of warfarin, NOAC or dual antiplatelet therapy pre-operatively

305

306 **3.3. Intervention**

307 Each site will be allocated to two consecutive periods of standard protocol of aspirin and
308 standard protocol of LMWH for VTE prophylaxis with the order of the two periods
309 determined by randomisation at a 1:1 ratio on an open label basis.

310

311 Each site will adhere to the initially randomised protocol for a time period based on surgical
312 volume aiming for 222 patients eligible for the primary analysis per group. Maximum time
313 period for each group will be 12 months. Total recruitment (all arthroplasties) to each group
314 is expected to be 250-300 patients.

315 Patients will be informed of the trial during initial data entry. Patients will be specifically
316 asked at the time of study entry for consent for follow up, for use of their data in research,
317 and use of linked data to measure and verify surgical outcomes (Appendix 1). Patients will
318 not be individually consenting to be randomised to either aspirin or LMWH, as both drugs
319 represent standard practice and randomisation is not at the patient level. Further details on
320 the consent process is listed in protocol (section 4.3).

321
322 Patients will be followed at 90 (75-105) days and 6 (5-7) months, electronically with
323 telephone back up. To ensure minimal inconvenience a maximum of three reminders will be
324 sent to the patient to complete their follow up CRISTAL questions.

- 325 • 1st reminder – upon registration
- 326 • 2nd reminder – 3 days from the first reminder
- 327 • 3rd reminder - 4 days from the second reminder

328 There will be no change to usual medical follow up (clinic attendance, investigations etc.)
329 except that routine venous imaging is not to be used (currently not recommended and not
330 commonly used).

331
332 Aspirin will be administered orally at 100mg (85-150 mg permitted if previously prescribed)
333 daily for 28-35 days (hips) or 10-14 days (knees) commencing the day of or day after
334 surgery.

335
336 LMWH will be administered as enoxaparin (Clexane) 40mg subcutaneously daily, for 28-35
337 days (hips) or 10-14 days (knees) commencing the day of or day after surgery. Patients will
338 be taught to self-administer while in hospital. For those unable to self-administer, the
339 injections will be given by family members, a community nursing service or their local
340 doctor, depending on local arrangements.

341
342

3.4. Adherence

343 Patients may discontinue the drug if they have an allergy or adverse event related to the
344 drug.

345

346 The study drug may be withheld if post-operative wound ooze continues to 36 hours post-
347 operatively, with recommencement 48 hours later if settled.

348

349 Inpatient adherence during the acute care period will be determined by a chart audit of a
350 sample of patients from a sample of hospitals.

351

352 Post-discharge adherence will be determined by patient report during follow up at 90 days.

353

354

3.5. Concomitant care

355 All patients will have intermittent compression devices intra-operatively and post-
356 operatively until mobile. All patients will be offered mobilisation on day one post-surgery
357 unless surgically or medically contraindicated.

358

359 Patients taking (non-aspirin) oral anti-platelet therapy pre-operatively may have their
360 medication withheld for one week pre-operatively if advised by their treating doctor and
361 will recommence their usual medication (in addition to any study medication) at day 7 post-
362 operatively or when safe to do so.

363
364 Routine doppler screening for DVT (in asymptomatic patients) will not be permitted by
365 participating sites.

366
367 Patients taking aspirin (85-125mg daily) pre-operatively will take this drug in the usual dose
368 post-operatively in place of the study drug for those in the aspirin group, and in addition to
369 LMWH for those in the LMWH group. The aspirin may be stopped pre-operatively if advised
370 by their treating doctors.

371

372 **3.6. Primary outcome**

373 The primary outcome is verified, symptomatic VTE (DVT or PE) at 90 day follow up.
374 All reports of VTE will be verified by contact with treating doctors and institutions and
375 obtaining any imaging reports. VTE will be deemed verified by the independent Outcome
376 Verification Committee. The absence of VTE will be verified in a random sample of 222
377 patients reporting an absence of VTE, by auditing treating doctors and institutions. Patients
378 will be asked if they are still taking anticoagulant medication at 90 day follow up and those
379 who are will be probed for the reasons for ongoing anticoagulation.

380

381 **3.7. Secondary outcomes**

382

- 383 1. Safety. Any bleeding complication leading to reoperation. Any reoperation or
384 readmission related to the surgery or anticoagulation (defined as haemorrhage,
385 infection, dislocation, manipulation, fracture, loosening or migration of implant,
386 death, other)
- 387 2. Costs. Cost of anticoagulation, cost of hospital stay, need for further health resource
388 utilisation (e.g. nurse or GP visits) and complications (see list below)
- 389 3. Adherence. Proportion of patients taking the drug continuously (no more than 2
390 consecutive days missed) for the recommended minimum period
- 391 4. PROMs. Health-related quality of life (EQ5D-5L), Oxford hip and knee scores and
392 patient-rated satisfaction and improvement

393 Complications will be classified into the following groups by the Outcome Verification
394 Committee:

- 395 • Readmission related to the original surgery or associated treatment (including
396 bleeding and VTE related)
- 397 • Reason for readmission (infection, dislocation, stiffness, fracture, wound dehiscence,
398 implant loosening, migration or failure, wound bleeding, other bleeding)
- 399 • Reoperation on the same joint
- 400 • Type of reoperation (treatment of infection, reduction of dislocation, manipulation
401 under anaesthesia, fracture treatment, wound repair, implant loosening, migration
402 or failure, non-joint related surgery)

- 403 • DVT below knee
- 404 • DVT above knee
- 405 • PE
- 406 • Death

407
408

3.8. Participant timeline

Time Point	Data Collection Questions and Instruments
Pre-operative	Current anticoagulation use (yes/no and drug) Age Sex Joint (hip or knee) Side Unilateral vs bilateral Primary or revision ASA grade BMI Oxford Hip or Knee Score EQ-5D-5L EQVAS Low back pain Joint pain (numeric rating scale 0-10) Expectations (pain and improvement)
90 days	VTE (DVT or PE) Adherence (did you use pills or injections to prevent a blood clot post-operatively, for how long?) Current use of anticoagulants (yes/no, which one) Complications (asked individually, as per complication list)
6 months	VTE (DVT or PE) Complications (asked individually, as per complication list) Oxford Hip or Knee Score EQ-5D-5L Joint pain (scale 0-10) Satisfaction with outcome of surgery Patient-rated improvement

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EQ-5D-5L (Appendix 2)

The EQ-5D is a standardised measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal.

(22) The survey includes 5 health outcome domains that can be summarised into a utility score. (21) These include:

- Mobility
- Self-care
- Usual Activities
- Pain/Discomfort
- Anxiety/Depression

420 There are five descriptive sentences under each heading and patients are directed to tick
421 one box that best describes their health on that day. There is also a visual analogue scale
422 (VAS) that addresses health state. (21)

423

424 Oxford Hip or Knee Scores (Appendix 3)

425 The Oxford hip (OHS) and knee (OKS) scores were developed in the mid-1990s. The scores
426 were developed to assess the outcome of hip and knee replacements as well as shoulder
427 surgery (including shoulder replacement) and were designed to be completed by patients in
428 order to minimise potential bias. (23) Both two instruments include 12 questions to assess a
429 patient's capacity to undertake general activities of daily living, about their affected hip or
430 knee.

431

432 Pre-operative anticoagulation use (Appendix 4)

433 Questions listed below will be presented pre-operatively to determine any history of VTE
434 and current use of Anti-coagulant medications. The questions were reviewed and approved
435 by consumer representatives and will be specific to the medications and the site of DVT.

- 436 1. Do you normally take (or are you currently taking) blood thinning medication
437 routinely?
- 438 2. Do you know what blood thinning medication are taking?
- 439 3. Have you ever been diagnosed with a clot in your legs (Deep Vein Thrombosis (DVT)
440 or lungs (Pulmonary Embolism (PE))?
- 441 4. When did your most recent (or only) clot in your legs (DVT) or lungs (PE) occur?

442 Post-operative VTE symptoms and occurrence (Appendix 4)

443 The following questions will be presented post-operatively at both 90 days and 6 months to
444 gauge patient's surgery outcome Questions 1 to 3 are only specific for the 90 days data
445 collection point and will not be asked on the 6 months data collection point.

- 446 1. Did you take your POST-surgery blood thinning medication (to avoid blood clots)
447 after leaving hospital following your joint replacement operation?
- 448 2. Do you know what blood thinning medication are taking?
- 449 3. How many days di you take the blood thinning medication after your (HIP/KNEE)
450 replacement operation?
- 451 4. Since your joint replacement surgery, have you been diagnosed with a blood clot in
452 your legs (DVT) or lungs (PE)?
- 453 5. Have you had any further surgery on your replaced joint (apart from when it was put
454 in)?
- 455 6. Please select the reason(s) for the additional surgery/surgeries? (select all that
456 apply)
- 457 7. Have you had any serious bleeding from anywhere else in your body not related to
458 your joint replacement?

459

460 **3.9. Sample size**

461 A pooled analysis of 47 RCTs and cohort studies estimated the incidence of symptomatic
462 VTE to be approximately 1%. The previous RCT of aspirin versus LMWH used an event rate
463 of 1.5% and a minimum clinically important difference of 2.0%. A recent large cohort study

464 of 1900 hip and knee replacement patients from 19 institutions across Australia (manuscript
465 under preparation) showed an incidence of symptomatic VTE of 2.9% up to 90 days post
466 surgery.

467

468 Using an estimated overall event rate of 2%, and a non-inferiority margin (for aspirin
469 compared to LMWH) of 1% and using a power of 80% and a one-sided significance level of
470 0.05, 4,800 patients would be required for an individual randomised trial. For a cluster
471 randomised crossover trial, we will require 8,000 patients to account for correlation
472 between and within clusters. We will therefore recruit a minimum of 400 patients (200 per
473 treatment arm) from each of 20 institutions (clusters).

474

475 Allowing for 10% loss to follow up (estimated at 5% based on current similar systems), 8,888
476 eligible patients (a minimum of 222 per group from a minimum of 20 sites) will be recruited.

477

478 **3.10. Recruitment**

479 Hospitals will be approached individually by the lead CI and the study team, as appropriate.
480 A site will be considered eligible if they can recruit 222 eligible patients (for the primary
481 analysis) within 12 months, and recruit for up to 24 months. Departmental (or surgeon
482 group) agreement with the study protocol and the individual treatment protocols (for each
483 group) will be required. Sites where a subgroup of attending surgeons agree to participate
484 will be included if the number of eligible patients for that group of surgeons per year is at
485 least 222. A site investigator will be nominated for each site

486

487 **3.11. Randomisation**

488 Each site will be randomised with a 1:1 allocation with a computer generated random
489 sequence. Simple randomisation will be used (no use of blocks, no stratification). The
490 allocation will refer to the first intervention.

491

492 **3.12. Blinding**

493 Sites will not be blinded to group allocation. Patients will be aware of a study comparing
494 different treatments for VTE prevention but will not know the specific details of the study
495 and will therefore be blind to the specific interventions and outcomes of the trial. Outcomes
496 will be self-reported with verification of the primary outcome by the Outcome Verification
497 Committee. Where outcome reporting is by phone (back up for failure to capture patients
498 reported outcomes electronically and where verification is performed) those outcome
499 assessors will be blinded to group allocation.

500

501 The Outcome Verification Committee will be presented with deidentified cases for
502 assessment. The statistical analysis will be blinded. The Writing Committee will be blinded
503 and will prepare separate manuscripts based on the possible group allocations.

504

505 **3.13. Data collection**

506 Data collection for baseline data and follow up at 90 days and 6 months will be patient-
507 reported electronically (via tablet, phone or computer) using direct data entry. For patients

508 not responding to email and SMS follow up, telephone contact will be used to administer
509 the surveys verbally.

510

511 Pre-Operative

512 When collected electronically by patients, data will be directly entered into the AOANJRR
513 Clinical Trials Platform.

514

515 Some patients may not have direct access to the internet. This is especially a factor for older
516 patients and patients from lower socioeconomic groups²⁷. Another group who could
517 potentially be excluded from implementing this approach to data collection are non-English
518 speaking patients. To overcome these barriers patients will be given the option to nominate
519 a 'proxy' e.g. family member or friend to assist them with completing the instruments and
520 receive reminders electronically on their behalf. Information will be collected on whether
521 the patient had assistance to complete the CRISTAL questions and these data will be
522 reviewed during the analysis.

523

524 There will be various methods and procedures implemented at the different hospitals to
525 register patients and request them to complete the CRISTAL data online. Ideally the patients
526 will complete pre-operative CRISTAL data immediately when first approached, however, this
527 may not always be possible. There is functionality built into the system to email a patient
528 the link to the website to complete the CRISTAL requirements at a time that is convenient
529 for them.

530

531 Some hospitals participating in CRISTAL already routinely collect PROMs and wish to
532 continue to do so using their own systems. In these cases, the AOANJRR will work with the
533 hospital to simplify the data collection process and avoid duplication of collection. A data
534 sharing agreement will be entered into between the hospital and the AOANJRR whereby
535 data can be exported from the current system and imported into the AOANJRR Clinical Trials
536 Platform. There will be a secure file sharing facility established within the web application to
537 ensure secure transfer of confidential information. The data provided will be reviewed by
538 the data manager prior to upload into the database to confirm quality and completeness.

539

540

541 Post-Operative

542 Follow up will be by telephone until the electronic data capture system is built and
543 telephone follow up will be used as back up for the electronic follow up once in place.
544 Patients will be able to login and complete their 90 day follow-up from 75 days and 6-month
545 follow-up from 5 months.

546

547 The Arthroplasty Clinical Outcomes Registry (ACORN) has been contracted to complete the
548 follow-up phone calls. ACORN was selected because this Registry already collects PROMs
549 centrally for hospitals, predominately in NSW, and the staff have expertise in this area.

550

551 **3.14. Data management**

552 Data quality will be checked monthly under the supervision of the Data Quality Committee.

553

554 **3.15. Statistical analysis**

555 The primary analysis will be restricted to elective primary THA and TKA for osteoarthritis
556 and will test between-group difference in the proportion of cases developing VTE within 90
557 days for non-inferiority of aspirin at a margin of 1%, on an intention to treat basis. The
558 primary analysis will use a multi-level modelling (MLM) framework. This framework
559 effectively models the complex correlation structure of the cluster randomised crossover
560 design but utilizes the power available from individual level data. The model allows for
561 correlation of patients within hospitals and also correlation between study periods within
562 the same hospital. Multiple imputation will be used to account for missing outcome data,
563 should a patient be lost to follow-up at 90 days. Possible confounders will be gathered from
564 routine AOANJRR data (including age, sex, baseline health pain and function, diagnosis and
565 surgical factors).

566
567 This analysis will be performed on the primary and secondary outcomes.

568
569 Secondary analyses:

- 570 1. An extension of the primary analysis to patients receiving elective Knee Arthroplasty
571 KA and Hip Arthroplasty (HA) (primary and revision, for any reason)
- 572 2. An extension of the primary analysis to patients receiving revision KA and HA
- 573 3. Economic analysis (see below)
- 574 4. Compare the safety (proportion of non-VTE complications) between groups, as a
575 total and for each individual complication
- 576 5. An extension of the primary analysis for: THA and TKA separately; unilateral and
577 bilateral separately; below-knee DVT, above-knee DVT and PE separately
- 578 6. Compare VTE and complication rates in those receiving LMWH alone to those
579 receiving LMWH and oral anticoagulation (patients in the LMWH group already
580 taking oral anti-platelet therapy).

581
582 Cost effectiveness of prophylactic aspirin compared to LMWH will be evaluated from a
583 health system perspective. Data for resource use associated with treatments and
584 complications will be taken from trial data within the AOANJRR, supplemented by linked
585 MBS and PBS data and valued at total public prices (Medicare and national average
586 diagnosis related group [DRG] costs). Costs include drug acquisition, out of hospital doctor
587 fees charged, tests, in hospital medical and pharmaceutical costs post-surgery. Survival at
588 one year and quality of life measured using EQ5D at baseline, 90 days and six months will
589 allow calculation of differences in Quality Adjusted Life Years (QALYs) between groups.
590 We will calculate the cost per QALY for each treatment comparison as the difference in
591 mean costs divided by the difference in mean outcomes (quality adjusted survival as QALYs)
592 over the duration of the trial, using mixed model regression analysis to adjust for
593 differences at baseline and clustering by site. We will extrapolate from the trial evidence
594 and simulate the long-term comparative cost effectiveness of each treatment including long
595 term complication and outcomes stage to age 101 years in a decision analytic model.

596

597 **3.16. Data monitoring and cleaning**

598 A separate Data Quality Committee will be established to monitor data management and
599 quality.

600 A separate safety monitoring committee will not be established and no stopping rules will
601 be used as both interventions are commonly used and recommended treatments. No
602 interim analysis will be performed; this will reduce the chance of early stopping due to
603 spurious findings. Adverse events (separate to complications listed under secondary
604 outcomes) will be monitored by the Trial Management Committee).

605

606 **3.17. Auditing and Data validation**

607 Positive outcomes (reported VTE) reported by patients will be confirmed by contacting
608 hospitals or treating doctors and retrieving imaging reports. These will be adjudicated by
609 the Outcome Verification Committee.

610

611 A sample of negative outcomes (patients reporting the absence of VTE) will be verified in a
612 similar manner in a random sample of patients with negative outcomes.

613 Complications will be adjudicated by the Outcome Verification Committee.

614 ANZMUSC will audit the study.

615

616 The AOANJRR Data Linkage project will be used to test the accuracy of outcome reporting
617 (readmission, re-operation, drug prescriptions). The AOANJRR also links to the National
618 Death Index (NDI) twice a year (February and September). If a patient, who has participated
619 in the CRISTAL project, is flagged as deceased in the AOANJRR database this can also be
620 transferred to the CRISTAL system and no further contact will be made, reducing distress
621 for families.

622

623 **4. Ethics and dissemination**

624

625 **4.1. Ethics approval**

626 The study will be submitted to Sydney Local Health District (RPAH Zone) human research
627 ethics committee for approval. Following approval, the study will be submitted to local
628 ethics committees and Research Governance Offices as required for each site. Refer to the
629 Table 1 for sites.

630

631 Table 1: List of Sites for Ethics approval by Sydney Local Health District (RPAH Zone)

State	Hospital
NSW	Canterbury Hospital
NSW	Coffs Harbour
NSW	Fairfield Hospital
NSW	Gosford Public Hospital
NSW	Hornsby Ku-ring-gai Hospital
NSW	Nepean Hospital
NSW	Prince of Wales Hospital
NSW	Royal Prince Alfred Hospital (Institute of Rheumatology and Orthopaedic Surgery)
NSW	Royal North Shore Hospital
NSW	Ryde Hospital
NSW	Sutherland Hospital
QLD	Mater Adults Hospital
QLD	Prince Charles Hospital
SA	Flinders Medical Centre
VIC	Bendigo Hospital
VIC	Epworth Private Hospital
VIC	Frankston Hospital
VIC	University Hospital Geelong Barwon Health
VIC	Western Hospital Footscray
VIC	Western Hospital Williamstown
WA	Fremantle Hospital
WA	Osborne Park Hospital
WA	Royal Perth Hospital
WA	Sir Charles Gairdner Hospital

632

633 **4.2. Amendments**

634 Any modifications to the protocol which may impact on the conduct of the study, potential
635 benefit of the patient or may affect patient safety, including changes of study objectives,
636 study design, patient population, sample sizes, study procedures, or significant
637 administrative aspects will require a formal amendment to the protocol. Such amendment
638 will be agreed upon by the Steering Committee and approved by the Ethics Committee prior
639 to implementation and site notification.

640 Administrative changes of the protocol are minor corrections and/or clarifications that have
641 no effect on the way the study is to be conducted. These administrative changes will be
642 agreed upon by Trial Management Committee and will be documented in a memorandum.
643 The Ethics Committee/IRB may be notified of administrative changes at the discretion of
644 Trial Management Committee.

645
646
647

4.3 Consent to project participation

648 Individual consent is not being sought for randomisation or use of the study drugs. This is
649 because randomisation is not occurring at the patient level and because both study drugs
650 represent current standard practice. Consent is being sought for the collection and use of
651 patient data, as per standard protocol for the AOANJRR Clinical Trials Platform. The Clinical
652 Trials Platform uses the same consent process (and near identical data collection) as the
653 AOANJRR PROMS Pilot Project which has received ethics approval (Reference: X18-0057 &
654 HREC/18/RPAH/90).

655

Consent to AOANJRR Clinical Trials Platform

657 Consent will be obtained electronically. All data collection for this project is electronic. This
658 provides efficiency and effectiveness (less error) and allows a better way to impart
659 information relevant to the consent process. The participant information and consent form
660 will be displayed on the screen. It contains all elements required for a consent form (see
661 Appendix 1). The information under each statement will be expandable. Patients will be
662 provided the option to 'agree to the statement' or 'learn more'. If the patient agrees they
663 will be navigated to the next statement. If the patient chooses to learn more the additional
664 information will be displayed. Once all statements have been agreed to the patient will be
665 able to choose whether they give consent or no longer wish to participate in the study. If
666 the patient consents to participate they will be directed to the next page where they can
667 complete the required pre-operative CRISTAL questions relevant to their procedure. If the
668 patient chooses not to consent after the initial registration, then all personal information
669 collected at registration will be deleted from the database. The only data that will be
670 retained is:

671
672
673
674

- Hospital Name (if available)
- Surgeon Name (if available)
- Date of registration If the patient elects to withdraw at the time of their post-operative assessment, then no further follow-up will be undertaken.

675

676 Electronic Consent Process Flowchart

677

678 **Patient registered in AOANJRR trials**
679 **system**

680 <https://aoanjrrtrials.sahmri.com>

681

682

683 **Patient reviews Patient**
684 **Information**

685

686

687 **Patient confirms they**
688 **understand what is required**

689 For each statement the patient will confirm
690 they understand what is required for each
691 statement

692

693

694

695 **Patient confirms**
696 **Consent to Participate**

697

698

699 **Progress to completion of**
700 **CRISTAL questions**

701

702

703

704 Consent to share data

705 After completing the pre- and post-operative CRISTAL questions, patients will be given the
706 option (at each time point) to share their data with their treating surgeon. If the patient
707 consents for their results to be shared the treating surgeon will be able to download patient
708 level data from the CRISTAL system. If patients do not consent to share these data, their
709 information will not be provided to the surgeon.

710

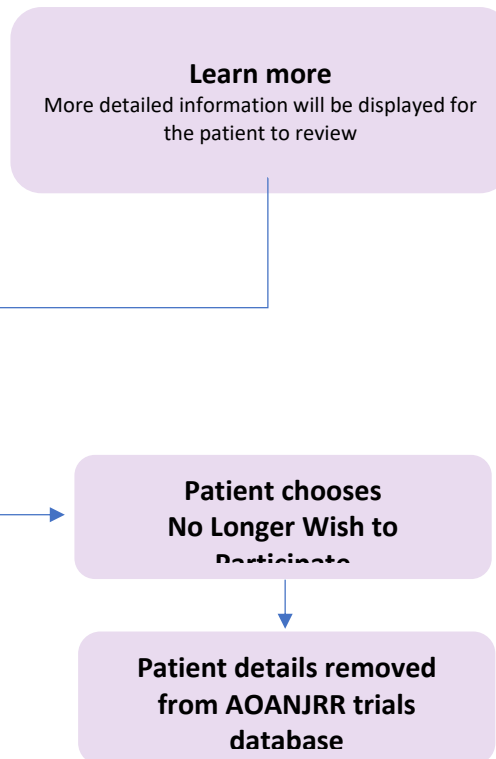
711 Waiver of Consent

712 We are requesting waiver of consent for two different aspects of this project. Firstly, we
713 require waiver of consent for the 'registration' process which involves getting basic contact
714 information from potential participants so that they can be contacted and formally invited
715 to participate and consent. An identical process of registration has been previously
716 approved for the AOANJRR PROMs pilot. Secondly, we request waiver of consent for
717 randomisation and treatment with the study drugs (the intervention) that make up the
718 CRISTAL project.

719

720 Each request for waiver of consent are listed below: firstly, for the 'registration' process
721 (clinical trials platform), and secondly for specific involvement (randomisation and
722 treatment) in the CRISTAL study.

723



724 Waiver of consent Part 1: patient registration prior to initial patient contact.

725 The request for waiver of consent only applies in some instances. Specifically, some
726 patients will be registered in the system by hospital administrative staff or their treating
727 surgeon. Once this registration occurs the patient will subsequently be sent an email by the
728 AOANJRR to obtain consent electronically prior to completing the CRISTAL questions. The
729 data that will be stored within the AOANJRR between registration and consent includes:

- 730 • Patient First Name
- 731 • Patient Middle Name
- 732 • Patient Surname
- 733 • Date of Birth
- 734 • Postcode
- 735 • Hospital
- 736 • Surgeon name
- 737 • The joint that will be operated on (Hip, Knee, Shoulder)
- 738 • The side that will be operated on (Left, Right, Both)
- 739 • Patient contact details such as phone number and email address

740 It is important to emphasise that the AOANJRR will collect almost all the registration
741 information when it is provided at the time of surgery except for phone number and email
742 address. We believe this request satisfies the criteria as detailed in the National Statement
743 on Ethical Conduct in Human Research (2013, chapter 2.3) for providing a waiver of consent.
744 This waiver of consent is only for collecting information through the registration process and
745 not to the completion of the CRISTAL instruments.

746
747 a. Involvement in the research carries no more than low risk

- 748 • This is a low risk project particularly as the waiver is specifically required to
749 defer involvement in the project after the registration as a mechanism to
750 ensure that patients that take this option can complete their involvement in
751 the project at a time that is most suitable to them.

752 b. the benefits from the research justify any risks of harm associated with not seeking
753 consent

- 754 • There is no risk of harm associated with storing the patient's details prior to
755 collecting consent. The Registry will receive almost all of this data at the time
756 of the procedure. It is being requested to enhance participant convenience.
757 The AOANJRR is a declared Federal Quality Assurance Activity and all data is
758 managed in accordance with that declaration which includes the use of high
759 level security systems.

760 c. it is impracticable to obtain consent (for example, due to the quantity, age or
761 accessibility of records)

- 762 • It is not feasible to collect patient consent prior to the registration as it is
763 necessary to link the electronic consent to the individual patient identified by
764 the registration process. If the consent is completed prior to registration then
765 the consent will be unidentified.

- 766 d. there is no known or likely reason for thinking that participants would not have
767 consented if they had been asked
- 768 • Patients will verbally consent to have their details recorded at registration
769 and this will be subsequently confirmed prior to completion of the CRISTAL
770 Questions instruments. It is the AOANJRR experience that very few patients
771 are reluctant to have their data included in the Registry.
- 772 e. there is sufficient protection of their privacy
- 773 • The AOANJRR is a declared Federal Quality Assurance Activity
- 774 • Systems are in place to ensure individual patient data remains confidential
- 775 • A third-party security review and penetration testing will be undertaken prior
776 to commencement of data collection
- 777 f. there is an adequate plan to protect the confidentiality of data
- 778 • SAHMRI which is the organisation responsible for managing AOANJRR data
779 has existing security systems, policies and procedures in place as well as
780 software barriers to protect personal information and ensure confidentiality.
781 These systems are already in place for data contained within the AOANJRR
782 and the CRISTAL data will be treated identically (see Appendix 5).
- 783 g. in case the results have significance for the participants' welfare there is, where
784 practicable, a plan for making information arising from the research available to
785 them (for example, via a disease-specific website or regional news media)
- 786 • Patients will be able to review their own results and how they compare to
787 the national average via online dashboards.
- 788 h. the possibility of commercial exploitation of derivatives of the data or tissue will not
789 deprive the participants of any financial benefits to which they would be entitled
- 790 • The AOANJRR is a not for profit organisation which does not use the data it
791 collects for commercial gain.
- 792 i. the waiver is not prohibited by State, federal, or international law
- 793 • There are no applicable laws prohibiting this waiver.

794 Waiver of consent Part 2: participant randomisation and treatment under the CRISTAL
795 study.

796 The CRISTAL study is seeking a waiver of individual consent for the intervention proposed by
797 the study (the administration of either aspirin or LMWH). It is recommended that all
798 patients who undergo THA or TKA require chemoprophylaxis to prevent VTE, with-holding
799 or not giving chemoprophylaxis is considered against the current standard of care. We
800 believe this request satisfies the criteria as detailed in the National Statement on Ethical
801 Conduct in Human Research (2013, chapter 2.3) for providing a waiver of consent.
802

- 803 a. involvement in the research carries no more than low risk
804
805 • This is a low risk project as it involves interventions that are currently used in
806 standard practice (aspirin and LMWH for VTE prophylaxis). The additional
807 questions asked of patients is not considered of sufficient risk or burden to justify
808 specific consent as they are also part of routine practice (follow up health and
809 complication questionnaires) for most sites. Furthermore, randomisation is not
810 at the patient level – it occurs at the site level (cluster randomisation).
811
- 812 b. the benefits from the research justify any risks of harm associated with not seeking
813 consent
814
815 • There is no additional harm from this study as both intervention arms are
816 standard practice. There may be an imbalance of harms between groups, but this
817 study is necessary to determine this, and this highlights the benefits that will
818 arise from the research as there is currently insufficient evidence to guide
819 practice which has resulted in widespread practice variation.
820
- 821 c. it is impracticable to obtain consent (for example, due to the quantity, age or
822 accessibility of records)
823
824 • Specific consent for CRISTAL would require an additional consent process (in
825 addition to the consent for the use of data). This would make entry into the
826 research cumbersome and confusing and would likely lead to a higher proportion
827 of patients abandoning data entry, reducing the scientific validity of the study.
828
- 829 d. there is no known or likely reason for thinking that participants would not have
830 consented if they had been asked
831
832 • Patients currently receive VTE prophylaxis without consent as part of standard
833 practice and we consider the process of this trial to be similar to standard
834 practice.
835
- 836 e. there is sufficient protection of their privacy
837
838 • The AOANJRR is a declared Federal Quality Assurance Activity
839 • Systems are in place to ensure individual patient data remains confidential
840 • A third-party security review and penetration testing will be undertaken prior to
841 commencement of data collection
842
- 843 f. there is an adequate plan to protect the confidentiality of data
844
845 • SAHMRI which is the organisation responsible for managing AOANJRR data has
846 existing security systems, policies and procedures in place as well as software

847 barriers to protect personal information and ensure confidentiality. These
848 systems are already in place for data contained within the AOANJRR Clinical
849 Trials platform and the CRISTAL data will be treated identically (see Appendix 5)

850

851 g. in case the results have significance for the participants' welfare there is, where
852 practicable, a plan for making information arising from the research available to
853 them (for example, via a disease-specific website or regional news media)

854

855 • It is the intent of the researchers that the results of the CRISTAL study will be
856 synthesised and published as a clinical trial in a peer reviewed journal. The only
857 trial data of relevance to the patients will be the development of adverse events
858 or VTE, which will be known to them at the time. Other data collected as part of
859 the Registry will be made available to patients as per usual practice.

860

861 h. the possibility of commercial exploitation of derivatives of the data or tissue will not
862 deprive the participants of any financial benefits to which they would be entitled

863

864 • The CRISTAL study is receiving no industry or pharmaceutical corporation
865 support and does not aim to make any financial profit or gain during the trial or
866 after publication of the results. It will not deprive participants of any financial
867 benefits.

868

869 i. the waiver is not prohibited by State, federal, or international law

870

871 • There are no applicable laws prohibiting this waiver.

872

873 **4.4 Confidentiality**

874 AOANJRR is required to have highly secure data protection systems to secure the identified
875 information which it currently holds as this is an absolute requirement under its Federal
876 Quality Assurance Activity.

877

878 SAHMRI has been contracted to build the AOANJRR Trials which will be utilised for CRISTAL.
879 SAHMRI has existing security systems, policies and procedures in place as well as software
880 barriers to protect personal information and ensure confidentiality. (Appendix 5)

881

882 As this will be a fully electronic system, accessible online, which will store patient's personal
883 and contact details, additional security activities have been included in the AOANJRR Trials
884 system development:

- 885 • A third-party security review of the infrastructure and application design, prior to
886 development starting
- 887 • A penetration test of the application prior to commencement of data collection

888

889 Patient Confidentiality

890 All patient data will be managed in accordance with the Guidelines for the Protection of
891 Privacy in the Conduct of Medical Research. Patient contact details will only be used for the

892 purpose for which they were collected and will be stored securely and confidentially.
893 Patients will not be identified in any reports, manuscripts or presentations derived from the
894 CRISTAL project.

895

896 Surgeon Confidentiality

897 No individual surgeons will be identified in any reports or manuscripts.

898

899

900 **4.5 Risk to Patients**

901 As patients will be treated with the standard protocol for both LWMH and Aspirin, this study
902 poses no foreseeable risk, harm or discomfort to patients beyond the inconvenience
903 associated with completing the study questionnaires at three-time points. We recognise the
904 burden of survey completion but also recognise that patient outcome collection is now
905 becoming a standard part of patient care and will be standard practice in most sites
906 recruiting for CRISTAL.

907

908 As patient follow-up is a requirement of this project all efforts will be made not to contact
909 the relatives of a deceased participant. The AOANJRR links to the National Death Index (NDI)
910 twice a year (February and September). If a patient, who has participated in the CRISTAL
911 project, is flagged as deceased this will be transferred to the AOANJRR trials when the
912 procedure date is linked. This will stop any automated and manual reminders being
913 triggered

914

915 **4.6 Declaration of interests**

916

917 Ian Harris (IH), Stephen Graves (SG), Richard de Steiger (Rds) and Michelle Lorimer are
918 employed by the AOANJRR. Nicole Pratt (NP)'s salary is partly supported by the MRFF grant
919 received for CRISTAL.

920

921 **4.7 Data access**

922 All principal investigators involved in data analysis will have access to deidentified datasets.
923 All principal investigators involved in subcommittees will have access to relevant
924 deidentified data necessary for undertaking their specific role (e.g. outcome validation).

925

926 **4.8 Additional care**

927 As both interventions are standard, recommended practice, no additional treatment will be
928 provided for participants.

929

930 **4.9 Dissemination**

931 A writing committee will be established to write the principal papers (primary and
932 secondary outcomes). Dissemination will be by peer reviewed journal publication,
933 conference presentation and through media. All study findings will be reported, regardless
934 of statistical significance or the size or direction of effect.

935

936 Study findings will be released to participating sites and investigators.

937

938 Input will be sought into guideline development by state and national bodies (e.g. ACSQHC).
939 The results of the study are expected to be published in a journal with high impact and to be
940 of interest to a wide audience (beyond orthopaedics and haematology, including hospitalists
941 and public health). They are expected to have clinical importance and statistical power that
942 will enable the results to influence practice, which currently lacks studies on this size and
943 quality.

944

945 **4.10 Implementation**

946 Surgeons will be surveyed prior to commencement (separate study) to assess their
947 willingness to change practice based on the results of the trial, allowing for current practice,
948 study findings, experience, gender.

949

950 Following the study, practice change at departmental and surgeon level will be measured
951 for each surgeon at each site by assessing departmental and individual surgeon prophylaxis
952 methods.

953

954 Practice change more broadly will be assessed through data linkage, assessing the increase
955 or decrease in post-operative LMWH prescriptions.

956

957 **4.11 Authorship**

958 Authorship for principal papers will be by the members of the writing committee and the
959 CRISTAL Study Group (consisting of all investigators according to the authorship guidelines
960 of the ICMJE).

961

962 **5. Statement for compliance with NHMRC National Statement on Ethical Conduct of**
963 **Research Involving Humans**

964 This study will be conducted in accordance with the ethical principles that have their origin
965 from the Declaration of Helsinki and are consistent with ICH/GCP. This study will comply
966 with National Health and Medical Research Council (NHMRC) National Statement on Ethical
967 Conduct in Research Involving Humans.

968
969

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1055 **FINAL PROTOCOL – 29 OCTOBER 2020**

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STUDY PROTOCOL

1060 **CRISTAL: A cluster randomised, crossover, non-inferiority trial of aspirin compared to low**
1061 **molecular weight heparin for venous thromboembolism prophylaxis and safety in hip or**
1062 **knee arthroplasty, a registry nested study**

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1088 **Study Protocol**

1089 CRISTAL: a cluster randomised, crossover, non-inferiority trial of aspirin compared to low
1090 molecular weight heparin for venous thromboembolism prophylaxis in hip or knee
1091 arthroplasty, a registry nested study.

1092 **1. Administrative information**

1093 **1.1. Registration**

1094 CRISTAL has been registered with the Australian and New Zealand Clinical Trials Registry
1095 (anzctr.org.au, ACTRN12618001879257).

1096

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1101 any role during its execution, analyses, interpretation of the data, dissemination or decision
1102 to publish.

1103

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 1184 IAH conceived the study. IAH, SEG, RB, SA, JMN, IA, BHC, NP, RdS and AH are Chief
 1185 Investigators on the MRFF grant. NP is the primary statistician. AH is the primary health
 1186 economist. All contributors participated in protocol development.

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1191
 1192 **1.5. Study Coordination**

1193 Committees

Committee	Members	Responsibilities
Writing Committee	IAH, SG, RB, NP, SA, VS	Protocol development and publication Preparation of principal publications (primary and secondary outcomes)
Steering committee	All investigators listed above (contributors)	Final protocol approval Study oversight Principal publication approval
Trial management committee	IAH, SEG, VS, SA, RdS, Project Coordinator (DA), AOANJRR Registry Manager, AOANJRR project manager, SAHMRI rep (LG), , SAHMRI IT, SAHMRI Data Management, SAHMRI Statistician	Integration with AOANJRR PROMs program Ethics approval Site liaison (recruitment and maintenance)
Data Quality Committee	IAH, Project Manager, ML, RdS	Data management Data quality audits
Outcome Verification Committee	ACORN Manager, JN, IAH, BHC	Validating verification of DVT and PE reported during patient follow-up

1194
 1195 Coordinating Centre
 1196 The day to day management of the trial will be the responsibility of the Australian
 1197 Orthopaedic Association National Joint Replacement Registry (AOANJRR) and South
 1198 Australian Health & Medical Research Institute (SAHMRI).

1199 Other expert subgroups may be established throughout the project to advise on specific
1200 elements and make recommendations should the need arise.

1201

1202 **1.6. Abbreviations**

1203 AOANJRR Australian Orthopaedic Association National Joint Replacement Registry

1204 AAOS American Academy of Orthopaedic Surgeons

1205 ACORN Arthroplasty Clinical Outcomes Registry

1206 DVT Deep Venous Thrombosis

1207 ICJME International Committee of Medical Journal Editors

1208 LMWH Low Molecular Weight Heparin

1209 NICE National Institute of Health and Care Excellence

1210 NOAC Novel Oral Anticoagulant

1211 OA Osteoarthritis

1212 PE Pulmonary Embolus

1213 PROMs Patient Reported Outcome Measures

1214 THA Total Hip Arthroplasty

1215 TKA Total Knee Arthroplasty

1216 HA Hip Arthroplasty

1217 KA Knee Arthroplasty

1218 VTE Venous Thromboembolism

1219

1220 **2. Introduction**

1221

1222 **2.1. Background**

1223 Over 100,000 total hip and total knee arthroplasty (THA, TKA) procedures are performed
1224 each year in Australia.¹ Venous thromboembolism (VTE) comprises deep venous thrombosis
1225 (DVT) and pulmonary embolus (PE) and is a recognised serious complication of hip and knee
1226 arthroplasty surgery. Patients undergoing THA and TKA receive chemoprophylaxis for VTE
1227 prevention, with most patients in Australia receiving either low molecular weight heparin
1228 (LMWH) or aspirin (manuscript in preparation).

1229

1230 Guideline recommendations and surgeon preference for VTE prophylaxis vary due to a lack
1231 of evidence regarding the comparative safety and effectiveness of these two common
1232 chemoprophylaxis agents. Aspirin is a low cost, over-the-counter, safe medication that is
1233 easy to take (one oral tablet daily). LMWH requires daily injection (often requiring
1234 professional or family support), is more expensive and requires prescription, but has a larger
1235 body of evidence of effectiveness. Previous studies comparing LMWH and aspirin have been
1236 underpowered for effectiveness and for safety.

1237

1238 Currently, practice guidelines provide conflicting recommendations for VTE prophylaxis. The
1239 National Institute of Health and Care Excellence (NICE) guidelines (United Kingdom) now
1240 (2018) recommend using LMWH, aspirin or Novel Oral Anticoagulants (NOACs) for VTE
1241 prophylaxis in TKA (aspirin is not recommended for THA) whereas aspirin was not
1242 recommended in the previous version.² In the US, two main guidelines are used: those
1243 recommended by the American College of Chest Physicians (ACCP)³ and those produced by
1244 the American Association of Orthopaedic Surgeons (AAOS).⁴ Both recommend the use of
1245 LMWH, NOACs or aspirin. Previously, the ACCP guidelines recommended against aspirin
1246 whereas the AAOS guidelines recommended its use. As of 2012, both guidelines now allow
1247 the use of aspirin for VTE prophylaxis, and as a result the prevalence of aspirin prescription
1248 has increased.⁵ The Australian National Health and Medical Research Council guidelines
1249 (2009) did not recommend aspirin, however these guidelines were rescinded in 2016 as they
1250 were considered outdated.⁶

1251

1252 A number of systematic reviews (including data from up to 22 trials) have summarised the
1253 evidence for VTE prophylaxis in joint arthroplasty, but most do not assess aspirin, despite
1254 being commonly used and recommended by some practice guidelines.^{3,4,7-13}

1255

1256 Two small systematic reviews were found, including data from six pharmacological trials
1257 that had aspirin as a comparator.^{14,15} In both reviews, the evidence was dominated by one
1258 trial of 778 patients comparing aspirin to LMWH in THA.¹⁶ This trial was stopped early due to
1259 poor recruitment. Furthermore, all patients in the trial received LMWH for the first 10 days
1260 before random allocation to aspirin or continued LMWH. This does not reflect the way that
1261 aspirin is commonly used in Australia as aspirin is commenced during the acute care period.
1262 Another five trials were also described, including a total of 936 patients, but these trials
1263 were small, measured different outcomes, and were subject to bias.¹⁵ Both reviews
1264 concluded that there is insufficient evidence to support recommendations on the use of

1265 aspirin, and suggest larger trials are needed.^{14,15} A recent large trial compared aspirin to
1266 rivaroxaban (a NOAC) for VTE prophylaxis in THA and TKA. A total of 3424 patients were
1267 recruited in this cluster-randomised trial, however both groups were treated with
1268 rivaroxaban for the first 5 days before being randomised to aspirin or rivaroxaban for the
1269 following 2-4 weeks.¹⁷

1270
1271 While studies using administrative datasets should be interpreted with caution due to risk of
1272 coding errors, incomplete data and difficulty fully adjusting for possible confounding, two
1273 studies of aspirin using large administrative datasets have been reported. The first, from the
1274 US, used data from 93,804 patients undergoing elective total knee replacement surgery.¹⁸
1275 The study compared early (30 day) mortality and VTE between patients given warfarin,
1276 LMWH and aspirin, adjusted for patient factors (age, sex, race, VTE risk, comorbidities),
1277 institution factors (size, urban/rural) and a separate propensity score. No difference was
1278 found in the mortality rates or rates of post-operative bleeding complications between the
1279 three groups, and there was no difference in the rate of VTE comparing LMWH to aspirin.
1280 A study using data from the National Joint Registry for England, Wales, Northern Ireland and
1281 the Isle of Man analysed data from 108,584 patients undergoing THA comparing LMWH to
1282 aspirin for VTE prophylaxis using multivariable modelling and propensity score matching.¹⁹
1283 The adjusted analysis showed no significant difference in mortality up to 90 days post-
1284 operatively but this difference became significant (favouring LMWH) on propensity score
1285 matching. There was no difference in VTE complications or re-operations (up to 90 days)
1286 between groups. The reported rates of VTE were very low, possibly due to under-detection.

1287
1288 The existing uncertainty regarding the relative safety and effectiveness of these different
1289 medications to prevent VTE following arthroplasty and inconsistencies in available clinical
1290 practice guidelines likely contribute to widespread clinical practice variation in Australia. A
1291 national survey²⁰ and recent large cohort study involving 1,900 patients from 19 institutions
1292 across Australia (manuscript under preparation) show that nearly all surgeons use some
1293 form of chemoprophylaxis, with approximately 80% using LMWH and nearly half using
1294 aspirin (approximately 40% of patients had more than one drug). The survey indicated that
1295 those using LMWH were more likely to do so for fear of litigation.²⁰ Aspirin does not require
1296 a prescription, is easier for patients to take (tablet rather than injection), is safe and is
1297 inexpensive. Therefore, establishing non-inferiority would provide patients with a preferred,
1298 effective, safe, cheaper and simpler method of VTE prophylaxis compared to LMWH.

1299
1300 The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) was
1301 established in 1999 and reports on revision surgery and mortality after joint arthroplasty in
1302 Australia, with close to complete national coverage. The AOANJRR has established a system
1303 to directly capture data entered by patients pre- and post-operatively; this system is a
1304 platform for the conduct of clinical trials and is incorporated as part of the AOANJRR (not a
1305 standalone project). The proposed CRISTAL trial will be embedded within the Clinical Trials
1306 Platform of the AOANJRR.

1307

1308 **2.2. Choice of comparators**

1309 Wide practice variation is evident for VTE chemoprophylaxis in Australia due to both
1310 surgeon uncertainty in the evidence for effect, and differences in surgeon preference.
1311 Aspirin and LMWH are the two most frequently used drugs for VTE prophylaxis in THA and

1312 TKA in Australia. Alternatives, such as warfarin and unfractionated heparin are not
1313 commonly used in Australia and are not reflected in practice guidelines in this country.
1314 NOACs are an alternative to LMWH and aspirin but are not commonly used in Australia.
1315 Given aspirin's popularity, ease of use, safety profile and low cost but lack of evidence of
1316 comparative effectiveness against the most commonly recommended drug (LMWH), we
1317 considered aspirin to be the most suitable comparator to LMWH for this trial.
1318
1319

1320 **2.3. Study hypothesis**

1321 Aspirin is non-inferior to LMWH for prevention of VTE after THA and TKA surgery.

1322

1323 **2.4. Primary aim**

1324 To compare the effectiveness and safety of aspirin to LMWH in preventing symptomatic VTE
1325 after primary elective THA and TKA for osteoarthritis (OA).

1326

1327 **2.5. Secondary aims**

- 1328 • To compare the effectiveness and safety of aspirin to LMWH in preventing
1329 symptomatic VTE after all hip arthroplasty (HA) and knee arthroplasty (KA) including
1330 primary, revision and partial arthroplasty, performed for any indication including
1331 fracture surgery
- 1332 • To compare the effectiveness and safety of aspirin to LMWH in preventing
1333 symptomatic VTE after revision HA and KA
- 1334 • Compare the safety (proportion of non-VTE complications) between groups
- 1335 • An extension of the primary analysis for: HA and KA separately; unilateral and
1336 bilateral separately; below-knee DVT, above-knee DVT and PE separately
- 1337 • To compare the cost effectiveness of aspirin to LMWH for VTE prophylaxis after
1338 primary elective THA and TKA for osteoarthritis if aspirin is found to be inferior to
1339 LMWH

1340

1341 **2.6. Trial design**

1342 A pragmatic multicentre, cluster-randomised, crossover, non-inferiority study with a
1343 primary endpoint of patient-reported symptomatic VTE at 90 days.

1344

1345 **3. Methods**

1346

1347 **3.1. Setting**

1348 Eligible hospitals (public and private) performing HA and KA in Australia. The study will be
1349 nested within the AOANJRR Clinical Trials Platform, an electronic platform for recruitment
1350 and data collection for patients undergoing joint replacement surgery.

1351

1352 **3.2. Eligibility**

1353 Hospital level

- 1354 • Departmental (or surgeon group) agreement to participate in the study and adhere
1355 to study protocols
- 1356 • Use of intermittent calf compression device intra-operatively and post-operatively
1357 until mobile
- 1358 • Offer mobilisation day 1 post-operatively or earlier
- 1359 • No change in other practices or protocols relevant to VTE over the course of the
1360 study (e.g. tourniquet use, anaesthetic type).

1361 Patient level

- 1362 • Adults (age 18 and older)
- 1363 • Receiving primary or revision HA or KA for any indication (including for fracture)

1364

1365 Exclusion criteria

1366 As a pragmatic study, all patients undergoing revision and primary arthroplasty for any
1367 indication during the study period will be included. The only exclusion for a department is if
1368 the volume of primary elective THA and TKA for osteoarthritis is less than 250 per year (as
1369 this may render the site unable to recruit the required sample size required for the primary
1370 analysis within a reasonable timeframe).

1371 At an individual level, patients unsuitable to receive routine prophylaxis will be treated
1372 according to local advice and recommendations, as per normal practice. Routine prophylaxis
1373 for the purpose of the CRISTAL study includes the LMWH and the aspirin protocols used in
1374 CRISTAL. Reasons for not receiving routine prophylaxis include the long-term use of
1375 warfarin, NOAC or dual antiplatelet therapy pre-operatively, allergy to the study drug and
1376 an underlying medical condition that precludes the use of either drug or the treating
1377 doctors consider the patient to be high risk for routine prophylaxis.

1378

1379 **3.3. Intervention**

1380 Each site will be allocated to two consecutive periods of a standard protocol of aspirin and a
1381 standard protocol of LMWH for VTE prophylaxis with the order of the two periods
1382 determined by randomisation at a 1:1 ratio, on an open label basis.

1383 Each site will adhere to the initially randomised protocol for a time period based on surgical
1384 volume aiming for 250 patients eligible for the primary analysis per group. The target

1385 recruitment time period for each group will be 12 months, but may extend beyond this if
1386 required. Total recruitment (all arthroplasties) to each group is expected to be 300 patients.
1387 Patients will be informed of the trial during initial data entry. Patients will be specifically
1388 asked at the time of study entry for consent for follow-up, for use of their data in research,
1389 and use of linked data to measure and verify surgical outcomes (Appendix 1). Patients will
1390 not be individually consenting to be randomised to either aspirin or LMWH, as both drugs
1391 represent standard practice and randomisation is not at the patient level. Further details on
1392 the consent process is listed in protocol (section 4.3).

1393

1394 Patients will be followed up at 90 (90-120) days and 6 (5-7) months, electronically, with
1395 telephone back up. To ensure minimal inconvenience a maximum of three successful
1396 reminders will be sent to the patient to complete their follow-up CRISTAL questions.
1397 Patients will be contacted beyond 100 days and 6.5 months via telephone, if surveys remain
1398 incomplete and if initial telephone contact has not been successful.

1399

- 1st reminder

1400

- Pre-operative - 2 days after registration

1401

- 90-day post-operative – 90 days post operation

1402

- 6-months post-operative - 5 months + 2 weeks post operation

1403

- 2nd reminder

1404

- Pre-operative - 3 days after the first reminder

1405

- 90-day post-operative – 95 days post-operation

1406

- 6-months post-operative – 2 weeks after first reminder

1407

- 3rd reminder

1408

- Pre-operative - 4 days after the second reminder,

1409

- 90-day post-operative – 100 days after operation

1410

- 6-months post-operative – 2 weeks after second reminder

1411 The electronic system used for data collection is also equipped with a Save and Complete
1412 feature which will allow an incomplete set of questions to be completed by the patient at a
1413 later date.

1414

1415 This was deemed necessary because if a patient is completing a set of questions and they
1416 need to stop for whatever reason it is helpful for them to be able to recommence from
1417 where they left off. For example, an issue may occur with the internet connection or, if the
1418 pre-operative data is being collected in a pre-admission clinic setting, a patient may be
1419 called away for different appointments mid-way through completing the questions.

1420

1421 If there is an incomplete set of questions recorded, the patient can log back in at any time
1422 within a 2-week period to complete the questions. If the questions are not completed
1423 within 48 hours of being started the system will send an additional reminder to the patient
1424 prompting them to complete the questions. After 2 weeks the session will be locked and the
1425 incomplete set of questions will be utilised.

1426

1427 There will be no change to usual medical follow-up (clinic attendance, investigations etc.)
1428 except that routine venous imaging is not to be used (currently not recommended and not
1429 commonly used).

1430 Aspirin will be administered orally at 100mg (85-150 mg permitted if previously prescribed)
1431 daily for 35 (+/-7) days (hips) or 14 (+/-4) days (knees) commencing the day of or day after
1432 surgery.

1433

1434 LMWH will be administered as enoxaparin (Clexane) 40mg subcutaneously daily, for 35 days
1435 (hips) or 14 days (knees) commencing within 24 hours of surgery. Patients with renal
1436 impairment (creatinine clearance of <30ml/min) will be administered enoxaparin (Clexane)
1437 in a reduced dosage of 20mg subcutaneously daily and patients undergoing haemodialysis
1438 will be treated according to standard local protocol. The reduced dosage of 20 mg will also
1439 apply to patients who weigh less than 50 kilograms. Patients who have a contradiction to
1440 either study drug will be treated as per local protocols. If this requires the study drug to be
1441 withheld the study site will notify the Registry. Patients will be taught to self-administer
1442 while in hospital. For those unable to self-administer, the injections will be given by family
1443 members, a community nursing service or their local doctor, depending on local
1444 arrangements.

1445

1446 **3.4. Adherence**

1447 Patients may discontinue the drug if they have an allergy or adverse event related to the
1448 drug.

1449

1450 The study drug may be withheld if post-operative wound ooze continues beyond 72 hours
1451 post-operatively, with recommencement 48 hours later if settled.

1452

1453 Inpatient adherence during the acute care period will be monitored by an audit of all sites
1454 over the first 2 weeks after commencing patient recruitment. A repeat audit will be
1455 performed after one month for sties that do not reach at least 80% compliance on the initial
1456 audit.

1457

1458 Post-discharge adherence will be determined by patient report during follow-up at 90 days.

1459

1460 **3.5. Concomitant care**

1461 All patients will have intermittent compression devices intra-operatively and post-
1462 operatively until mobile. All patients will be offered mobilisation on day one post-surgery
1463 unless surgically or medically contraindicated.

1464

1465 Patients taking (non-aspirin) oral anti-platelet therapy pre-operatively may have their
1466 medication withheld for one week pre-operatively if advised by their treating doctor and
1467 will recommence their usual medication (in addition to any study medication) at day 7 post-
1468 operatively or when safe to do so.

1469

1470 Routine doppler screening for DVT (in asymptomatic patients) will not be permitted by
1471 participating sites.

1472

1473 Patients taking aspirin (85-150mg daily) pre-operatively will take this drug in the usual dose
1474 post-operatively in place of the study drug for those in the aspirin group, and in addition to

1475 LMWH for those in the LMWH group. The aspirin may be stopped pre-operatively if advised
1476 by their treating doctors.

1477

1478 **3.6. Primary outcome**

1479 The primary outcome is verified, symptomatic VTE (DVT or PE) at 90-day follow-up.

1480 All reports of VTE will be verified by contact with treating doctors and institutions. VTE will
1481 be deemed verified by the independent Outcome Verification Committee. The absence of
1482 VTE will be verified in a random sample of 200 patients reporting an absence of VTE, by
1483 auditing treating doctors and institutions. Patients will be asked if they are still taking
1484 anticoagulant medication at 90-day follow-up. VTEs will be subclassified into all DVT, below
1485 knee DVT, above knee DVT and PE.

1486

1487 **3.7. Secondary outcomes**

1488

1489 1. Non-VTE complications (see below)

1490 2. PROMs. Health-related quality of life (EQ5D-5L), Oxford hip and knee scores and
1491 patient-rated satisfaction and improvement.

1492 3. Costs. If aspirin is found to be inferior to LMWH, the cost of anticoagulation, cost of
1493 hospital stay, need for further health resource utilisation (e.g. nurse or GP visits) and
1494 complications will be analysed (see list below)

1495 4. Adherence. Proportion of patients taking the drug continuously (no more than 2
1496 consecutive days missed) for the recommended minimum period.

1497

1498 Non-VTE Complications will be classified into the following groups by the Outcome
1499 Verification Committee:

- 1500 • Readmission related to the original surgery or associated treatment (including
1501 bleeding and VTE related) within 90 days
- 1502 • Reason for readmission (infection, dislocation, stiffness, fracture, wound dehiscence,
1503 implant loosening, migration or failure, wound bleeding, other bleeding) within 90
1504 days
- 1505 • Major bleeding events within 90 days ('major' defined as those resulting in
1506 readmission, reoperation or death)
- 1507 • Reoperation on the same joint within 90 days and 6 months
- 1508 • Type of reoperation (treatment of infection, reduction of dislocation, manipulation
1509 under anaesthesia, fracture treatment, wound repair, implant loosening, migration
1510 or failure, non-joint related surgery) within 90 days and 6 months
- 1511 • Death within 90 days and 6 months

1512 All reports of non-VTE complications will be verified by contact with treating doctors and
1513 institutions, except for death, which will be verified through the National Death Index (NDI).

1514 **3.8. Participant timeline**

Time Point	Data Collection Questions and Instruments
Pre-operative	Current anticoagulation use (yes/no and drug) History of previous VTE Age Sex Joint (hip or knee) Side Unilateral vs bilateral Primary or revision ASA grade BMI Oxford Hip or Knee Score EQ-5D-5L EQVAS Low back pain Joint pain (numeric rating scale 0-10) Expectations (pain and improvement)
90 days	VTE (DVT or PE) Adherence (did you use pills or injections to prevent a blood clot post-operatively, for how long?) Current use of anticoagulants (yes/no, which one) Complications (asked individually, as per complication list)
6 months	Complications (asked individually, as per complication list) Oxford Hip or Knee Score EQ-5D-5L Joint pain (scale 0-10) Satisfaction with outcome of surgery Patient-rated improvement

1515

1516 EQ-5D-5L (Appendix 2)

1517 The EQ-5D is a standardised measure of health status developed by the EuroQol Group in
 1518 order to provide a simple, generic measure of health for clinical and economic appraisal.²¹

1519 The survey includes 5 health outcome domains that can be summarised into a utility score.

1520 These include:

- 1521 • Mobility
- 1522 • Self-care
- 1523 • Usual Activities
- 1524 • Pain/Discomfort
- 1525 • Anxiety/Depression

1526 There are five descriptive sentences under each heading and patients are directed to tick
 1527 one box that best describes their health on that day. There is also a visual analogue scale
 1528 (VAS) that addresses health state.²¹

1529

1530 Oxford Hip or Knee Scores (Appendix 3)

1531 The Oxford hip (OHS) and knee (OKS) scores were developed in the mid-1990s. The scores
1532 were developed to assess the outcome of hip and knee replacements as well as shoulder
1533 surgery (including shoulder replacement) and were designed to be completed by patients in
1534 order to minimise potential bias.²² Both two instruments include 12 questions to assess a
1535 patient's capacity to undertake general activities of daily living, about their affected hip or
1536 knee.

1537

1538 Pre-operative anticoagulation use (Appendix 4)

1539 Questions listed below will be presented pre-operatively to determine any history of VTE
1540 and current use of Anti-coagulant medications. The questions were reviewed and approved
1541 by consumer representatives and will be specific to the medications and the site of DVT.

- 1542 1. Do you normally take (or are you currently taking) blood thinning medication
1543 routinely?
- 1544 2. Do you know what blood thinning medication you are taking?
- 1545 3. Have you ever been diagnosed with a clot in your legs (Deep Vein Thrombosis - DVT)
1546 or lungs (Pulmonary Embolism - PE)?
- 1547 4. When did your most recent (or only) clot in your legs (Deep Vein Thrombosis - DVT)
1548 or lungs (Pulmonary Embolism - PE) occur?

1549 Post-operative VTE symptoms and occurrence (Appendix 4)

1550 The following questions will be presented post-operatively at both 90 days and 6 months to
1551 gauge patient's surgery outcome. Questions 1 to 5 are only specific for the 90 days data
1552 collection point and will not be asked on the 6 months data collection point.

- 1553 1. Did you take your post-surgery blood thinning medication (to avoid blood clots) after
1554 leaving hospital following your joint replacement operation?
- 1555 2. Do you know what blood thinning medication you were taking?
- 1556 3. How many days did you take the blood thinning medication after your (HIP/KNEE)
1557 replacement operation?
- 1558 4. Since your joint replacement surgery, have you been diagnosed with a blood clot in
1559 your legs (Deep Vein Thrombosis - DVT) or lungs (Pulmonary Embolism - PE)?
- 1560 5. Since your joint replacement surgery, have you had any serious bleeding from
1561 anywhere in your body not related to your joint replacement?
- 1562 6. Have you had any further surgery on your replaced joint (apart from when it was put
1563 in)?
- 1564 7. Please select the reason(s) for the additional surgery/surgeries (select all that apply)

1565

1566 **3.9. Sample size**

1567 A recent large cohort study of 1900 THA and TKA patients from 19 institutions across
1568 Australia showed an incidence of symptomatic VTE within 90 days of THA and TKA of 2.6%
1569 (manuscript under preparation). A recent randomised trial of aspirin versus rivaroxaban
1570 used a minimum clinically important difference of 1%, based on a survey of
1571 thromboembolism experts and orthopaedic surgeons.¹⁷

1572
1573 For the sample size calculation in the CRISTAL study, we used an estimated overall event
1574 rate of 2% (a conservative estimate based on the recent Australian cohort study and the
1575 current available literature)^{15-17,19,23-26}, the same non-inferiority margin of 1% from the
1576 recent randomised controlled trial (for aspirin compared to LMWH, 2.5% for aspirin and
1577 1.5% for LMWH)¹⁷, a power of 90% and a one-sided significance level of 0.025. For an
1578 individual randomised trial, this yields a sample size of 4,117 per treatment group or a total
1579 of 8,234 patients. For a cluster randomised crossover trial, the sample size must account for
1580 correlations within clusters during the same time period (intracluster correlation) and
1581 between study periods in the same cluster (interperiod correlation).^{27,28} Assuming an
1582 intracluster correlation of 0.01, an interperiod correlation of 0.008 and 31 clusters, the
1583 sample size required increases to 11,160 patients. From each cluster, we will aim to recruit
1584 minimum of 251 registered patients from each group (a total of 15,562 patients), which will
1585 allow a 27% loss to follow-up.

1586
1587 Due to uncertainty around the exact event rate^{15-17,19,23,24} and to allow for a smaller non-
1588 inferiority margin, we have constructed a sample-size table (Table 1) to demonstrate that
1589 the trial will be adequately powered using a non-inferiority margin of 1%, for an event rate
1590 up to 3% at 80% power and for an event rate up to 2% at 90% power, provided that loss to
1591 follow-up is less than 17%. As a secondary measure, after 1,000 patients have completed
1592 the 90-day follow-up, we will obtain a preliminary symptomatic VTE rate for the whole
1593 sample and a loss to follow-up rate (without performing any comparative statistical analyses
1594 and maintaining blinding) to determine whether the estimates for the primary event rate
1595 (2%) and loss to follow-up rate (27%) are accurate and adjust the sample size accordingly if
1596 the primary event rate is greater than 3%, whilst accounting for loss to follow-up.
1597

1598 **Table 1 – Sample Size Table for the CRISTAL Trial** † ‡
 1599

Event rate in experimental	Event rate in control	Overall event rate	Non inferiority margin	N in each group (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

1600
 1601 † A one sided $\alpha = 0.025$ is required for a 95% CI. The number of clusters is assumed to 31,
 1602 the ICC = 0.01 and the IPC=0.008.

1603 ‡ Table does not account for an estimation of loss to follow-up

1604
 1605

3.10. Recruitment

1606 Hospitals will be approached individually by the lead CI and the study team, as appropriate.
 1607 A site will be considered eligible if they can recruit 251 eligible patients (for the primary
 1608 analysis for each group) with an aim to recruit this number within 12 months. Departmental
 1609 (or surgeon group) agreement with the study protocol and the individual treatment
 1610 protocols (for each group) will be required. Sites where a subgroup of attending surgeons
 1611 agree to participate will be included if the number of eligible patients for that group of
 1612 surgeons per year it at least 250. A site investigator will be nominated for each site

1613
 1614

3.11. Randomisation

1615 Each site will be randomised with a 1:1 allocation with a computer generated random
 1616 sequence. Simple randomisation will be used (no use of blocks, no stratification). The
 1617 allocation will refer to the first intervention.

1618
 1619

3.12. Blinding

1620

1621 Sites will not be blinded to group allocation. Patients will be aware of a study comparing
1622 different treatments for VTE prevention but will not know the specific details of the study
1623 and will therefore be blind to the specific interventions and outcomes of the trial such as
1624 whether they are in the intervention or control group and the secondary outcomes of the
1625 trial. Outcomes will be self-reported with verification of the primary outcome by the
1626 Outcome Verification Committee. Where outcome reporting is by phone (back up for failure
1627 to capture patients reported outcomes electronically and where verification is performed),
1628 those outcome assessors will be blinded to group allocation.

1629

1630 The Outcome Verification Committee will be presented with deidentified cases for
1631 assessment. The statistical analysis will be blinded. The Writing Committee will be blinded
1632 and will prepare separate manuscripts based on the possible group allocations.

1633

1634 **3.13. Data collection**

1635 Data collection for baseline data and follow-up at 90 days and 6 months will be patient-
1636 reported electronically (via tablet, phone or computer) using direct data entry. For patients
1637 not responding to email and SMS follow-up, telephone contact will be used to administer
1638 the surveys verbally.

1639

1640 Pre-Operative

1641 When collected electronically by patients, data will be directly entered into the AOANJRR
1642 Clinical Trials Platform.

1643

1644 Some patients may not have direct access to the internet. This is especially a factor for older
1645 patients and patients from lower socioeconomic groups.²⁹⁻³¹ Another group who could
1646 potentially be excluded from implementing this approach to data collection are non-English
1647 speaking patients. To overcome these barriers patients will be given the option to nominate
1648 a 'proxy' e.g. family member or friend to assist them with completing the instruments and
1649 receive reminders electronically on their behalf. Information will be collected on whether
1650 the patient had assistance to complete the CRISTAL questions and these data will be
1651 reviewed during the analysis.

1652

1653 There will be various methods and procedures implemented at the different hospitals to
1654 register patients and request them to complete the CRISTAL data online. Ideally the patients
1655 will complete pre-operative CRISTAL data immediately when first approached, however, this
1656 may not always be possible. There is functionality built into the system to email a patient
1657 the link to the website to complete the CRISTAL requirements at a time that is convenient
1658 for them.

1659

1660 Some hospitals participating in CRISTAL already routinely collect PROMs and wish to
1661 continue to do so using their own systems. In these cases, the AOANJRR will work with the
1662 hospital to simplify the data collection process and avoid duplication of collection. A data
1663 sharing agreement will be entered into between the hospital and the AOANJRR whereby
1664 data can be exported from the current system and imported into the AOANJRR Clinical Trials
1665 Platform. There will be a secure file sharing facility established within the web application to
1666 ensure secure transfer of confidential information. The data provided will be reviewed by
1667 the data manager prior to upload into the database to confirm quality and completeness.

1668

1669 Post-Operative

1670 Follow-up will be by telephone until the electronic data capture system is built and
1671 telephone follow-up will be used as back up for the electronic follow-up once in place.

1672 Patients will be able to login and complete their 90-day follow-up from 75 days and 6-month
1673 follow-up from 5 months.

1674

1675 The Arthroplasty Clinical Outcomes Registry (ACORN) has been contracted to complete the
1676 follow-up phone calls. ACORN was selected because this Registry already collects PROMs
1677 centrally for hospitals, predominately in NSW, and the staff have expertise in this area.

1678

1679 **3.14. Data management**

1680 Data quality will be checked monthly under the supervision of the Data Quality Committee.

1681

1682 **3.15. Statistical analysis**

1683 The analysis for the primary objective will be limited to patients undergoing elective primary
1684 THA or TKA for a diagnosis of OA, excluding patients for whom the study drugs were
1685 contraindicated (e.g., allergy or need for alternative anticoagulant – warfarin, NOAC, dual
1686 antiplatelet, for a pre-existing condition). This analysis will test between-group difference in
1687 the proportion of cases developing VTE within 90 days for non-inferiority of aspirin at a
1688 margin of 1%, on an intention to treat basis.

1689

1690 The primary analysis will use cluster summary methods.³² These methods estimate the
1691 treatment effect using cluster level differences and have been shown to be appropriate for
1692 cluster randomised crossover trials with rare outcomes and the intracluster and interperiod
1693 correlation coefficients expected in this trial.³³

1694

1695 Multiple imputation to account for missing outcome data will be investigated, using
1696 auxiliary variables gathered from routine AOANJRR data (including age, sex, baseline health,
1697 pain and function, diagnosis and surgical factors). Since VTE is rare, if prediction in the
1698 imputation models using these auxiliary variables is a problem, no imputation will be
1699 performed due to the possibility of bias.³⁴ Since the most likely reason for loss to follow-up
1700 is difficulty in contacting patients postoperatively (rather than any association with
1701 treatment assignment or outcome), missing outcome data is expected to be missing
1702 completely at random, which will not cause bias in the estimates.

1703

1704 Secondary analyses will be performed for the primary outcome, to test for differences in
1705 treatment effect between subgroups of patients: THA only, TKA only and bilateral joint
1706 replacement. The analysis method will be the same as the primary outcome and will include
1707 an interaction term between subgroup and treatment group.

1708

1709 Further secondary analyses will include an extension of the primary analysis for patients
1710 undergoing all forms of HA and KA (total, revision, partial) for any indication (non-elective
1711 surgery, non-OA diagnoses) and will include patients for whom the study drug was
1712 contraindicated. This will assess the effect of implementing the protocol at a departmental
1713 (hospital) level. Other secondary analyses will include an analysis of the subcategories of

1714 VTE as the outcome; PE only, all DVT, above knee DVT only and below knee DVT only and
1715 non-VTE related complications (death, re-operation, major bleeding and readmission rates).
1716 Cluster summary methods will be used for all secondary analyses.
1717

1718 If aspirin is found to be inferior to LMWH, a cost effectiveness analysis of aspirin compared
1719 to LMWH will be performed from a health system perspective. Data for resource use
1720 associated with treatments and complications will be taken from trial data within the
1721 AOANJRR. Survival at one year and quality of life measured using EQ5D at baseline and six
1722 months will allow calculation of differences in quality adjusted life years (QALYs) between
1723 groups. We will calculate the cost per QALY for each treatment comparison as the
1724 difference in mean costs divided by the difference in mean outcomes (quality adjusted
1725 survival as QALYs) over the duration of the trial, using regression analysis to adjust for
1726 differences at baseline and clustering by site.
1727

1728 **3.16. Data monitoring and cleaning**

1729 A separate Data Quality Committee will be established to monitor data management and
1730 quality.
1731

1732 A separate safety monitoring committee will not be established and no stopping rules will
1733 be used as both interventions are commonly used and recommended treatments. No
1734 interim analysis will be performed; this will reduce the chance of early stopping due to
1735 spurious findings. Adverse events (separate to complications listed under secondary
1736 outcomes) will be monitored by the Trial Management Committee).
1737

1738 **3.17. Auditing and Data validation**

1739 Positive outcomes (reported VTE) reported by patients will be confirmed by contacting
1740 hospitals or treating doctors. These will be adjudicated by the Outcome Verification
1741 Committee.
1742

1743 A sample of negative outcomes (patients reporting the absence of VTE) will be verified in a
1744 similar manner in a random sample of 200 patients with negative outcomes.

1745 Complications will be adjudicated by the Outcome Verification Committee.

1746 ANZMUSC will audit the study.
1747

1748 The AOANJRR Data Linkage project will be used to test the accuracy of outcome reporting
1749 (readmission, re-operation, drug prescriptions). The AOANJRR also links to the National
1750 Death Index (NDI) twice a year (February and September). If a patient, who has participated
1751 in the CRISTAL project, is flagged as deceased in the AOANJRR database this can also be
1752 transferred to the CRISTAL system and no further contact with be made, reducing distress
1753 for families.
1754

1755 **4. Ethics and dissemination**

1756

1757 **4.1. Ethics approval**

1758 The study will be submitted to Sydney Local Health District (RPAH Zone) human research
 1759 ethics committee for approval. Following approval, the study will be submitted to local
 1760 ethics committees and Research Governance Offices as required for each site. Refer to the
 1761 Table 2 for sites.

1762

1763 **Table 2: List of Sites for Ethics approval by Sydney Local Health District (RPAH Zone)**

State	Hospital	Comment
NSW	Canterbury Hospital	
NSW	Coffs Harbour	
NSW	Fairfield Hospital	
NSW	Gosford Public Hospital	
NSW	Hornsby Ku-ring-gai Hospital	
NSW	Kareena Private Hospital	Private Hospital (notified that an EEA is in place)
NSW	Nepean Hospital	
NSW	North Shore Private Hospital	Private Hospital (notified that an EEA is in place)
NSW	Prince of Wales Hospital	
NSW	Royal Prince Alfred Hospital (Institute of Rheumatology and Orthopaedic Surgery)	
NSW	Royal North Shore Hospital	
NSW	Ryde Hospital	
NSW	St George Private Hospital & Medical Centre	Private Hospital (notified that an EEA is in place)
NSW	Sutherland Hospital	
NSW	Westmead Private Hospital	Private Hospital (notified that an EEA is in place)
QLD	Greenslopes Private Hospital	Private Hospital (notified that an EEA is in place)
QLD	Mater Adults Hospital	
QLD	Prince Charles Hospital	
SA	Flinders Medical Centre	
VIC	Bendigo Hospital	
VIC	Epworth Private Hospital	
VIC	Frankston Hospital	
VIC	Hollywood Private Hospital	Private Hospital

		(notified that an EEA is in place)
VIC	University Hospital Geelong Barwon Health	
VIC	Warringal Hospital	Private Hospital (notified that an EEA is in place)
VIC	Western Hospital Footscray	
VIC	Western Hospital Williamstown	
WA	Fremantle Hospital	
WA	Osborne Park Hospital	
WA	Royal Perth Hospital	
WA	Sir Charles Gairdner Hospital	

1764

1765 **4.2. Amendments**

1766 Any modifications to the protocol which may impact on the conduct of the study, potential
1767 benefit of the patient or may affect patient safety, including changes of study objectives,
1768 study design, patient population, sample sizes, study procedures, or significant
1769 administrative aspects will require a formal amendment to the protocol. Such amendments
1770 will be agreed upon by the Steering Committee and approved by the Ethics Committee prior
1771 to implementation and site notification.

1772

1773 Administrative changes of the protocol are minor corrections and/or clarifications that have
1774 no effect on the way the study is to be conducted. These administrative changes will be
1775 agreed upon by Trial Management Committee and will be documented in a memorandum.
1776 The Ethics Committee/IRB may be notified of administrative changes at the discretion of
1777 Trial Management Committee.

1778

1779 **4.3. Consent to project participation**

1780 Individual consent is not being sought for randomisation or use of the study drugs. This is
1781 because randomisation is not occurring at the patient level and because both study drugs
1782 represent current standard practice. Consent is being sought for the collection and use of
1783 patient data, as per standard protocol for the AOANJRR Clinical Trials Platform. The Clinical
1784 Trials Platform uses the same consent process (and near identical data collection) as the
1785 AOANJRR PROMS Pilot Project which has received ethics approval (Reference: X18-0057 &
1786 HREC/18/RPAH/90).

1787

1788 Consent to AOANJRR Clinical Trials Platform

1789 Consent will be obtained electronically. All data collection for this project is electronic. This
1790 provides efficiency and effectiveness (less error) and allows a better way to impart
1791 information relevant to the consent process. The participant information and consent form
1792 will be displayed on the screen. It contains all elements required for a consent form (see
1793 Appendix 1). The information under each statement will be expandable. Patients will be
1794 provided the option to 'agree to the statement' or 'learn more'. If the patient agrees they
1795 will be navigated to the next statement. If the patient chooses to learn more the additional
1796 information will be displayed. Once all statements have been agreed to the patient will be
1797 able to choose whether they give consent or no longer wish to participate in the study. If

1798 the patient consents to participate they will be directed to the next page where they can
1799 complete the required pre-operative CRISTAL questions relevant to their procedure. If the
1800 patient chooses not to consent after the initial registration, then all personal information
1801 collected at registration will be deleted from the database. The only data that will be
1802 retained is:

- 1803 • Hospital Name (if available)
- 1804 • Surgeon Name (if available)
- 1805 • Date of registration

1806 If the patient elects to withdraw at the time of their post-operative assessment, then no
1807 further follow-up will be undertaken.

1808

1809 Electronic Consent Process Flowchart

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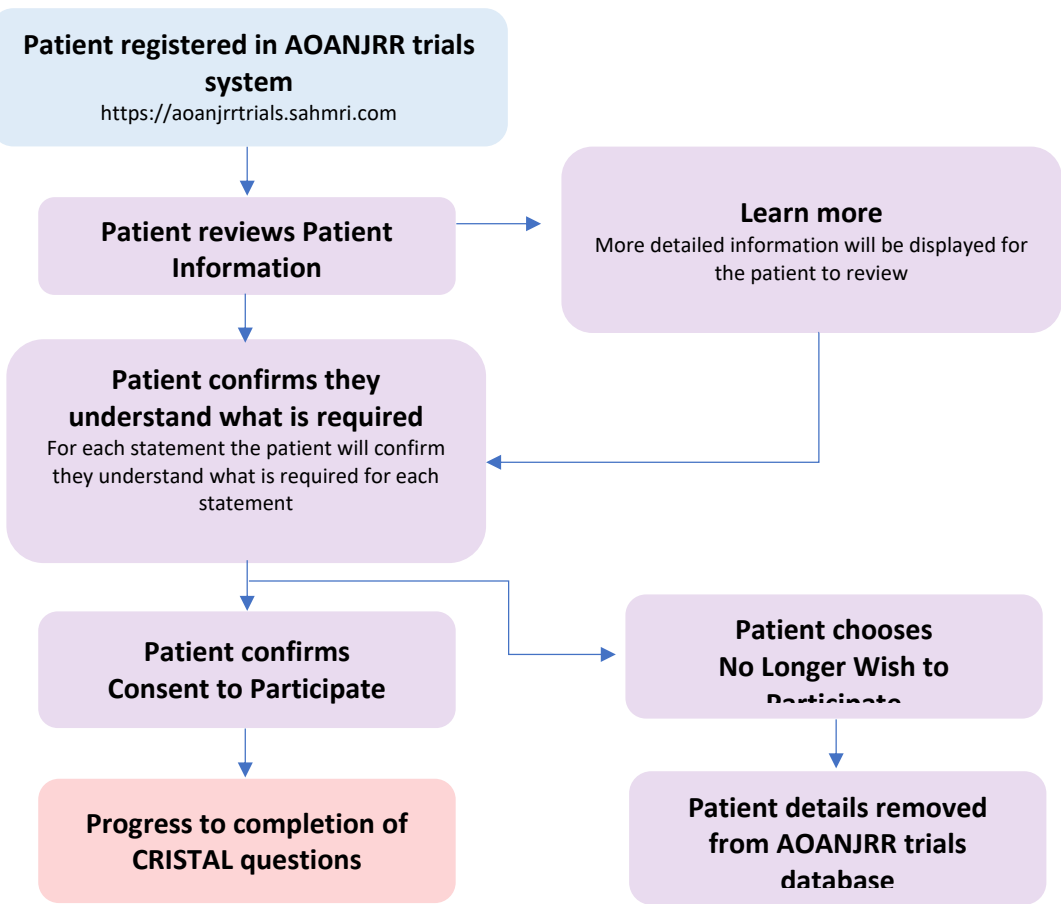
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1838 Consent to share data

1839 After completing the pre- and post-operative CRISTAL questions, patients will be given the
1840 option (at each time point) to share their data with their treating surgeon. If the patient
1841 consents for their results to be shared the treating surgeon will be able to download patient
1842 level data from the CRISTAL system. If patients do not consent to share these data, their
1843 information will not be provided to the surgeon.

1844 Waiver of Consent

1845 We are requesting waiver of consent for two different aspects of this project. Firstly, we
1846 require waiver of consent for the 'registration' process which involves getting basic contact
1847 information from potential participants so that they can be contacted and formally invited
1848 to participate and consent. An identical process of registration has been previously
1849 approved for the AOANJRR PROMs pilot. Secondly, we request waiver of consent for
1850 randomisation and treatment with the study drugs (the intervention) that make up the
1851 CRISTAL project.

1852

1853 Each request for waiver of consent are listed below: firstly, for the 'registration' process
1854 (clinical trials platform), and secondly for specific involvement (randomisation and
1855 treatment) in the CRISTAL study.

1856

1857 Waiver of consent Part 1: patient registration prior to initial patient contact.

1858 The request for waiver of consent only applies in some instances. Specifically, some
1859 patients will be registered in the system by hospital administrative staff or their treating
1860 surgeon. Once this registration occurs the patient will subsequently be sent an email by the
1861 AOANJRR to obtain consent electronically prior to completing the CRISTAL questions. The
1862 data that will be stored within the AOANJRR between registration and consent includes:

1863

- Patient First Name
- Patient Middle Name
- Patient Surname
- Date of Birth
- Postcode
- Hospital
- Surgeon name
- The joint that will be operated on (Hip, Knee)
- The side that will be operated on (Left, Right, Both)
- Patient contact details such as phone number and email address

1864

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1872

1873 It is important to emphasise that the AOANJRR will collect almost all the registration
1874 information when it is provided at the time of surgery except for phone number and email
1875 address. We believe this request satisfies the criteria as detailed in the National Statement
1876 on Ethical Conduct in Human Research (2013, chapter 2.3) for providing a waiver of consent.
1877 This waiver of consent is only for collecting information through the registration process and
1878 not to the completion of the CRISTAL instruments.

1879

1880

a. Involvement in the research carries no more than low risk

1881

- This is a low risk project particularly as the waiver is specifically required to defer involvement in the project after the registration as a mechanism to ensure that patients that take this option can complete their involvement in the project at a time that is most suitable to them.

1882

1883

1884

- 1885 b. the benefits from the research justify any risks of harm associated with not seeking
1886 consent
- 1887 • There is no risk of harm associated with storing the patient’s details prior to
1888 collecting consent. The Registry will receive almost all of this data at the time
1889 of the procedure. It is being requested to enhance participant convenience.
1890 The AOANJRR is a declared Federal Quality Assurance Activity and all data is
1891 managed in accordance with that declaration which includes the use of high
1892 level security systems.
- 1893 c. it is impracticable to obtain consent (for example, due to the quantity, age or
1894 accessibility of records)
- 1895 • It is not feasible to collect patient consent prior to the registration as it is
1896 necessary to link the electronic consent to the individual patient identified by
1897 the registration process. If the consent is completed prior to registration then
1898 the consent will be unidentified.
- 1899 d. there is no known or likely reason for thinking that participants would not have
1900 consented if they had been asked
- 1901 • Patients will verbally consent to have their details recorded at registration
1902 and this will be subsequently confirmed prior to completion of the CRISTAL
1903 Questions instruments. It is the AOANJRR experience that very few patients
1904 are reluctant to have their data included in the Registry.
- 1905 e. there is sufficient protection of their privacy
- 1906 • The AOANJRR is a declared Federal Quality Assurance Activity
1907 • Systems are in place to ensure individual patient data remains confidential
1908 • A third-party security review and penetration testing was undertaken prior to
1909 commencement of data collection in the clinical trials system.
1910
- 1911 f. there is an adequate plan to protect the confidentiality of data
- 1912 • SAHMRI, which is the organisation responsible for managing AOANJRR data,
1913 has existing security systems, policies and procedures in place as well as
1914 software barriers to protect personal information and ensure confidentiality.
1915 These systems are already in place for data contained within the AOANJRR
1916 and the CRISTAL data will be treated identically (see Appendix 5).
- 1917 g. in case the results have significance for the participants’ welfare there is, where
1918 practicable, a plan for making information arising from the research available to
1919 them (for example, via a disease-specific website or regional news media)
- 1920 • Patients will be able to review their own results and how they compare to
1921 the national average via online dashboards.

1922 h. the possibility of commercial exploitation of derivatives of the data or tissue will not
1923 deprive the participants of any financial benefits to which they would be entitled

1924 • The AOANJRR is a not for profit organisation which does not use the data it
1925 collects for commercial gain.

1926
1927 i. the waiver is not prohibited by State, federal, or international law

1928 • There are no applicable laws prohibiting this waiver.

1929

1930

1931 Waiver of consent Part 2: participant randomisation and treatment under the CRISTAL
1932 study.

1933 The CRISTAL study is seeking a waiver of individual consent for the intervention proposed by
1934 the study (the administration of either aspirin or LMWH). It is recommended that all
1935 patients who undergo THA or TKA require chemoprophylaxis to prevent VTE, with-holding
1936 or not giving chemoprophylaxis is considered against the current standard of care. We
1937 believe this request satisfies the criteria as detailed in the National Statement on Ethical
1938 Conduct in Human Research (2013, chapter 2.3) for providing a waiver of consent.

1939

1940 a. involvement in the research carries no more than low risk

1941

1942 • This is a low risk project as it involves interventions that are currently used in
1943 standard practice (aspirin and LMWH for VTE prophylaxis). The additional
1944 questions asked of patients is not considered of sufficient risk or burden to justify
1945 specific consent as they are also part of routine practice (follow-up health and
1946 complication questionnaires) for most sites. Furthermore, randomisation is not
1947 at the patient level – it occurs at the site level (cluster randomisation).

1948

1949 b. the benefits from the research justify any risks of harm associated with not seeking
1950 consent

1951

1952 • There is no additional harm from this study as both intervention arms are
1953 standard practice. There may be an imbalance of harms between groups, but this
1954 study is necessary to determine this, and this highlights the benefits that will
1955 arise from the research as there is currently insufficient evidence to guide
1956 practice which has resulted in widespread practice variation.

1957

1958 c. it is impracticable to obtain consent (for example, due to the quantity, age or
1959 accessibility of records)

1960

1961 • Specific consent for CRISTAL would require an additional consent process (in
1962 addition to the consent for the use of data). This would make entry into the
1963 research cumbersome and confusing and would likely lead to a higher proportion
1964 of patients abandoning data entry, reducing the scientific validity of the study.

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- 2008
- d. there is no known or likely reason for thinking that participants would not have consented if they had been asked
- Patients currently receive VTE prophylaxis without consent as part of standard practice and we consider the process of this trial to be similar to standard practice.
- e. there is sufficient protection of their privacy
- The AOANJRR is a declared Federal Quality Assurance Activity
 - Systems are in place to ensure individual patient data remains confidential
 - A third-party security review and penetration testing has been undertaken prior to commencement of data collection in the clinical trials system.
- f. there is an adequate plan to protect the confidentiality of data
- SAHMRI which is the organisation responsible for managing AOANJRR data has existing security systems, policies and procedures in place as well as software barriers to protect personal information and ensure confidentiality. These systems are already in place for data contained within the AOANJRR Clinical Trials platform and the CRISTAL data will be treated identically (see Appendix 5)
- g. in case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them (for example, via a disease-specific website or regional news media)
- It is the intent of the researchers that the results of the CRISTAL study will be synthesised and published as a clinical trial in a peer reviewed journal. The only trial data of relevance to the patients will be the development of adverse events or VTE, which will be known to them at the time. Other data collected as part of the Registry will be made available to patients as per usual practice.
- h. the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled
- The CRISTAL study is receiving no industry or pharmaceutical corporation support and does not aim to make any financial profit or gain during the trial or after publication of the results. It will not deprive participants of any financial benefits.
- i. the waiver is not prohibited by State, federal, or international law
- There are no applicable laws prohibiting this waiver.

2009 **4.4. Confidentiality**

2010 AOANJRR is required to have highly secure data protection systems to secure the identified
2011 information which it currently holds as this is an absolute requirement under its Federal
2012 Quality Assurance Activity.

2013 SAHMRI has been contracted to build the AOANJRR Trials which will be utilised for CRISTAL.
2014 SAHMRI has existing security systems, policies and procedures in place as well as software
2015 barriers to protect personal information and ensure confidentiality. (Appendix 5)

2016
2017 As this will be a fully electronic system, accessible online, which will store patient’s personal
2018 and contact details, additional security activities have been included in the AOANJRR Trials
2019 system development:

- 2020 • A third-party security review of the infrastructure and application design was
- 2021 undertaken, prior to development starting
- 2022 • A penetration test of the application was performed prior to commencement of
- 2023 data collection in the clinical trials system.

2024

2025 Patient Confidentiality

2026 All patient data will be managed in accordance with the Guidelines for the Protection of
2027 Privacy in the Conduct of Medical Research. Patient contact details will only be used for the
2028 purpose for which they were collected and will be stored securely and confidentially.

2029 Patients will not be identified in any reports, manuscripts or presentations derived from the
2030 CRISTAL project.

2031

2032 Surgeon Confidentiality

2033 No individual surgeons will be identified in any reports or manuscripts.

2034

2035 **4.5. Risk to Patients**

2036 As patients will be treated with the standard protocol for both LWMH and Aspirin, this study
2037 poses no foreseeable risk, harm or discomfort to patients beyond the inconvenience
2038 associated with completing the study questionnaires at three-time points. We recognise the
2039 burden of survey completion but also recognise that patient outcome collection is now
2040 becoming a standard part of patient care and will be standard practice in most sites
2041 recruiting for CRISTAL.

2042

2043 As patient follow-up is a requirement of this project all efforts will be made not to contact
2044 the relatives of a deceased participant. The AOANJRR links to the National Death Index (NDI)
2045 twice a year (February and September). If a patient, who has participated in the CRISTAL
2046 project, is flagged as deceased this will be transferred to the AOANJRR trials when the
2047 procedure date is linked. This will stop any automated and manual reminders being
2048 triggered. Notification of all deaths to the respective HRECs will occur biannually following
2049 the linking of the AOANJRR core date to the NDI. NDI matching provides ‘fact of death’ data
2050 only and no causality is determined.

2051

2052

2053

2054

2055 **4.6. Safety Monitoring and Management of Serious Adverse Events**

2056 The principal investigators will be responsible of notifying the AOANJRR of any known
2057 serious adverse event that occurred at their respective site. The event will then be
2058 reviewed by the Trial Management Committee to determine if it warrants a review by the
2059 Data Safety Monitoring Board (DSMB).

2060

2061 The DSMB will also be notified as soon as practicable by the relevant principle investigators
2062 of any VTE related participant deaths as they become aware of the events. This includes
2063 post-surgical inpatient deaths or deaths after discharge of which the Principle Investigator
2064 or researcher becomes aware.

2065

2066 A DSMB was established after the commencement of the study. The DSMB consists of one
2067 orthopaedic surgeon, one haematologist and one statistician. All members are independent
2068 to the study and will review serious adverse events when deemed necessary by the Trial
2069 Management Committee. DSMB recommendations will be reviewed by the Trial
2070 Management Committee for their approval.

2071

2072

2073 **4.7. Declaration of interests**

2074

2075 Ian Harris (IH), Stephen Graves (SG), Richard de Steiger (Rds) and Michelle Lorimer are
2076 employed by the AOANJRR. Nicole Pratt (NP)'s salary is partly supported by the MRFF grant
2077 received for CRISTAL.

2078

2079

2080 **4.8. Data access**

2081 All principal investigators involved in data analysis will have access to deidentified datasets.

2082 All principal investigators involved in subcommittees will have access to relevant

2083 deidentified data necessary for undertaking their specific role (e.g. outcome validation).

2084

2085 **4.9. Additional care**

2086 As both interventions are standard, recommended practice, no additional treatment will be
2087 provided for participants.

2088

2089 **4.10. Dissemination**

2090 A writing committee will be established to write the principal papers (primary and
2091 secondary outcomes). Dissemination will be by peer reviewed journal publication,
2092 conference presentation and through media. All study findings will be reported, regardless
2093 of statistical significance or the size or direction of effect.

2094

2095 Study findings will be released to participating sites and investigators.

2096

2097 Input will be sought into guideline development by state and national bodies (e.g. ACSQHC).
2098 The results of the study are expected to be published in a journal with high impact and to be
2099 of interest to a wide audience (beyond orthopaedics and haematology, including hospitalists

2100 and public health). They are expected to have clinical importance and statistical power that
2101 will enable the results to influence practice, which currently lacks studies on this size and
2102 quality.

2103

2104 **4.11. Implementation**

2105 Surgeons will be surveyed prior to commencement (separate study) to assess their
2106 willingness to change practice based on the results of the trial, allowing for current practice,
2107 study findings, experience, gender.

2108

2109 Surgeons will be asked to sign a commitment to change. Following the study, practice
2110 change at departmental and surgeon level will be measured for each surgeon at each site by
2111 assessing departmental and individual surgeon prophylaxis methods.

2112

2113 Practice change more broadly will be assessed through data linkage, assessing the increase
2114 or decrease in post-operative LMWH prescriptions.

2115

2116 **4.12. Authorship**

2117 Authorship for principal papers will be by the members of the writing committee and the
2118 CRISTAL Study Group (consisting of all investigators according to the authorship guidelines
2119 of the ICMJE).

2120

2121 **5. Statement for compliance with NHMRC National Statement on Ethical Conduct of**
2122 **Research Involving Humans**

2123 This study will be conducted in accordance with the ethical principles that have their origin
2124 from the Declaration of Helsinki and are consistent with ICH/GCP. This study will comply
2125 with National Health and Medical Research Council (NHMRC) National Statement on Ethical
2126 Conduct in Research Involving Humans.
2127

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2223
2224

2225 **CRISTAL: Aspirin or LMWH for VTE Prophylaxis After Hip or Knee Arthroplasty**

2226

2227

2228 **Historical Summary of Amendments for Trial Protocol**

2229

2230

2231 **Previous Protocol (Initial):** 28 September 2018

2232

2233 **Updated Protocol:** 11 January 2019

2234

2235 **AMENDMENT 1**

2236

2237 1. **ITEM:** Section 3.3. Intervention: Reminder Schedule for 90-day follow-up

2238 **CHANGE:** Previously patients were to be reminded at 90 days only for follow-up and
2239 this was changed to allow three reminders, at 90 days, 95 days and 100 days

2240 **RATIONALE:** This allowed two further attempts of follow-up and aimed to reduce
2241 loss to follow-up if initial contact was unsuccessful

2242 2. **ITEM:** Section 3.6. Primary outcome: Question at 90-day follow-up about ongoing
2243 anticoagulation

2244 **CHANGE:** This question was removed from the 90-day follow-up questionnaire

2245 **RATIONALE:** This could not distinguish between patients who were on long-term
2246 anticoagulants preoperatively or who had started anticoagulants postoperatively for
2247 an alternative reason and was therefore removed

2248 3. **ITEM:** Section 3.8. Participant timeline – Table of Pre-operative/90 day/6 month

2249 Questions: Question at 6 months regarding venous thromboembolism (VTE) and
2250 deep venous thrombosis (DVT) or pulmonary embolism (PE)

2251 **CHANGE:** This question was removed

2252 **RATIONALE:** VTE was to be assessed at 90 days only and not 6 months

2253 4. **ITEM:** Section 3.8. Participant timeline – Pre-operative anticoagulation use

2254 (Appendix 4): Question 4, timing of previous DVT or PE

2255 **CHANGE:** Question updated to remove abbreviations, DVT changed to “deep venous
2256 thrombosis” and PE to “pulmonary embolism”

2257 **RATIONALE:** Avoid confusion in patients about meaning of abbreviations

2258 5. **ITEM:** Section 3.8. Participant timeline – Post-operative VTE symptoms and

2259 occurrence (Appendix 4): Question 7, serious bleeding postoperatively and

2260 preceding text “Questions 1 to 3 are only specific for the 90 days data collection
2261 point...” implied that VTE and serious bleeding were to be measured at 6 months

2262 **CHANGE:** Question 7 moved to Question 5, and preceding text changed to

2263 “Questions 1 to 5 are only specific for the 90 days data collection point...”

2264 **RATIONALE:** Serious bleeding and postoperative VTE occurrence were only

2265 measured at 90 days and not at 6 months

2266 6. **ITEM:** Section 4.3. Consent to project participation – Waiver of Consent – Section e:

2267 Protection of patient privacy

2268 **CHANGE:** Addition of text stating that a third-party security review and penetration
2269 test was undertaken of the Australian Orthopaedic Association National Joint
2270 Replacement Registry (AOANJRR) clinical trials system prior to data collection
2271 **RATIONALE:** Provide patients and ethics committees with security that patient
2272 privacy was protected prior to trial commencement
2273 7. **ITEM:** Section 4.4. Confidentiality: Protection of patient privacy
2274 **CHANGE:** Addition of text stating that a third-party security review and penetration
2275 test was undertaken of the AOANJRR clinical trials system prior to data collection
2276 **RATIONALE:** Provide patients and ethics committees with security that patient
2277 privacy was protected prior to trial commencement
2278

2279 **Previous Protocol:** 11 January 2019

2280

2281 **Updated Protocol:** 6 February 2019

2282

2283 **AMENDMENT 2**

2284

2285 1. **ITEM:** Section 1.3. Contributors

2286 **CHANGE:** Addition of two medical students as contributors, Qazi Sarem Shahab and
2287 Emma Tsz Lou Cheng

2288 **RATIONALE:** Allowed these contributors to assist with the hospital inpatient audit
2289 process

2290 2. **ITEM:** Section 3.3. Intervention: Save and complete function added

2291 **CHANGE:** Save and complete function added to the electronic data system used for
2292 data collection

2293 **RATIONALE:** Allowed for patients to save progress on postoperative questionnaires
2294 and to log-in again to complete questionnaire for up to 2 weeks after
2295 commencement (in case of unexpected stopping so that entered data was not lost)

2296 3. **ITEM:** Section 3.3. Intervention: Dose reduction for low-molecular weight heparin
2297 (enoxaparin) based on weight

2298 **CHANGE:** Dose for enoxaparin reduced to 20mg for patients weighing less than 50kg

2299 **RATIONALE:** After consultation with haematologist and participating surgeon
2300 groups/institutions, decision made to reduce dose to 20mg for patients weighing less
2301 than 50kg prior to trial commencement

2302 4. **ITEM:** Section 3.4. Adherence: Definition of wound ooze

2303 **CHANGE:** Wound ooze defined as ooze occurring beyond 72 hours instead of 36-48
2304 hours postoperatively

2305 **RATIONALE:** Aimed to deter surgeons and clinicians from with-holding prophylaxis
2306 for postoperative wound ooze occurring within 72 hours of surgery, which occurs
2307 frequently

2308

2309 **Previous Protocol:** 6 February 2019

2310

2311 **Updated Protocol:** 9 July 2019

2312

2313 **AMENDMENT 3**

2314

2315 1. **ITEM:** Section 3.2. Eligibility – Patient Level: Update to include patients with fracture

2316 **CHANGE:** Addition of patients with diagnosis of fracture to be included

2317 **RATIONALE:** Allowed for protocol to be applied to all patients undergoing any hip or

2318 knee arthroplasty procedure at participating hospitals to reduce confusion about

2319 which patients would be included or not for hospital staff members (nursing staff,

2320 junior doctors, residents, registrars and consultants/attending doctors)

2321 2. **ITEM:** Section 3.4. Adherence: Audit of inpatient compliance extended to all sites

2322 **CHANGE:** Inpatient compliance changed from “a sample of hospitals” to “all sites”

2323 **RATIONALE:** Extended audit process to all sites (clusters) to allow measurement of

2324 inpatient compliance across all participating hospitals

2325 3. **ITEM:** Section 3.9. Sample size: Change in number of clusters used for sample size

2326 **CHANGE:** Based on number of expected hospitals, cluster number was reduced to 22

2327 hospitals and a new sample size was calculated, giving 212 patients per arm for each

2328 hospital for the primary outcome

2329 **RATIONALE:** The number of hospitals recruited was less than expected at this time

2330 and the sample size was re-calculated

2331 4. **ITEM:** Section 3.12. Blinding: Clarification on how patients will be blinded to

2332 outcomes and interventions

2333 **CHANGE:** Insertion of phrase “whether they (patients) are in the intervention or

2334 control group and the secondary outcomes of the trial”

2335 **RATIONALE:** Clarification on how patients would not be aware that they were

2336 receiving control or intervention medication for the trial and that this would not bias

2337 them when reporting outcomes at 90 days or 6 months

2338 5. **ITEM:** Section 3.15. Statistical Analysis: Update on methods used

2339 **CHANGE:** Insertion of use of cluster summary methods

2340 **RATIONALE:** Use of cluster summary methods in final statistical analyses of the

2341 outcomes

2342

2343 **Previous Protocol:** 9 July 2019

2344

2345 **Updated Protocol:** 1 October 2019

2346

2347

2348 **AMENDMENT 4 – Protocol published after this amendment (BMJ Open. 2019 Nov**

2349 **6;9(11):e031657)**

2350

2351

2352 1. **ITEM:** Section 1. Administrative Information – 1.1. Registration

2353 **CHANGE:** Trial registration number from Australian and New Zealand Clinical Trials
2354 Registry (ANZCTR) included

2355 **RATIONALE:** Linked protocol to published online protocol through inclusion of
2356 ANZCTR number

2357 2. **ITEM:** Section 1.3. Contributors

2358 **CHANGE:** Addition of Dr Thu-Lan Kelly as contributor (statistician)

2359 **RATIONALE:** Allowed addition of lead statistician prior to development of statistical
2360 analysis plan

2361 3. **ITEM:** Section 1.6. Abbreviations

2362 **CHANGE:** Included “OA” as abbreviation for osteoarthritis

2363 **RATIONALE:** Avoided any misunderstandings of abbreviation of “OA” throughout
2364 protocol

2365 4. **ITEM:** Section 3.3 Intervention: Clarification on number of times patients could be
2366 contacted for 90 day and 6 month follow-up

2367 **CHANGE:** Allowed up to 3 successful attempts to contact patients to complete 90
2368 day and 6 month follow-up surveys and allowed for attempts to contact patients
2369 beyond 100 days and 6.5 months if their surveys remained incomplete

2370 **RATIONALE:** Allowed for further contact attempts to reduce loss to follow-up

2371 5. **ITEM:** Section 3.6. Primary Outcome: False negative audit

2372 **CHANGE:** Included an audit of 200 patients who did not report a VTE to allow
2373 estimation of the false negative rate through contact with their general practitioners
2374 and treating surgeons

2375 **RATIONALE:** False negative audit allowed estimation of whether any VTE’s had been
2376 missed

2377 6. **ITEM:** Section 3.7. Secondary Outcomes

2378 **CHANGE:** Classification of non-VTE complications (death, serious bleeding, joint
2379 related re-operation and re-admission within 90 days and death, re-operation within
2380 6 months) and specification of time points at which these would be collected

2381 **RATIONALE:** Allowed specification of time points prior to development of statistical
2382 analysis plan

2383 7. **ITEM:** Section 3.9. Sample size

2384 **CHANGE:** Sample size calculation updated to reflect that 31 hospitals had been
2385 recruited, which was increased from 22 from the previous protocol. The new sample
2386 size used an event rate of 2.5% in the aspirin group, 1.5% in the enoxaparin group,
2387 with a non-inferiority margin of 1%, a power of 90% and a one-sided significance of
2388 0.025. Using an intracluster correlation of 0.01, an interperiod correlation of 0.008,
2389 the sample size increased to 251 patients per arm per hospital, increasing the overall
2390 sample size to 15,562 allowing for a loss to follow-up of up to 27%. A sample size
2391 table was also included (Table 1) to allow for a range of parameters for power, non-
2392 inferiority margin and event rate.

2393 **RATIONALE:** The number of hospitals recruited had increased from the last version
2394 of the protocol and a new sample size was calculated.

- 2395 8. **ITEM:** Section 3.9. Sample size: determination of preliminary VTE rate after 1000
2396 recruited patients to help guide sample size

2397 **CHANGE:** Calculation of VTE rate was performed after first 1000 patients recruited
2398 (without any between-group analyses) to help ensure overall event rate was correct
2399 in order to guide sample size for remainder of trial

2400 **RATIONALE:** This would allow adjustment of sample size if estimated pre-trial event
2401 rate (2%) was incorrect

- 2402 9. **ITEM:** Section 3.15. Statistical analysis: accounting for missing data and specification
2403 of secondary/subgroup analyses

2404 **CHANGE:** Section on accounting for missing data using multiple imputation was
2405 included in protocol and secondary/subgroup analyses were clarified

2406 **RATIONALE:** Clarification of methods for handling missing data and methods used
2407 for secondary/subgroup analyses prior to statistical analysis plan

2408
2409

2410 **Previous Protocol:** 1 October 2019

2411

2412 **Updated Protocol:** 24 September 2020

2413

2414 **AMENDMENT 5 – After protocol publication, amendment made due to meeting of Data**
2415 **Safety Monitoring Board (DSMB), first interim analysis (11 September 2020) and**
2416 **recommendations from lead Human Research Ethics Committee (HREC)**

2417

2418 1. **ITEM:** Section 3.2. Eligibility – Exclusion criteria: clarification of exclusion criteria
2419 given recommendations from DSMB that the decision to include or exclude patients
2420 should be as explicit as possible

2421 **CHANGE:** The three dot points at the end of this section were removed and were
2422 changed to “At an individual level, patients unsuitable to receive routine prophylaxis
2423 will be treated according to local advice and recommendations, as per normal
2424 practice. Routine prophylaxis for the purpose of the CRISTAL study includes the low-
2425 molecular weight heparin (LMWH) and the aspirin protocols used in CRISTAL.
2426 Reasons for not receiving routine prophylaxis include the long-term use of warfarin,
2427 novel oral anticoagulants (NOAC) or dual antiplatelet therapy pre-operatively, allergy
2428 to the study drug and an underlying medical condition that precludes the use of
2429 either drug. Obesity, bilateral surgery or past history of VTE (not currently being
2430 treated) alone are not considered sufficient criteria to exempt patients from routine
2431 prophylaxis.”

2432 **RATIONALE:** Change of wording for eligibility criteria as per the recommendations of
2433 the DSMB. This was adopted by the Trial Management Committee (TMC) into the
2434 trial protocol

2435 2. **ITEM:** Section 4.5. Risk to patients

2436 **CHANGE:** Requirement to notify HRECs of the death of any patient participating in
2437 CRISTAL

2438 **RATIONALE:** Protocol updated to inform HRECs of any death participating in CRISTAL

2439 3. **ITEM:** Section 4.6. Safety Monitoring and Management of Serious Adverse Events:

2440 **CHANGE:** Insertion of statement of how serious adverse events would be managed
2441 by the TMC, including the establishment of a DSMB and notification of the AOANJRR

2442 **RATIONALE:** Updated protocol to include information on how serious adverse events
2443 would be managed following first interim analysis

2444

2445 **Previous Protocol:** 24 September 2020

2446

2447 **Updated Protocol (Final):** 29 October 2020

2448

2449 **AMENDMENT 6 – Final amendments due to further recommendations from lead HREC**

2450

2451 1. **ITEM:** Section 3.2. Eligibility – Exclusion criteria: the information from the previous
2452 protocol was further edited upon recommendation from the lead human ethics
2453 research committee

2454 **CHANGE:** The text was changed to “...Reasons for not receiving routine prophylaxis
2455 include the long-term use of warfarin, NOAC or dual antiplatelet therapy pre-
2456 operatively, allergy to the study drug and an underlying medical condition that
2457 precludes the use of either drug or the treating doctors consider the patient to be
2458 high risk for routine prophylaxis.”

2459 **RATIONALE:** Change of wording as per the advice of the lead HREC after review of
2460 the recommendations of the DSMB

2461 2. **ITEM:** Section 4.6. Safety Monitoring and Management of Serious Adverse Events:

2462 **CHANGE:** Additional wording on how VTE related deaths would be managed,
2463 addition of “The DSMB will also be notified as soon as practicable by the relevant
2464 principle investigators of any VTE related participant deaths as they become aware
2465 of the events. This includes post-surgical inpatient deaths or deaths after discharge
2466 of which the Principle Investigator or researcher becomes aware.”

2467 **RATIONALE:** The TMC agreed that the DSMB should be made aware of any VTE
2468 related death as soon as practicable, in addition to notifying the HREC as listed
2469 above

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