STATISTICAL ANALYSIS PLAN CUT-N-MOVE TRIAL

Progressive early passive and active exercise therapy after surgical rotator cuff repair – a randomized controlled trial (the CUT-N-MOVE trial)

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Progressive early passive and active exercise therapy after surgical rotator cuff repair – a randomized controlled trial (the CUT-N-MOVE trial)

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6 The Shoulder-Elbow Unit, Department of Orthopaedic Surgery, Herlev-Gentofte Hospital, Kildegårdsvej 28, DK-2900 Hellerup, Copenhagen, Denmark
Statistical advisor, analyst and epidemiologist: Eleanor Boyle (EB).

Datamanager:
The computer-generated randomization are performed using Procordo Research Platform. Senior researcher Susan Warming (SW) with no clinical involvement in the trial notifies the patient and clinical study staff of the treatment allocation. The allocation is concealed in a password-protected research platform only accessible by the senior researcher and the independent data manager (Procordo).

Correspondence
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1. Study synopsis

Shoulder disorders are extremely common, with a life-time prevalence in the population of 30%, and a 12-month prevalence of 50% having shoulder pain (Lewis, 2009). Specifically rotator cuff tears are considered some of the principal causes of chronic shoulder pain and disability, especially with advancing age (Lewis, 2009, van der Windt et al., 1995, Fehringer et al., 2008). The predominant complaints among patients are pain and loss of strength during elevation of the arm resulting in loss of function (Hawkins et al., 1999, van der Windt et al., 1995, Danish_Health_Authority, 2013). Criteria for surgery are full-thickness tears, or partial-thickness tears, if extending greater than 50% of the transversal or longitudinal tendon size, provided it is caused by a relevant and extrinsic trauma (Mazzocca et al., 2008, Gerber et al., 2000, Danish_Health_Authority, 2011, Danish_Health_Authority, 2013). Postsurgical rehabilitation is recommended using supervised, progressive and early training (Holmgren et al., 2012, Danish_Health_Authority, 2013).

A number of systematic reviews looking at different rehabilitation parameters after rotator cuff surgery conclude that there is a further need to evaluate approaches that foster early initiation of rehabilitation and gradual introduction to functional loads, in high-quality, adequately powered trials, also considering key outcomes such as return to work (Littlewood et al., 2015, Riboh and Garrigues, 2014, Kluczynski et al., 2016, Mazuquin et al., 2018).

The few existing clinical studies of early postoperative loading of rotator cuff repair are of moderate-low quality (lack of blinding, small sample sizes, responsiveness on outcomes, or with only per protocol analyses) (Duzgun et al., 2011, Klintberg et al., 2009).

Thus, no high-quality study has evaluated the combined effect of early (= the time of initiation) and progressive (= with an increased intensity, also including dynamic, active muscle contraction) postoperative exercises on physical function, pain, and quality of life.

Ethical approval: H-16033995
Clinicaltrials.gov registration (NCT02969135).

2. Study design

This is a multicentre, randomized, controlled, pragmatic, outcome assessor blinded, parallel group, superiority trial, called CUT-N-MOVE, with a two-group parallel design comparing progressive early passive and active movement protocol (PR) with a usual care protocol (UC) (figure 1).
Participants were recruited from two Orthopedic Department; the Section for Sports Traumatology, Department of Orthopedic Surgery, Bispebjerg-Frederiksberg Hospital and The Shoulder-Elbow Unit, Herlev-Gentofte Hospital.

A provisional deadline for patient recruitment is set to August 2019, but in case the target number of 100 patients has not been met the recruitment period may be extended to reach the number required (2 times 41 patients) to obtain power of at least 0.8 (80%).

**Participants**

Participant included are:

*Inclusion criteria:*

- Women and men above 18 years
- Operated due to traumatic full thickness RC-tear
- Involving supraspinatus (full thickness and width)
- Reduced arm elevation strength and pain
- Clinical diagnosis verified by arthroscopy
- Fully repairable RC-tear

*Exclusion criteria:*

- Patients with non-traumatic RC-tears of the shoulder
- Patients with isolated teres minor or subscapularis tear
- Patients with partial thickness/width tear
- Prior shoulder surgery (all shoulder joints)
- Glenohumeral osteoarthritis (OA), rheumatoid arthritis or periarthritis
- Inability to speak or read Danish
- Inability to perform and maintain the physical training
- Other condition negatively influencing compliance or conditions that in the opinion of the investigator makes him/her unsuitable for participation.

**Intervention**

Based on best evidence from previous studies the postoperative training program was developed by the principal investigator and two clinical physiotherapists specialized in orthopaedic shoulder rehabilitation in collaboration with patients operated due to traumatic full thickness RC-tear. The
PR group starts loading (assisted active range of motion (AAROM) and active range of motion (AROM)) from week 2, while this is introduced in the UC group from week 6. The PR group is attending individual physiotherapist-supervised exercise therapy three times weekly, supplemented with daily home exercises (week 2, 3, 4 and 5), and the UC group is attending individual physiotherapist-supervised exercise therapy once a week supplemented with daily home exercises (week 2, 3, 4 and 5). From weeks 6 to 12 all patients receive physiotherapist-supervised exercise therapy twice a week (individually or in small groups) next to the self-administered exercise once a week. The shoulder-specific exercises are progressed as defined by the exercise program targeting specific levels of shoulder function (e.g. passive movement; assisted active movement; active movement). All methods are described in the protocol published by Kjær et al. (Kjaer et al., 2018).

3. Study objective and outcome
This study tests the hypothesis that early and progressive movement and physical training postoperatively is superior to limited early passive movement protocol (‘care as usual’) on the pain, physical function, and quality of life.

The same patient-reported primary (WORC Physical symptoms) and secondary outcomes (WORC other subdomains and total, DASH, pain, ROM) are performed at baseline, 6 weeks, 12 weeks and 12 months after baseline. Further secondary outcomes (strength) are performed at baseline, 12 weeks and 12 months after baseline.

4. Primary objective and outcome
The primary objective of this trial is to evaluate the effect of a 12-week progressive rehabilitation (PR) strategy on shoulder function compared to usual care (UC) in patients recovering from surgical treatment of rotator cuff tears, as measured by the WORC Physical symptoms (see below).

The primary outcome measure is the 12 weeks patient-reported postoperative change in the subdomain Physical symptoms in the Western Ontario Rotator Cuff Index (WORC). The WORC is a self-administered questionnaire developed to measure health related quality of life in patients with rotator cuff disease (Kirkley et al., 2003). WORC consists of 21 items covered in 5 domains: physical symptoms (6 items), sports and recreation (4 items), work (4 items), lifestyle (4 items) and emotions (3 items). Each question is scored on a 100 mm VAS scale and summed up to a total score
of maximally 2100, with a higher score indicating reduced quality of life. A percentage score ranging from 0 (worst possible) to 100 (best possible) is used as advocated by its developers (Kirkley et al., 2003, MacDermid et al., 2006). A Danish validated version was used (Brix et al., 2018).

5. Secondary objective and outcome
The secondary objectives are to compare changes from baseline to 6 and 12-weeks follow-up between the two treatment arms in a number of patient reported outcomes and objective outcomes. The secondary outcomes are to be used as support for the interpretation of the primary outcome.

Patient reported outcomes

WORC other subdomains and total
Secondary Patient Reported Outcome (PRO) include the WORC subdomain “sports and recreation”, “work”, “lifestyle” and “emotions” and ‘total’ at 6 and 12-weeks follow-up and the WORC Physical symptoms at 6 weeks follow-up.

Disabilities of the Arm, Shoulder and Hand questionnaire (DASH)
Secondary PRO also include assessment of pain, functional activity level and health related quality of life (HRQOL), using DASH (Hudak et al., 1996, Lundquist et al., 2014). The DASH questionnaire is a self-administered questionnaire and is region-specific to upper extremity disorders. The questionnaire consists of 30 items, including six items on symptoms and 24 on function. The questionnaire score ranges from 0 to 100, where 0 equals no disability and 100 equals most severe disability. If there is no response for more than three items, the DASH score is recommended not to be calculated (Hudak et al., 1996, Lundquist et al., 2014).

Patient Global Rating Scale (GRS)
GRS is used to get a global/ general impression of recovery from baseline to respectively 6, 12 and 52 weeks postoperatively, with the question: “Compared to when this treatment first started, how would you describe your shoulder this last week?”. The question is rated on a 15-point scale where minus seven represents vastly worse, 0 represents unchanged, and seven represents a whole lot better (de Vet et al., 2006, Bernard et al., 2016, Revicki et al., 2008). GRS will be reported in text, not tables.
Numeric Pain Rating Scale (NPRS)

Patients are asked about perceived pain (self-reported pain registration) on a Numeric Pain Rating Scale (NPRS) (Downie et al., 1978, Mintken et al., 2009). The questions were:

- How much pain do you feel in your shoulder during resting?
- How much pain do you feel in your shoulder during activity?
- What is the maximal shoulder pain you have experienced within the past 24 hours?

Objective outcomes

- Active and passive Range of Movement (ROM) in scaption (0 to 180 degrees), external (0 to 90 degrees) and internal rotation (0 to 90 degrees) measured by Baseline Digital Inclinometer.
- Maximum isometric voluntary contraction (MVC) of external and internal rotation and scaption measured by IsoForce EVO2 dynamometer.

Other secondary outcomes

Secondary outcomes also includes patient-reported number of sick days from work /time until return to work.

Demographics

Registered demographic data include age, gender, tendon(s) involved, dominant side affected, occupation/employment.

Compliance

Intervention adherence and attendance (supervised and home-based) within the 12 weeks is recorded in exercise logbooks for both groups. In the exercise logbook, the patients are asked to report completed home-based exercise sessions and reasons for non-completed sessions (pain or other reasons). Initial supervision of the subsequent home exercises at the commencement of every session is performed to facilitate program adherence. Reinforcement techniques are used as the physiotherapist gives positive feedback and commends patients for their efforts.
Satisfactory intervention adherence/compliance is defined by having attended at least 75% of the scheduled rehabilitation appointments, either at clinical supervised visits or home-based as tailored to the individual.

6. Tertiary outcomes

Adverse Event (infection and retear)

Infection is registered by the PI. Tendon retear is assessed by ultrasound (US) and registered at 6 weeks postoperatively by the PI.

Use of analgesics

Patients are asked to report use of analgesics (type and amount). NSAID (non-steroid-anti-inflammatory-drug) is not allowed. Paracetamol and opioids are allowed.

7. Allocation, Randomization and Blinding

To control for potential imbalance in the randomization, stratification are done. Stratification by site is necessary because of possible regional differences in clinical practice, and also stratification by gender and age are done. Randomization to one of two treatment arms are computer-generated based upon permuted random blocks of variable size (3 to 6 in each block) using the Procordo Research Platform, an online data trial management system (www.procordo.com). Participants are randomized equally (1:1) to receive either the PR protocol (progressive early passive and active movement) or UC, ‘care as usual’ protocol (limited early passive movement). The randomization will be performed after baseline tests and surgery, and the allocation (based on the randomization) will be performed by a person otherwise not included in the project.

Orthopaedic surgeons will perform initial screening. All further pre- and post-examinations are performed blinded to group allocation by the principal investigator. The participants are instructed not to reveal anything of their group allocation during assessment appointments.

As this is an “open-label” trial the health professionals delivering the interventions and the participants will not be blinded to treatment allocation. Outcome assessors will be blinded to treatment allocation, and participants are requested not to disclose their allocation when outcomes are assessed at weeks 6 and 12 postoperatively, and 12 months postoperatively.
8. Sample size estimation
The sample size was calculated to test the superiority of the PR protocol over the UC protocol in the assessment of change in the WORC physical symptoms subscale at week 12 (primary outcome) (de Witte et al., 2012). With 41 patients per group, the study would have 80% power and a significance level of 5%, assuming the expected group difference in the mean changes from baseline is 12 points, corresponding to the suggested minimum clinical relevant difference (Kirkley et al., 1998), the common standard deviation is 20 (0–100 scale) (de Witte et al., 2012).

Deviation from sample size
To account for dropouts, we sought to include a total of 50 to each group, however, we experienced no dropout and thus the recruitment period was stopped when we reached the number required (2 times 41 patients) to obtain power of at least 0.8 (80%). Thus, it would be unethical to continue the study when sample size had been reached.

9. Statistical analysis plan

Study Population definitions

Intention-to treat (ITT)
The primary efficacy analysis performed is assessment of the between-group difference in change in WORC score after 12 weeks in the ITT population. ITT population is defined as all randomized participants irrespective of compliance or withdrawals. A patient will be considered randomized as soon as intervention/training group is assigned according to the allocation sequence. Missing follow up data will be imputed using baseline observation carried forward (BOCF). There are no missing data on self-reported outcomes at baseline due to the electronic nature of this outcome. Missing data at baseline for objective measures will be replaced by the group mean the individuals are allocated to.

As-observed population (AO)
The AO population is defined as participants who have the outcome of interest assessed at a given time point of interest (i.e. no imputation of missing data), primarily used for demographics presentation.

Per-protocol population (PP)
The PP population is defined as the AO population participants that comply with this protocol, defined by the following criteria to the two groups:

Patients in the PR- group and the UC- group:
- Are included in the AO population, AND
- Have attended at least 75% of the scheduled rehabilitation appointments, whether at clinical supervised visits or home-based as tailored to the individual. The exercise diary will be used for documentation, AND
- Fulfill the training intervention during the 12 weeks main trial period, AND
- Do not engage in concomitant training

For both groups the participants will be considered to have completed the training if they have attended 3 out of 4 supervised sessions at the hospital.

Each participant’s planned home training with shoulder exercises will be registered by him/her in a logbook and completion of min 75% of the home-based scheduled exercises, as reported in the exercise diary is considered as compliant.

Sensitivity analyses will be performed on the PP-population for detecting differences in demographics and baseline outcomes between participants lost to follow-up and those from the complete dataset, using Fisher’s exact test or t-test depending on the variable tested.

**Primary analysis**

The primary analysis of the WORC physical symptoms will be done by a repeated measures analysis of covariance (ANCOVA) on change in WORC physical symptoms as dependent variable, with a factor for group (2 levels) a factor for time (2 levels; 6 and 12 weeks) and adjustment for WORC physical symptoms value at baseline as independent variables and confounders (age, gender and center).

**Secondary outcome analysis**

Secondary outcome measures will be analysed with ANCOVA for the continuous outcome measures (pain, patient reported outcomes, strength, ROM) as dependant variables (individually),
with group allocation and demographic variables as fixed factors. Analyses will be adjusted for repeated measures (baseline-6 weeks/ baseline-12 weeks).

**Tertiary outcomes analysis**
Tertiary outcome measures will be analysed with multiple logistic regression analysis for binary outcome measures (infection and retear) and for GPE with multiple logististics, with the same fixed factors as for the analyses of the primary and secondary outcomes.

**General statistical approach**
Test for normality will be performed. For quantitative variables we will calculate mean, standard deviation (SD), minimum and maximum. Descriptive tables for quantitative variables are expected to include at least mean and SD/95% CI by treatment group.
All descriptive tables for qualitative variables will display counts, percentages by treatment group. Baseline data are defined as the all measurements performed at the baseline visit.
All statistical tests will be two-sided and statistical significance will be claimed if the computed p-value is equal to or less than 0.05 (using 95% CI). All data analysis will be carried out according to the pre-established analysis plan and will be performed by the IBM SPSS Statistics Version 25.0 software (SPSS Inc., Chicago, IL).

10. Implementation of analysis plan
A statistical advisor and epidemiologist (EB) will perform the analysis of the primary endpoint outcomes. Principal investigator will perform analyses on secondary outcomes.
The implementation procedure of the SAP for the CUT-N-MOVE trial:

- Database model will be lined up in collaboration between EB, PI and BJK.
- Senior researcher SW will code each treatment arm into “A” and “B” thus leaving all others blinded to treatment allocation during analysis.
- Blinded data will be delivered to EB according to the statistical model requirements.
- Primary analysis will be conducted blinded from allocation to any of the two treatment arms by an external statistician (EB). Secondary, sensitivity and exploratory analyses will be carried out by the PI in collaboration with EB and BJK.
Before unblinding a consensus document will be described and signed by all authors of the study.

11. Figure legends

*Figure 1:* Flow of participants throughout the study

*Figure 2:* WORC at baseline, 6 and 12 weeks postop. The graphs illustrates the results from the Intention-To-Treat population with datapoints representing least square means and error bars indicate 95% CI’s.
Figure 1.
Table 1: Baseline demographics for PR and UC groups. Estimates are reported for each group as the total with Mean ± SD, n (%).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PR Group (n=xx)</th>
<th>UC Group (n=xx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
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<tr>
<td>Male, n (%)</td>
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<td>Height in cm, mean (SD)</td>
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<td>Weight in kg, mean (SD)</td>
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<tr>
<td>BMI in kg/m², mean (SD)</td>
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<td>Dominant side affected, n (%)</td>
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<td>Employment</td>
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<td>Manual labour, n (%)</td>
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<td>Office work, n (%)</td>
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<tr>
<td>Retired, n (%)</td>
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<tr>
<td>Number of sick days, n (%)</td>
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<tr>
<td>Tendons</td>
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<tr>
<td>Number of tendons involved, n (%)</td>
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<tr>
<td>Supraspinatus tear, n (%)</td>
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<td>Infraspinatus tear, n (%)</td>
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<td>Subscapularis tear, n (%)</td>
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<tr>
<td>Primary Outcome</td>
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<tr>
<td>WORC Physical symptoms (0-100 % (best))</td>
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<tr>
<td>Secondary Patient Reported Outcomes</td>
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<td></td>
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<tr>
<td>WORC Sports and recreation</td>
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<td>WORC Work</td>
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<tr>
<td>WORC Lifestyle</td>
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<tr>
<td>WORC Emotions</td>
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<td>WORC Total</td>
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<td>DASH Total</td>
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<tr>
<td>DASH Work</td>
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<tr>
<td>DASH Leisure time</td>
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<tr>
<td>NPRS At rest</td>
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<td>NPRS During activity</td>
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<tr>
<td>NPRS Worst past 24 hours</td>
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</table>

PR, progressive; UC, usual care; BMI, Body Mass Index; WORC, Western Ontario Rotator Cuff Index; DASH, Disability Arm Shoulder Hand; NPRS, Numeric Pain Rating Scale; SD, Standard Deviation
Figure 2: WORC at baseline, 6 and 12 weeks postop. The graphs illustrate the results from the Intention-To-Treat population with datapoints representing least means and error bars indicate 95% CI’s.

PR, progressive; UC, usual care; WORC, Western Ontario Rotator Cuff Index
Table 2: Changes in primary and secondary outcomes from baseline to 12 weeks postoperatively for PR and UC groups. Intention-To-Treat population.

<table>
<thead>
<tr>
<th>Change from baseline in</th>
<th>PR Group (n=xx) Change (95% CI)</th>
<th>UC Group (n=xx) Change (95% CI)</th>
<th>Between-Group difference (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
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<tr>
<td>WORC Physical symptoms</td>
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<td><strong>Secondary Outcomes</strong></td>
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<td><strong>Patient Reported</strong></td>
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<tr>
<td>WORC Sports and recreation</td>
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<td>WORC Lifestyle</td>
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<td>WORC Emotions</td>
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<td>WORC Total</td>
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<td>DASH Total</td>
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<td>DASH Work</td>
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<td>NPRS At rest</td>
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<td>NPRS During activity</td>
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<td>NPRS Worst past 24 hours</td>
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<td><strong>ROM (°)</strong></td>
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<td>Scaption</td>
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<td>External rotation</td>
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<td>Internal rotation</td>
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<td><strong>Strength (Nm)</strong></td>
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<td>Scaption</td>
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<td>Internal rotation</td>
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</table>

PR, progressive; UC, usual care; WORC, Western Ontario Rotator Cuff Index; DASH, Disability Arm Shoulder Hand; NPRS, Numeric Pain Rating Scale; °, degrees; MVC, Maximum isometric voluntary contraction; 95%CI, 95% Confidence Intervals
Table 3: Changes in secondary outcomes from baseline to 6 weeks postoperatively for PR and UC groups. Intention-To-Treat population.

<table>
<thead>
<tr>
<th>Change from baseline in</th>
<th>PR Group (n=xx)</th>
<th>UC Group (n=xx)</th>
<th>Between-Group difference (95% CI)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td>Change (95% CI)</td>
<td>Change (95% CI)</td>
<td>(95% CI)</td>
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<tr>
<td><strong>Patient Reported</strong></td>
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<td>WORC Physical symptoms</td>
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<td>WORC Sports and recreation</td>
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<td>WORC Work</td>
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<td>WORC Lifestyle</td>
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<td>WORC Emotions</td>
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<td>WORC Total</td>
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<tr>
<td>DASH Total</td>
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<td>DASH Work</td>
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<td>DASH Leisure time</td>
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<tr>
<td>NPRS At rest</td>
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<tr>
<td>NPRS During activity</td>
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<td>NPRS Worst past 24 hours</td>
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<td><strong>ROM (°)</strong></td>
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<td>Scaption</td>
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<td>External rotation</td>
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<td>Internal rotation</td>
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</table>

PR, progressive; UC, usual care; WORC, Western Ontario Rotator Cuff Index; DASH, Disability Arm Shoulder Hand; NPRS, Numeric Pain Rating Scale; °, degrees; 95%CI, 95% Confidence Intervals

Table 4 Adverse events. Retear measured at 6-week, and infection measured at 12-week follow-up, for PR and UC groups

<table>
<thead>
<tr>
<th>Change from baseline in</th>
<th>PR Group (n=xx)</th>
<th>UC Group (n=xx)</th>
<th>Between-Group difference (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Change (95% CI)</td>
<td>Change (95% CI)</td>
<td>(95% CI)</td>
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<td>6 weeks</td>
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<td>Retear (by US)</td>
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<td>12 weeks</td>
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<td>Infection (by surgeons)</td>
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12. References


