Generalizability of Patients with Severe Hip Osteoarthritis Accepting Participation in a Randomized Trial on Total Hip Arthroplasty and Progressive Resistance Training: *Statistical Analysis Plan for the PROHIP Cross-Sectional Study Comparing Baseline Characteristics and Propensity of Patients Accepting and Declining Enrollment*

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Statistical Analysis Plan (SAP) version: The PROHIP Generalizability SAP version 1.0, dated 3rd of August 2022.

SIGNATURES

Date	Name	Roles and Responsibility	Signature
Aug. 3, 2022	Thomas Frydendal	SAP first author (Team leader)	
Aug. 3, 2022	Robin Christensen	Senior Biostatistician (Risk Manager)	
Aug. 3, 2022	Søren Overgaard	Chief Investigator (Sponsor)	
Aug. 3, 2022	Kim Gordon Ingwersen	SAP last author (Project leader)	

INTRODUCTION

Background and rationale

Hip osteoarthritis (OA) is the leading cause for undergoing total hip arthroplasty (THA)[1]. This procedure is widely acknowledged to be highly effective for reducing hip pain, and improving functional outcomes and quality-of-life in the management of severe hip OA[2-4]. Around 90-95% of the patients are satisfied with the outcome one year postoperatively[5], but one fifth of the patients undergoing THA report residual pain after surgery[6]. This may possibly be due to significant variation in the indication criteria for THA[7-9]. Moreover, patient willingness to undergo surgery has been shown as the strongest predictor for undergoing THA[10], which could indicate a need for a more objective criteria.

Exercise is recommended as first-line treatment in the management of mild to moderate hip OA[11-13]. Supervised progressive resistance training (PRT) has shown a moderate effect for improving multiple outcomes and may be of clinical relevance even in patients with severe hip OA[14, 15]. Furthermore, first-line treatment comprising exercise and patient education may postpone the need for surgery and reduce the willingness to undergo THA[16, 17].

The PROgressive resistance training versus total HIP arthroplasty (PROHIP) trial aims to determine if THA surgery is a superior treatment to PRT in patients suffering from severe hip OA[18]. However, previous clinical trials comparing surgical procedures with first-line treatment have had enrollment rates between 7% and 22%[19-23]. Low enrollment rates may decrease the generalizability of these trials making it unclear to which patients the result can be applied[24-27].

Objectives

The primary objective of this study is to compare baseline characteristics of patients with severe hip OA eligible for THA *accepting versus* those *declining* enrollment in the PROHIP trial in order to evaluate whether enrolled patients differ systematically (i.e. bias) from the patients declining participation in hip pain and function, measured using the Oxford Hip Score (OHS), assessed at baseline.

The primary null hypothesis is that there is no difference in hip pain and function between the two groups. The alternative hypothesis is that patients declining enrollment in the PROHIP trial have significantly worse hip pain and function than those accepting participation.

Secondary objectives are:

1) To compare baseline characteristics of patients with severe hip OA eligible for THA *accepting versus* those *declining* enrollment in the PROHIP trial in order to evaluate whether enrolled patients differ systematically from the patients declining participation in hip pain, hip symptoms, activities-of-daily-living (ADL) function, hip-related quality-of-life (QoL), and sport and recreation function (sport/recreation), measured using the Hip disability and Osteoarthritis Outcome Score (HOOS) subscales, assessed at baseline.
2) To compare baseline characteristics of patients with severe hip OA eligible for THA *accepting versus* those *declining* enrollment in the PROHIP trial in order to evaluate whether enrolled patients differ systematically from the patients declining participation in physical activity level, measured using the University of California Los Angeles (UCLA) Activity Score, assessed at baseline.
3) To compare baseline characteristics of patients with severe hip OA eligible for THA *accepting versus* those *declining* enrollment in the PROHIP trial in order to evaluate whether enrolled patients differ systematically from the patients declining participation in pain intensity in the index hip at rest and during activity, measured using the Visual Analogue Scale (VAS), assessed at baseline.
4) To compare baseline characteristics of patients with severe hip OA eligible for THA *accepting versus* those *declining* enrollment in the PROHIP trial in order to evaluate whether enrolled patients differ systematically from the patients declining participation in health-related quality of life, measured using the EuroQol Group 5-dimension 5 level (EQ-5D-5L) including summary index and VAS, assessed at baseline.
5) To compare baseline characteristics of patients with severe hip OA eligible for THA *accepting versus* those *declining* enrollment in the PROHIP trial in order to evaluate whether enrolled patients differ systematically from the patients declining participation in sex, age, height, weight, body mass index (BMI), educational level, employment status, smoking status, alcohol consumption, hip symptoms duration, previous THA and total knee arthroplasty (TKA), medicine consumption, and number of comorbidities, measured using a patient-reported questionnaire, assessed at baseline.

STUDY METHODS

Study design

The PROHIP trial was designed as a multicenter (four sites), stratified (by site), randomized (allocation 1:1), controlled, parallel-group superiority trial. Patients were recruited from the orthopedic departments at Vejle Hospital and Odense University Hospital (OUH) in the Region of Southern Denmark, Aarhus University Hospital (AUH) in the Central Denmark Region, and Næstved Hospital in Region Zealand and randomized to THA followed by standard care or 12-weeks of supervised PRT followed by 12-weeks of optional unsupervised PRT. The treatments are described in full details in the trial protocol[18]. Patients who declined participation in the PROHIP trial was invited into a parallel prospective cohort. This study was designed as a cross-sectional study using patient-reported baseline characteristics and outcomes of patients with severe hip OA eligible for enrollment in the PROHIP trial who either accepted (PROHIP group) or declined (non-PROHIP group) participation in the clinical trial. Patient enrolment and data collection was started on the September 2nd 2019 and ended on June 30th 2021 as the final deadline for recruitment was reached for the clinical trial[18].

The PROHIP trial protocol was reported in accordance with the *'Standard Protocol Items: Recommendations for Interventional Trials'* (SPIRIT) statement[28]. This statistical analysis plan (SAP) adheres to the *'Guidelines for the Content of Statistical Analysis Plans in Clinical Trials'*[29], while reporting of the cross-sectional study will follow the *'Strengthening the Reporting of Observational Studies in Epidemiology'* (STROBE) statement[30].

Randomization

The randomization process for the PROHIP trial is described in full details in the trial protocol[18]. No randomization was performed in the present study, since this is an observational study comparing patients who accepted with those who declined participation in the PROHIP trial.

Sample size and power calculation

The sample size and power calculation for the PROHIP trial is described in full details in the trial protocol[18]. For the present cross-sectional study, no formal sample size calculation was performed and patients for the observational cohort was enrolled prospectively and consecutively until enrollment for the PROHIP trial ended (i.e. the ratio of patients who accepted versus those who declined is unclear, and will be an important outcome of the present study).

Statistical interim analysis and stopping guidance

No formal statistical interim analysis is planned on the primary endpoint (baseline difference for the OHS score between the two groups [PROHIP and non-PROHIP]). The final deadline for patient recruitment was a priori set 18 months (i.e. February 2021) after the inclusion of patients was started. However, the recruitment deadline was prolonged 4 months to June 2021 due to the COVID-19 lockdown in Denmark in March 2020. The author group have monitored recruitment and attrition rates in the study.

Timing of final analysis

The final analysis for the between-group comparison (PROHIP versus non-PROHIP) for the primary endpoint (baseline) is planned complement of baseline measurements and the final deadline for recruitment is reached for the clinical trial[18]. The publication of this cross-sectional study will be prepared when these data have been retrieved and cleaned (anticipated by August 2022).

Timing of outcome assessments

The overview of PROHIP trial procedures and time-point of each outcome assessment is presented in the Table 3 in the trial protocol[18]. This cross-sectional comparison between PROHIP and non-PROHIP participants evaluates patients-reported outcomes measured at baseline. For the PROHIP group, patient-reported questionnaires had to be completed prior to randomization in the PROHIP trial in order to be included in the analysis. For the non-PROHIP group, patient-reported questionnaires had to be completed prior to THA surgery in order to be included in the analysis.

STATISTICAL PRINCIPLES

Confidence intervals and p-values

All *P* values and confidence intervals will be two-sided; *p-values* <0.05 will be considered statistically significant. For the OHS, a 95% confidence interval excluding a difference greater than 5 OHS points between the two groups will be interpreted as indicating absence of a minimal clinically important difference (i.e. possible equivalence). No adjustment for multiplicity will be performed.

Adherence and protocol deviations

Treatment adherence in both the PROHIP and non-PROHIP group will not be presented due the cross-sectional design with the objective to compare baseline characteristics.

The following are pre-defined major protocol deviations: (1) patients in the PROHIP group not completing the patient-reported questionnaires prior to randomization, (2) patients in the non-PROHIP group not completing the patient-reported questionnaires prior to THA surgery, and (3) patients in both groups withdrawing from the study between inclusion and baseline assessment. The number (percentage) of patients with major protocol deviations will be summarized by group. No formal statistical testing will be conducted.

Analysis populations

The primary analyses will be based on a per-protocol population. The per-protocol analysis set consists of patients from the PROHIP and non-PROHIP groups with a baseline measurement on the patient characteristics questionnaire, primary outcome, key secondary outcomes, and exploratory outcomes.

STUDY POPULATION

Screening data

The following enrolment data will be presented for each hospital for each month during the study period: (1) the number of patients assessed for eligibility, (2) the number of patients enrolled (PROHIP and non-PROHIP), and (3) enrollment rate. This detailed enrollment summary is illustrated in **Appendix Figure 1** and **Appendix Figure 2**.

Eligibility

Patients conforming to the following inclusion and exclusion criteria are considered eligible for the PROHIP trial and the current cross-sectional study.

Inclusion criteria: (1) Patients aged ≥50 years; (2) Clinical history and symptoms consistent with primary hip OA (including hip OA due to mild hip dysplasia that may be treated with standard components) and radiographic verified hip OA defined as joint space narrowing <2 mm; (3) Considered eligible for THA by an orthopedic surgeon (i.e. hip-related pain, symptom duration >3 months, functional impairment or decreased range-of-motion, and attempted treatment with analgesics).

Exclusion criteria: (1) Severe walking deficits (i.e. dependency of two crutches or walker); (2) Body Mass Index (BMI) >35 kg/m^2; (3) Lower extremity fractures within previous 12 months; (4) Planned other lower extremity surgery within 6 months; (5) Cancer diagnosis and current chemo-, immuno- or radiotherapy; (6) Neurological diseases (e.g. previous stroke, multiple

sclerosis, Parkinson's, Alzheimer's); (7) Other reasons for exclusion (i.e. inadequacy in written and spoken Danish, mentally unable to participate, physically unable to comply with the PRT protocol due to comorbidity (e.g. severe heart disease, previous major lower extremity surgery within previous 6 months) etc.).

The total number of patients screened for eligibility from the four hospitals will be collected and presented in a CONSORT flowchart to describe representativeness of the study sample. Furthermore, the number of ineligible patients will be reported including reason for ineligibility.

Recruitment

The CONSORT flowchart will comprise number of patients screened assessed for eligibility, excluded due to ineligibility (with reasons), assessed eligible, declined participation in PROHIP, declined participation in cross-sectional study, accepted inclusion in PROHIP, accepted inclusion in non-PROHIP, withdrawals (with reasons), and included in the per-protocol analysis. The CONSORT flowchart is depicted in **Figure 1.**

Withdrawal/follow-up

The level of consent withdrawal will be classified by the following two options: (1) consent to continue follow-up and data collection and (2) complete withdrawal with no further follow-up and data collection.

Timing of withdrawal and loss to follow-up will be presented in the CONSORT flowchart with numbers and reasons for withdrawal and/or loss to follow-up given at the baseline (primary end point) outcome assessment. Furthermore, the number (with reasons) of loss to follow-up during the course of the study will summarized by group.

Baseline patient characteristics

The following data will be used to describe patients by group (PROHIP and non-PROHIP) at baseline: sex, age, height, weight, BMI, educational level beyond high school, employment status, alcohol consumption above Danish recommendations[31], index hip, duration of hip symptoms, previous THA, previous total knee arthroplasty, use of analgesics in the previous week, comorbidities, OHS, HOOS subscales (pain, symptoms, ADL function, sport/rec, hip-related QoL), UCLA activity score, VAS pain (rest), VAS pain (activity), EQ-5D-5L index score, and EQ-VAS score.

Numbers and percentages will be calculated and presented for categorical variables. Means and standard deviations (SD) will be computed and presented for continues variables if data follows a normal distribution. The baseline characteristics will be presented as illustrated in **Table 1.**

ANALYSIS

Outcome definitions

Primary outcome

Oxford Hip Score (OHS)

The primary outcome measure will be the between-group difference at baseline ($OHS_{baseline}$). The OHS is considered a valid, reliable, and responsive patient-reported questionnaire assessing hip pain and function in a composite score ranging from 0 (worst) to 48 (best)[32 33-36].

Key secondary outcomes

Hip disability and Osteoarthritis Outcome Score (HOOS)

A key secondary outcome will be the between-group difference at baseline in each HOOS subscale ($HOOS_{baseline}$). The HOOS is a valid, reliable and responsive patient-reported questionnaire consisting of five subscales covering, hip pain, hip symptoms, ADL function, hip-related QoL, and sport/recreation with each subscale score ranging from 0 (worst) to 100 (best)[37-40].

University of California Los Angeles (UCLA) Activity Score

A key secondary outcome will be the between-group difference at baseline in UCLA activity score ($UCLA\ activity\ score_{baseline}$). The UCLA is reliable, valid, and responsive measure of patient-reported physical activity level ranging from 1 (inactive) to 10 (regular participation in impact sport or heavy labour)[41-43].

Exploratory outcomes

Visual Analogue Scale (VAS)

An exploratory outcome will be the between-group difference at baseline in VAS hip pain intensity ($VAS\ rest_{baseline}$ and $VAS\ activity_{baseline}$). The VAS is a reliable, valid and responsive measure of patient-reported pain intensity ranging from 0 (no pain) to 100 (worst pain imaginable)[44].

EuroQol Group 5-dimension (EQ-5D-5L)

An exploratory outcome will be the between-group difference at baseline in EQ-5D-5L (EQ-5D-5L $index_{baseline}$ and $EQ\text{-}VAS_{baseline}$). The EQ-5D-5L is a reliable and valid measure of patient-reported health-related quality-of-life including the summary index ranging from -0.624 (worst) to 1.000 (best) (Danish value set) and EQ-VAS ranging from 0 (worst imaginable health) to 100 (best imaginable health)[45-49]. The major outcomes will be presented as illustrated in **Table 1.**

Analysis methods

All descriptive statistics and statistical analysis will be reported in accordance with the recommendations of the *'Enhancing the QUAlity and Transparency Of health Research'* (EQUATOR) network[50] and the CONSORT statement.[51] Visual inspection (QQ-plot, histograms, and scatterplots) will be used to assess the assumption of normality of continuous variables.

The term balance diagnostics will be used to describe the statistical methods applied to evaluate whether the distribution of baseline covariates is similar between the PROHIP and non-PROHIP groups. Means and/or medians of continuous variables and the distribution of categorical variables will be reported for each of the two groups. These crude comparisons between PROHIP and non-PROHIP allow an evaluation of the comparability of the two groups, which will provide an indication of the generalizability of the PROHIP trial[52].

Descriptive Statistical Measures: Between-group comparisons of continuous variables will be estimated using standardized differences defined as:

$$d = \frac{\bar{x}_{PROHIP} - \bar{x}_{non-PROHIP}}{\sqrt{\frac{s^2_{PROHIP} + s^2_{non-PROHIP}}{2}}}$$

Where $\bar{X}$ denotes the sample means of the variable in PROHIP and non-PROHIP participants, respectively, whereas the s^2 represents the sample variance of the variables in the groups. Between-group comparisons of categorical variables will be estimated using standardized differences defined as:

$$d = \frac{\hat{p}_{PROHIP} - \hat{p}_{non-PROHIP}}{\sqrt{\frac{\hat{p}_{PROHIP}(1-\hat{p}_{non-PROHIP}) + \hat{p}_{PROHIP}(1-\hat{p}_{non-PROHIP})}{2}}}$$

Where $\hat{p}$ denotes the prevalence or mean of the categorical variable in PROHIP and non-PROHIP participants, respectively. A standardized difference of ≥0.2 will be used to indicate that there might

be a difference in the baseline variable (i.e. potentially low generalizability), while a standardized difference of ≥0.8 will be considered as a definitive difference.

Inferential Statistical Measures: The SAS PROC NPAR$_1$WAY procedure will be used to compute the empirical function (EDF) statistics to test the distribution of baseline variables. This procedure provides a summary of the Wilcoxon scores for the analysis of the baseline variable by group level (PROHIP and non-PROHIP) and displays the one-way ANOVA statistics. If the *P-value* is <0.05 this indicates that there might be a difference between the groups (i.e. leads to rejection of the null hypothesis that there are no difference between the groups).

Logistic regression will be used to develop propensity scores, which represent the probability that a patient accept participation in the PROHIP trial depending on the patients observed covariates. Group status (PROHIP and non-PROHIP) will be the dependent variable and baseline variables the covariates.

Missing data

No imputation will be conducted as patients with missing data on the patient characteristics questionnaire, primary outcome, key secondary outcomes, and exploratory outcomes will be considered ineligible for the analysis of the missing individual variables.

Additional analyses

No additional analyses on the primary outcome and key secondary and exploratory outcomes are planned at baseline.

Harms

No summary of adverse events (AEs) will be performed for this study due to the cross-sectional design using data obtained from patient-reported questionnaires measured at baseline.

Statistical software

All statistical analyses and calculations will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA) and/or STATA (Statacorp, College Station, Texas, USA).

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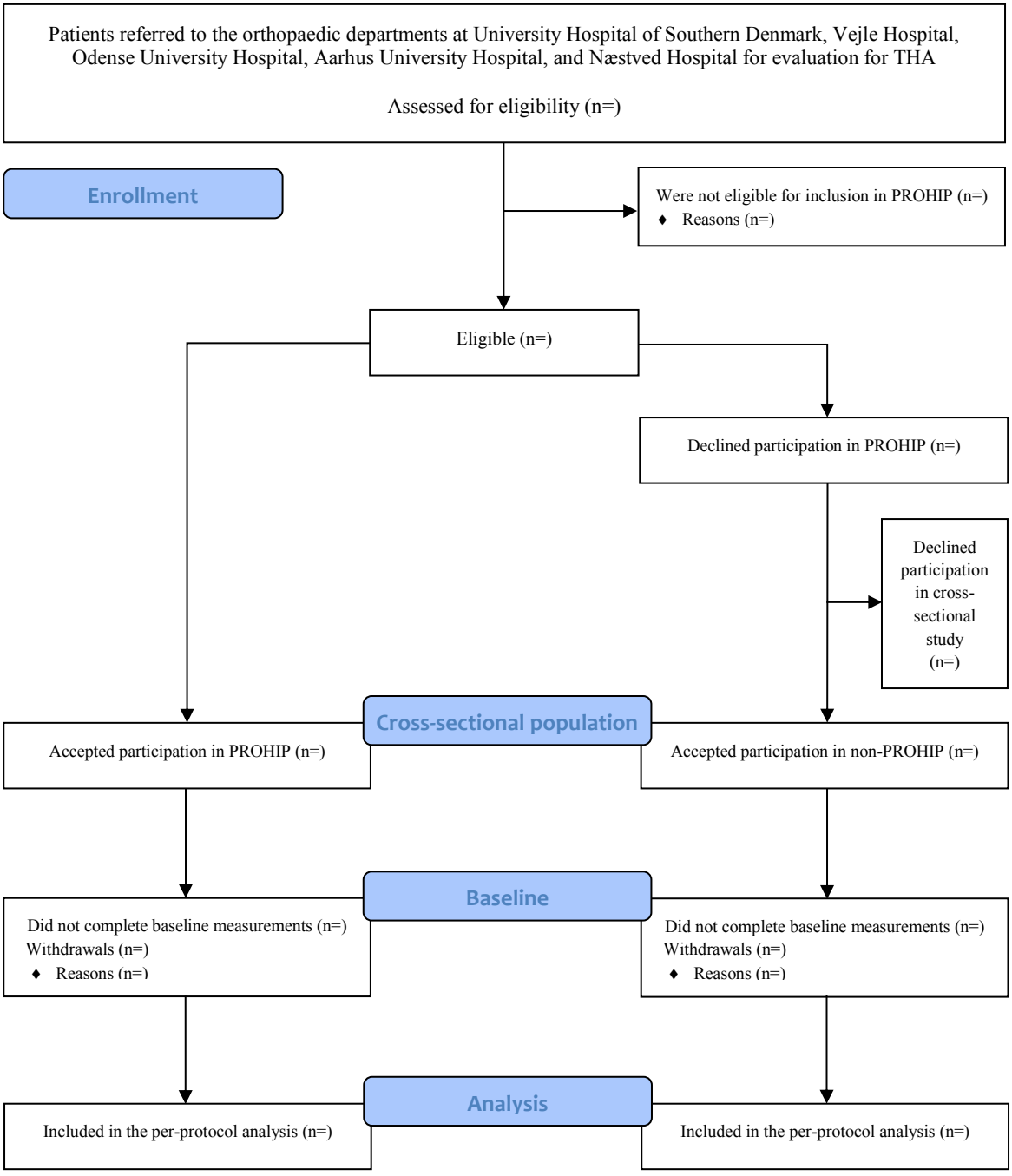


Figure 1. Flowchart of this cross-sectional study. Total hip arthroplasty (THA). The PROgressive resistance training versus total HIP arthroplasty (PROHIP) trial.

Table 1. Baseline characteristics of the patients accepting and declining participation in the PROgressive resistance training versus total HIP arthroplasty (PROHIP) trial.*

	PROHIP (N=??)	Non-PROHIP (N=??)	Between-Group Difference (95% CI)	Standardized Difference
Female sex — no. (%)				
Age — yr				
Height — m				
Weight — kg				
Body-mass index — kg/m^2				
Education level beyond high school — no. (%)				
Employment — no. (%)				
Employed for wages				
Self-employed				
Sick leave				
Retired				
Other				
Substance use — no. (%)				
Current smoker				
Alcohol consumption above recommendations†				
Index hip right — no. (%)				
Duration of hip symptoms — yr				
Previous total hip arthroplasty — no. (%)				
Previous total knee arthroplasty — no. (%)				
Use of analgesics due to hip-related pain — no. (%)				
Paracetamol				
Ibuprofen				
Morphine or opioids				
Other				
Comorbidities — no. (%)				
None				
1				
2				
3 or more				
OHS score‡ — 0 to 48				
HOOS subscale scores§ — 0 to 100				
Pain				
Symptoms				
Function in activities of daily living				
Hip-related quality of life				
Function in sports and recreation				

UCLA activity score¶ — 1 to 10
VAS hip pain at rest‖ — 0 to 100
VAS hip pain during activity‖ — 0 to 100
EQ-5D-5L index score∫ — -0.624 to 1.000
EQ-VAS‡‡ — 0 to 100

* Plus–minus values are mean ±SD unless otherwise indicated.

† The Danish Health Authority recommends an alcohol consumption to be no higher than 10 units per week for adults aged 18 or above to have a low risk of developing diseases[31].

‡ The Oxford Hip Score (OHS) ranges from 0 to 48, with higher scores indicating better disease status.

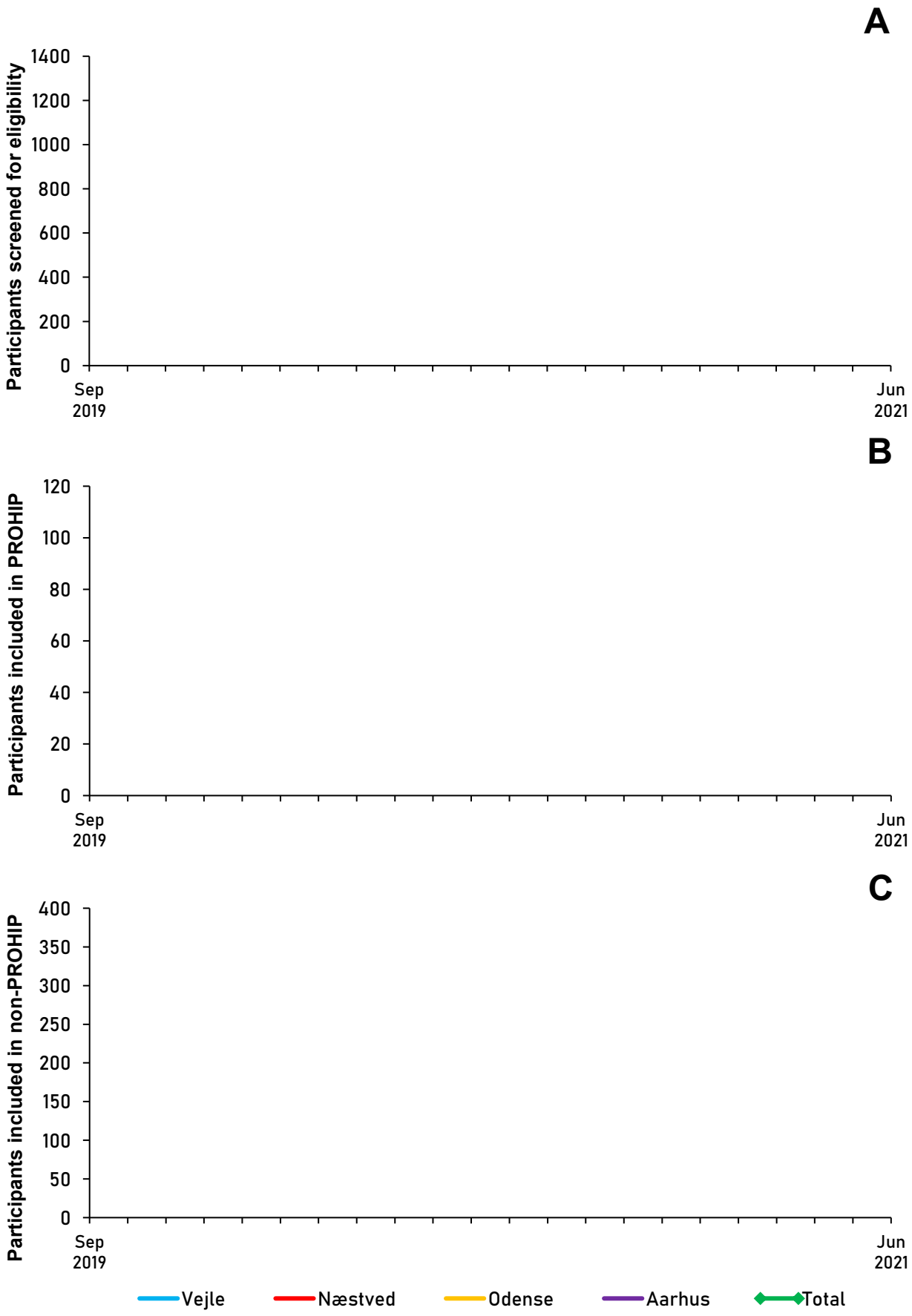
§ For all five subscales, the Hip disability and Osteoarthritis Outcome Score (HOOS) ranges from 0 to 100, with higher scores indicating better disease status.

¶ The University of California Los Angeles (UCLA) Activity Score ranges from 1 to 10, with higher scores indicating greater physical activity level.

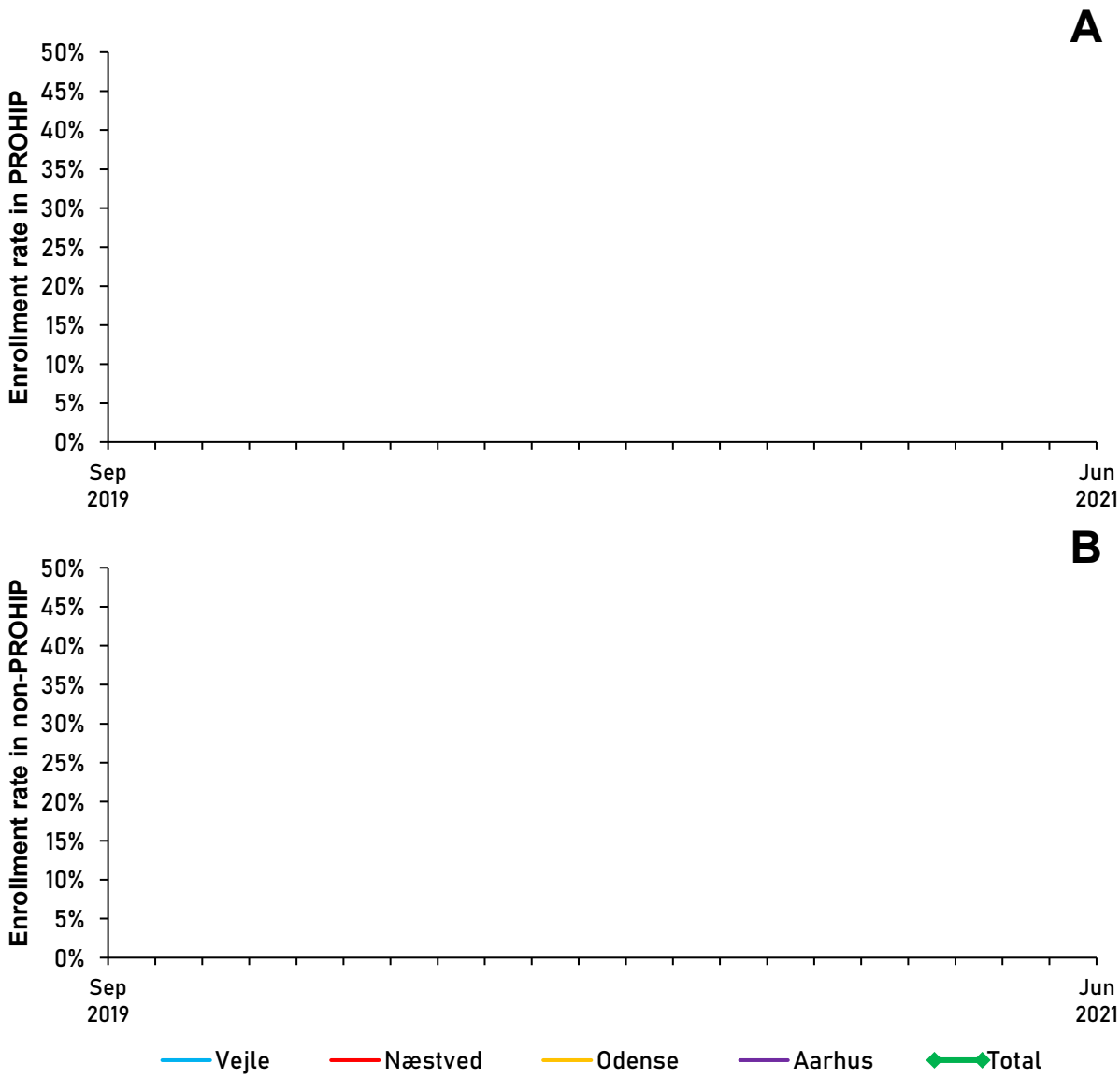
‖ The Visual Analogue Scale (VAS) ranges from 0 to 100, with higher scores indicating worse pain intensity.

∫ The EuroQol Group 5-dimension (EQ-5D-5L) index score ranges from -0.624 to 1.000, with higher scores indicating better health-related quality of life.

‡‡ The EuroQol Group 5-dimension VAS (EQ-VAS) index score ranges from 0 to 100, with higher scores indicating better health status.



Appendix Figure 1. The number of patients assessed for eligibility (A) and the number of participants enrolled in PROHIP (B) and non-PROHIP (C). The PROgressive resistance training versus total HIP arthroplasty (PROHIP) trial.



Appendix Figure 2. Enrollment rate in PROHIP (A) and non-PROHIP (B). The PROgressive resistance training versus total HIP arthroplasty (PROHIP) trial.