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SECTION 1: ADMINISTATIVE INFORMATION

Statistical analysis plan (SAP)

Effect of prothesis and active (PROACT) exercise program in patients with glenohumeral osteoarthritis

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Trial registration: The trial is registered at www.clincaltrials.gov with the number NCT04845074.

Protocol version: This document has been written based on the information contained in the trial protocol published in Acta Orthopaedica (1).

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Roles, responsibilities, and signatures:

Role	Name	Date	Signature
SAP author	Josefine Beck Larsen	02-07-2024	
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SECTION 2: INTRODUCTION

Background

Glenohumeral osteoarthritis (OA) is characterized by osseous changes, joint incongruence, and capsular thickening (2, 3). Anatomical total shoulder arthroplasty (TSA) is the surgical treatment of choice for patients suffering from glenohumeral OA (4, 5). The aim of TSA is to relieve pain and thereafter improve physical function (6-9). Although the incidence of TSA is rising, and 70% of patients report that they are very satisfied with their postoperative results (10), the proportion of patients living with an unsatisfactory shoulder arthroplasty is largely unknown (11).

In hip and knee OA exercise is recommended as the first-line treatment (4). The effectiveness of exercise and the effectiveness of TSA in patients with glenohumeral OA is unknown, as no randomized trials have directly compared TSA to a non-surgical treatment (5). In order to provide a trustworthy and evidence-based foundation for clinical decisions it is important to conduct a randomized controlled trial where surgical treatment is compared to non-surgical treatment in patients with glenohumeral OA.

The primary aim of this trial is to examine if surgical treatment followed by standard care is superior to a 12-week exercise programme in patients with primary glenohumeral OA. The primary outcome is the Western Ontario Osteoarthritis of the Shoulder index score (WOOS), measured 12 months after initiating the treatment. The primary hypothesis is that surgical intervention is superior to the exercise intervention at 12 months (1).

The key secondary objectives are (1):

1. To investigate the effectiveness of total anatomical shoulder arthroplasty followed by standard rehabilitation compared to a 12-week physiotherapist-supervised exercise programme, on (1) pain intensity, (2) activities of daily living, (3) use of analgesics and (4) shoulder-related quality of life in patients with glenohumeral OA.
2. To investigate the safety of total anatomical shoulder arthroplasty followed by standard rehabilitation compared to a 12-week physiotherapist-supervised exercise programme on occurrence of adverse events from baseline to 12 months after initiating the treatment, in patients with glenohumeral OA.

Exploratory objectives:

1. To investigate the external validity of the randomised controlled trial on total anatomical shoulder arthroplasty and physiotherapist-supervised exercise in patients glenohumeral OA by comparing patient characteristics and patient-reported WOOS scores from baseline to 12 months after initiating the treatment, in patients included in the randomised controlled trial versus those declining to participate but included in the follow-up cohort.
2. To investigate objectively measured physical upper extremity activity level from baseline to 12 months using tri-axial (Axivity, UK) accelerometers, in patients with glenohumeral OA eligible for total anatomical shoulder arthroplasty.
3. To assess the cost-utility of total anatomical shoulder arthroplasty followed by standard care compared to a 12-week physiotherapist-supervised progressive exercise programme on quality-adjusted life years (QALYs) gained from baseline to 12 months after initiating the treatment, in patients with glenohumeral OA.

SECTION 3: STUDY METHODS

Trial Design

The PROACT trial is a multicenter randomized controlled and investigator blinded trial, the reporting of the trial will follow the "*Consolidated Standards of Reporting Trials*" (CONSORT) statement (12). Patients are recruited from the orthopaedic departments at Aarhus University Hospital, Aalborg University Hospital, Viborg Regional Hospital and Silkeborg Regional Hospital in Denmark, at Tampere University Hospital, Central Finland Hospital in Finland and Oslo University Hospital in Norway.

The Statistical Analysis Plan (SAP) is reported in accordance with the "*Guidelines for the Content of Statistical Analysis Plan in Clinical Trials*" (13).

The PROACT trial is registered at www.clincaltrials.gov with the number NCT04845074. The Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-29-21) and the Danish Data Protection Agency (Journal No 1-16-02-199-21), The Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital (ref ETL R21089) and The Regional Committee for Medical and Health Research Ethics Region South-East Norway (Ref. 269784) have approved the trial.

Randomisation

The included patients will be randomised with a 1:1 allocation to TSA or exercise after their baseline assessment. The randomisation is stratified by recruitment site with randomly selected block sizes and done by a computer-generated list of random numbers using the randomization tool in Research Electronic Data Capture (REDCap), developed by an independent data manager (14). During the trial period administrators of the randomisation procedure are blinded to block sizes and randomisation sequence at all times.

Sample Size

The sample size is based on the expected between group difference in the WOOS end scores. The WOOS score 1 year after TSA surgery was 84.6 points in the Danish Shoulder Arthroplasty Registry in 2020 (7). The WOOS score after completing this exercise intervention in a feasibility study was 67 points (15). The assumed common SD was 27.1. The required power was set to 80%. Given a power of 0.80 to detect a difference between the two groups and using a two-sided significance level α=0.05, the estimated sample of each intervention group is 39 patients. Allowing for possible crossovers, loss-to follow-up and drop-outs the total number of patients in each group is 51 (1).

Framework

The overall objective of the trial is to determine whether surgical intervention results in a clinically and statistically significant greater improvement compared to exercise on WOOS, Disabilities of the Arm, Shoulder and Hand (DASH) (16), patient-reported pain intensity at rest, during activity, and nightly pain using the 100 mm VAS, the use of analgesics during the last week (paracetamol, NSAID, opioids) and adverse events. The primary hypothesis is that surgical intervention is superior to the exercise intervention at 12 months.

Blinded interpretation of the results

The blinded interpretation will be of the intention-to-treat analysis. The blinded analysis involves the primary outcome and key secondary outcomes. The principal investigator (JBL) will export data from REDCap and deliver the blinded dataset for analysis to the statistical analysist (AR). The senior statistician (EP) will supervise the analysis. The blinded results from the analysis of treatment A compared with treatment B will be presented to the project group followed by the development of the blinded interpretation. Interpretation version 1 assumes that group A had surgery, while interpretation 2 assumes that group A performed exercise. A draft of the blinded interpretation will be sent for approval by all co-authors. No other outcomes will be analyzed prior to an agreement of the blinded interpretation by all co-authors. All other analyses described in this document will be performed after the blinded interpretation is published (17).

Statistical interim analysis and stopping guidance

There has not been planned any formal statistical interim analysis for the PROACT trial. The final deadline for patient recruitment was a priori set to April 2024 but has since been moved to November 2024 due to delays in recruitment.

Timing of final analysis

The final analysis for the primary outcome, the end scores on WOOS at 12 months, will be performed after the last follow-up assessment at 12-months. The main publication of the trial will be prepared when these data are available.

In addition, papers on 2-, 5-, and 10-years follow-up will be performed, when these follow-up assessments are available.

Timing of outcome assessments

The trial consists of six time points; baseline, 12-weeks, 12-months, 2 years, 5 years and 10 years. An overview of the assessments and procedures has been presented in the protocol (Table 1).

SECTION 4: STATISTICAL PRINCIPLES

Confidence intervals and P values

For the primary outcome the statistical tests will be two-sided and a p-value <0.05 will be considered statistically significant. Confidence intervals will be 95% (95% CI) and two-sided. For the secondary outcomes the use of p values will be interpreted with care (18).

Adherence and protocol deviations

Adherence is defined as the ability to follow the allocated treatment. For the exercise group adherence is related to the number of attended supervised exercise sessions, good adherence has been predefined as participation in at least 70% of the supervised exercise sessions, during the first 12-weeks. Table 7 illustrates this.

There are predefined protocol deviations regarding adherence:

1. Patients randomized to exercise undergoing TSA in the follow-up period
2. Patients randomized to TSA not undergoing TSA in the follow-up period

Analysis populations

The primary analysis will be based on the Intention to Treat (ITT) principle. Patients allocated to a treatment group (TSA or exercise) should be followed up, assessed and analysed as members of that group, regardless of their adherence to the planned course of treatment.

Response to treatment will be described for both treatment groups, regardless of their adherence to the planned course of treatment.

A per protocol analysis will be conducted with patients in the surgical group undergoing surgery and for the exercise groups patients with a good adherence to the exercises are included. Poor adherence is defined as participating in less than 70% of the supervised exercise sessions. Another per protocol analysis will be of patients undergoing surgery regardless of randomization.

Lastly four as-treated analysis will be performed in which patients will be analyzed based on their adherence to the randomized treatment expecting four groups: (1) patients randomized to TSA and getting TSA, (2) patients randomized to exercise without undergoing TSA in the follow-up period, (3) patients randomized to exercise undergoing TSA in the follow-up period, (4) patients randomized to TSA not undergoing TSA in the follow-up period. One as treated analysis will be done on TSA patients versus good exercise adherence versus poor exercise adherence. And one as treated analysis on TSA patients randomized to TSA versus crossover TSA patients versus good exercise adherence versus poor exercise adherence.

SECTION 5: TRIAL POPULATION

Screening data

At all hospitals patients eligible for TSA will be screened for the inclusion and exclusion criteria. If they fulfil the criteria, they will be invited to participate. The number of patients who do not meet the criteria and the reason for ineligibility will be reported in a CONSORT flow chart (Figure 1).

Eligibility

Patients fulfilling the in- and exclusion criteria and are willing to participate are eligible for the PROACT trial. The inclusion criteria are:

Inclusion criteria:

1. Patients ≥55 years
2. Moderate to severe primary OA of the glenohumeral joint (Osteophyte larger than 3 mm, according to Samilson and Prieto (Samilson et al. 1983)
3. Eligible for surgery with standard TSA

Exclusion criteria:

1. Surgical need for bone graft or use of augmented glenoid component
2. Previous shoulder fracture (fracture of the proximal humerus or glenoid fracture)
3. Planned other upper extremity surgery within six months
4. Rheumatoid arthritis or other types of arthritis not diagnosed as primary glenohumeral OA
5. Cancer diagnosis and actively receiving chemo-, immuno-, or radiotherapy
6. Neurological diseases affecting shoulder mobility (e.g., disability after previous stroke, multiple sclerosis, Parkinson's, Alzheimer's disease)
7. Other reasons for exclusion include mentally unable to participate or planned absence for more than 14 days in the first 3 months after baseline test
8. Unable to communicate in the respective languages of the participating countries.

Recruitment

The CONSORT flowchart will present the number of patients screened, excluded (with reasons), eligible for inclusion, randomized, receiving allocated treatment, withdrawals (with reasons), lost to follow-up (with reasons), included in the ITT analysis, included in the per protocol analysis.

Withdrawal/follow-up

Throughout the trial period the patients are allowed to withdraw from the study at any time. Patients who decide to withdraw will be encouraged to continue in the study as if they have received the intervention. Withdrawal will be classified into two options; (1) complete withdrawal from the study with no further follow-up and data-collection, (2) consent to follow-up assessments and data-collection. The number of withdrawals and the timing of withdrawal will be presented in the CONSORT flowchart (with reasons).

Baseline patient characteristics

Baseline characteristics will be presented as seen in Table 2. Categorical variables will be presented as numbers and percentages. Continuous variables will be presented as mean with

standard deviation (SD), if normally distributed and ad median with interquartile range (IQR) if not normally distributed. No tests of significance will be conducted for the baseline characteristics, imbalances of importance will be noted. Baseline and follow-up values for the primary and secondary outcomes will be presented as part of the analysis, as seen in Table 3.

SECTION 6: ANALYSIS

Outcome definitions

The Western Ontario Osteoarthritis of the Shoulder index score (WOOS)

The primary outcome will be presented as the between group difference on the 12-month follow-up score. WOOS is a valid and reliable patient-reported questionnaire assessing shoulder pain and function in a total raw score ranging from 0-1900, raw scores can be converted to a score from 0-100, where 0 indicates severe problems and 100 indicates no problems.

Key secondary outcomes

Disabilities of the Arm, Shoulder and Hand (DASH) (Lindenhovius et al. 2008); patient-reported pain intensity at rest, during activity, and nightly pain using the 100 mm VAS; the use of analgesics during the last week (paracetamol, NSAID, opioids); serious adverse events and adverse events.

Analysis methods

Descriptive statistics will be presented as means with standard deviation (SD) for all normally distributed continuous variables. Continuous variables that do not follow a normal distribution will be presented as median with interquartile ranges. Normal distribution will be determined by visual inspection of QQ-plots and histograms. Categorical outcomes will be presented as numbers with percentages.

The primary comparison in WOOS between groups will be conducted using a linear mixed model. Intervention group and time (3 months, 12 months) will be included as fixed effects and patient as random. Baseline score, sex, age and study site will also be included as fixed covariates. Interaction between study group and time will be included in the model to estimate treatment effect at each time point. 95% confidence intervals are estimated for each time point.

Due to the repeated mixed model analysis no missing data imputation will be conducted. A sensitivity analysis will be done using an analysis of covariance (ANCOVA) including baseline score, sex, age and study site as covariates with the same ITT approach for time (3 months and 12 months) separately.

Analysis for patient-reported DASH, pain intensity at 3 and 12 months will be analysed similar to the primary comparison. For binary variables (ie. the use of analgesics and adverse events) we use proportions to describe the number of events. For each binary outcome an unadjusted risk difference in proportions with 95% confidence interval of outcomes between study groups. Table 3 illustrates the primary analysis.

Response to treatment for the WOOS change score from baseline to 12 months and 3 months follow-up will be computed for each patient in both treatment groups. Response to treatment will be presented dichotomized (i.e. responder and non-responder) as number and percentage. The patients will be classified as a responder if they reach a minimal important change of 13.3 points or more from baseline to 12 months follow-up (19).

Missing data

As stated above, imputations will not be applied in this study due to the repeated mixed model analysis. Each randomized patient will be included in the intention-to-treat analysis with the collected data. In an attempt to collect data from all randomized patients, patients deciding to withdraw from the study, are still encouraged to attend the follow-up test.

Harms

Adverse and serious adverse events will be presented as number and percentage for each event.

Statistical software

All statistical analysis will be conducted using the statistical software program R (R Foundation for Statistical Computing, Vienna, Austria) (20).

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Figure 1 Expected enrolment, randomization, intervention, and follow-up. Total shoulder arthroplasty (TSA).

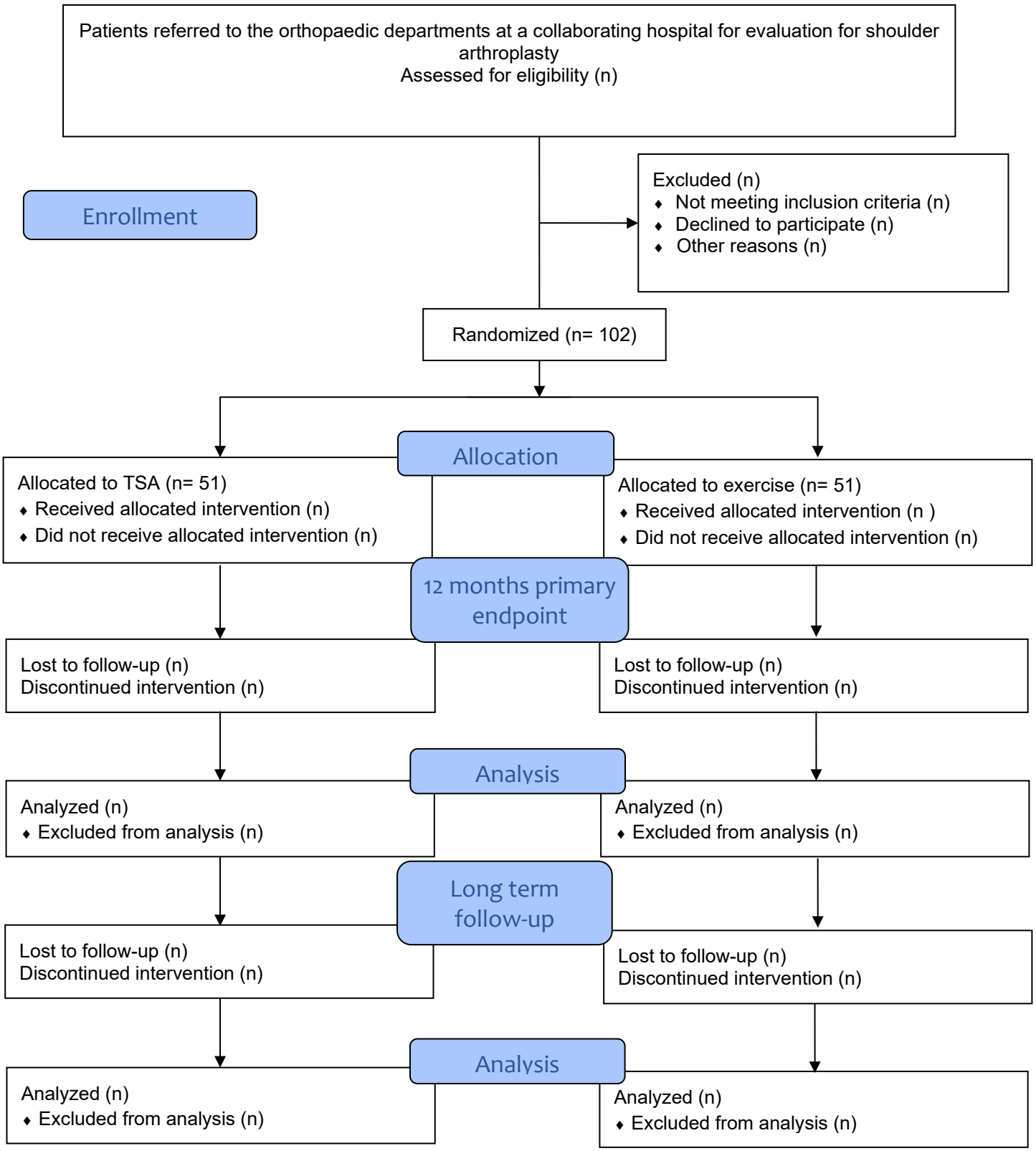

Table 1. Assessments and procedures.

	Baseline	Surgery	3 m	12 m	2 y	5 y	10 y
Baseline characteristics							
Sex	X						
Age	X						
Height	X						
Weight	X						
Hand dominance	X						
Duration of shoulder symptoms	X						
Marital status	X						
Educational level	X						
Employment status	X						
Alcohol intake	X						
Smoking behaviors	X						
Comorbidities	X						
Surgery information							
X-ray and surgeon appointment	X						
Surgery report (only surgical group)		X	X*	X*			
CT	X						
Patient reported outcomes							
WOOS[a]	X		X	X	X	X	X
DASH[b]	X		X	X	X	X	X
EQ-5D-5L[c]	X		X	X	X	X	X
iPCQ[d]			X	X			
VAS[e]	X		X	X	X	X	X
Physical activity							
Tri-axial accelerometry	X			X			
Treatment related variables							
Adverse events[f]			X	X	X	X	X
Serious adverse events[f]			X	X			
Training-compliance			X				
Pain before exercise and at the end of exercise for the exercise group using NRS[g]			X				
Other shoulder related treatments	X		X	X			
Analgesic consumption in last week	X		X	X	X	X	X
Crossover			X	X	X	X	X

m = months. y = years. *X-ray at 3 months for the surgical group only to assess adverse events. [a] the Western Ontario Osteoarthritis of the Shoulder index (WOOS). [b] Disabilities of the Arm, Shoulder and Hand (DASH). [c] European Quality of life 5 Dimensions with 5 Levels (EC-5D-5L). [d] Productivity Costs Questionnaire (iPQC) only in Denmark. [e] Visual Analogue Scale will be at rest, during activity and at night. [f] Described in "Adverse events". [g] Numeric Rating Scale will be used at the supervised exercise sessions to determine pain at rest before and after the session.

Table 2: Baseline characteristics for the two intervention groups

	TSA group n =	Exercise group n =
Gender, n (%) female		
Age, mean (SD) years		
Body mass index, mean (SD) kg/m^2		
Handedness, n (%) right		
Affected shoulder, n (%) right		
Duration of shoulder symptoms, n (%)		
6-12 months		
1-2 years		
2-5 years		
More than 5 years		
Previous treatment in the affected shoulder, n (%) yes		
Exercise and/or physiotherapy		
Pharmacological treatment		
Surgical treatment		
Civil status, n (%)		
Living alone		
Living with someone		
Not informed		
Educational level, n (%)		
Low		
Medium		
High		
Employment status, n (%)		
Employed		
Outside the labor market		
In activation, sick leave, available, etc.		
Retired		
Alcohol consumption, n (%)		
Under 2 items per week		
2-7 items per week		
8-14 items per week		
15-21 items per week		
Over 21 items per week		
Smoking behaviour, n (%)		
Never smoked		
Quit smoking		
Sometimes		
Daily		
Co-morbidities, n (%) yes		

Table 3: Intention to treat analysis and per protocol analysis of the between group difference for the surgical group and exercise group in end-scores one year after intervention.

Intention-to-treat analysis							
	TSA			**Exercise**			**Improvement between the two groups**
	Baseline	**Three months**	**One year**	**Baseline**	**Three months**	**One year**	**Adjusted**
WOOS DASH Pain at rest Pain during activity Pain at night Use of analgesics* Adverse events*							
Per-protocol analysis							
	TSA			**Exercise**			**Improvement between the two groups**
	Baseline	**Three months**	**One year**	**Baseline**	**Three months**	**One year**	**Adjusted**
WOOS DASH Pain at rest Pain during activity Pain at night Use of analgesics* Adverse events*							

Higher scores indicate desired (better) treatment outcome for WOOS. For the other outcomes lower scores indicate desired (better) treatment outcome.

*Analysed with risk difference, use of analgesics (yes/no), adverse events (yes/no).

Table 4: As treated analysis of the between group difference for the surgical group and exercise group in end-scores one year after intervention.

	TSA			Exercise			Cross-over			No treatment			Improvements between the four groups
	B	3M	1Y	B	3M	1Y	B	3M	1Y	B	3M	1Y	Adjusted
WOOS													
DASH													
Pain at rest													
Pain during activity													
Pain at night													
Use of analgesics*													
Adverse events*													

B=Baseline, 3M=Three months, 1Y=One year

Table 5: Usage of painkillers

	TSA group			Exercise group		
	Baseline	Three months	One year	Baseline	Three months	One year
Use of painkillers, n (%) yes						
Type of painkillers, n (%) Paracetamol NSAID Morfin/opiods Other painkillers						
Usage of painkillers, n (%) Never Monthly Weekly Daily						

Table 6: Adverse and serious adverse events

	TSA group	Exercise group
Adverse events, n (%)		
Postoperative infections		
Instability		
Periprosthetic fracture		
Loosening		
Humeral component		
Glenoid component		
Both		
Injuries related to the exercise intervention		
Serious adverse events, n (%)		
Death		
Embolism		
Liver failure		
Renal failure		

***Serious adverse events resulting in the need for hospitalization or death in the first 4 weeks after surgery. Adverse events that occurred between baseline and 12 months follow-up but did not necessarily have a causal relationship between the treatments.**

Table 7: Adherence to randomized treatment

	Exercise group
Training adherence	
Showed up for supervised sessions within the first three months of exercise, mean (SD)	
Participated in at least 70% of supervised sessions within the first three months of exercise, n (%)	
Number of self-reported exercise sessions within the first three months of exercise, mean (SD)	
Completed three or more exercise sessions per week within the first three months of exercise, n (%)	
Completed 4 booster sessions, n (%)	
Number of self-reported exercise sessions from three months to one year, mean (SD)	
Completed three or more exercise sessions per week from three months to one year, n (%)	
Number of patients randomized to exercise undergoing surgery in the follow-up period, n (%)	
	Surgical group
Surgical adherence	
Number of patients randomized to surgery electing not to undergo surgery in the follow-up period, n (%)	