HAKA

Routine follow-up at 10 years after hip- or knee arthroplasty: wasting resources or appropriate healthcare?

PROTOCOL TITLE 'HAKA: Routine follow-up at 10 years after hip- or knee arthroplasty: wasting resources or appropriate healthcare?'

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Coordinating investigator/project leader	L.A.C. Roubos Toneellaan 2 2725 NA Zoetermeer [redacted] [redacted]
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) ***Multicenter research: per site***	Reinier Haga Orthopedisch Centrum Dr. ir. J.H. Pasma Toneellaan 2 2725 NA Zoetermeer [redacted] [redacted] See ABR form
Sponsor (in Dutch: verrichter/opdrachtgever)	Reinier Haga Orthopedisch Centrum (RHOC) Toneellaan 2 2725 NA Zoetermeer
Subsidising party	ZonMw
Independent expert(s)	Dr. ing. Sebastiaan van de Groes Radboud Universitair Medisch Centrum Postbus 9101, 6500 HB Nijmegen [redacted] [redacted] [redacted]

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
COD	**Check-up on demand**
EPD	**Electronic patient record system**
FU	**Follow-up**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
HCP	**Health care professional**
IC	**Informed Consent**
LROI	**Dutch Arthroplasty Register**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
Review committee	**Medical research ethics committee (MREC) or CCMO**
RFU	**Routine follow-up**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
THA	**Total hip arthroplasty**
TKA	**Total knee arthroplasty**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Clinical guidelines recommend routine follow-up (RFU) consisting of an X-ray and a clinical visit within 3 months and at 1 year after total hip arthroplasty (THA) and knee arthroplasty (TKA). RFU after 5 years (THA) or every 5 years (TKA) might also be worth considering. As revisions are rare and seldom without symptoms, the added value of RFU can be questioned. Consequently, this already leads to variability in clinical practice, as some hospitals already conduct check-ups only upon the request of the orthopaedic surgeon or patient (COD). However, replacing RFU by only COD might not without risks. A recent NIHR report (2022) recommends that no further RFU is required before 10 years in patients with well-studied implants not at high risk of developing problems. However, they do not give evidence for or insight in the cost-effectiveness of RFU at 10 years and recommend to further research the additional value of RFU after 10 years. We expect that replacing RFU at 10 years by COD will be (cost-)effective without compromising outcomes relevant to patients.

Objective: Primary: investigate the (cost-)effectiveness of replacing RFU after THA and TKA at 10 years by COD by comparing the complications and clinical visits between patients with COD versus RFU at 10 years after THA and TKA. Secondary: investigate the effect of COD compared to RFU at 10 years after THA and TKA on surgical interventions, physical function, quality of life, pain and costs. Investigate the effect of informing patients about COD on complications, clinical visits, surgical interventions, and costs.

Study design: Randomized controlled trial with 3 arms

Study population: Patients who had a primary THA or TKA 10 years ago because of osteoarthritis, were 50 years or older at the time of THA or TKA, are still alive and had no revision arthroplasty, bilateral surgery or are already participating in the study due to another hip or knee surgery. Patients will be identified using the Dutch Arthroplasty Register (LROI) and the electronic patient record system (EPD). In total 1,500 patients will be included.

Intervention: COD (intervention): no follow-up visit 10 years after THA or TKA but only check-ups requested by both the health care professional (HCP) or the patient. The intervention group will be split into two groups: one group will be informed about the study and will fill out questionnaires (active COD), one group will not be contacted to avoid any trigger to contact a HCP (passive COD). RFU (control): follow-up visit 10 years after THA or TKA combined with questionnaires.

Main study parameters/endpoints: primary outcomes: complications (clinical outcome), healthcare consumption (process outcome); secondary outcomes: PROMIS physical function, surgical interventions, NRS pain, NRS satisfaction, EQ-5D-5L, and costs for healthcare and societal perspectives.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: No additional risks are expected compared to standard care, as both RFU and COD 10 years after THA or TKA are part of current clinical practice. Patients are required to spend time completing questionnaires. Only the RFU group will be asked to visit the hospital.

1. INTRODUCTION AND RATIONALE

Clinical Dutch guidelines recommend routine follow-up (RFU) consisting of an X-ray and clinical visit within 3 months and at 1 year after total hip arthroplasty (THA) and total knee arthroplasty (TKA) [1, 2]. RFU after 5 years (THA) or every 5 years (TKA) might also be worth considering. However, the added value of RFU can be questioned, as registry data show excellent survival after THA and TKA [3] and revisions are rare and seldom without symptoms [4-7]. Currently, clinical practice demonstrates significant variation in RFU, as some hospitals have already decided to discontinue RFU and instead perform check-ups only upon the request (COD) of the patient or orthopedic surgeon. This practice variation was confirmed by a national survey performed in 2019 among orthopaedic surgeons (non-published results). So, both RFU and COD are currently used in clinical practice, which is also acknowledged by the Dutch Orthopaedic Society (NOV).

There is equipoise among orthopaedic surgeons; a widely shared feeling of genuinely not knowing what the best course of action is. What is the risk of missing a complication? Do patients report issues promptly? For example, osteolysis (break down of bone tissue) and wear of the prosthesis can occur without symptoms. When discovered early, this can be monitored and managed by a relatively simple revision surgery. However, when discovered late, this can result in catastrophic failure (i.e. unexpected and unannounced failing of the prostheses with large consequences) and therefore a more complex revision surgery, with higher costs and more risks for the patient. There is willingness to adjust clinical practice, but also hesitation due to the risks of providing suboptimal care and missing a complication at the long term. In other words, replacing RFU with only COD might not be without risks, i.e. missed complications, reduced patient satisfaction or physical function.

Current guideline recommendations are of low level evidence. Both guidelines suggest that the added value of RFU is likely limited, but convincing research is lacking [1, 2]. Furthermore, previous studies did not give evidence for mid- and long-term RFU and did not report the effect on a combination of (potentially missed) complications, costs, and PROMs such as physical function. Most studies retrospectively evaluated complications, revisions, radiographic abnormalities or change in management, and were underpowered [6, 8-12]. Current RCTs only compared a web-based follow-up (FU) to routine X-rays and a clinical visit, but did not eliminate FU [13, 14].

Little information is available on the effectiveness of long-term (>10 years) RFU [15, 16]. A retrospective medical chart review showed that of 501 patients with RFU, 84% had either no symptoms or a musculoskeletal concern unrelated to the prosthesis [7]. Without symptoms, a

change in clinical management was 7x less likely and the risk of revision was 10x lower than with symptoms. When combining the reported percentages of asymptomatic patients who undergo revision surgery (0.6-3.6%, [6, 7]) with the 12 year LROI survival data, COD may negatively affect 0.03-0.2% of the population of interest. On the other hand, RFU may negatively affect patients due to overdiagnosis and overtreatment.

A recent NIHR report (2022) recommends that no further RFU is required before 10 years in patients with well-studied implants not at high risk of developing problems [17]. These recommendations are mainly based on expert opinions and retrospective data. However, this report does not give evidence for or insight in the cost-effectiveness of RFU at 10 years and they recommend to further research the additional value of RFU after 10 years. In this study, we will address this knowledge gap by providing high level evidence. We expect that RFU at 10 years can be safely replaced by COD after THA and TKA and that it will be (cost-)effective without compromising outcomes relevant to patients.

2. OBJECTIVES

Primary Objective: Investigate the (cost-)effectiveness of replacing RFU after THA and TKA at 10 years by COD by comparing complications and clinical visits between patients with COD versus RFU at 10 years after THA and TKA, after a follow-up of 1 year.

Secondary Objective(s): Investigate the effect of COD compared to RFU at 10 years after THA and TKA on surgical interventions, physical function, quality of life, pain and costs , after a follow-up of 1 year.
Investigate the effect of informing patients about COD on complications, clinical visits, surgical interventions, and costs.

3. STUDY DESIGN

During the grant application process, all relevant stakeholders were involved in setting up this study protocol during a co-creation process. The co-creation team consisted of representatives from patient associations, healthcare insurers, the knowledge institute of the federation of medical specialists, the national healthcare institute, methodological and statistical expertise, the Netherlands Orthopaedic Association (NOV), the ZE&GG program for appropriate healthcare, and the project team. ZE&GG organized meetings to discuss crucial points with the stakeholders, which resulted in a well-considered research protocol approved by all involved stakeholders. The NOV signed a declaration of support and commits to implementation of the results.

In this study a randomized controlled trial with 3 arms will be performed. Patients will be randomized 1:1:1 in the following groups:

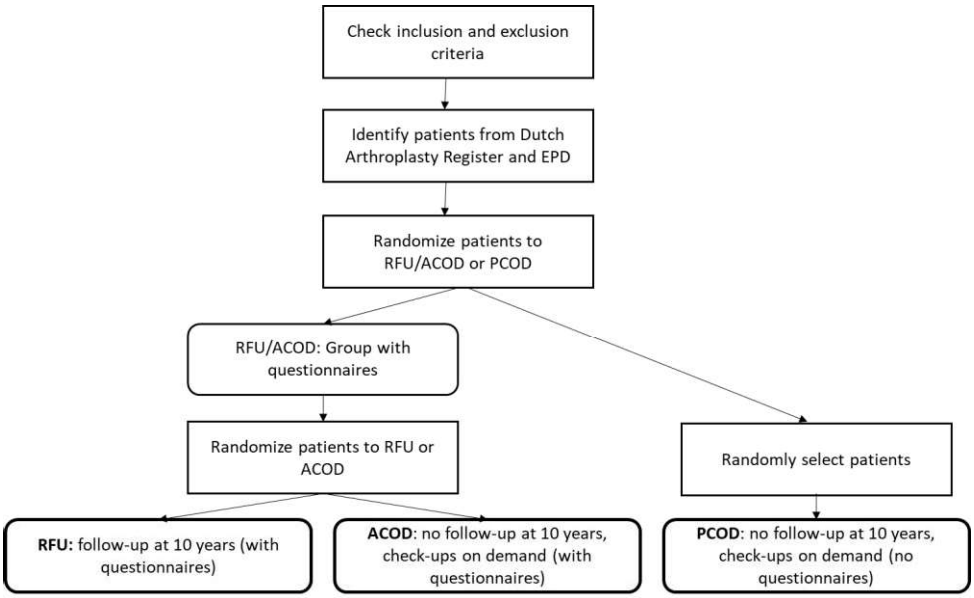
1. RFU: routine follow-up at 10 years after THA or TKA (control)
2. Active COD: No RFU at 10 years. Patients will be informed about the study and complete questionnaires. Check-ups are scheduled only on demand by the patient or health care professional (HCP) (intervention)
3. Passive COD: No RFU at 10 years. Patients will not be informed about the study to avoid any trigger to contact a HCP and will not complete questionnaires (intervention)

Patients will be followed for 1 year after RFU or COD (11 years after surgery). Informing the patients about the study and letting them complete questionnaires might result in trigger bias to contact a HCP. Therefore, patients in the intervention group will be divided into two groups: 1) one group will be informed about the study and complete questionnaires (active COD), 2) the other group will not be contacted and informed about the study to avoid trigger bias (passive COD). Of the latest group, only data from the LROI and EPD will be used. The control group will receive RFU at 10 years after THA or TKA and will complete questionnaires. Both groups completing questionnaires (active COD and RFU group) will be actively asked to participate in the study and to complete questionnaires and therefore will be randomized after informed consent.

A total of 10 hospitals will participate in the study. As randomization will be on individual patient level, all centers will perform both RFU and COD. Some centers will therefore perform RFU at 10 years while they already discontinued RFU, while other centers will have to implement COD while their current practice is RFU.

Patients will be included using the Dutch Arthroplasty Register and the EPD. The period of inclusion will be 18 months. The total study duration will be 30 months.

Figure 1: Overview of the study design.



4. STUDY POPULATION

4.1 Population (base)

Patients will be identified using the LROI register and the EPD. In 2015, 28,872 THA and 24,244 TKA were performed in the Netherlands [3]. The participating centres indicated that they performed between 400 and 800 THA and TKA per year. Taking into account a mortality rate of 16% 10 years after THA or TKA [18, 19], a revision rate of 6% 10 years after THA and TKA [3] and that 33% of the patients might not want to participate, the patient population will still be large enough to obtain our required sample size.

4.2 Inclusion criteria

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

- Underwent primary THA or TKA approximately 10 years ago
- Age 50 years or older at time of THA or TKA
- Capable and willing to complete questionnaires (when applicable)
- Understanding Dutch or English
- Willing to provide written informed consent in case the patient will complete questionnaires

4.3 Exclusion criteria

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

- Other indication for surgery than osteoarthritis
- Surgery was bilateral
- Deceased
- Revision arthroplasty of hip or knee, except a conversion from unicompartmental knee arthroplasty to TKA or from hip hemiarthroplasty/resurfacing to THA
- Already participating in this study due to another hip or knee surgery

4.4 Sample size calculation

We carefully determined the required number of patients to ensure reliable outcome estimates in collaboration with co-creating stakeholders and by consulting orthopaedic surgeons using an online survey on what constitutes convincing evidence. The agreed sample size is 250 patients per group. Therefore, we plan to randomize 250 patients per study group resulting in a total of 750 THA and 750 TKA patients.

To provide a rough indication of the statistical power, we used the online power calculator tool available on Sealed Envelope [20]. The sample size calculation is based on the comparison of RFU vs. active COD as the primary analysis. For this calculation, we assumed that the actual complication rate in both groups is 10%. With the agreed number, it is possible to detect a clinical relevant difference of 10% in complications between the two groups. If there is truly no difference between active COD and RFU, 190 patients per group are needed to be 80% sure that the limits of a two-sided 95% confidence interval will exclude a difference between active COD and RFU of more than 10%. Anticipating 20-25% loss to follow up, we plan to randomize 250 patients.

5. TREATMENT OF RESEARCH PARTICIPANTS

This study will compare COD and RFU at 10 years after THA and TKA, both of which are currently used in clinical settings, as confirmed by the Dutch Orthopaedics Society (NOV). In recent years, some hospitals discontinued RFU at 10 years for various reasons, thereby deviating from the Dutch guidelines. In many cases, patients were not personally informed about these policy changes.

Check-ups on demand (COD) are scheduled only at request of the patient or health care professional (HCP). Patients are welcome to contact a HCP (i.e. general practitioner, physical therapist or hospital) in case of pain, concerns or other symptoms at any time (consistent with current standard care practices).

COD will be compared to RFU at 10 years after THA and TKA. RFU consists of an evaluation by an orthopaedic surgeon or resident and an X-ray. In case of concerns, a physical examination will be conducted. In the meantime, patients are still welcome to contact a HCP (i.e. general practitioner, physical therapist or hospital) in case of pain, concerns or other symptoms at any time (consistent with current standard care practices).

6. INVESTIGATIONAL PRODUCT

NA

7. NON-INVESTIGATIONAL PRODUCT

NA

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Clinical endpoint:

- Number and type of complications
  Described as unplanned, unexpected and undesired outcomes related to THA or TKA that are directly associated with the care or services provided to the patient (i.e. knee- or hip related complaints or changes on X-ray that lead to extra FU, a referral to another specialism or (surgical) intervention) (like infection, peri-prosthetic fracture, loosening, malalignment or malposition of components, prosthetic wear, dislocation, etc)

Process endpoint:

- Healthcare consumption related to THA and TKA FU (number of X-rays and clinical visits)

8.1.2 Secondary study parameters/endpoints (if applicable)

- PROMIS physical function
- Number and type of surgical interventions (like DAIR, partial component exchange, revision surgery (full prosthesis replacement), irrigation and debridement (without component retention))
- Additional healthcare consumption related to THA or TKA FU (like clinical visit, telephone consultations, X-ray, CT scan, MRI scan, laboratory tests)
- Costs (based on electronic patient records and additional questionnaires, including all visits to healthcare professionals outside the hospital)
- Numeric Pain Rating Scale (NPRS)
- Numeric Satisfaction Rating Scale (NSRS)
- Health related quality of life (EQ-5D-5L)

For the passive COD group only available data from the EPD and LROI will be collected.

8.1.3 Other study parameters (if applicable)

- Patient characteristics (like age, gender, BMI, ASA score, ethnicity, employment status, home-hospital distance and educational level)

- Surgical information of primary arthroplasty (like surgery date, approach, type of prosthesis, fixation method, surgical duration, and intra-operative complications)
- Postoperative characteristics (like length of stay, in-hospital complications and discharge destination)
- Healthcare consumption, complications, and surgical interventions from the time of THA/TKA up to 10 years postoperatively

8.2 Randomisation, blinding and treatment allocation

Participants are randomly assigned in a 1:1:1 ratio to one of the three groups: RFU, active COD or passive COD. In order to do so, randomisation takes place in two steps and will be done using Castor EDC.

First, patients will be randomly allocated in a 1:2 ratio to the active group and the passive COD (intervention) group, with use of dynamic block designed randomisation with blocks of 6, 9 and 12. From the passive COD group, 25 THA and 25 TKA patients will be randomly selected. Patients in the passive COD group are not informed about the study and are blinded. Only data from EPD and LROI register will be collected.

Second, patients who are not placed in the passive COD group will be informed about the study. After informed consent, they will be randomly allocated in a 1:1 ratio to group 1 (RFU, control) or group 2 (active COD, intervention) with use of dynamic block designed randomisation with blocks of 4 and 6 and stratification by center and procedure (TKA or THA). There patients are not blinded. Inclusion will stop once the groups are filled.

8.3 Study procedures

This study will be conducted in 10 Dutch hospitals across the Netherlands. Patients will be recruited using the LROI register and EPD. After inclusion, baseline characteristics will be obtained from the EPD and LROI register. Information on patient background will be collected to explore potential differences in follow-up needs, including among patients with different ethnic backgrounds. Previous research shows that people with a migrant background visit specialists and hospitals less often than native Dutch patients with similar health and SES [21]. Acknowledging the sensitivity of this topic, a ‘prefer not to say’ option is provided.

Patients will be scheduled for a clinical visit or not depending on the randomization group. The clinical visit contains of a check by the orthopaedic surgeon or orthopaedic resident and an X-ray. Additionally, a physical examination can be performed in case of concerns.

Information about the clinical visit will be collected. The patient or the HCP can also schedule a clinical visit in case of concerns, pain or symptoms. Information about these visits will also be collected.

Patients randomized to the active COD or RFU group will be asked to complete the questionnaires online or on paper. Completion time will be around 10-25 minutes. Table 1 depicts the data collection and assessments at baseline and during follow-up appointments.

Study data will be collected onto an electronic case report form (eCRF) in Castor EDC. The primary outcome will be measured at 11 years after surgery, i.e. 1 year after RFU or COD at 10 years. EQ-5D-5L and costs will be measured at 10 years after surgery (baseline), and at 3, 6, and 12 months after baseline in the RFU and active COD group. The other outcomes will be measured only at 10 years (baseline) and 11 years after surgery (end point).

Table 1: Overview of data collection and assessments.

	Baseline (10 years after surgery) (+/- 30 days)	In case of check-up on demand (10-11 years after surgery)	3 months (+/- 30 days)	6 months (+/- 30 days)	12 months (11 years after surgery) (+/- 30 days)
Clinical visit	X*	X			
Physical examination#	X	X			
X-ray	X*	X#			
Healthcare consumption	X	X	X	X	X
Questionnaires:**					
PROMIS	X				X
EQ-5D-5L	X		X	X	X
NPRS	X				X
NSRS	X				X
Costs	X		X	X	X

* Only RFU group # In case of concerns

** Not for passive COD group

In case of a clinical visit information will be collected about the visits, like whether the visit was a routine visit or on demand, the reason for the visit, date of the visit, consequences of possible findings (like change in policy and secondary health consumption). In case of a routine visit, we will collect data whether the patient cancelled the appointment and the reason of cancellation.

PROMIS physical function will be obtained using the short form (SF) [22]. In case hospitals already use computer adaptive testing (CAT) of PROMIS physical function in clinical practice, this will be used. Version 10b will be used. The SF PROMIS physical function consists of 10 questions and is expressed by raw summed score ranging from 10 to 50, which can be converted to a T-score and SE. The T-score is a standardized score with a mean of 50 and a SD of 10.
EuroQol-5D (EQ-5D-5L) is a general health-related quality of life questionnaire and consists of five questions regarding mobility, self-care, usual activities, pain/discomfort and anxiety/depression and one visual analog scale (VAS) to document the perceived quality of life [23]. The quality of life is described by 2 scores, the index value, which range from 0 to 1, and the VAS score, which range from 0 to 100. For both scores applies the higher the better.
Numeric Rating Scale for pain (NPRS) is a scale ranging from zero to ten on which patients can score their pain [24]. It is a widely used instrument in varying populations due to its ease of administration and clinical relevance to the patient. The lower the score, the better.
Numeric Rating Scale for satisfaction (NSRS) will be measured by a single question: “How satisfied are you with the results of the treatment?” The patient will answer this question with a NRS scale ranging from zero to ten. The higher the score, the better.
Health consumption and costs will be measured using the EPD. Health consumption includes both the primary outcomes clinical visits and X-rays, as well as additional health care use, including telephone consultations and scans. The LROI register will be used to collect data about revision surgery. A questionnaire will be used to get more insight in the health consumption and costs which cannot be obtained from the EPD. This questionnaire is made in collaboration with a HTA expert and patient representatives.

8.4 Withdrawal of individual research participants

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

8.5 Replacement of individual research participants after withdrawal

Participants will not be replaced after withdrawal.

8.6 Follow-up of research participants withdrawn from treatment

Patients withdrawn from the study will get the usual care according to their hospital. This care is hospital-dependent. In case data are already collected, these data will be used in the study unless the patient also revokes the consent to use the collected data. Patients will be asked whether data may still be collected from the EPD and LROI register after withdrawal.

8.7 Premature termination of the study

As both the COD and RFU are part of standard care, we do not expect premature termination of the study. Only in case the study will jeopardize participant's health or safety, the study will be prematurely terminated. In case of premature termination of the study, participants will be followed up according to the standard care according to their hospital. Participants are not at additional risk when the study is terminated prematurely.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of research participant safety

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 participant health or safety. The sponsor will notify the review committee 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 review committee. The investigator will take care that all participants are kept informed.

9.2 AEs, SAEs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to the experimental intervention (RFU or COD). In this study, complications, surgical interventions, and healthcare use are systematically collected as part of the study outcomes and are therefore already recorded. As such, these do not need to be reported separately as adverse events. Only events that can be directly linked to the presence or absence of the clinical visit and X-ray 1 year after surgery should be reported as adverse events.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or 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.

Only events that are related to the study procedures (RFU or COD) will be considered as serious adverse events. An elective hospital admission will not be considered as a serious adverse event.

Due to the intervention (COD or RFU) hardly any SAEs are to be expected. This means all (S)AEs related to participation in this study protocol, meaning from COD

and RFU, will not be reported to the METC, as no patient benefit is expected from this.

9.3 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.

10. STATISTICAL ANALYSIS

All analyses will be performed separately for THA and TKA and will be performed using IBM SPSS statistics (SPSS software version 28.0) or R. Categorical data will be presented as numbers and percentages. Continuous variables will be presented by mean and standard deviation in case of a normal distribution. In case of non-normality, median and interquartile range will be given.
Mixed models are used to deal with missing data; when necessary and possible we will perform multiple imputation.

10.1 Primary study parameter(s)

The total number of complications at 1 year follow-up (11 years after surgery) and process evaluation expressed by the health care consumption, like the number of clinical visits and X-rays, will be presented by median and interquartile range. For the primary aim, the number of complications will be compared between 2 groups, namely the RFU and active COD, using generalized linear mixed models (GLMM), with a Poisson distribution. A random intercept for centre will be included in the model to account for clustering of patients within centres and a main affect for group is added to determine treatment effect. We will also determine adjusted intervention effects, by accounting for relevant baseline characteristics such as age, gender, BMI, ASA-score, ethnicity, employment status, home-hospital distance and educational level.

The type of complications at 1 year follow-up (11 years after surgery) will be presented categorically by numbers and percentages. The type of complications will be compared between 2 groups (RFU vs. active COD) using GLMM with a logistic regression approach, including a main effect for group, a random intercept for centre and adjusting for baseline characteristics such as age, gender, BMI, ASA-score, ethnicity, employment status, home-hospital distance and educational level.
Process evaluation outcomes will also be expressed dichotomously (i.e. clinical visit: yes/no, X-ray: yes/no etc.) and analysed using logistic GLMM.
The primary outcomes are based on intention-to-treat analyses.

10.2 Secondary study parameter(s)

For the secondary analysis, the aforementioned GLMM analyses on number and type of complications and clinical visits will be repeated comparing the 3 groups, namely the RFU, active COD and passive COD.
Secondary patient-reported outcomes, namely PROMIS physical function, NPRS, NSRS and EQ-5D-5L, will be presented as mean with standard deviation in case of normality or median and interquartile range otherwise. These parameters will be analysed using linear mixed models, with repeated measures clustered within participants and participants within

hospitals (random intercepts). Intervention group (RFU vs. active COD vs. passive COD), baseline score, and time (3, 6, 12 months) are included as fixed effects, to determine the crude effect of the intervention. To correct for possible confounders, baseline variables will be add to the model as fixed effects.
The total number of surgical interventions at 1 year follow-up (11 years after surgery) will be presented by median and interquartile range. The number of complications will be compared between 3 groups, namely the RFU, active COD and passive COD, using GLMM, with a Poisson distribution. A random intercept for the centre will be included in the model to account for clustering within centres. GLMM will also be used to correct for and to investigate the effect of possible confounders..
The type of surgical interventions at 1 year follow-up (11 years after surgery) will be presented categorically by numbers and percentages. The type of surgical interventions will be compared between 3 groups using GLMM with logistic regression, adjusting for possible confounders and incorporating centre as a random intercept.

10.2.1 Cost-effectiveness

A trial-based economic evaluations will be performed at 11 years after surgery (i.e. 1 year after RFU or COD at 10 years), separated for THA and TKA. Both economic evaluations will be performed for the primary outcome (PROMIS physical function) and for QALYs, and in accordance with the intention-to-treat principle. We will consider two perspectives: 1) healthcare perspective and 2) societal perspective. QALYs will be estimated by multiplying the patients' utility values by the duration for which they experienced a certain health state [25, 26]. Utility values will be based on the EQ-5D-5L, which health states will be valued using the Dutch tariff. All other kinds of resource utilization will be assessed using cost questionnaires administered at baseline, and 3, 6 and 12 months, and valued according to the "Dutch manual of costing" [27].

Missing data will be imputed using multivariate imputation by chained equations [28]. From the societal perspective, costs will include healthcare costs, absenteeism, presenteeism, unpaid productivity, and informal care costs. From the healthcare perspective, only costs accruing to the formal Dutch healthcare sector will be included. Costs will be assessed using cost questionnaires, and valued in accordance with the Dutch manual of costing. Cost and effect differences will be estimated using linear mixed models. It is very important to use mixed-model analyses, and hence to account for the possible clustering of cost and effect data (e.g., at the hospital level), as most economic evaluations fail to do so, whereas ignoring the possible clustering of data might lead to inaccurate levels of uncertainty and inaccurate point estimates. Incremental cost effectiveness ratios (ICERs) will be calculated by dividing

the difference in costs by that in effects. Bootstrapping techniques will be used to estimate the uncertainty surrounding the cost-effectiveness estimates (please note that non-parametric bootstrapping will be nested within the multiple imputation procedure). Uncertainty will be shown in cost-effectiveness planes and cost-effectiveness acceptability curves [29,30]. The latter indicate the probability of COD being cost-effective compared with RFU at different values of willingness to pay. Multiple sensitivity analyses will be performed to test the robustness of the cost-effectiveness results derived from the main analysis (e.g. complete-case analysis) [26].

For the budget impact analysis we plan to use the BIA tool as suggested and provided by ZonMw. The BIA will be based on the Dutch population, and hence Dutch incidence data will be used. Perspectives that will be considered are the societal, government (Budget Kader Zorg), and insurer perspective. Different scenarios will be evaluated including the following: 1) the intervention is not implemented, i.e. all patients will receive RFU only, 2) the intervention is offered to the whole patient population, i.e. all patients receive COD, and 3) the intervention is only offered to specific subgroups of the potential patient population, such as patients with the lowest risk of complications. These subgroups will be defined based on the results of the study, e.g. subgroups who particularly benefit from the intervention. The cost of the intervention mix will be valued using Dutch standard costs for the societal perspective, actual NZA tariffs for the government perspective, and average tariffs NZA for the insurer perspective.

This cost-effectiveness and budget impact analysis will comply with the ‘Dutch guideline for economic evaluations in health care' [31].

10.3 Other study parameters

Other study parameters, like patient characteristics and surgical information, will be given as numbers and percentages in case of categorical data. Continuous variables will be presented by mean and standard deviation in case of a normal distribution. In case of non-normality, median and interquartile range will be given. These parameters will be used to describe the included population and the clinical visits, but also to adjust the intervention effects.

10.4 Exploratory analysis

As an exploratory analysis, we will assess subgroup effects on the primary outcomes of complications, clinical visits and X-rays. The GLMMs described above will be extended by including interaction terms for age, gender, BMI, ASA, ethnicity, employment status and educational level with the intervention in separate models.

10.5 Interim analysis (if applicable)

NA

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 8, October 2024) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

First, each participating center will select patients who had a THA or TKA 10 years ago using the LROI register and EPD. From this list, all patients will be selected who meet the inclusion and exclusion criteria. From the remaining list, patients will be randomized in a 1:2 ratio into a passive and active group. Patients in the active group will be approached for participation.

The initial contact regarding the study will be made by a physician working in the orthopaedic department of the hospital where the surgery was performed, by asking permission if he/she can be approached for the study. A researcher or research coordinator will contact the patient by phone, or at the outpatient department to assess their suitability for participation based on their medical history and the study's inclusion and exclusion criteria. The researcher will provide a brief overview of the study's purpose and procedures and offer the opportunity for patients to ask any initial questions about the study. If the patient expresses interest in the study, the patient information letter including the informed consent form will be sent by mail, along with a return envelope, and/or e-mail ensuring the patient has adequate time to review the study details. The patient will be contacted after at least 5 days by the research team. The researcher will discuss the patient information letter and the patient has the opportunity to ask further questions. Once the patient agrees to participate, they will sign the consent form and return it to the research team. The researcher will sign and return a copy of the fully signed consent form to the patient, ensuring that both the investigator and the patient have a complete signed informed consent.

There is also an option for e-consent using Castor EDC, which safely collects and stores data in compliance with Good Clinical Practice (GCP). The e-consent and screening procedures will maintain an audit trail to record data entries with timestamps and editors. Access to the Castor EDC study page will be limited to the research team. Research has shown that e-consent improves participants' understanding of clinical trial information and is rated as a more acceptable and user-friendly consenting process compared to traditional paper-based methods. The first part of recruitment is identical to the hard-copy procedure, but if the patient expresses interest in learning more about the study, the researcher will send an email to the patient containing a personalized URL. By clicking this URL, patients will

access an introductory screen in Castor EDC, where the patient information letter is provided. Here, it is explained how a participant can revoke their consent during the study. The patient will still be contacted after at least 5 days by the research team, the researcher will discuss the patient information letter and the patient has the opportunity to ask further questions. If the patient is interested in participation, they can confirm this with an electronic informed consent (e-consent) using a Castor EDC survey presented after the digital patient information letter. In this survey, the patient can confirm their understanding of the information and willingness to participate in the study. Using locked checkboxes (yes/no), the patient can give permission to additional questions (similar as in the hard-copy procedure). Additionally, the patient need to select the date they signed the consent. The consent procedure will be completed only if all boxes are selected. The participant will receive a copy of this informed consent form, signed by a researcher, by email.

11.3 Benefits and risks assessment, group relatedness

We expect that participants will not have benefits from participating to the study. There are no additional risks expected compared to standard care, as both RFU and COD at 10 years after THA or TKA are part of current clinical care. Patients are asked to spend time to fill out questionnaires. Only the RFU group will be asked to spend time to visit the hospital.

11.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The METC gives dispensation for research participant insurance, because no additional risks are expected as RFU and COD are both part of standard care.

11.5 Incentives (if applicable)

Participants will not receive any incentives or compensation as both COD and RFU are standard care.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data are handled confidentially and anonymously. All participants participating in this study will be linked to a participant identification code based on the center from which they participate (e.g. RHOC001 till RHOC150). The key to the code is safeguarded by the local investigator of the participating center. During the study, the investigator also has access to the key and contact details of the participants to be able to send reminders and contact patients to fill in the questionnaires. All contact details will be deleted at the investigator site after study completion.

Data will be stored for 15 years by each participating center. All data will be processed and analysed with the participant identification code by the investigator. Also, in reports and publications only the participant identification code will be used. The research team, and where appropriate, monitors and staff of the IGJ have access to source documents. These persons will keep all data secret.

All data will be collected in the web-based database Castor EDC. Questionnaires will be sent from the Castor EDC and filled in by the patient. For these data direct entry is applicable. Other data will be collected from the EPD and LROI register. Participants will also give permission to use the data for other studies or not.

Patients can leave the study of his own volition. In case data are already collected, these data will be used in the study unless the patient also revoke the consent to use the collected data.

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. (in Dutch: Uitvoeringswet AVG, UAVG).

12.2 Monitoring and Quality Assurance

Monitoring will be performed in compliance with Good Clinical Practice (GCP) and other rules and regulations in order to achieve high quality research and secure patient safety. Qualified and independent monitors will have access to the data and source documents. The study will be monitored annually by an independent member of the research department of the Reinier Haga Orthopedisch Centrum, who is not involved in this study.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the review committee has been given. All amendments will be notified to the review committee that gave a favourable opinion.

Non-substantial amendments will not be notified to the review committee, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the review committee once a year. Information will be provided on the date of inclusion of the first participant, numbers of participants included and numbers of participants that have completed the trial, serious adverse events, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the review committee of the end of the study within a period of 8 weeks. The end of the study is defined as the end of follow-up of the last patient.

The sponsor will notify the review committee immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the review committee within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the review committee.

12.6 Public disclosure and publication policy

In accordance with the requirements of the International Committee of Medical Journal Editors, the study will be registered in a public trial registry prior to the recruitment of the first patient. The results will be published in peer-reviewed scientific journals and presented at relevant (inter)national congresses. The arrangements for public disclosure and publication of the research data for the overall HAKA project are outlined in the ZonMw consortium agreement between the sponsors of the individual studies. For the participating centers within the studies, publication policies are specified in the Participation Agreements.

13. STRUCTURED RISK ANALYSIS

NA

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