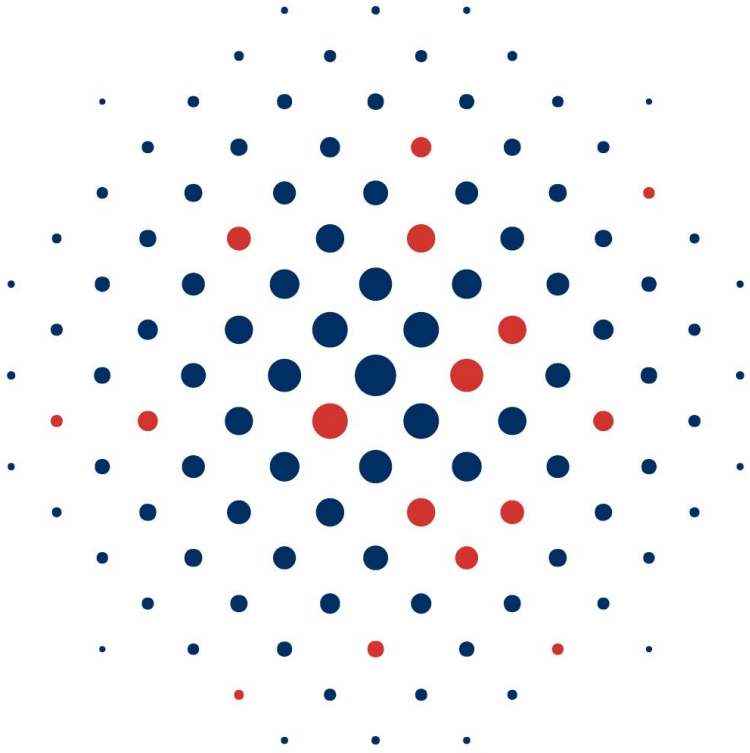
RESEARCH PROTOCOL

The **DISTINCT** trial

*in**D**ividual, targeted thrombos**IS** prophylaxis versus the standard 'one size fits all' approach in patients undergoing **T**otal h**I**p or total k**N**ee repla**C**emen**T**: a national, multicenter, randomized, multi-arm, open-label trial.*



PROTOCOL TITLE the **DISTINCT** trial: in**D**ividual, targeted thrombos**IS** prophylaxis versus the standard 'one size fits all' approach in patients undergoing **T**otal h**I**p or total k**N**ee repla**C**emen**T**: a national, multicenter, randomized, multi-arm, open-label trial

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Legal representative(s) of the sponsor:	***H.B.M. Onstein, manager bedrijfsvoering Divisie 2, A.M.Bontje@lumc.nl***
Principal investigator (in Dutch: hoofdonderzoeker/uitvoerder)	**B. Nemeth, Leiden University Medical Center** **S.C. Cannegieter, Leiden University Medical Center** **J.I. Wiegerink, Bergman Kliniek** **S.B.W. Vehmeijer, Reinier Haga Orthopedisch Centrum** **H.B. Ettema, Isala ziekenhuis**
Coordinating investigator/project leader	**B. Nemeth, MD, PhD** **B.nemeth@lumc.nl**
Funding party	**ZonMW**
Pharmacy	**Pharmacy of the Leiden University Medical Center**

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department Clinical Epidemiology: Prof. F.R. Rosendaal, MD, PhD		
Coordinating Investigator/Project Leader: B. Nemeth, MD, PhD		

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

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ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ATMP	Advanced Therapy Medicinal Product
AxMP	Auxiliary Medicinal Product
CA	Competent Authority
CCMO	Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research Involving Human Subjects)
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trial
CTA	Clinical Trial Authorisation
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
e-CRF	Electronic Case Report Form
EU	European Union
EMA	European Medicines Agency
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MS	Member State
OHS	Oxford Hip Score
OKS	Oxford Knee Score
PI	Principal Investigator
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
VTE	Venous thromboembolism

1. SYNOPSIS

2023-510186-98-00 The **DISTINCT** trial: in**D**ividual, targeted thrombos**IS** prophylaxis versus the standard 'one size fits all' approach in patients undergoing **T**otal h**I**p or total k**N**ee repla**C**emen**T**: a national, multicenter, randomized, multi-arm, open-label trial.

Rationale

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are associated with an overall symptomatic venous thromboembolism (VTE) risk of about 1.3% despite the use of prophylactic anticoagulants in all patients. While not preventing all VTEs, the uniform application of anticoagulant prophylaxis is at the same time associated with a major bleeding risk of at least 0.5%. Considering that a large proportion of all patients actually have a low VTE risk, this group is unnecessarily exposed to the burden and risks of thrombosis prophylaxis. On the contrary, some patients with a high VTE risk experience a VTE despite the use of the same prophylactic anticoagulants. These VTE cases could have possibly been prevented by intensified prophylaxis.

Objective

Overall objective: To study whether the application of a targeted anticoagulation strategy leads to less thrombotic and bleeding complications in this large patient group.

Primary objective DISTINCT study arm 1 : To determine whether in-hospital thrombosis prophylaxis only is as effective compared with the standard thrombosis prophylaxis approach to prevent symptomatic VTE after total knee and hip arthroplasty in patients with a low VTE risk.

Primary objective DISTINCT study arm 2: To determine the incidence of symptomatic VTE after total knee and hip arthroplasty in patients with an intermediate VTE risk.

Primary objective DISTINCT study arm 3: To determine whether intensified thrombosis prophylaxis is more effective and equally safe compared with standard thrombosis prophylaxis to prevent symptomatic VTE in patients with a high VTE risk by comparing symptomatic VTE and bleeding complications.

Main trial endpoints

The primary efficacy outcome is symptomatic venous thromboembolism. The primary safety outcome is major bleeding, both assessed within 3 months postoperatively. In DISTINCT 1, we expect non-inferiority on the primary efficacy outcome. In DISTINCT 3, we expect a 50% risk reduction of symptomatic VTE.

Secondary trial endpoints

The secondary outcomes include: clinically relevant non major bleeding, impact of events on QALY's, healthcare costs, prosthetic joint infections, patient reported outcome measures, myocardial infarction, ischemic stroke and death. All outcomes are assessed within 3 months postoperatively. For patients in whom an outcome event occurred, patient reported outcome measures will also be assessed at 1 year postoperatively.

Trial design

The study is a national, multicenter, randomized, multi-arm, open-label trial and will consist of three sub studies, to which patients will be assigned based on their individual estimated VTE risk. Following risk stratification by the TRIP(plasty) score, patients in the DISTINCT 1 study arm (predicted 3-months VTE risk <1.0%) will be randomized to either short duration thrombosis prophylaxis or standard duration prophylaxis (control arm). Patients in the DISTINCT 2 study arm (predicted 3-months VTE risk >1.0% - <1.5%) will be treated with standard duration prophylaxis and participate in an observational study arm. Patients in the DISTINCT 3 study arm (predicted 3-months VTE risk >1.5%) will undergo randomization between the intervention arm (higher intensity and longer duration prophylaxis) and the standard prophylaxis.

Trial population

Patients, aged 18+ years, undergoing elective primary THA or TKA.

Interventions

DISTINCT 1

Control: any type of low-molecular-weight heparin (LMWH) or direct oral anticoagulant (DOAC), type of anticoagulant according to local hospital protocol for a duration of 4 weeks.

Short duration prophylaxis: similar thrombosis prophylaxis type as used in the control group but only during hospitalization.

DISTINCT 2

Treatment: any type of low-molecular-weight heparin (LMWH) or direct oral anticoagulant (DOAC), type of anticoagulant according to local hospital protocol for a duration of 4 weeks.

DISTINCT 3

Control: any type of low-molecular-weight heparin (LMWH) or direct oral anticoagulant (DOAC), type of anticoagulant according to local hospital protocol for a duration of 4 weeks.

Intervention: Day 0-2: similar thrombosis prophylaxis type as used in the control group, Day 3: Apixaban 5mg b.i.d. for a total of 6 weeks.

Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks

In the DISTINCT 1 study arm, the participants are either exposed to standard thrombosis prophylaxis, introducing no extra burden, or a short duration of thrombosis prophylaxis which decreases the risks and burden of prophylaxis (often done with subcutaneous injections as well as the risk of bleeding). In the DISTINCT 2 study arm, participants receive thrombosis prophylaxis conform standard care and therefore there is no extra burden due to this study arm. In the DISTINCT 3 study arm, half of participants receive standard care thrombosis prophylaxis. The other half receives the intervention (high dose apixaban). A possible burden of this treatment is an increased risk of bleeding, while a benefit is the expected lower VTE risk. As follow-up of all participants will be in accordance with current follow-up regimen of THA or TKA procedures, there is no extra need for patient visits. One questionnaire will be sent at baseline and three questionnaires will be sent during follow-up. In case of an outcome event an extra questionnaire will be sent 12 months postoperative.

2. INTRODUCTION AND RATIONALE

2.1 Therapeutic condition and current treatment status

Venous thromboembolism (VTE) is a clotting disease that mainly affects the deep veins of the leg (deep vein thrombosis [DVT]) and the pulmonary arteries (pulmonary embolism [PE]). VTE is associated with considerable mortality (~10% of patients die within 1-year) and chronic morbidity: 20-50% of all VTE patients develop post-thrombotic syndrome and ~3% of all PE survivors suffer from chronic thromboembolic pulmonary hypertension. Furthermore, in about 30% of patients a recurrent VTE occurs within 5 years.

Patients who undergo total hip arthroplasty (THA) or total knee arthroplasty (TKA) have a high risk of postoperative VTE. Therefore, essentially all guidelines recommend the use of prophylactic anticoagulant therapy after THA and TKA, although the type and length of treatment differ between guidelines. (Chest. 2012 6 Feb;141(2 Suppl) In the Netherlands, a prophylactic dose of Low Molecular Weight Heparin (LMWH) or a Direct Oral Anticoagulant (DOAC) for the duration of 28-35 days is advised. (Dutch Federatie Medisch Specialisten guideline).

However, this current scheme is not optimal, as about 1.3% of all patients still develop VTE despite the uniform prophylaxis. (Thromb Res. 2015;135:322-8.) Considering the large number of patients involved (35.000 THA and 30.000 TKA), almost 1.000 potentially preventable VTE's yearly occur in the Netherlands alone. At the same time, all patients are subjected to anticoagulant treatment, which is associated with a major bleeding risk of at least 0.5%. (Acta Orthop. 2019 Aug;90(4):298–305) Furthermore, since LMWH is given through subcutaneous injections, this treatment is inconvenient and painful. Considering that a large proportion of all patients actually have a low VTE risk, this group is unnecessarily exposed to the burden and risks of LMWH.

2.2 Clinical trial rationale

Rationale for study interventions

The rationale for all chosen study interventions and assumptions for the power calculations are described below. A detailed overview of the literature that forms the basis for this rationale, including a summary of ongoing and future trials on thrombosis prophylaxis following THA/TKA and guideline recommendations, can be found in *supplement 1*.

Rationale for shortening the duration of thrombosis prophylaxis in DISTINCT study arm 1 (low VTE risk arm)

Multiple observational studies among patients in fast-track treatment protocols have shown that the risk of postoperative VTE is <= 1% with use of in-hospital thrombosis prophylaxis only. In fast-track treatment protocols a multi-disciplinary approach of pre-, peri- and post-operative interventions is performed to reduce surgical stress and achieve early mobilization which all contribute to a short length of stay (LOS). In a Danish registry study, 34.397 patients underwent THA or TKA in a fast-track setting. 96% received in-hospital prophylaxis only and 4% received a prolonged duration of prophylaxis (Petersen 2019). In the entire cohort, 90-day VTE incidence was only 0.42%. Another large prospective cohort in a fast-track cohort showed similar results with an incidence of symptomatic VTE of 0.40% (Petersen 2018). A similar study among 4.924 patients

showed an equal rate of 0.41% (Jorgensen 2013). Again, comparable low VTE rates were reported by a large French observational study in 11 hospitals including 2.003 patients who underwent THA/TKA in an Enhanced Recovery After Surgery (ERAS) protocol. In this study, the risk of VTE was 0.4% following THA and 1.0% following TKA within 3-months of surgery (Jean-Yves 2020). There are no head-to-head comparisons between an in-hospital only thrombosis prophylaxis approach and a standard approach (28 days of thrombosis prophylaxis).

An overall incidence of symptomatic VTE of 0.75% is expected in DISTINCT study arm 1 as only patients with a predicted VTE risk <1.0% are included within this part of the trial. Based on the available literature/evidence, we estimate that by shortening the duration of thrombosis prophylaxis, there is no effect on the VTE and major bleeding rates. The estimated reduced risk for minor + clinically relevant non-major bleeding is approximately 29%-50%. For details on the evidence and assumptions underlying these estimations we refer to supplement 1. Based on these data the DISTINCT 1 study arm will be classified as a 'Low intervention clinical trial'.

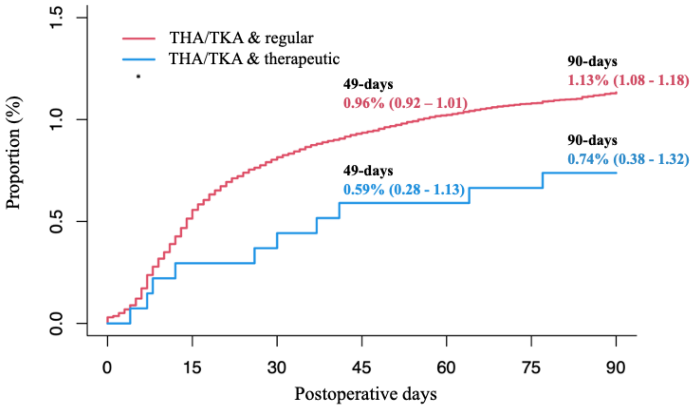
Rationale for DISTINCT study arm 2 (intermediate VTE risk arm)

This part of the trial will be observational only in patients who will receive treatment according to current guidelines. Including patients in this study arm will provide: 1) insight in the observed risk of VTE as predicted by the TRiP(plasty) score, 2) insight in risk factors for VTE, 3) insight in the burden of thrombosis prophylaxis in terms of bleeding risk, and 4) insight in the incidence of wound problems such as persistent bleeding or wound drainage in patients with a standard regimen of thrombosis prophylaxis. These data will be of interest when the complete results of the study will be implemented in practice, to know what can be expected for a large part of the THA/TKA population.

In the DISTINCT 2 study arm, only patients with a predicted VTE risk >1.0% - <1.5% are included. Therefore we expect an overall incidence of VTE within this study arm of 1.3%. The clinical care for these patients remains exactly as it would have been outside the study.

Rationale for extending and increasing the dose of thrombosis prophylaxis in DISTINCT study arm 3 (high VTE risk arm)

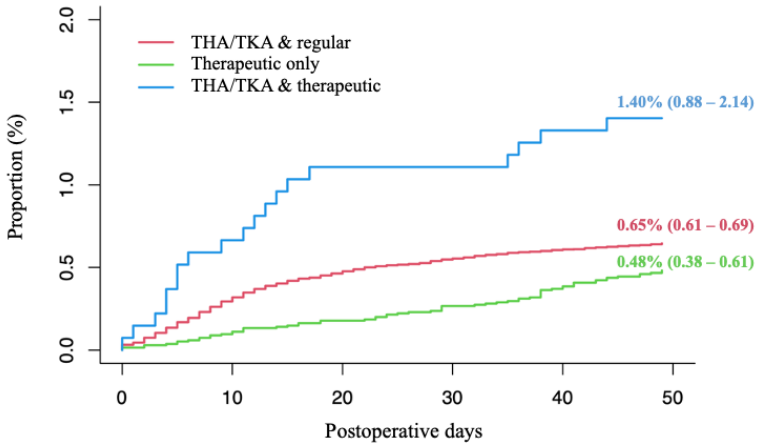
In preparation for the current trial, we conducted a registry-based cohort study on Danish data from 2000 through 2018, in order to obtain a better estimate of the effect of high-dose and longer duration of thrombosis prophylaxis for VTE prevention. The primary cohort of interest consisted of patients with atrial fibrillation (AF), a condition that necessitates therapeutic dosages of DOACs, who needed to undergo THA or TKA (n=1.354). Two control cohorts were formed: 1) patients undergoing THA/TKA using a prophylactic dose of anticoagulation (n=173.020) and 2) patients with atrial fibrillation on a therapeutic dose of DOACs not undergoing THA/TKA (n=13.516). Cumulative incidences of VTE with death as competing risk were assessed. The 90-day VTE incidence estimates were 0.74% (95%CI 0.38 – 1.32) in the THA/TKA & therapeutic anticoagulation cohort, 1.13% (95%CI 1.08 – 1.18%) in the THA/TKA & regular thrombosis prophylaxis cohort and 0.10% (95%CI 0.06 – 0.17%) in the therapeutic only cohort (background risk) (*figure right*, the 2nd control group is not shown [AF + DOAC] due to privacy regulations). Thus, patients with AF and therapeutic anticoagulation following surgery were on average less likely to develop VTE than patients without AF, taking a prophylactic dose of thrombosis prophylaxis, for a RR of 0.74/1.13=0.65. Moreover, the reduction in risk is probably underestimated as no adjusted analyses were performed while patients with AF have more comorbidities than regular patients undergoing THA/TKA taking standard thrombosis prophylaxis.



This finding of a reduced risk with higher dosage was confirmed by a phase II (dose finding) study (APROPOS trial, Lassen 2007) which investigated the efficacy and safety of apixaban in multiple dosages in patients undergoing TKA. In this study, the incidence of VTE decreased with increasing apixaban dose (Apixaban 2.5mg b.i.d. vs. Apixaban 5mg b.i.d. (RR of 0.53 (95%CI 0.19-1.50)).

For more details on the reduced risk of VTE by an intensified dose of thrombosis prophylaxis we refer to supplement 1. For our trial, we assume a relative risk reduction of 50% with a higher thrombosis prophylaxis dose and longer duration. A longer duration up to 6 weeks was chosen as a significant proportion of patients develop VTE after 4 weeks of treatment (Bjørnarå 2016, Mula 2020, Falck-Ytter - ACCP 2012).

A second aim of our pilot study was to assess the extent of a possibly increased risk of bleeding *(figure right)*. As a primary outcome for this part of the study, bleeding incidence rates and cumulative incidences at 49-days postoperatively were obtained. This timepoint was chosen to mimic a situation in which patients would be treated for 6 weeks postoperatively (42 days + 1 week of bleeding risk after cessation of treatment) with a therapeutic dosage of DOACs. Bleeding was defined as a surgical site bleeding (including hematomas), articular bleeding, intracranial bleeding, gastrointestinal bleeding, urinary and bleeding of the airways, i.e., a mixture of major and clinically relevant non-major bleeding. The cumulative incidence of bleeding at 49-days postoperatively was 1.40% (95%CI 0.88% - 2.14%) in the AF cohort on therapeutic dosage undergoing THA/TKA, 0.65% (95%CI 0.61% - 0.69%) in the regular THA/TKA cohort and 0.48% (95%CI 0.38% - 0.61%) in the AF only cohort.



These pilot data give some indication of the expected bleeding risks within our trial for patients treated with high dose apixaban. The incidence rate ratio (IRR) for major bleeding between the therapeutic and regular thromboprophylactic group who underwent THA/TKA is (IRR) 2.1, meaning that patients experienced bleeding twice as much. However, this estimation is subject to confounding by indication which was not adjusted for; it can be assumed that the therapeutically anticoagulated group had more comorbidities and therefore a higher bleeding risk. Therefore, the IRR of 2.1 is presumably an overestimation of the actual effect and can be considered as the maximum increased risk.

A more realistic estimate can be found from the AMPLIFY-EXT trial (Agnelli 2013), in which patients with a VTE, after having been treated for 6-12 months were subsequently randomized between placebo, 2.5mg Apixaban b.i.d. or 5mg Apixaban b.i.d.. In the high dose arm, 35/813 (4.3%) major + clinically relevant non major bleeds occurred versus 27/840 (3.2%) in the low VTE risk arm for a RR of 1.35 (95%CI 0.82-2.17).

For more details on the increased risk of bleeding by an intensified dose of thrombosis prophylaxis we refer to supplement 1. For our trial, we assume an increased relative risk of 65% with increasing the thrombosis prophylaxis dose and duration (versus the prophylactic thrombosis regimen), thus ranging between RRs of 1.35 (AMPLIFY-EXT trial) and 2.10 (abovementioned pilot study).

2.3 Mechanism of action, Drug class

See 7.1.1.

3. STRUCTURED RISK ANALYSIS

3.1 Potential issues of concern

One issue of concern is that the TRiP(plasty) model may not classify the patients correctly. However, we developed and validated the model in two nationwide populations with more or less similar care systems and populations compared to the Netherlands. The model performed equally well in both populations. In particular, the calibration of the model was excellent (near perfect concordance between the observed and predicted risks) up to a VTE risk of 4%, above this threshold, the model tends to overestimate an individual's VTE risk. From a clinical perspective, and for the chosen study arms in the DISTINCT study this is not an issue as the risk thresholds (<1%, >1% - <1.5% and >1.5%) lay well below this 4% risk. This means that the average predicted VTE risks across all DISTINCT study arms will closely match the observed risks.
For details on the TRiP(plasty) score we refer to the original publication. (B. Nemeth et al. Development and validation of a clinical prediction model for 90-day venous thromboembolism risk following total hip and total knee arthroplasty: a multinational study. J Thromb Haemost. 2024 Jan;22(1):238-248. doi: 10.1016/j.jtha.2023.09.033. Epub 2023 Nov 22. PMID: 38030547.)
In addition, more information on the TRiP(plasty) model and information on how VTE risks will be estimated has been described under section 5.1, Trial Design.

Standard care in all study arms consists of LMWHs and DOACs which are registered for the indication 'prevention of VTE after surgery' (amongst which orthopaedic surgery) to administer subcutaneously (LMWHs) or orally (DOACs) and in the dosages presented at 7.1.1. The dosage of the LMWHs/DOAC will be in accordance with (current) standard care in the participating center and therefore will not pose an additional risk for potential participants.

In the DISTINCT 1 study arm, half of the participants will be randomized to standard care (i.e., a prophylactic dose of thrombosis prophylaxis, type of anticoagulant according to hospital protocol for a duration 4 weeks), while the other half will be assigned to a short treatment duration (i.e., only during hospital admission). Participants in the standard care group have a major bleeding risk of 0.5% and minor bleeding risk of 6.0%, while they have a venous thrombosis risk lower than 1.0%, of which the risk is highest during immobilisation and therefore during hospital admission (for details see the literature review in supplement 1). Shortening treatment will likely benefit patients with respect to bleeding and burden of the treatment and pose a minimal risk on additional venous thrombosis, as their baseline risk is low. Furthermore, rates of complications will be closely monitored by the DSMB and assessed during the interim analyses.

In the DISTINCT 2 study arm participants will receive standard care (i.e., already prescribed DOAC/LMWH, type of anticoagulant according to hospital protocol for a duration 4 weeks). This means that no additional risk is introduced in this study arm compared to standard clinical care.

The DISTINCT 3 study arm participants will receive standard care or the intervention: day 0-2 standard thrombosis prophylaxis, type of anticoagulant according to hospital protocol and from day 3 onwards, 5 mg Apixaban b.i.d.. In case of a contra-indication (such as an impaired kidney function) the dose is adjusted to 2.5 mg b.i.d.. Participants in this study arm have a predicted VTE risk of >1.5%. The majority of these VTEs occur during prophylactic anticoagulant treatment or shortly after ceasing this, indicating that the dosage of prophylaxis is too low and the duration too short. A

dosage adjustment from prophylactic to therapeutic combined with longer treatment duration will likely decrease the number of VTEs in this group. The other side of intensifying the treatment is an increased risk of major bleeding. Based on our pilot study (2.2) we expect that these patients have a major bleeding risk of 0.83%, indicating that the decreased thrombosis risk outweighs the increased major bleeding risk, thus justifying the intensification and prolonged duration of anticoagulant treatment. Again, the occurrence rate of bleeding will be assessed by the DSMB.

3.2 Overall synthesis of the direct risks for the research subjects

The risks posed for the patients have all been researched and the balance between venous VTE and bleeding, based on the models, is expected to be beneficial towards the new proposed dosage regimen by means of the TRiP(plasty) model. Furthermore, if the study fails to show an overall beneficial effect for study participants, this will be noticed during the interim analyses and by the DSMB (more details 12.10 DSMB and 13.7 interim analysis). These measures together will, as much as possible, guarantee the safety of participants.

4. OBJECTIVES AND ENDPOINTS

Overall objective:
To study whether the application of a targeted anticoagulation strategy leads to less thrombotic and bleeding complications in this large patient group.

We hypothesize that:
1. In patients with a low VTE risk (individual predicted risk <1.0%), prophylactic thrombosis prophylaxis can be safely shortened to in-hospital duration only, without increasing the VTE risk (in comparison with the standard duration). In addition, this will lead to less clinically relevant non-major and minor bleeds.
2. In patients with a high VTE risk (individual predicted risk >1.5%), a therapeutic dose of thrombosis prophylaxis for 6 weeks is more effective to prevent symptomatic VTE, in comparison with the standard duration and prophylactic dose. In addition, we expect that the benefits of this approach (less symptomatic VTEs) outweigh the induced bleeds.

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint for the primary objective(s)**
DISTINCT study arm 1 • To determine whether in-hospital thrombosis prophylaxis only is as effective compared with the standard thrombosis prophylaxis approach to prevent symptomatic VTE after total knee and hip arthroplasty in patients with a low VTE risk.	• Number of VTEs in the first 3 months postoperative. • Number of major bleeds in the first 3 months postoperative.
DISTINCT study arm 2 • To determine the incidence of symptomatic VTE after total knee and hip arthroplasty in patients with an intermediate VTE risk.	• Number of VTEs in the first 3 months postoperative.

DISTINCT study arm 3 • To determine whether intensified thrombosis prophylaxis is more effective and equally safe compared with standard thrombosis prophylaxis to prevent symptomatic VTE in patients with a high VTE risk by comparing symptomatic VTE and bleeding complications.	• Number of major bleeds in the first 3 months postoperative. • Number of VTEs in the first 3 months postoperative. • Number of major bleeds in the first 3 months postoperative.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To compare risks of clinically relevant non-major bleeds between the targeted thrombosis prophylaxis approach and the standard approach.	• Clinically relevant non major bleeding
• To compare the cost-effectiveness of the targeted thrombosis prophylaxis approach with the standard approach.	• Impact of events on QALY's • Healthcare costs
• To determine the incidence of prosthetic joint infection, overall and in subgroups.	• Prosthetic joint infections
• To compare patient reported outcome measures in the targeted thrombosis prophylaxis approach with the standard approach.	• Patient reported outcome measures
• To investigate the effect of VTE, bleeding and prosthetic joint infections on the functional outcomes after THA and TKA.	• Patient reported outcome measures
• To determine the incidence of myocardial infarction, ischemic stroke and death overall and in subgroups.	• Myocardial infarction • Ischemic stroke • Death

Definition of primary endpoints

VTE is defined according to the ISTH criteria (Le Gal et al.2020, J Thromb Haemost. https://doi.org/10.1111/jth.15138).

DVT is defined by the presence of thrombotic material in the lumen of a deep vein confirmed radiologically.

PE is defined by the presence of thrombotic material in the lumen of a pulmonary vein confirmed radiologically according to the following radiologic diagnosis criteria:

- Computed Tomography Pulmonary Angiogram (CTPA): PE is defined as a central contrast filling defect or complete occlusion up to the subsegmental level of the pulmonary arteries.
- Ventilation/Perfusion Scan (V/Q): PE is defined as at least two large mismatched segmental perfusion defects or the arithmetic equivalent in moderate or large and moderate defects (revised PIOPED criteria).
- Digital Subtraction Angiography: PE is defined as a filling defect or a cut-off of a vessel of > 2.5 mm.

Bleeding is defined as major of it fulfils one of the following criteria (S. Schulman et al J Thromb Haemost. 2010 Jan;8(1):202-4. doi: 10.1111/j.1538-7836.2009.03678.x.):
1. fatal bleeding
2. a symptomatic bleeding that occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome
3. extrasurgical site bleeding causing a fall in hemoglobin level of 20g/L or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48h to the bleeding,
4. surgical site bleeding that requires a second intervention– open, arthroscopic or endovascular.
5. surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability. There should be an associate fall in hemoglobin level of at least 20g/L or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24h to the bleeding,

Definition of secondary endpoints
Clinically relevant non-major bleeding is defined as any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for major bleeding but does meet at least one of the following criteria: requiring medical intervention by a healthcare professional, and/or leading to hospitalization or increased level of care, and/or prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.

Prosthetic joint infection is defined according to the European Bone and Joint Infection Society (EBJIS) definition of periprosthetic joint infection described in Bone Joint J 2021;103-B(1):18–25.

Myocardial infarction, ischemic stroke and death are defined according to current routine practice.

5. STUDY PLAN AND DESIGN

5.1 Trial Design

We plan a national, multicenter, randomized, multi-arm, open-label trial with objective primary efficacy endpoint assessment and blinded outcome adjudication. The study will consist of three study arms (CONSORT flow chart below), to which patients will be attributed based on their individual estimated VTE risk based on the TRiP(plasty) score (see below). This way, patients will be assigned to the low VTE risk study arm: DISTINCT 1 (predicted 3-months postoperative VTE risk <1%), intermediate VTE risk study arm: DISTINCT 2 (predicted VTE risk ≥1%-≤1.5%) or high VTE risk study arm: DISTINCT 3 (predicted VTE risk >1.5%). Following inclusion in the study, patients in the DISTINCT 1 study arm will be randomized to either short duration prophylaxis or the control group (standard prophylaxis). This study arm will analysed as a non-inferiority trial. In the DISTINCT 2 study arm participants will be treated with standard thrombosis prophylaxis. This study arm will be observational. Participants in the DISTINCT 3 study arm will undergo randomization between the intervention (higher intensity and longer duration prophylaxis) and the control group (standard prophylaxis). This study arm will be analysed as a superiority trial. All primary outcomes will be assessed up to 3-months following surgery. During the study, trial outcomes will be regularly evaluated by an independent data safety monitoring board (DSMB) to assess safety.

All patients will be asked to complete a quality-of-life questionnaire (EQ-5D questionnaire) at baseline and at 90-days postoperatively. At 2 weeks, 6 weeks and 3 months following surgery, primary and secondary outcomes will be collected by means of a questionnaire. Furthermore, all patients who developed a primary or secondary outcome will be asked to complete additional patient reported outcomes measures such as the Oxford Hip Score or Oxford Knee Score, a SF-36 and EQ-5D score 1 year postoperatively. A random control group (patients who did not develop an outcome event) of equal size (matched on study center, type of surgery, age and sex) will be asked to complete the same set of PROMS 1 year postoperatively. Please see 10.3 Study procedures and assessments for a detailed overview of all study procedures.

Study interventions

In DISTINCT 1 we will compare short duration prophylaxis versus a control arm and in DISTINCT 3 we will compare an intervention versus a control arm, where the control arm is the 'one size fits all approach' that is the current standard in The Netherlands as advised by the Dutch FMS Guideline 'Antitrombotisch Beleid' (https://richtlijnendatabase.nl/richtlijn/antitrombotisch_beleid). In DISTINCT 2 patients will also receive this standard 'one size fits all' treatment and will only be observed. The vast majority of all orthopaedic surgeons in the Netherlands prescribe any type of low-molecular-weight heparin or direct oral anticoagulant for 4 weeks following surgery.

DISTINCT 1 randomized study arm

- Short duration prophylaxis: only during hospitalization: any type of LMWH or DOAC in a prophylactic dose as approved by the Dutch guideline "Antitrombotisch beleid". First dose of LMWH within 6-24h following surgery. First dose of apixaban within 12-24h following surgery. First dose of rivaroxaban 6-10h following surgery. First dose of dabigatran within 1-4h following surgery. The applied type of anticoagulant is according to the local standard use (same type as used for control group).

- Control: 4 weeks: any type of LMWH or DOAC in a prophylactic dose as approved by the Dutch guidelines. First dose of LMWH within 6-24h following surgery. First dose of apixaban within 12-24h following surgery. First dose of rivaroxaban 6-10h following surgery. First dose of dabigatran within 1-4h following surgery. The applied type of anticoagulant is according to the local standard use.

DISTINCT 2 observational study arm

Treatment: 4 weeks: any type of LMWH or DOAC in a prophylactic dose as approved by the Dutch guidelines. First dose of LMWH within 6-24h following surgery. First dose of apixaban within 12-24h following surgery. First dose of rivaroxaban 6-10h following surgery. First dose of dabigatran within 1-4h following surgery. The applied type of anticoagulant is according to the local standard use.

DISTINCT 3 randomized study arm

- Intervention: the use of any thrombocyte aggregation inhibitors should be discontinued 5 days prior to surgery. Day 0-2: any type of LMWH or DOAC in a prophylactic dose as approved by the Dutch guidelines. First dose of LMWH within 6-24h following surgery. First dose of apixaban within 12-24h following surgery. First dose of rivaroxaban 6-10h following surgery. First dose of dabigatran within 1-4h following surgery. The applied type of anticoagulant is according to the local standard use.

Day 3: Apixaban 5mg b.i.d., continued until 6 weeks after surgery, conditional on the fact that no active bleeding of the surgical wound can be observed. In case of active bleeding, the prophylactic dose of thrombosis prophylaxis is continued. Thereafter, in case no active bleeding has been observed for 24 hours (thus following an active bleeding), the 5mg b.i.d. apixaban treatment will be started (off note, the total duration of thromboprophylaxis will not be extended and is maximized up to 6 weeks following surgery).

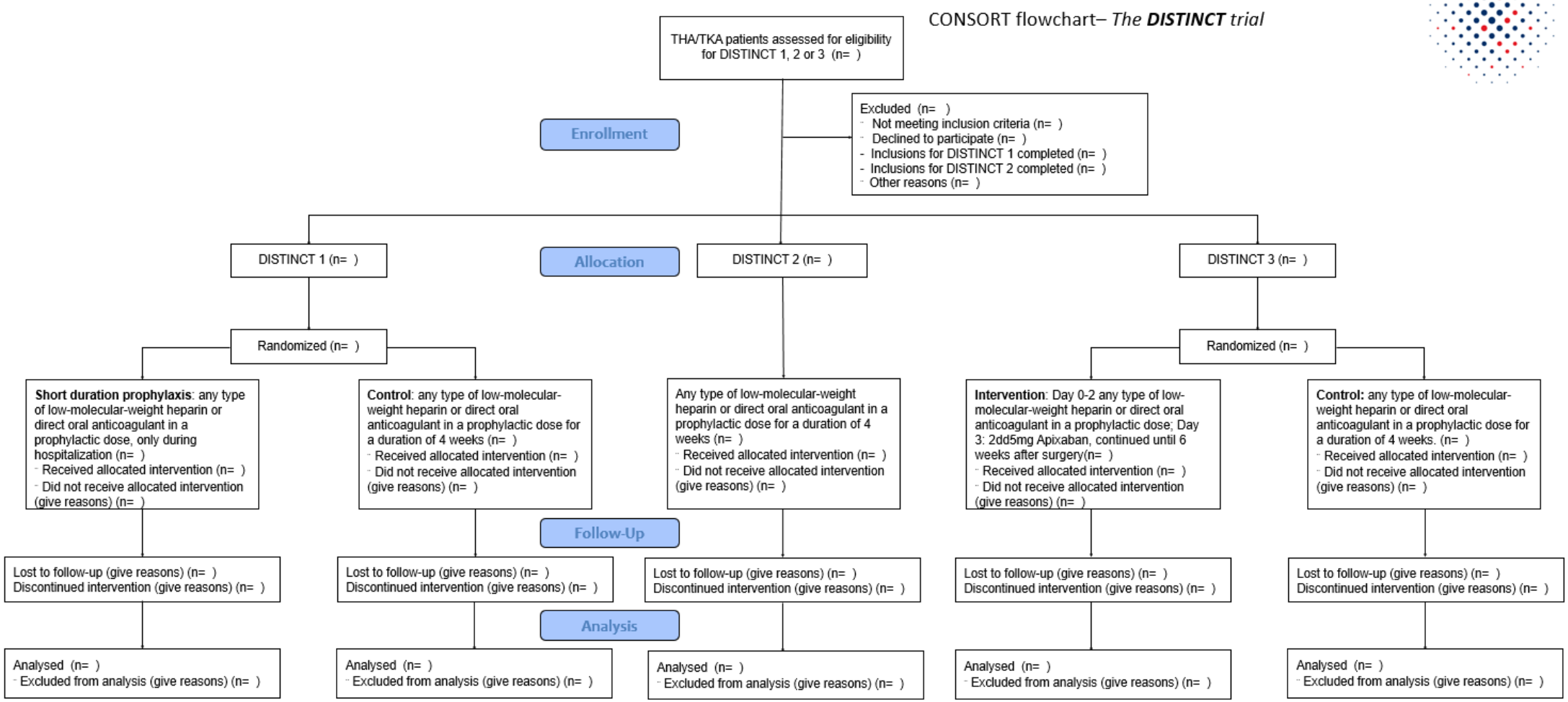
The timing of the first dose of Apixaban is dependent on the type of used thrombosis prophylaxis during day 0-2: the first dose of study medication (apixaban) must be administered 12-24 hours following the last dose of the initial provided thrombosis prophylaxis. The 5mg b.i.d. apixaban dose will be adjusted to 2.5mg b.i.d. in case of an impaired kidney function (defined as eGFR 10-30ml/min).

- Control: 4 weeks: any type LMWH or DOAC in a prophylactic dose as approved by the Dutch guidelines. First dose of LMWH within 6-24h following surgery. First dose of apixaban within 12-24h following surgery. First dose of rivaroxaban 6-10h following surgery. First dose of dabigatran within 1-4h following surgery. Thrombosis prophylaxis is continued until 4 weeks after surgery. The applied type of anticoagulant is according to the local standard use.

TRiP(plasty) score

Thrombosis Risk Prediction following total hip or knee arthroplasty score to estimate VTE risk at 90-days following either THA or TKA, (https://doi.org/10.1016/j.jtha.2023.09.033)

Age at surgery (years)
Body mass index (kg/m2)
Sex (male = 1, female = 0)
Cystitis within 1 year before surgery (urinary tract infection requiring treatment) (yes = 1, no = 0)
History of phlebitis (superficial vein thrombosis) (yes = 1, no = 0)
History of venous thromboembolism (yes = 1, no = 0)
History of varicose veins (only if medically attended) (yes = 1, no = 0)
History of asthma (yes = 1, no = 0)
History of transient ischemic attack (yes = 1, no = 0)
History of myocardial infarction (yes = 1, no = 0)
Hypertension (also if using antihypertensives) (yes = 1, no = 0)
Procedure type (total knee arthroplasty = 1, total hip arthroplasty = 0)
Regression formula:
Prognostic index = -11.21512366 - 0.0025112037∗ Age + 3.1802692e-05∗ pmax(Age – 52, 0)3 + 3.0289566e-05∗ pmax(Age – 66, 0)3 - 0.00045484162 ∗ pmax(Age – 72, 0)3 + 0.00056371658∗ pmax(Age – 78, 0)3 - 0.00017096722∗ pmax(Age – 87, 0)3 + 0.28151553∗ BMI - 0.00088295423∗ pmax(BMI - 15.1, 0)3 + 0.0015184276∗ pmax(BMI - 21.7, 0)3 + 0.00010410438∗ pmax(BMI - 26.8, 0)3 - 0.00078436427∗ pmax(BMI -30.8, 0)ˆ3 + 4.4786473e-05∗ pmax(BMI - 39.1, 0) 3 + 0.10483374∗ Sex + 0.82177659∗ Cystitis + 0.39953645∗ Phlebitis + 1.2908304∗ VTEhistory + 0.1565422∗ Varicose + 0.17636548∗ Asthma + 0.2653638∗ TIA + 0.52510786∗ MIhistory - 0.052137583∗ Hypertension - 0.0066283685∗ Procedure type + 0.23627308∗ Hypertension ∗ Procedure type - 0.76886068∗ MIhistory ∗ Procedure type


CONSORT flowchart– *The **DISTINCT** trial*
THA/TKA patients assessed for eligibility for DISTINCT 1, 2 or 3 (n=)
Enrollment
Excluded (n=)
Not meeting inclusion criteria (n=)
Declined to participate (n=)
Inclusions for DISTINCT 1 completed (n=)
Inclusions for DISTINCT 2 completed (n=)
Other reasons (n=)
Allocation
DISTINCT 1 (n=)
DISTINCT 2 (n=)
DISTINCT 3 (n=)
Randomized (n=)
Randomized (n=)
Short duration prophylaxis: any type of low-molecular-weight heparin or direct oral anticoagulant in a prophylactic dose, only during hospitalization (n=)
Received allocated intervention (n=)
Did not receive allocated intervention (give reasons) (n=)
Control: any type of low-molecular-weight heparin or direct oral anticoagulant in a prophylactic dose for a duration of 4 weeks (n=)
Received allocated intervention (n=)
Did not receive allocated intervention (give reasons) (n=)
Any type of low-molecular-weight heparin or direct oral anticoagulant in a prophylactic dose for a duration of 4 weeks (n=)
Received allocated intervention (n=)
Did not receive allocated intervention (give reasons) (n=)
Intervention: Day 0-2 any type of low-molecular-weight heparin or direct oral anticoagulant in a prophylactic dose; Day 3: 2dd5mg Apixaban, continued until 6 weeks after surgery(n=)
Received allocated intervention (n=)
Did not receive allocated intervention (give reasons) (n=)
Control: any type of low-molecular-weight heparin or direct oral anticoagulant in a prophylactic dose for a duration of 4 weeks. (n=)
Received allocated intervention (n=)
Did not receive allocated intervention (give reasons) (n=)
Follow-Up
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Analysis
Analysed (n=)
Excluded from analysis (give reasons) (n=)
Analysed (n=)
Excluded from analysis (give reasons) (n=)
Analysed (n=)
Excluded from analysis (give reasons) (n=)
Analysed (n=)
Excluded from analysis (give reasons) (n=)
Analysed (n=)
Excluded from analysis (give reasons) (n=)

5.2 Number of Patients

Total planned number of inclusions: 10078
DISTINCT 1: 3478
DISTINCT 2: 2500
DISTINCT 3: 4100

Feasibility of patient recruitment

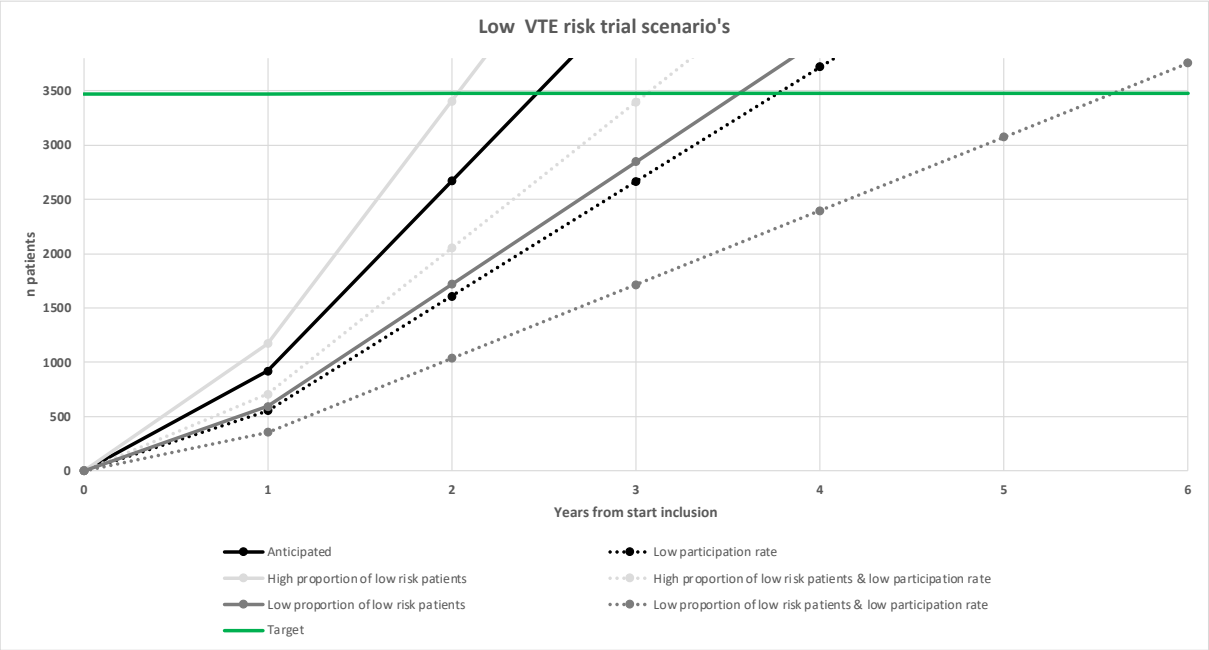
Ten orthopedic centres have confirmed their commitment to enroll patients for the trial: Bergman kliniek, Bravis ziekenhuis, Noordwest ziekenhuisgroep, Reinier Haga Orthopedisch Centrum, St Anna ziekenhuis, Elizabeth Tweesteden ziekenhuis, Isala ziekenhuis, Alrijne ziekenhuis, Onze Lieve Vrouwe Gasthuis & Medisch Spectrum Twente. In total, these centers perform 16.400 THA/TKAs annually of which 13.500 are expected to fulfill the in- and exclusion criteria.

The planned inclusion rates are based on the expected distribution of patients over DISTINCT 1, DISTINCT 2 and DISTINCT 3. We expect that 55% of patients will be eligible for DISTINCT 1, 30% for DISTINCT 2 and 15% for DISTINCT 3. However, as these proportions are difficult to foresee exactly, we also modelled an inclusion rate scenario in case we include a higher proportion of low VTE risk patients, and another scenario in case we include a higher proportion of high VTE risk patients. These scenarios are derived from the development and validation study of the TRiP(plasty) score. (Supplement 2)

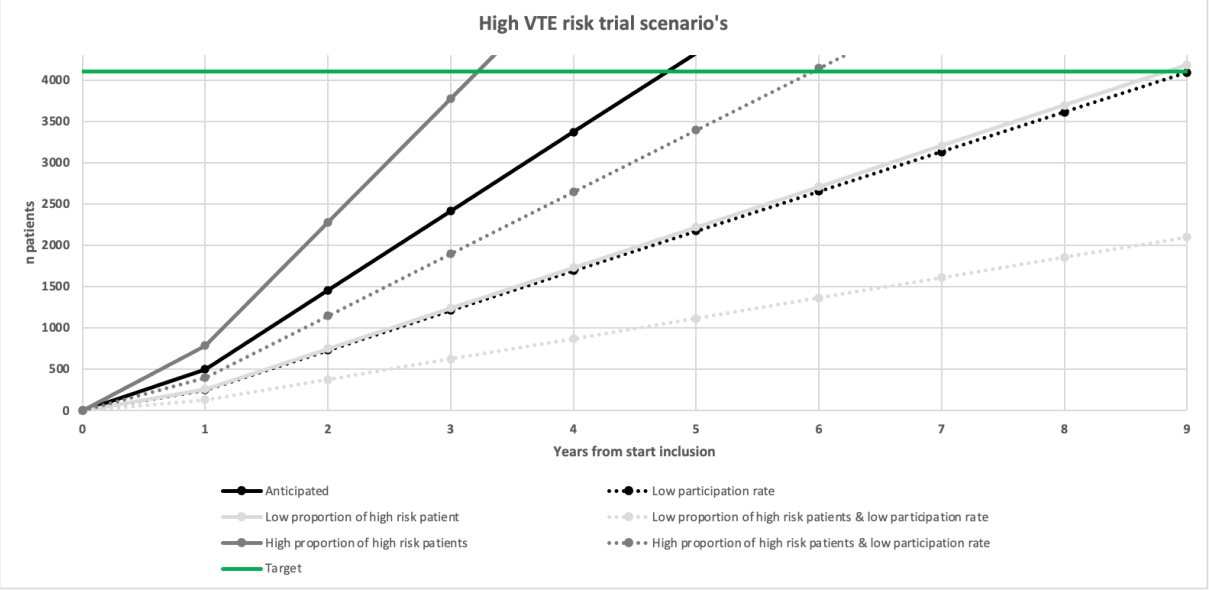
All inclusion rate scenarios are extensively described in Supplement 2. From these analyses, (summarized in the figures below) we expect inclusion in DISTINCT 1 to be completed after 2 years and 5 months. However, this may vary, depending on the scenario, between 2 years and 5.5 years. For DISTINCT 3, we expect inclusion to be completed after 4 years and 10 months, but this may vary, depending on the scenario, between 3 years + 2 months and 9 years for 5/6 scenarios. For all scenarios, inclusions for DISTINCT 2 will be completed before completion of DISTINCT 1.

During the study we will monitor which inclusion scenario is actually ongoing. If we notice a high proportion of low VTE risk patients, the inclusion period of the DISTINCT 1 study arm will be shortened but extended for the DISTINCT 3 study arm. This may jeopardize the inclusion target of the DISTINCT 3 study arm and in that case, we could decide to include more centers with predominantly high VTE risk patients. We refer to Supplement 2 which described all inclusion scenarios and patient participation rates.

DISTINCT 1 inclusion scenario's



DISTINCT 3 inclusion scenario's



5.3 Overall study duration and follow-up

All primary study outcomes will be assessed at 3 months following surgery. For most study participants, follow-up stops at this moment. For all participants who develop a primary or secondary outcome (cases), and for a random subset of participants (controls) (see section 5.1, Trial Design), follow-up will be extended up to 1 year postoperatively. At this point in time, additional quality of life and hip or knee function related PROMS will be collected by means of a questionnaire.

5.4 Patient participation

An expert panel of patients from Harteraad and the Vereniging Afwijkende Heupontwikkeling participated in the trial design. Members from the expert panels read the protocol and the PIF and included comments for improvement. Furthermore, a representative of the Vereniging Afwijkende Heupontwikkeling is included in the Steering Committee of the trial and as such involved in all aspects of the trial.

6. STUDY POPULATION

6.1 Population

Patients, aged over 18 years, who undergo a total hip arthroplasty or total knee arthroplasty within the Netherlands. Study participants will be recruited from large orthopaedic centres. Inclusion will start in:

Bergman Klinieken
Reinier Haga Orthopedisch Centrum
Isala Ziekenhuis

Inclusion in the following orthopedic centers will start in the first year after the beginning of the trial, for these centres a study amendment will be filed once ready:

Noordwest Ziekenhuisgroep
Bravis Ziekenhuis
St Anna Ziekenhuis
Elizabeth Tweesteden Ziekenhuis
Alrijne Ziekenhuis
Onze Lieve Vrouwe Gasthuis
Medisch Spectrum Twente

6.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Scheduled to undergo an elective total hip arthroplasty or total knee arthroplasty
- Aged 18 years or older

6.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Primary arthroplasty for fractures
- Revision surgery
- Hemiarthroplasty
- Pregnancy
- Current use of therapeutic anticoagulant therapy of any type (e.g., LMWH, DOAC, vitamin K antagonist)
- A contraindication for either study drug
- Insufficient knowledge of the Dutch language
- Insufficient mental or physical ability to fulfil trial requirements
- Active malignancy (i.e. cancer diagnosis within six months before surgery (excluding basal-cell or squamous-cell carcinoma of the skin), recently recurrent or progressive cancer or any cancer that required anti-cancer treatment within six months before surgery)
- Patients using thrombocyte aggregation inhibitors that cannot be temporarily discontinued at the discretion of their treating physician

6.4 Vulnerable populations and clinical trials in emergency situations

Not applicable

7. STUDY TREATMENTS

7.1 Investigational Medicinal Product(s) (IMP(s))

7.1.1 Name and description of the IMP

The IMP listed below is specific to the DISTINCT 3 study arm, which involves testing or using a medicinal product in a clinical trial, in this case, apixaban 5mg. The anticoagulants mentioned in section 7.2 will be given as part of standard care in the control study groups and for the initial 2 days in the intervention group. The anticoagulants in section 7.2 are part of standard care and are used in DISTINCT 1 & 2.

Apixaban 5 mg tablet

Apixaban is an oral, direct, and highly selective factor Xa (FXa) inhibitor (of both free and prothrombinase-bound FXa independently of antithrombin III) for the prevention and treatment of thromboembolic diseases.

7.1.2 Status of development of the IMP

The IMPs are registered in the Netherlands, so see the Summary of Product Characteristics (SmPC).

7.1.3 Description and justification of dosage and route of administration

All LMWHs and DOACs (except apixaban 5 mg) are registered for the indication 'prevention of VTE after surgery' (amongst which orthopaedic surgery) to administer subcutaneously (LMWHs) or orally (DOACs) and in the dosages presented under 7.1.1 and 7.2. The dosage of the LMWHs/DOAC will be in accordance with (current) standard care in the participating center.

In DISTINCT 1, half of the participants will be randomized to standard care (i.e., already prescribed DOAC/LMWH, duration 4 weeks), while the other half will have a shorter treatment duration (i.e., during hospital admission). This group has a major bleeding risk of 0.5% and minor bleeding risk of 6.0%, while they have a predicted VTE below 1.0% (supplement 1, literature review). The VTE risk is highest during immobilisation and therefore hospital admission. Due to the balance between bleeding and thrombosis, shortening treatment will highly likely benefit this group of patients.

Participants in DISTINCT 2 will receive standard care (i.e., the type of DOAC/LMWH that is prescribed in the participating study center, duration 4 weeks).

Participants in DISTINCT 3 will receive standard care or a therapeutic dosage of Apixaban during six weeks (i.e., day 0-2 standard prophylaxis with LMWH or DOAC according to local hospital protocol, after which 5mg b.i.d. Apixaban is prescribed, unless contra-indications require a dose adjustment). In the DISTINCT 3 trial participants have a predicted VTE risk ≥1.5%. The majority of these VTEs currently occur during (or shortly after) prophylactic anticoagulant treatment, indicating that the dosage of current clinical practice may be too low and the duration too short. An intensified treatment regimen, both a higher dose and longer duration will likely decrease the number of VTEs. Consequently, this will probably also lead to more major bleeds. Based on our pilot study (see section 2.2, Study Rationale) we

expect that on average, these patients have a major bleeding risk of 0.83% following intensified prophylaxis while the VTE risk declines from 2.5% to 1.25%. This indicated that expected reduced VTE risk outweighs the increased major bleeding risk, hence, justifying the intensified thrombosis prophylaxis treatment.

7.2 Comparator IMP(s)

Apixaban 2.5 mg tablet

Apixaban is an oral, direct, and highly selective factor Xa (FXa) inhibitor (of both free and prothrombinase-bound FXa independently of antithrombin III) for the prevention and treatment of thromboembolic diseases.

Nadroparin 2850 IE for subcutaneous injection and 5700 IE for subcutaneous injection

Nadroparin is a low molecular weight heparin (LMWH) which, when bound to plasma protein antithrombin (ATIII) potentiates the activity of ATIII, inhibiting the formation of both factor Xa and thrombin. As a result, the coagulation cascade is inhibited. It is indicated for prevention of thrombotic events postoperative.

Dalteparin 2500 IE for subcutaneous injection and 5000 IE for subcutaneous injection

Dalteparin is a low molecular weight heparin (LMWH) which when bound to plasma protein antithrombin (ATIII) potentiates the activity of ATIII, inhibiting the formation of both factor Xa and thrombin. As a result, the coagulation cascade is inhibited. It is indicated for prevention of thrombotic events postoperative.

Enoxaparin 2000IE for subcutaneous injection and 4000 IE for subcutaneous injection

Enoxaparin is a low molecular weight heparin (LMWH) which when bound to plasma protein antithrombin (ATIII) potentiates the activity of ATIII, inhibiting the formation of both factor Xa and thrombin. As a result, the coagulation cascade is inhibited. It is indicated for prevention of thrombotic events postoperative.

Rivaroxaban 10 mg tablet

Rivaroxaban is an oral, direct, and highly selective factor Xa (FXa) inhibitor (of both free and prothrombinase-bound FXa independently of antithrombin III) for the prevention and treatment of thromboembolic diseases.

Dabigatran 110 mg capsule

Dabigatran etexilate is an oral prodrug that is metabolized by a serum esterase to dabigatran. It is a synthetic, competitive and reversible direct thrombin inhibitor. Inhibition of thrombin disrupts the coagulation cascade and inhibits the formation of clots. It is indicated for the prevention and treatment of thromboembolic diseases.

7.3 Placebo

Not applicable

7.4 Auxiliary Medicinal Product(s) (AxMP(s))

7.4.1 Name and description of the AxMP

Not applicable

7.4.2 Statement on authorisation and justification unauthorised AxMP (if applicable)

Not applicable

7.4.3 Description and justification of dosage and route of administration

Not applicable

7.5 Additional considerations for trials involving a medical device

Not applicable

7.6 Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic

Not applicable

7.7 Preparation and labelling of the study treatment(s)

Study medication in the commercial package is already ready to use (i.e., orally or subcutaneously). The DISTINCT study arms 1 and 2 will be considered 'low intervention trials' and therefore do not require labelling (see also paragraph 3.1). The DISTINCT 3 study arm has a control arm that is 'standard care', and will therefore not be additionally labelled according to the CTR. This is because there are no specific circumstances for security of the participants or reliability of the results that require additional labelling for the control arm. The study medication i.e., Apixaban 5 mg and 2.5mg (for patients with a eGFR < 30 ml/min) is non-standard care and therefore will be 'repackaged' to amounts required for the treatment of the participants and will require GMP Annex 13 labelling. Both (repackaging and labelling) will be performed by the LUMC Pharmacy under licence number 4576 F.

8. OTHER TREATMENTS AND RESTRICTIONS

8.1 Concomitant therapy

8.1.1 Permitted medication(s)

All medication except medication mentioned in 8.1.2.

8.1.2 Prohibited medication(s)

The chronic use of any anticoagulation in therapeutic dosing is prohibited.

The use of medication with a known interaction with the study medication will be left the at discretion of the treating specialist.

For all patients in DISTINCT 1, concomitant treatment with thrombocyte aggregation inhibitors (e.g.aspirin, clopidogrel, prasugrel or ticagrelor) is allowed, the decision to stop or continue this treatment will lie with the treating physician. We estimate the proportion of prevalent users of aspirin, clopidogrel, prasugrel and ticagrelor at 20%-25% (Acta Orthopaedica, 90:4, 298-305). The decision to continue or stop around/following surgery must not be made based on the randomization outcome and needs to be uniform according to the local hospital protocol/physician's preference. This will prevent variation (of comedication use) between the control and short duration prophylaxis groups which can affect the treatment effect. In DISTINCT 2, the decision to stop or continue must be uniform as well (same decision as for DISTINCT 1). This also applies for patients allocated to the control arm of the DISTINCT 3 study arm. However, for patients in Intervention group, concomitant treatment with thrombocyte aggregation inhibitors (e.g. aspirin, clopidogrel, prasugrel and ticagrelor) is not allowed and must be stopped 5 days prior to surgery to prevent a high-bleeding risk. Hence, patients who are not allowed to stop antiplatelet therapy at the discretion of their treating specialist (for example, in case of a recent coronary percutaneous intervention or stroke) will be excluded before randomization (exclusion criterium).

8.2 Lifestyle restrictions

8.2.1 Contraception measures

Elective hip or knee replacement is not indicated in pregnant women, no extra contraception measures compared to clinical practise have to be taken.

8.2.2 Other requirements

Not applicable

9. TRACEABLILITY, STORAGE, ACCOUNTABLILITY AND COMPLIANCE

9.1 Traceability and storage of the study treatment(s)?

Only medication for the intervention group of the DISTINCT study arm 3 differs from standard care and therefore is considered as study medication. This study medication is repackaged and labelled by the LUMC Pharmacy. Thereafter, the study medication will be stored in the LUMC pharmacy and will be distributed from the LUMC pharmacy to the pharmacy of the participating center with 'conditional transport' (i.e., conditioned on room temperature and under temperature monitoring). In all pharmacies, drugs are stored under continuous temperature monitoring. If the participating center does not have a pharmacy the study medication is transported from the LUMC pharmacy to the home address of the patient after randomisation.

9.2 Accountability of the study treatment(s) and compliance

Drug accountability will be performed in all pharmacies. After collecting the IMP, the local investigator is responsible for the drug storage to the patient at the ward.

Compliance of medicine use is assessed in the follow-up questionnaire after 6 weeks. Because of the prespecified duration of the anticoagulation treatment an exact amount of medication will be delivered to the participant, no study medication has to be returned.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1 Screening procedure

Every patient placed on the waiting list for total knee or total hip replacement at one of the participating centers will undergo screening by a trained study staff member. A screening log will be accessible in Castor EDC, with access restricted to the participating center only.

10.2 Randomisation, blinding and treatment allocation

Patients will be enrolled upon signing the informed consent form. Randomization will be conducted centrally using a clinical data management system. Block randomization with variable block sizes and stratification by center will be employed. This is an open-label study, meaning patients and treating physicians will not be blinded to the intervention, but outcome assessors will be blinded. Each patient will be assigned a unique study number for identification purposes within the study.

10.3 Study procedures and assessments

Evaluation	**Pre-Operative**	**Day 0 (surgery)**	**2 weeks**	**6 weeks**	**3 months**	**12 months**
Study information and informed consent	**X**					
Baseline questionnaire	**X**					
Randomization	**X**					
Surgery		**X**				
Outpatient clinic (as part of standard care)*			**X**	**X**		
Outcome event(s) by questionnaire			**X**	**X**	**X**	
Treatment compliance (questionnaire)				**X**		
VAS	**X**				**X**	
OHS/OKS	**X**					
EQ-5D	**X**				**X**	
In case of an outcome event(s) and controls						
OHS/OKS						**X**
SF-36						**X**
EQ-5D						**X**

* optional according to standard care in the participating center.

VAS: Visual Analogue Scale, OHS: Oxford Hip Score, OKS: Oxford Knee Score, EQ-5D: EuroQol 5 Dimensions Quality of Life questionnaire, SF-36: 36-Item Short Form Survey.

Pre-operative

After the treating physician has establishment the need for surgery together with the patient, he or she will be registered on the waiting list for total hip or knee arthroplasty. A patient is then asked permission if he/she can be approached for the DISTINCT study. If a patient does not consent to be approached, this will be documented in the electronic patient file. Shortly after the preoperative screening the patient will be approached (via telephone) to discuss potential participation in the trial, during which time they will receive study information (for detailed information regarding recruitment, time windows, and informed consent procedures, refer to section 14.2). After inclusion and allocation to the DISTINCT 1, 2 or 3 study arm, patients receive a baseline questionnaire including the EQ-5D and OHS or OKS (based on type of surgery). Randomisation for DISTINCT 1 and 3 is performed in the participating centre 1-2 weeks before surgery to minimize the chance for post-randomisation exclusions (for example when surgery is cancelled). Should a participant be randomized into the intervention group of DISTINCT 3, their usage of thrombocyte aggregation inhibitors will be assessed. If the use of any such inhibitors is identified, the participant will be instructed to discontinue usage 5 days prior to surgery. Study medication will be available in the pharmacy of the participating center or transported to the patient's home address (depending on hospital/study center). The time between study inclusion and surgery will be approximately 4-6 weeks dependent on the waiting list of the participating center.

If the status of the following medical conditions included in the TRiP(plasty) prediction model changes between the time of inclusion and surgery, the outcome of the TRiP(plasty) prediction model is revised: hypertension, history of VTE, history of medically attended varicose veins, history of myocardial infarction, history of phlebitis, history of asthma, history of transient ischemic attack or urinary tract infection requiring treatment in the past year. If this revised risk estimation results in allocation to a different study arm, a new informed consent procedure is initiated. When there is insufficient time to obtain new informed consent or if randomisation for DISTINCT 1 or DISTINCT 3 is already performed the participant will be excluded.

Day 0 (date of surgery)

Surgery

Receive thrombosis prophylaxis in accordance with randomization result (DISTINCT 1 and 3) or local standard care (DISTINCT 2). The general practitioner will receive notification of the patient's participation in the study and the assigned treatment (via the discharge letter).

Day 14

Assess outcome event(s) by questionnaire via email or regular mail. Outpatient clinic visit (as part of standard care, only for some study centers). If participants have experienced a study outcome, information regarding the event will be gathered from the hospital or general practitioner's electronic patient file.

Day 42

Assess outcome event(s) by questionnaire via email or regular mail. Outpatient clinic visit (as part of standard care, only for some study centers). If participants have experienced a study outcome, information regarding the event will be gathered from the hospital or general practitioner's electronic patient file.

Day 90

Assess outcome event(s) by questionnaire via email or regular mail. If participants have experienced a study outcome, information regarding the event will be gathered from the hospital or general practitioner's electronic patient file.

Extended follow-up in case of an outcome event

If a (possible) study outcome is reported by the patient, he or she will receive an additional questionnaire 1 year postoperatively. This questionnaire will include the OHS/OKS, the SF-36 and the EQ-5D. A control group of a comparable size will be randomly selected from all participants. The control group will be matched on age, sex, participating center and THA or TKA.

Landelijke Registratie Orthopedische Interventies (LROI) data

For all THA and TKA procedures performed in the Netherlands, peri-operative and patient specific data are registered in the LROI database. These data will be utilized in the study (and not collected by the study team to avoid duplicate data collection). These LROI data will be linked to the study data upon trial completion; patients provide informed consent for this linkage.

10.3.1 Efficacy assessments

The efficacy assessment is included in the questionnaire 6 weeks and 3 months.

10.3.2 Safety assessments

The safety assessment is included in the questionnaire after 2 weeks, 6 weeks and 3 months. All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol. This only accounts for all reported (S)AEs under chapter 11.1.1. and 11.1.2.

11. STUDY DISCONTINUATION AND COMPLETION

11.1 Definition End of Trial

All study arms (DISTINCT 1, 2 and 3) will end when the last patient completes the final follow-up questionnaire within each study arm (1 year following surgery).

11.2 Criteria for temporary halt and early termination of the clinical trial

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed. During the study, trial outcomes will be regularly evaluated by an independent data safety monitoring board (DSMB) to assess safety. An interim analysis will be performed for DISTINCT 1 and DISTINCT 3 after 25%, 50% and 75% of the planned number of participants have completed the 3 months follow-up. Based on the results of the interim analysis and/or safety outcomes the DSMB can advise to premature terminate DISTINCT 1 and/or DISTINCT 3. See 12.10 for description of the interim analysis and the stopping rules.

11.3 Discontinuation/withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

11.4 Arrangements for subjects after their participation in the clinical trial ended

Not applicable

12. SAFETY REPORTING

12.1 Definitions

12.1.1 Adverse events (AEs)

Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

12.1.2 Serious adverse events (SAEs)

Serious adverse event is any untoward medical occurrence in a patient or trial subject that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.
- An elective hospital admission will not be considered as a serious adverse event.

12.1.3 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious;
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the reference safety information (RSI).

12.2 Recording of AEs/SAEs/SUSARS

Thrombosis prophylaxis following total hip and total knee replacement is a well-known medical intervention that has been applied for multiple decades. The risks of thrombosis prophylaxis are well known. Furthermore, the risks of an increased dose of anticoagulation are also well known from other study populations. Because patients undergoing total hip or total knee arthroplasty are expected to encounter many (S)AEs not related to the experimental drug or study intervention but to the surgery itself, not all (S)AE will be registered.

The following (S)AEs will NOT be registered as such, however, these will be registered as an outcome event within the study (and will thus be assessed by the outcome adjudication committee and DSMB within the interim analyses:

- Venous thromboembolism, consisting of a deep vein thrombosis or pulmonary embolism
- Any minor, clinically relevant non-major and major bleed
- Myocardial infarction

- Stroke
- Transient ischemic attack
- Prolonged surgical wound leakage necessitating (re)hospitalization
- Wound infection
- Prosthetic joint infection
- Re-operation

The following (S)AEs will NOT be registered as such, these are expected complications of total hip or total knee surgery and not related to the study intervention.

- Atrial fibrillation
- Heart failure
- Pneumonia
- Intestinal obstruction
- Cystitis
- (Periprosthetic) fracture

The following (S)AEs will NOT be registered as such.

- Elective hospital admission

All other adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to trial procedure.

12.3 Reporting of AEs and SAEs

(S)AE's reported via the follow-up questionnaires will be recorded in Castor EDC and SAE's will be reported in the annual safety report (except the aforementioned expected SAE's) (details on reporting see 11.3.1).

12.3.1 Reporting of SAEs by the investigator to the sponsor

The principal investigator from each participating hospital will report all SAEs to the study project leader by secured email without undue delay after obtaining knowledge of the events, except for the expected SAEs as mentioned above.

The sponsor will report the SAEs in the annual safety report to the accredited METC that approved the protocol.

12.3.2 List of SAEs which do not require immediate reporting and procedure for reporting

Not applicable

12.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

12.5 Reporting of SUSARs by the sponsor to the EudraVigilance database

The sponsor will keep detailed records of all AEs which are reported to him/her by the investigator or investigators

The sponsor will report electronically and without delay to EudraVigilance database all relevant information about any SUSAR

The period for the reporting of SUSARs by the sponsor to the EMA will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction.
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction.
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report.

12.6 Annual safety report

Regarding investigational medicinal products other than placebo, the sponsor shall submit annually through CTIS to all Member States concerned a report on the safety of each investigational medicinal product used in a clinical trial. The safety report is presented in the DSUR format. One safety report will be submitted for all IMP because all the IMPs are registered in the Netherlands and there is an extended experience with the use of the medication for preventing VTE worldwide.

12.7 Unblinding procedures for safety reporting

Not applicable

12.8 Temporary halt for reasons of subject safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will submit the notification through CTIS without undue delay of a temporary halt but not later than in 15 days of the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state The investigator will take care that all subjects are kept informed.

12.9 Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the subjects. In addition, the sponsor will notify the Member States concerned, through CTIS, of the event and the measures

taken. That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken.

12.10 Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

A data Safety Monitoring Board will be installed prior to the start of the study. See all details in the DSMB charter (D3_ DSMB Charter). The DSMB will consist of a (bio)medical statistician and two independent physicians. Advice of the DSMB after interpreting the results of the interim analysis will be notified to the METC. Each member has no conflict of interest with the sponsor of the study.

In case a (potential) study outcome occurred, additional information will be acquired from the medical patient files (via hospital and/or GP). All outcomes will be assessed by a blinded outcome adjudication committee. These outcomes will be assessed by the DSMB during the interim analyses.

The DSMB will meet and review the progress and acquired data of the DISTINCT 1 and 3 study arms when 25%, 50% and 75% of the target number of subjects have been recruited and completed 3-month follow-up. An interim analysis will be performed and an advice will be provided on the conduct of the trial to the trial steering committee. The DSMB should inform the Chair of the steering committee if, in their view: the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly contraindicated and there is a reasonable expectation that this new evidence would materially influence patient management. Furthermore, based on the results of the interim analysis the formal stopping rules for DISTINCT 1 and DISTINCT 3 are followed.

Formal stopping rule for the DISTINCT 1 study arm: The study will terminate when the lower limit of a two-sided 95% confidence interval around the VTE incidence estimates in either of the two study groups exceeds 0.75%. If the scenario occurs the DSMB will advise the sponsor of the study to stop the study arm.

Formal stopping rule for the DISTINCT 3 study arm: We will test superiority using the O'Brien-Flemming alpha spending function to control the type I error; i.e., we will perform a two-sided test, where superiority will be concluded in case the absolute value of the test statistic exceeds the boundary level of 4.084, 2.888 and 2.358 for the 25%, 50% and 75% interim analysis respectively. In the superiority analysis, at the end of the study (after inclusion of the planned number of participants), superiority will be concluded in case the absolute value of the test statistic that exceeds the boundary level of 1.98. In addition, as a main safety rule, the absolute risk for major bleeds must not exceed the absolute risk for symptomatic VTE in either of the two treatment arms. To determine the statistical significance of the risk difference a Wald-statistic will be used. If the scenario occurs the DSMB will advise the sponsor of the study to stop the study arm.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Next to the safety and main outcomes, the DSMB reviews the trial's progress including updated recruitment numbers and data quality more specific:

- assess data quality, including completeness (and by so doing encourage collection of high-quality data (in collaboration with study monitors)
- monitor recruitment numbers, recruitment speed and losses to follow-up
- monitor compliance with the protocol by participants and investigators
- monitor trial conduct – organisation and implementation of trial protocol
- suggest additional data analyses
- monitor planned sample size assumptions
- monitor compliance with previous DSMB recommendations

13. STATISTICAL ANALYSIS

13.1 Description of statistical methods

Descriptions of the statistical methods can be found under 13.6.1. analysis primary endpoint, 13.6.2. Analysis secondary endpoint(s) and for the interim analysis 12.10 DSMB.

13.2 Analysis sets

Subjects for whom surgery is cancelled, irrespective of the cause, will be excluded from the analysis following randomization. Additionally, in accordance with section 10.3, subjects for whom the TRiP(plasty) score (i.e., an individuals predicted VTE risk) changed following randomization will be excluded as well. This will be done for patient safety.

13.3 Participant demographics and other baseline characteristics

Continuous baseline data will be tested for normality, if normally distributed they will be presented as means (95% confidence interval), if not normally distributed the data will be presented as medians (interquartile range). Categorical baseline data will be presented as number (percentage).

13.4 Randomisation and blinding

See 10.2 for information regarding randomisation.

13.5 Sample size, trail power and level of significance used

Rationale for sample calculations

The rationale for all assumptions for the power calculations are described in 2.2. A detailed overview of the literature that forms the basis for this rationale, including a summary of ongoing and future trials on thrombosis prophylaxis following THA/TKA and guideline recommendations, can be found in supplement 1.

Sample size calculation DISTINCT study arm 1

A 3-months cumulative incidence of symptomatic VTE of 0.75% is expected in the control arm. We expect no risk reduction or increase of VTE. Therefore, the expected risk in the short duration prophylaxis group is also 0.75%. The non-inferiority limit is set at 1% which is the minimal clinically significant difference (Anderson 2018 NEJM). Considering a one-sided alpha of 0.025 and power of 90%, this leads to a necessary sample size of 3.130 patients. To account for a maximum dropout rate of 10% we aim to include 1.739 patients in each group, totalling 3.478 patients.

Sample size calculation DISTINCT study arm 2

In the intermediate risk group, the cumulative incidence of VTE within 3 months is expected to be 1.3%. With n=2.500, the width of the 95% confidence interval is expected to be 0.9% - 1.7%, with a probability of less than 15% that the upper bound of a two-sided 95% confidence interval will exceed the 2% margin. We consider this a sufficiently precise estimate of VTE risk in this patient group.

Sample size calculation DISTINCT study arm 3

A 3-month cumulative incidence of symptomatic VTE is expected of 2.5% in the control group (on standard thrombosis prophylaxis). We expect that the intervention gives a relative risk reduction of 50% (i.e., expected outcome in the intervention arm: 1.25%). At a two-sided alpha level of 0.05 and power of 80%, 3.694 patients would be necessary. To account for the interim analysis and thus testing against a slightly stricter statistical significance level at the final analysis, a total of 3.748 patients is required (1.874 per treatment arm). To account for a maximum dropout rate of approximately 9% we aim to include 2.050 patients in each arm, totalling 4.100 patients.

13.6 Planned analysis

13.6.1 Analysis primary endpoint

For all endpoints a modified intention-to-treat and per-protocol analysis will be performed (see 12.2 for excluded subjects).

Intercurrent events:

Treatment discontinuation will be ignored in the primary analyses. In a secondary, per protocol analyses, we will only include patients who completely adhered to the study protocol. This means that they are not allowed to skip study medication. If this happens, patients will be excluded from the analyses. We will report the proportion of patients who did not adhere to the study protocol, details on the number of skipped dosages, and the reason for non-adherence, will be provided.

Death as an intercurrent event will be included as an outcome event in the analyses (both in ITT and PP) if the outcome adjudication committee adjudicates this death as an outcome event (death related to a fatal pulmonary embolism or bleed). If death is non-related to VTE or bleed, it will be ignored in the analyses (as such an event is very rare within 90-days following surgery).

DINSTINCT 1 statistics

A primary modified intention-to-treat and secondary per-protocol analysis will be performed. Overall cumulative incidences between the control and short duration prophylaxis group will be compared using a one-sided non-inferiority analysis for the absolute risk difference with a significance level set as a one-side p value of 0.025.

DISTINCT 2 statistics

Overall cumulative incidences for VTE and bleeding for the whole cohort will be estimated with a 95%CI.

DISTINCT 3 statistics

A primary modified intention-to-treat and a secondary per-protocol analysis will be performed. Overall cumulative incidences of VTE and bleeding between the control and the intervention group will be compared using a superiority analysis for the risk difference. The 95% CI around the absolute difference in event risks will be determined.

13.6.2 Analysis secondary endpoint(s)

Risks of CRNMB and minor bleeds will be estimated and compared in a similar fashion. The incidence and, prosthetic joint infection, myocardial infarction, ischemic stroke and death will also be estimated and compared between the groups in a similar fashion.

We expect the intervention will improve health at lower health care and societal costs. A cost-utility analysis will be performed, using a Markov model to estimate the life-long impact of VTE and bleeds on discounted QALYs and societal costs. The targeted thromboprophylaxis will be compared to the standard approach, separately for the DISTINCT 1 study arm and the DISTINCT 3 study arm.

Three-months modified intention-to-treat VTE and bleeding rates will be estimated from the trial. The impact per event on QALYs (estimated using the EQ-5D), on healthcare and productivity costs will be obtained estimated from patient questionnaires at 0, 2, 6, 13 and 52 weeks. Medication and other health care will be valued using the farmacotherapeutisch kompas and Dutch reference prices. QALYs and costs will be compared using net-benefit analysis, taking data and parameter uncertainty into account and with multiple imputation to account for missing data. Sensitivity and scenario analyses will include perspective (societal versus health care) and the valuation of productivity (friction costs versus human capital approach) (doi: 10.1007/s00259-022-05794-w).

The functional and quality of life outcomes 1 year postoperative of patients who experienced a VTE, bleeding or prosthetic joint infection and controls will be compared between groups, across all groups.

13.6.3 Analysis other study parameters/endpoints

Not applicable

13.7 Interim analysis

See 12.10 DSMB

13.8 (Statistical) criteria for termination of the trial

See 12.10 DSMB

13.9 Procedure for accounting for missing, unused and spurious data

Missing data will not be imputed as the proportion of missingness is expected to be very low.

13.10 Procedure for reporting any deviation(s) from the original statistical plan

Deviations from the statistical plan can be suggested by the DSMB to ensure patient safety and/or safeguard adequate analysis of study outcomes. The DSMB will present their suggestions to the steering committee. Only if the steering committee agrees there can be a deviation from the

statistical plan. Possible deviations from the original statistical plan can be described with the results of the study or can be added in protocol amendments.

14. ETHICAL CONSIDERATIONS

14.1 Declaration of Helsinki

The study will be conducted according to the principles of the Declaration of Helsinki (version 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and Clinical trials - Regulation EU No 536/2014

14.2 Recruitment and informed consent procedures

When a subject is placed on the waiting list for total hip or knee arthroplasty, the treating physician will introduce the study and provide a flyer containing general information at the outpatient clinic. This flyer also contains a link/QR-code to a general information video on the study webpage. At this moment, either the treating physician or nurse will ask the patients whether he/she can be approached for potential participation in the study. In cases where this consent is not granted, this will be documented in the electronic patient file.

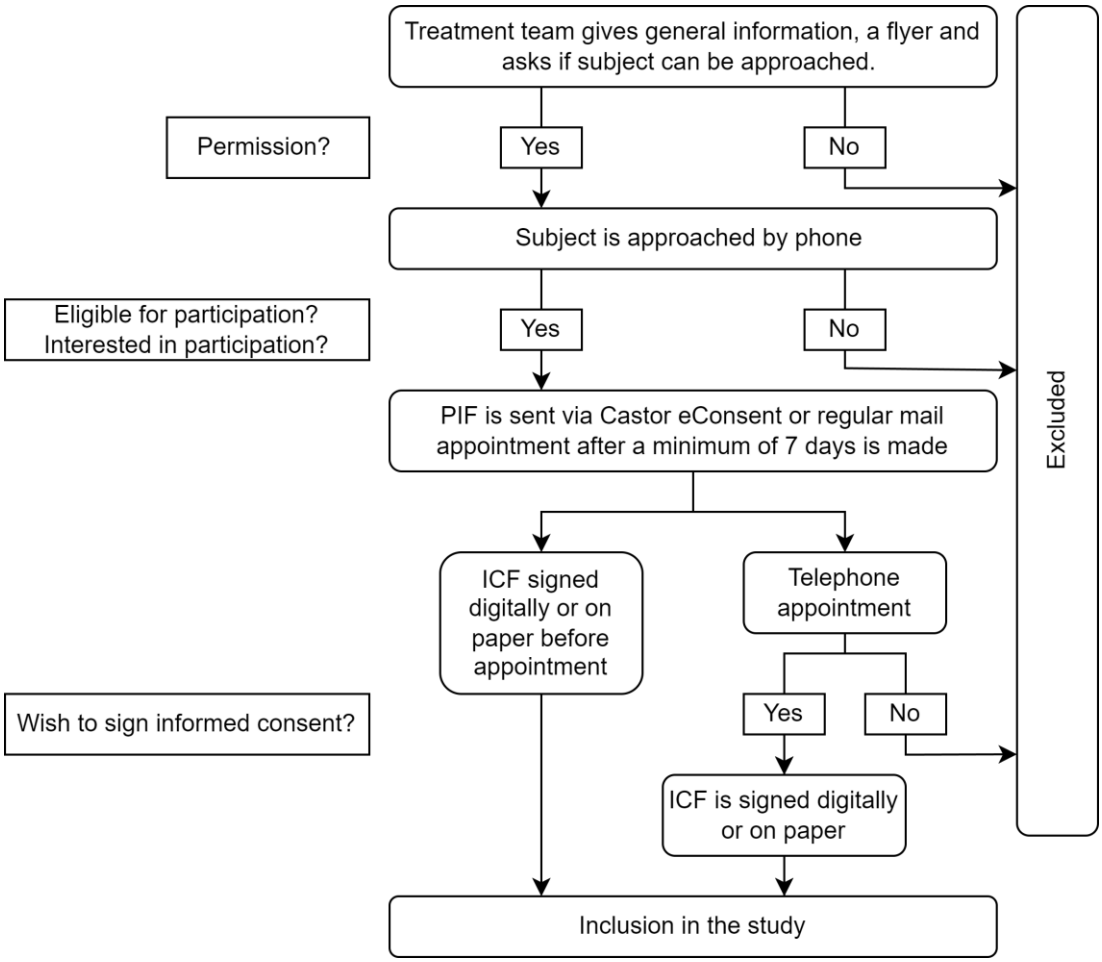
If the intended subject does not object to be approached for the study, a trained (research) nurse will contact this patient by telephone to determine whether the subject actually meets the inclusion and not exclusion criteria. In addition, consent is asked to inquire about the medical history of the subject to complete the TRiP(plasty) model (only if the information is not collected as part of standard care). Failure to provide this consent means the subject cannot participate in the trial. This information is recorded in a Castor EDC screening database.

If the intended subject is interested in study participation, the TRiP(plasty) score is calculated after which a patient's eligibility for either the DISTINCT 1, 2 or 3 study arm is determined. Eligible subjects will receive a comprehensive explanation of the study arm (DISTINCT 1, 2, or 3) through both oral communication (conducted by a medical doctor or a (research) nurse authorized and trained by the main investigator) and written information. The PIF is provided to subjects via Castor eConsent, and in cases where email is not feasible, a physical copy of the PIF is sent to the subject's home address. All subjects have to review and understand the information given prior to giving Informed Consent.

In the digital PIF, a link is provided to redirect the subject to the study webpage containing audio-visual material (animation). This material offers a summarized explanation of the PIF to enhance the subject's understanding of the specific study arm (DISTINCT 1, 2, or 3). It is important to note that the audio-visual content does not replace the information in the PIF, and subjects are encouraged to thoroughly read all details within the document.

If a subject receives a physical copy of the PIF, it will include a link and QR code redirecting to the webpage. The audio-visual material does not introduce new information; all necessary details for informed consent are already present in the PIF. Therefore, watching the audio-visual material is not obligatory for giving informed consent. To avoid any confusion, the audio-visual material can only be accessed through the direct link or QR code. As a result, subjects can only view the audio-visual content related to the study arm for which they are eligible.

At least 7 days following the initial phone call, subjects will receive a second phone call to provide an opportunity for addressing any remaining questions. If informed consent has already been provided, subjects affirms that they have no outstanding questions. Once informed consent is signed and received by a participating center, the subject is officially enrolled in the study. Subjects are free to leave the study at any time they wish to do so, subjects can withdraw their informed consent via email, phone call or letter.



Castor eConsent

Castor eConsent will be utilized for the hybrid remote informed consent process in the study. Following the initial appointment, a study staff member uses Castor eConsent to send an email to the subject, containing a link to access the Castor eConsent portal. Upon entering the portal for the first time, an account must be created by the subject using an email and a password. Within the portal, the PIF assigned to the specific subject is accessible for review. The PIF can be digitally signed in the portal at any time, requiring the email address and password to confirm the signature and verify the subject's identity. Once the subject signs the PIF, no alteration to the PIF or signature can be made, the study employee who informed the subject will then sign it, marking the completion of the informed consent procedure. The digital signature is located at the bottom of the PIF and is saved as a complete document. The (signed) PIF remains available for ongoing review and can be downloaded by participants. It is only after the completion of the informed consent procedure that a study record can be generated in the Castor EDC study database.

If subjects receive the PIF through regular mail, the signed informed consent form can be sent back using the provided return envelope. At the participating center, the ICF is signed by the study

employee. The original ICF is then stored in the ISF and a copy is uploaded in Castor eConsent. Additionally, a copy of the IC form is sent to the participant.

Additional information regarding digital informed consent and identifying data
All data within Castor eConsent are exclusively accessible for the study site, the coordinating study site (LUMC) has no access to the personal data in the Castor eConsent database. Upon signing the informed consent, personal data are accessible by the coordinating site and the data are transmitted to Castor EDC. Patient identifiable data are stored in encrypted form in Castor EDC. The coordinating site (LUMC) is able to decrypt these patient identifiable data to facilitate the distribution of study questionnaires and study medication. The patient identifiable data are limited to the essential information necessary for the trial and include name, email address, phone number, home address and a patient's general practitioner. All screening data are collected in a separate Castor EDC database, with access restricted to the participating center. This database functions as the centrally stored screening log.
Both Castor eConsent and EDC maintain a comprehensive audit trail. For additional details and a statement of compliance with regulations we refer to supplement 3.

14.3 Benefits and risks assessment, group relatedness

LMWHs and DOACs are no experimental pharmaceuticals. LMWHs like Nadroparin or Dalteparin have been registered for prevention of VTE following THP or TKP since 1989 and DOACs such as rivaroxaban and apixaban since 2008/2011. Side effects such as minor bleeds are well known and occur occasionally (0-10%), other complications such as thrombocytopenia, hypotension, gastro-intestinal bleeds are rare (0.1%-1%) and complications such as hypersensitivity reactions, haemoptysis and rectal bleeds are considered very rare (0.01-0.1%). Patients not participating in the trial will still receive a thrombosis prophylaxis regimen with LMWH of DOAC and the above-mentioned risks.

In the DISTINCT 1 study arm, the goal is to compare the standard thrombosis prophylaxis strategy with a reduced thrombosis prophylaxis strategy. Multiple studies from several countries have shown the safety of this reduced strategy. It is therefore not plausible that participation will lead to an increased health risk in terms of an increased risk of VTE. In the DISTINCT 3 study arm the goal is to compare the standard thrombosis prophylaxis strategy with an intensified thrombosis prophylaxis strategy. We expect that the benefits of this strategy (less VTEs) will outweigh the risks (more bleeds) so that the net clinical effect is beneficial.
The burden of participation in the trial can be considered minimal. No extra hospital visits are required. During follow-up, patients will be send a total of three to assess the primary outcome measures. For participants who developed an outcome event, and for a random subset of controls, an additional questionnaire is send 1 year after surgery.

14.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

14.5 Compensation for subjects

Not applicable

14.6 Compensation for investigators

Investigators in participating centers can be compensated based on a specified amount per patient, based on workload in the center or a hybrid model. An estimation of workload is made per participating centre based on the number of total hip and knee replacements last year.

14.7 Other ethical considerations

Not applicable

15. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY

The study will be conducted in compliance with the protocol, with Clinical Trials Regulation No 536/2014 and with the principles of good clinical practice.

15.1 Approval initial application and substantial modifications

The trial protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other documents required by the Regulation will be submitted for the regulatory approval before the clinical trial is started via CTIS.

The sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS.

A 'substantial modification' is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

15.2 Monitoring

Monitoring in all sites in the Netherlands will be executed by (internal) monitors of the LUMC according to the monitor plan. See supplement 4 monitor plan for all details.

15.3 Recording, handling and storage of information

All personal data will be stored like the rest of the medical data according to the rules in the hospital. Only the investigational team has access to the source data of this study. Data will be kept until 25 years after finishing the study. Data collection will be performed using the electronic clinical data management system Castor. When data will be used for publication, they will never relate to individual traceable patients. The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (AVG, UAVG). A detailed overview of data handling, storage and access can be found in the Data Handling and Quality assurance plan in supplement 5. Direct data entry will be performed for some data. See the monitoring plan (supplement 4 Monitor plan) for details on direct data entry.

15.3.1 Handling of data and data protection

Data in the trial will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679. Data is collected in Castor EDC with access restriction. The subjects will be identified by a study specific subjects' number in the database. Patient identifiable data will be encrypted and access to these data is strictly limited.

15.3.2 Source documents and case report forms (CRF)

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code. Castor EDC is used a CRF in this study.

15.3.3 Clinical trial master file and data archiving

The sponsor and investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data. The TMF is stored in PaNaMA. Personal data are encrypted and stored in Castor EDC.

The sponsor and investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other EU law requires archiving for a longer period. The medical files of subjects shall be archived in accordance with national law.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request

15.3.4 Collection and storage of biological samples

Not applicable

15.4 Audits and inspections and direct access to source data/documents

This trial may be subject to internal or external monitoring, auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents including direct access to source data will be given at that time.

15.5 Reporting of serious breaches

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **seven days** of becoming aware of that breach

15.6 Notification of the start and the end of the recruitment

The sponsor will notify within 15 days each Member State concerned of the start of a clinical trial in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the first visit of the first subject in relation to that Member State through CTIS.

The sponsor will notify within 15 days each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU.

15.7 Temporary halt/(early) termination

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS.

15.7.1 Temporary halt/early termination for reasons not affecting the benefit-risk balance

The sponsor will notify within 15 days each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through CTIS.

When a temporarily halted clinical trial for reasons not affecting the benefit-risk balance is resumed the sponsor will notify each Member State concerned through CTIS.

The sponsor will notify to the EU portal CTIS of early termination of the clinical trial for reasons not affecting the benefit-risk balance through CTIS. The reasons for such action and, when appropriate, follow-up measures for the subjects will be provided as well.

15.7.2 Temporary halt/early termination for reasons of subject safety

In accordance to article 38 of the CTR, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance will be notified to the Member States concerned through the EU portal CTIS without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorisation procedure laid down in Chapter III of the CTR.

15.8 Summary of the results

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V.

15.9 Public disclosure and publication policy

In accordance to the CCMO policy the results of the trial will be published unreservedly. As a condition for publication the trial will be registered in a public trial registry.

16. REFERENCES

All references have been included in the text