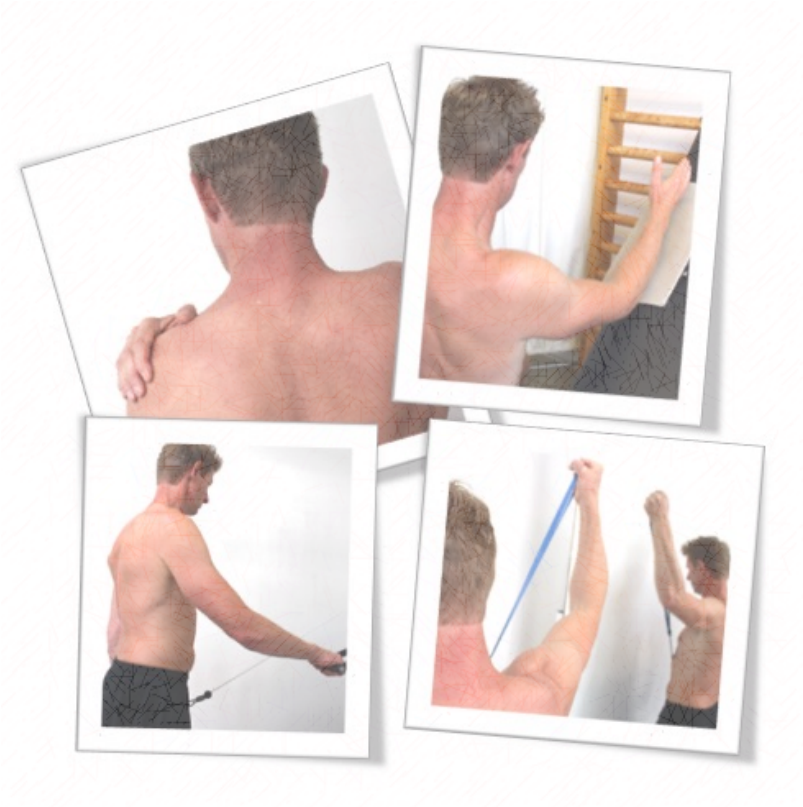
Physiotherapy for patients with traumatic rotator cuff tear and associations within patient characteristics.

Birgitte Hougs Kjær



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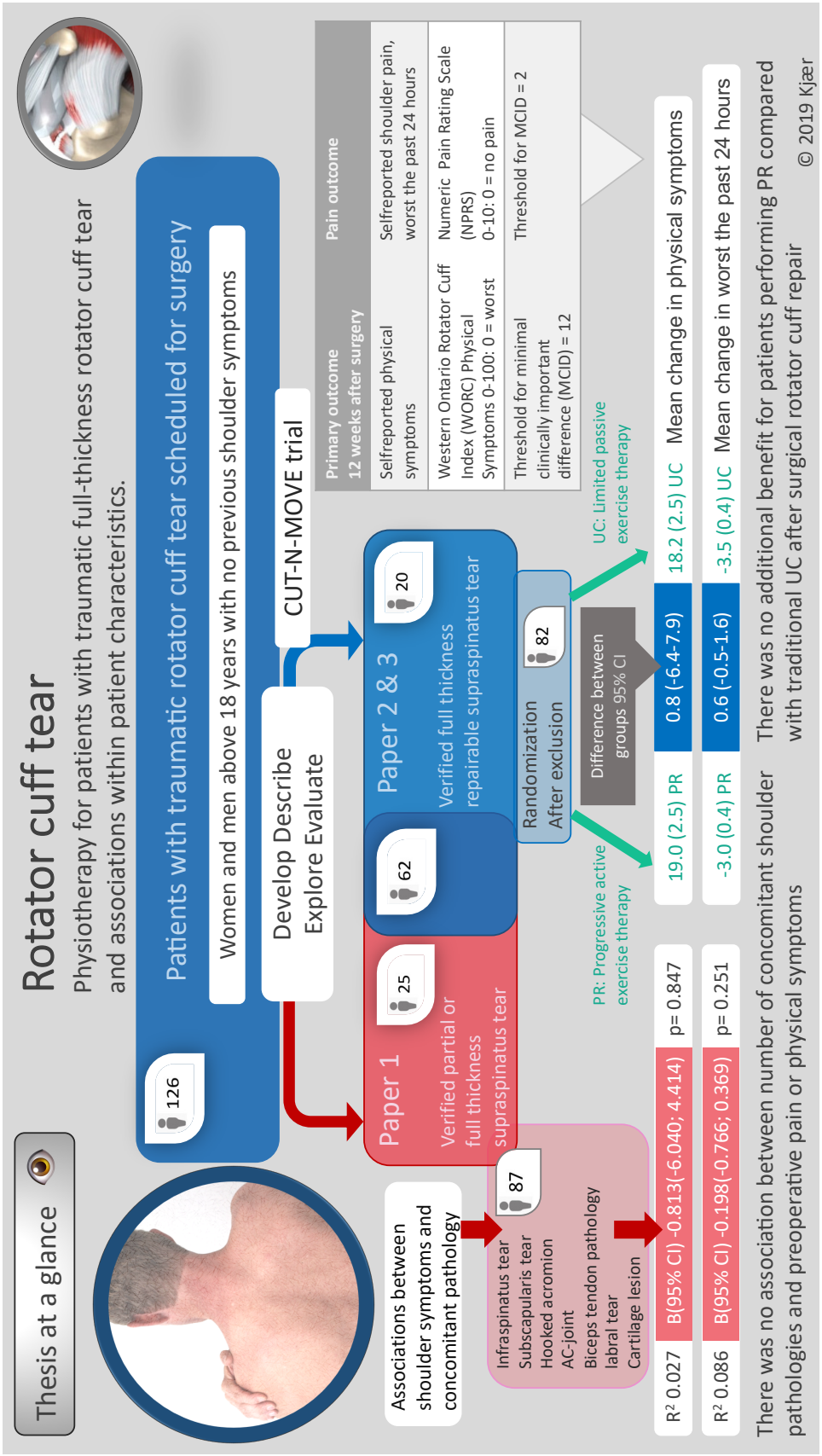
Paper 2: Hougs Kjær B, Magnusson SP, Warming S, Henriksen M, Krogsgaard MR, Juul-Kristensen B. Progressive early passive and active exercise therapy after surgical rotator cuff repair - study protocol for a randomized controlled trial (the CUT-N-MOVE trial). Trials. 2018 Sep 3;19(1):470. doi: 10.1186/s13063-018-2839-5.

Paper 3: Hougs Kjær B, Magnusson SP, Henriksen M, Warming S, Boyle E, Krogsgaard MR, Al-Hamdani A, Juul-Kristensen B. Effects of 12 weeks of progressive early active exercise therapy after surgical rotator cuff repair – primary results from the randomized controlled CUT-N-MOVE trial. Submitted to AJSM.

THESIS AT A GLANCE



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Paper 1

Study design	Birgitte Hougs Kjær, Marius Henriksen, Birgit Juul-Kristensen, Peter Magnusson, Michael Krogsgaard
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Manuscript writing	Birgitte Hougs Kjær
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Paper 3

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Abbreviations and terminology

ANCOVA	Analysis of COVAriance
AROM	Active Range of Motion
AAROM	Assisted Active Range of Motion
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CI	Confidence Intervals
CUT-N-MOVE	RCT focusing on moving shoulders following RC repair
DASH	Disability Arm Shoulder Hand
GRS	Global Rating Scale
ITT	Intention to Treat
MVC	Maximal isometric Voluntary Contraction
MCID	Minimal Clinical Important Difference
No	Number
NPRS	Numeric Pain Rating Scale
PROM	Patient Reported Outcome Measurement
HRQoL	Health Related Quality of Life
PP	Per Protocol
PR	Progressive Active Exercise Therapy
RC	Rotator Cuff
RCT	Randomized Controlled Clinical Trial
ROM	Range Of Movement
SD	Standard Deviation
SEM	Standard Error of Measurement
UC	Usual care (limited passive exercise therapy)
US	Ultrasound
VAS	Visual Analog Scale
WORC	Western Ontario Rotator Cuff Index
WORCPhysical	WORC Physical symptoms subdomain

Table of content

Summary (English)

Introduction: Rotator cuff tears are a frequent cause of shoulder disability and result in patients complaining of pain, loss of motion and strength. However, precise identification of patients eligible for surgical rotator cuff repair is a challenge to the clinicians, as the clinical presentation is highly variable and numerous injuries and pathologies often coexist. Further, the association between concomitant pathological characteristics and preoperative pain and disability has only sparsely been evaluated.
In addition, surgical repair of the traumatic full thickness rotator cuff tear followed by rehabilitation is a valuable procedure to improve shoulder function and decrease pain. Conventional postoperative rehabilitation protocols often vary considerably even in terms of basic content such as the length of immobilization, movement limitations and how early loading should be initiated. Therefore, the timing and loading of the postoperative rehabilitation strategy required to reach an optimal clinical outcome is still not fully uncovered. Early controlled and gradually increased tendon loading enhance tendon healing and recovery, but evidence regarding the combined effect of early and progressive postoperative exercises are lacking on this patient group.

Purpose: The overall purpose of this thesis was to extend our knowledge regarding shoulder symptoms and to contribute to the evidence regarding postoperative rehabilitation following rotator cuff repair. Specifically, the purpose was to explore the associations between pre-operative shoulder symptoms and additional structural pathology identified during surgery. Further, the purpose was to evaluate the effect of 12-week of progressive active exercise therapy on physical shoulder function, pain, and quality of life, compared with usual care that limits tendon loading in the early postoperative phase.

To accomplish this, three papers were completed. First, the cross-sectional study exploring the associations between pre-operative shoulder symptoms and structural pathology was planned. Secondly, a protocol for a randomized controlled trial (RCT) with stringent methodological criteria was developed and planned, and thirdly the RCT named (CUT-N-MOVE) was completed.

Methods:
In Paper 1, the cross-sectional study exploring the associations was planned to include patients with traumatic supraspinatus tears (partial and full thickness) awaiting rotator cuff surgery. Preoperatively, the patients reported pain using a 0-10 Numeric Pain Rating Scale (NPRS) and disability using the Western Ontario Rotator Cuff Index (WORC) Physical symptoms subdomain. During surgery the presence of prespecified structural injuries and pathologies, including full thickness or partial supraspinatus tear, infraspinatus tear, subscapularis tear, hooked acromion, AC-joint osteoarthritis, biceps tendon pathology, labral tear and cartilage lesions were recorded.
In Paper 2 the protocol for the pragmatic, randomized, controlled, outcome-assessor blinded, multicenter (three sites), superiority trial (CUT-N-MOVE), with a two-group paralleled design was prepared and described conforming to contemporary guidelines and checklists. Primary outcome measure was change from pre-surgery to 12 weeks post-surgery in the WORC Physical symptoms.

Secondary outcomes included change in WORC total and subdomains, Disabilities Arm, Shoulder and Hand questionnaire (DASH), pain (NPRS), range of motion, strength.
In Paper 3 the CUT-N-MOVE trial was completed, and the primary results presented. Patients with surgically repaired traumatic full-thickness rotator cuff tears were recruited from two orthopedic departments (three hospitals) in Denmark and randomized to either progressive early active exercise therapy (PR) or limited early passive exercise therapy (UC) (usual care).

Findings:
In the cross-sectional study eighty-seven patients (52 males; 60%) were included (mean age 60 years, SD 9.2). Sixty-nine (79%) had a full thickness supraspinatus tear; 18 (21%) had a partial thickness tear. Seventy-nine patients (91%) had concomitant structural pathology. There was no association between number of structural shoulder pathologies and preoperative NPRS or WORC, and no particular concomitant pathology was associated with worse patient-reported pain or disability.

In the CUT-N-MOVE trial a total of 82 patients were randomized to PR (n = 41) or UC (n = 41). All 82 patients (100%) participated in the 12-weeks follow-up assessment. Mean changes in the WORC Physical symptoms 12 weeks from baseline were 19.0 points (SE, 2.5) and 18.2 points (SE, 2.5) in the PR and UC groups, respectively; this corresponded to a statistically nonsignificant (adjusted model) between- group difference of 0.8 points (95% CI, -6.4-7.9; p = 0.834). Similar nonsignificant results were seen for the remaining subdomains in WORC and in DASH, pain, range of motion (ROM), and strength, except for a significant between-group difference in active scaption movement from baseline to 6 weeks, with a change of 13.8 degrees (95% CI, 0.2-27.4; p = 0.046). Both training groups had significant and clinically relevant improvements over time in WORC, pain, ROM, and strength. There was no difference in adverse events between groups (p= 0.295).

Conclusion:
In the cross-sectional study we concluded that pathology of infraspinatus and subscapularis and other structural joint pathologies in concomitance with supraspinatus tear were not associated with preoperative self-reported pain and disability in patients scheduled for rotator cuff surgery, suggesting that concomitant structural pathology adds only little to self-reported symptoms in patients with traumatic supraspinatus tear.

In the CUT-N-MOVE trial we conclude that there is no additional benefit for patients performing PR compared with traditional UC following surgical rotator cuff repair. Primary and secondary outcomes significantly improved at a clinically relevant level following rotator cuff repair, regardless of postoperative rehabilitation protocols. This finding suggests that shared decision making between patients and therapists, based on preferences, can safely be performed to ensure improved patient reported and measured outcome, off course within the multidisciplinary framework and compliant to clinical guidelines.

Dansk resumé

Baggrund
Rotator cuff (RC) overrivning er en hyppig års til skuldergener som resulterer i at patienterne klager over smerter, nedsat bevægelighed og nedsat styrke. Det er dog en udfordring for klinikere præcist at identificere de patienter der er egner sig til kirurgisk reparation af sene-overrivningen. Det skyldes at patienterne ofte kan have skader i flere strukturer. Desuden er en mulig sammenhæng mellem antal af skadede strukturer og de præoperative gener og smerter kun blevet sparsomt belyst. Kirurgisk reparation af en traumatisk baseret total RC overrivning efterfulgt af genoptræning er et værdifuldt redskab til at forbedre skulderfunktion og reducere smerter. Traditionelle postoperative genoptræningsprotokoller varierer ofte betydeligt selv med hensyn til grundlæggende indhold såsom varigheden af immobilisering, bevægerestriktioner og hvor tidligt man kan begynde at belaste vævet. Derfor er det stadigvæk ikke helt afdækket, hvilken timing og belastningsstrategi man skal bruge for at opnå det bedste kliniske resultat. Tidlig kontrolleret og gradvis øgning af belastningen fremmer sene helingen men der mangler evidens for hvilken effekt kombineret tidlig og progressiv genoptræning har på denne patientgruppe.

Formål
Det overordnede formål med denne afhandling er at øge vores viden om skuldersymptomer og bidrage til evidensen for genoptræning efter RC-operation. Mere konkret er formålet at undersøge sammenhængen mellem præoperative skuldersymptomer og antallet af skadede strukturer fundet under operationen. Formålet er også at evaluere effekten af 12 ugers progressiv aktiv genoptræning (PR) på skulderfunktion, smerte og livskvalitet sammenlignet med vanlig genoptræning (UC) der begrænser sene belastningen i den tidlige postoperative fase.

Metode
Afhandlingen er baseret på tre studier.
Studie 1 omfatter et tværsnitsstudie der undersøger sammenhængen mellem skuldersymptomer og skadede strukturer hos patienter der venter på operation efter traumatisk overrivning af supraspinatussenen. Præoperativt rapporterede patienterne smerte på en numerisk smerteskala, NPRS og dysfunktion på et sygdomsspecifikt spørgeskema, WORC. Under operationen blev antallet af skadede strukturer registreret, herunder delvis eller total supraspinatussene overrivning, infraspinatus- og subscapularis overrivning, kroget akromion, artrose i AC-leddet, bicepssene-, ledlæbe- og bruskskade.
I studie 2 er protokollen for det pragmatiske, randomiserede, kontrollerede, blindede, multicenter studie (CUT-N-MOVE) forberedt og beskrevet i henhold til aktuelle retningslinjer og tjeklister. Det primære effektmål er ændringen i WORCs (fysiske symptomer) fra før til 12 uger efter operation. De sekundære effektmål er den samlede WORC samt DASH, smerte, bevægelighed og muskelstyrke.
I studie 3 præsenteres de primære resultater fra den gennemførte CUT-N-MOVE-undersøgelse. Patienter opereret for total traumatisk overrivning af RC er rekrutteret fra ortopædkirurgiske afdelinger på tre af Region Hovedstadens hospitaler og randomiseret til enten PR eller UC.

Resultater
I tværsnitsstudiet inkluderede vi 87 patienter (52 mænd; 60%) med gennemsnitsalder på 60 år. 69 (79%) havde en total overrivning af supraspinatussenen; 18 (21%) havde en delvis overrivning af supraspinatussenen. 79 (91%) af patienterne havde yderligere skadede strukturer. Der var ingen sammenhæng mellem antal af skadede strukturer og de præoperative gener (WORC) og smerter (NPRS), og ingen bestemt skade gav forværring af skuldersymptomerne.

I CUT-N-MOVE-studiet inkluderede vi 82 patienter, som blev randomiserede til 41 i PR-gruppen og 41 i UC-gruppen. Alle 82 patienter deltog i 12-ugers undersøgelsen. Begge træningsgrupper havde signifikante og klinisk relevante forbedringer i WORC, smerte, bevægelighed og muskelstyrke fra baseline til 12 uger efter operationen, men der var ikke forskel mellem grupperne. Vi fandt heller ikke gruppeforskelle i de sekundære effektmål (den samlede WORC, DASH, smerte, bevægelighed og muskelstyrke), bortset fra en signifikant gruppe-forskel i aktivt løft af armen fra baseline til 6 uger efter operationen. Der var ingen gruppeforskel i antal af bivirkninger.

Konklusion
I tværsnitsstudiet kan vi konkludere, at der ikke var sammenhæng mellem de præoperative symptomer og forekomsten af patologi i infraspinatus, subscapularis eller andre strukturelle led patologier hos patienter der ventede på operation efter traumatisk overrivning af supraspinatussenen. Studiet antyder at forekomsten af andre skadede strukturer ikke bidrager nævneværdigt til de symptomer patienter med traumatisk overrivning af supraspinatussenen har.

I CUT-N-MOVE-studiet kan vi konkludere, at det ikke er nogen ekstra fordel for patienter at genoptræne i PR-gruppen sammenlignet med den traditionelle UC-gruppe. Primære og sekundære effektmål havde klinisk relevante forbedringer efter RC-operation uanset træningsgruppe. Disse fund antyder, at fysioterapeuter og patienter trygt kan samarbejde om hvilke træningspræferencer patienten måtte have indenfor de tværfaglige rammer af den superviserede genoptræning og i overensstemmelse med kliniske retningslinjer.

Introduction/ background

Prevalence and incidence shoulder injuries and rotator cuff tears

Shoulder disorders are the third most common musculoskeletal disorder with a life-time prevalence in the general population of 30% (1). The incidence of shoulder disorders in general practice has been reported to be as high as 11.2/1000 patients per year (2), and in addition, they are often persistent and recurrent, with 54% of the patients reporting on-going symptoms after 3 years (3). Specifically rotator cuff (RC) tears are considered one of the principal causes of shoulder complaints, particularly with advancing age (1, 4). The prevalence of RC tears in the general population is 11-13% for people in their 50s increasing to 37-50% for those in their 80s (5, 6). The National Patient Register in Denmark has registered 730 RC repairs in 2006 and 990 in 2012, representing a 35% increase (7). Likewise, an increasing number with more than 75,000 repairs are performed annually in United States (8).

Rotator Cuff tear

RC tear is defined as a rupture of the tendon (s) of the shoulder, and most frequently the supraspinatus and the infraspinatus tendon are involved (9) (Figure 1), which may result in tissue weakness (10). RC tears arise primarily due to trauma or degeneration (11). A traumatic RC tear is defined by "an acute tear in patients who were previously asymptomatic and experience a sudden onset of symptoms and signs following a traumatic event, e.g. fall or trauma to an abducted, externally rotated arm" (12). Traumatic RC tears occur largely in male patients with an average age of 55 years who suffer a fall or trauma (13).

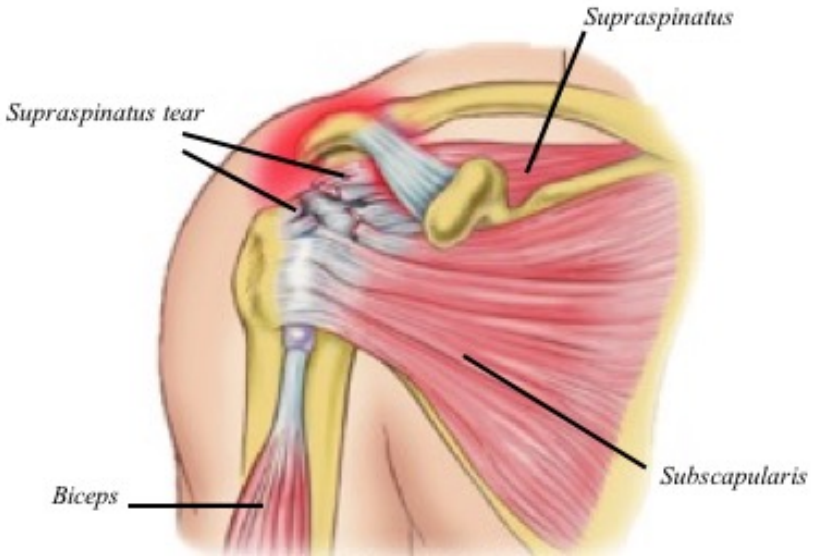


Figure 1 Anterior view of right shoulder

Anatomy and Biomechanics of the rotator cuff

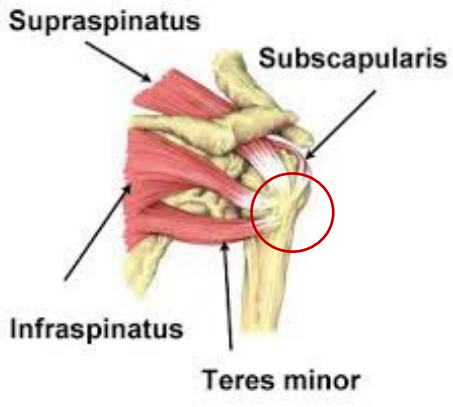


Figure 2 The rotator cuff

Four muscles constitute the RC (14): 1)The supraspinatus which originates from the supraspinous fossa of the scapula, where its tendon passes through the subscapular space and inserts on the superior and middle facets of the greater tuberosity (Figure 2). The 2)infraspinatus and 3)teres minor both originate from the infraspinous fossa and fibrous septum, and their tendons insert on the middle and inferior facets of the greater tuberosity, respectively. 4)The subscapularis originates from the subscapular fossa, and its tendon inserts on the lesser tuberosity. The humeral head is covered by the RC since its tendons unite to form a continuous structure near their insertions. The RC (tendons and muscles) creates a force couple around the glenohumeral (GH) joint, with coordinated activation and inactivation of agonist and antagonist muscles and provides balanced forces that impact mobility and stability to the GH joint. Disruption of this muscle force couple results in impaired/ abnormal joint kinematics, as the stable fulcrum for rotation of the humeral head in the glenoid is impaired (15). The description of an anatomic footprint has aided in diagnosing and repairing RC tears to the tendon-to-bone insertion site (the anatomic footprint) (Figure 2 & 3D, red circle) (16).

Symptoms and clinical evaluation of rotator cuff tear

Not all RC tears produce symptoms and the prevalence of asymptomatic RC tears is relatively high in elderly people (4, 17-19). Thus, 50% of all tears in the fifth decade are symptomatic, although this decreases with advancing age (5, 6). Only symptomatic RC tears are relevant clinically, and the predominant complaints among the patients are pain and loss of strength during arm elevation resulting in

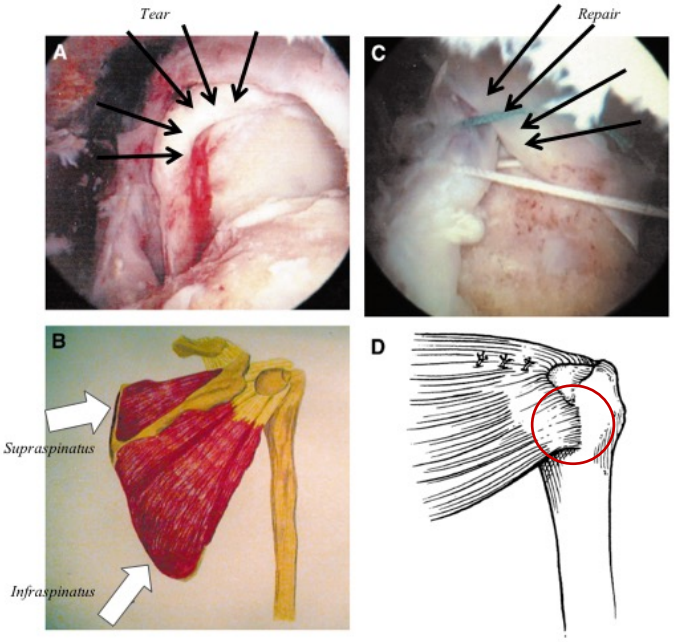


Figure 3 Large U-shape RC-tear and repair (Burkhart 2001)

functional disability (2, 10). If there is suspicion of an RC tear during the clinical shoulder examination (clinical tests: Painful arc, Jobe's test, Neer's test, Hawkin's test), then magnetic resonance imaging (MRI) or ultrasound (US) investigations will be requested. The clinical shoulder tests are reported to have poor to fair clinimetric properties (20) and insufficient diagnostic precision (21), and they are therefore typically supplemented by MRI (Figure 4) or US (Figure 5) with higher sensitivity and specificity, corresponding to above 90% (22). Further information about surgical indication: see below in section: Surgical treatment (surgical indication).

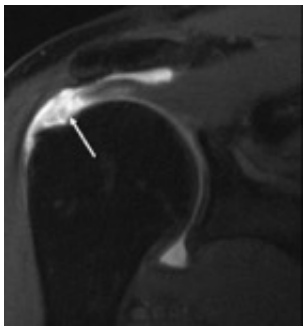


Figure 4 MRI of RC-tear

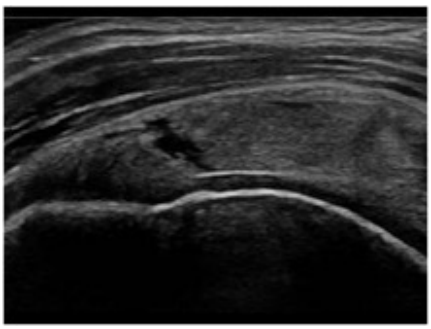


Figure 2 Ultrasound of RC-tear

Observations performed during surgery combined with US and MRI examinations have shown that several injuries/pathologies in the shoulder often coexist/ coincide with the RC tears (23, 24). In traumatic RC tears such injured structures may include biceps pathology (e.g. SLAP lesion), labral tear and cartilage lesions, and pathologies may include hooked acromion and acromioclavicular (AC) joint pathology (25, 26). But to which extent pre-operative shoulder symptoms are influenced by these concomitant injuries/pathologies in patients with a traumatic RC tear is unclear (13). Previous studies on both traumatic and non-traumatic RC tears have shown opposing results, as some studies found associations between pre-operative shoulder symptoms and tear size, biceps pathology and fatty degeneration (27, 28), while other studies did not find associations between pre-operative symptoms and tear size, biceps pathology and presence of bursitis (29-31). None of these studies have studied associations between the concomitant pathologies/injuries of acromion, AC-joint, labrum or cartilage lesions and pre-operative shoulder symptoms. This means that prognosis based on either preoperative shoulder symptoms or operative findings of concomitant pathologies is challenged.

In summary, there is a need to study whether an association between preoperative shoulder symptoms and concomitant structural pathologies exist in patients undergoing surgical RC repair, as this information is important in estimating treatment prognosis.

Outcome assessment tools

It is important and necessary to apply valid and reliable shoulder specific assessment tools that are responsive to the change in the patient perceived symptoms and physical function, both for clinical purposes and in research. However, it is a challenge because a large number of available assessment tools exists (32, 33). Responsiveness and minimal clinical important difference (MCID) are important aspects of any outcome measure. Responsiveness refers to the validity of changes in scores and is defined as the ability of a measurement tool to detect change over time in the construct being measured (34). MCID refers to interpretability of changes in scores and is defined as the smallest change in a score that a patient perceives as important. An outcome measure that is more responsive than others will be preferred as it may more accurately detect changes over time.

Two commonly used patient reported outcome measures after shoulder surgery are the Western Ontario Rotator Cuff Index (WORC) and the Disability Arm, Shoulder and Hand (DASH) (35, 36). The WORC is a disease-specific questionnaire developed to measure pain, functional activity level and health related quality of life (HRQoL) in patients with RC-disease (35, 37). WORC has demonstrated reliability, validity and responsiveness to detect group differences in evaluation of patients having elective RC surgery and non-surgical treatment in patients with RC-disease (37, 38). The DASH is a semi-generic upper extremity questionnaire also measuring pain, functional activity level and HRQoL, and the DASH has demonstrated validity and responsiveness and in both proximal and distal disorders, confirming its usefulness across the whole extremity (36, 39, 40). Objective outcomes such as measurements of joint ROM and muscle strength may be useful for more exploratory analyses (41), and for monitoring physiological outcomes related to the rehabilitation.

Treatments of RC tears

Non-surgical treatment

In an attempt to relieve pain and restore movement and function of the shoulder, patients with non-traumatic full-thickness or partial (traumatic and non-traumatic) RC-tears are recommended non-operative treatment as first line of treatment. This may consist of a combination of pain management (medications and cortisone injections), rest from activity, besides passive and active exercises (physiotherapy) (42-44). Failing 6 weeks to 3 months of non-operative treatment, surgical repair may be performed (45).

Surgical treatment (surgical indication)

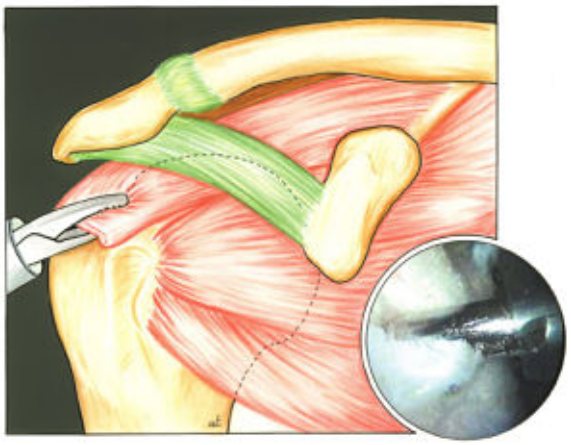


Figure 6 Surgical repair

Early surgical repair using open, mini-open, or arthroscopic approach (7, 46, 47) of traumatic RC tears is recommended in full-thickness tears, or partial-thickness tears extending greater than 50% of the transversal or longitudinal tendon size (Figure 6) (25, 48, 49). However, surgical repair is only recommended if the patient presents with pain and loss of arm elevation strength resulting in functional disability (see section: Symptoms and clinical evaluation of rotator cuff tear) (9). The rationale for early surgery is to preserve tissue quality and mobility while minimizing tear progression and retraction, in order to optimize functional outcomes and structural healing of the affected tendon (50-52). Human autopsy studies have indicated that the tendon, with an appropriate cuff repair, will regain its ability to transmit almost the same amount of force as an intact tendon, while an inappropriate repair most often will retract its tendon-muscle unit, resulting in different levels of shoulder disability (48, 51).

Postoperative therapy/ rehabilitation

The primary goal of postoperative therapy/ rehabilitation following RC-repair is restoration of upper extremity function including regaining joint range of motion (ROM), shoulder function and muscular strength, with sufficient time for tendon healing (53). A further purpose of postoperative therapy/ rehabilitation is specifically to reduce pain, avoid shoulder stiffness and muscle atrophy, and to prevent re-tear of the repaired site.

The postoperative therapy/ rehabilitation can be divided into five overlapping periods. These include an 1) immobilization period for tendon protection, 2) a protected passive range of motion (PROM) period, 3) an assisted active range of motion (AAROM) period, 4) an active range of motion (AROM) period and 5) a strengthening period (Figure 7).

The timing of those overlapping periods for rehabilitation is based on the evidence from basic science, including cadaver studies of biomechanical and biological tendon healing capacity showing a slow metabolic turnover of tendon tissue (51, 54), besides dividing healing into three phases (Figure 8) (55, 56). In addition, it has been shown that collagen being stressed (loaded) regains

formation and tensile strength faster than unstressed collagen (57), and that duration until full strength varies between 12 and 26 months (58).

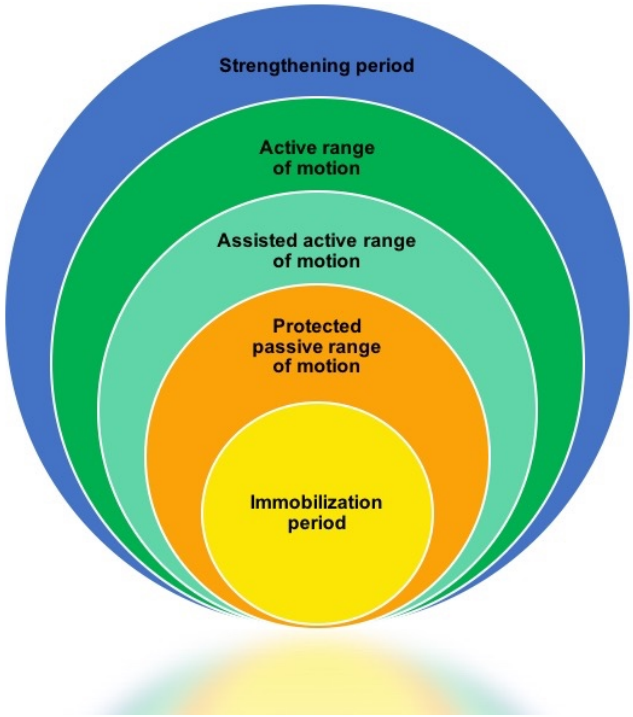


Figure 7 Five overlapping periods in rehabilitation after RC repair

While evidence is relatively good (basic science and in vivo human studies) for training principles in the first 3 periods (immobilization period for tendon protection, protected passive range of motion (PROM) period, and assisted active range of motion (AAROM) period), the evidence for training in the last 2 periods, (active range of motion (AROM), strengthening) however, is limited and mostly based on animal studies. Evidence for each of the 5 periods is described in the following.

1) Immobilization period for tendon protection

Considering basic science stating that loading the collagen increases tendon healing (57), postoperative unloading, as in immobilization (Figure 9), may reduce possibilities for optimal tendon healing (59-61), resulting in increased risk of re-tear (53, 62, 63).

In addition, immobilization may unfortunately result in increased adhesion development and decreased ROM (64, 65), but it may result in a stronger tendon-bone complex, with less scar tissue and a more organized tendon-bone interface compared with any loading regime (66).

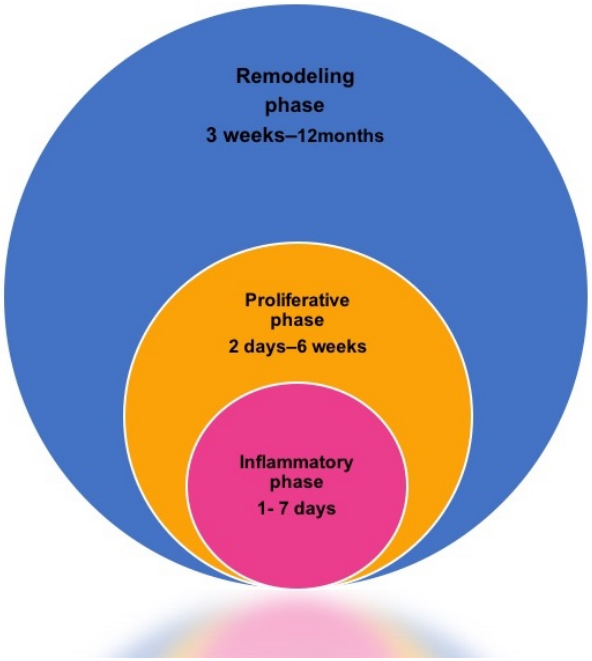


Figure 8 Phases of tendon healing after rupture and repair (Kannus 1997)

Figure 9 Sling immobilization

The biomechanical knowledge from animal and cadaver studies is supported by a systematic review with meta-analysis including three primary studies, concluding that immobilization does not increase possibilities for tendon healing (67-70). It is further reported that the negative impacts of early postoperative immobilization are unavoidable, and that increased stiffness and adhesion development will compromise short-term functional results. However, as stiffness is mostly transitory it does not often persist in the long-term follow-up (61, 69). Thus an early period of maximum 4 to 6 weeks of immobilization has been recommended to avoid gap formation negatively affecting tendon-to-bone healing, and to allow the optimal tendon-bone healing process (Figure 9) (54, 60, 61).

2) Protected passive ROM period

According to biomechanical studies it is recommended to perform continuous passive ROM already during the early postoperative (immobilization) period, as it has been shown to enhance type III collagen synthesis at the tendon-to-bone interface in rabbits (71).

Also in patients, early protected ROM (Figure 7) of the shoulder has previously been reported beneficial following RC repair on small, medium and large RC tears (measured on Shoulder Pain and Disability Index; SPADI) (65), and was further shown to prevent excessive stiffness in patients (72). Recent systematic reviews have also reported significantly improved range of motion at 3 to 6 months and at 12-month follow-up when using early passive ROM postoperatively compared with a delayed rehabilitation (67, 73-76). However, this does not translate into clinically important selfreported functional outcomes (74). Anyhow, four of the five existing primary studies (low-moderate quality RCT´s), are pointing in the direction of no advantage of early passive ROM intervention compared with immobilization (68, 70, 77, 78), and one study found a statistically superior (but not clinically relevant) effect of early passive ROM intervention versus immobilization (69).

Regarding repair integrity, it has previously been anticipated that early passive ROM postoperatively would lead to increased re-tear rate, however, none of the five aforementioned primary studies regarding early passive ROM have reported such increased risk of re-tear (68-70, 77, 78). Likewise, several recent meta-analyses concerning early passive ROM exercises did not show an increased risk of re-tear compared to delayed passive ROM (67, 74-76, 79, 80), also when including patients with tears > 5 centimeters (74, 81, 82).

3) Assisted active range of motion (AAROM)

Progressing from passive to active exercises provides a controlled and gradually increased tendon loading, and with several rest and immobilization periods it is anticipated to lead to optimal tendon healing (83). Time wise, it will include commencement into the proliferative phase (4-12 weeks) of healing, and later (after 12 weeks) into the remodeling phase (Figure 8) (57). Progression from passive to active exercises as described in the biomechanical studies may often be implemented in practice by assisted active range of motion (AAROM) exercises (Figure 7). This includes that the operated arm is typically supported by the healthy arm or given exercises in closed chain (distal support) principles. Two small studies (one RCT and one randomized pilot-study) actually showed this more proactive and progressive physiotherapy regime to be associated with slightly faster recovery, but only in the short term (84, 85).

4) Active range of motion (AROM) period and 5) Strengthening period

Animal studies on ligament-to-bone healing, and tendon healing suggest that submaximal mechanical loading may lead to better overall healing response than unloading, and this thereby provides theoretical support for early active ROM after RC repair (66, 86). In progressing the training by increasing load on the shoulder it has further been recommended to combine close and open chain AROM exercises (Figure 7) in different starting positions (84, 85). However, in summary due to the few, small RCT´s or uncontrolled studies there is lack of consensus regarding the proper timing and progression of load during Active ROM after RC repair. This seems necessary to know in order to be able to balance the risk of structural failure (when using too early AROM), with an increased risk of stiffness (when using delayed ROM) (87).

Postoperative rehabilitation protocols do not focus on recovery of strength until adequate tendon-to-bone healing is obtained and the majority of glenohumeral ROM is recovered (88). Appropriate timing of further loading of the tendon, as in strengthening, is important to remember that tendon

healing processes (the remodeling phase) continue until at least one year postoperatively depending on tendon loading (Figure 8) (16). Shoulder strength measured by dynamometer is typically lower at 3 months postoperatively compared with preoperative strength, increasing to preoperative level around 6 months postoperatively, and even 24 months postoperatively the shoulder strength (elevation and external rotation) remain less than that of the contralateral healthy shoulder in most patients (89, 90).

Accumulation of evidence for postoperative physiotherapy

In summary, the evidence regarding timing and loading following RC repair, and the overall rational for progression through the overlapping rehabilitation periods, is largely based on animal models on tendon healing and on few clinical studies with a high risk of bias not fulfilling essential components (73, 82).

It means that there is lack of consensus for humans and thereby patients, on proper timing and particularly loading in rehabilitation following RC repair which can also be seen in the large volume of systematic reviews and meta-analyses published within the past 5 years including almost the same few above mentioned RCT-studies. The most recent systematic reviews from 2018 and 2019 conclude that more Level 1 evidence including high quality adequately powered rehabilitation trials, evaluating patient reported outcomes and biomechanical effects are required (73, 82).

Study premises

In order to increase estimations of prognosis for patients diagnosed with traumatic RC tear, the following was defined:

- ⇒ Investigate/ analyze associations between preoperative shoulder symptoms and concomitant structural pathologies.

In order to contribute substantially to the above described knowledge gap the following premises for a study evaluating the effects of progressive early active exercise therapy were defined:

- ⇒ Methodological high quality RCT including adequate outcome assessor blinding, blinded analyses based on a priori defined analysis plan.
- ⇒ Transparent and detailed description of specific tailored interventions to enhance future implementation for clinicians and to allow comparisons with other studies.
- ⇒ Comparison with an active control group treated with clinically relevant exercises.

⇒ Evaluation using disease specific patient reported outcomes supported by additional specific objective outcomes.

The papers included in this thesis therefore aim to fulfil these aspects.

Aims of the thesis

In the specific population of patients with traumatic RC tears the aims of the thesis were to:

I. Explore associations between shoulder symptoms and concomitant pathology
    a. Explore associations between preoperative patient symptoms and total number of concomitant pathologies?
    b. Examine the influence of number of structural shoulder pathologies (categorized in 3 levels) on preoperative patient symptoms
    c. Analyze whether one particular concomitant pathology was associated with worse preoperative patient symptoms

II. Develop and describe a study protocol of progressive early active exercise therapy in a randomized controlled trial

III. Evaluate the effects of 12 weeks of progressive early active exercise therapy compared with usual care in a randomized controlled trial

Hypotheses in the thesis

In the population of patients with traumatic RC tears it was hypothesized that preoperative shoulder pain and disability was positively associated with the number of concomitant structural pathologies present in patients with supraspinatus tear.

Further, on the basis of the limited evidence regarding the postoperative rehabilitation, we hypothesized that patients who receive progressive active exercise therapy (PR) from day 8 would benefit more with respect to improved shoulder function, pain reduction, and quality of life than those receiving passive exercise therapy (UC) (‘usual care’) from day 8.

Methods

In this section the methods of the individual studies are presented. For further details, see the method sections of the appended papers. An overview of the timing of studies and included populations in the two studies is presented in Figure 10. The data collection for the Paper 1 (Associations-study) was performed concurrent to running the Paper 2 & 3 (RCT-study), and thus a part of the population was included in both study 1 and 3.

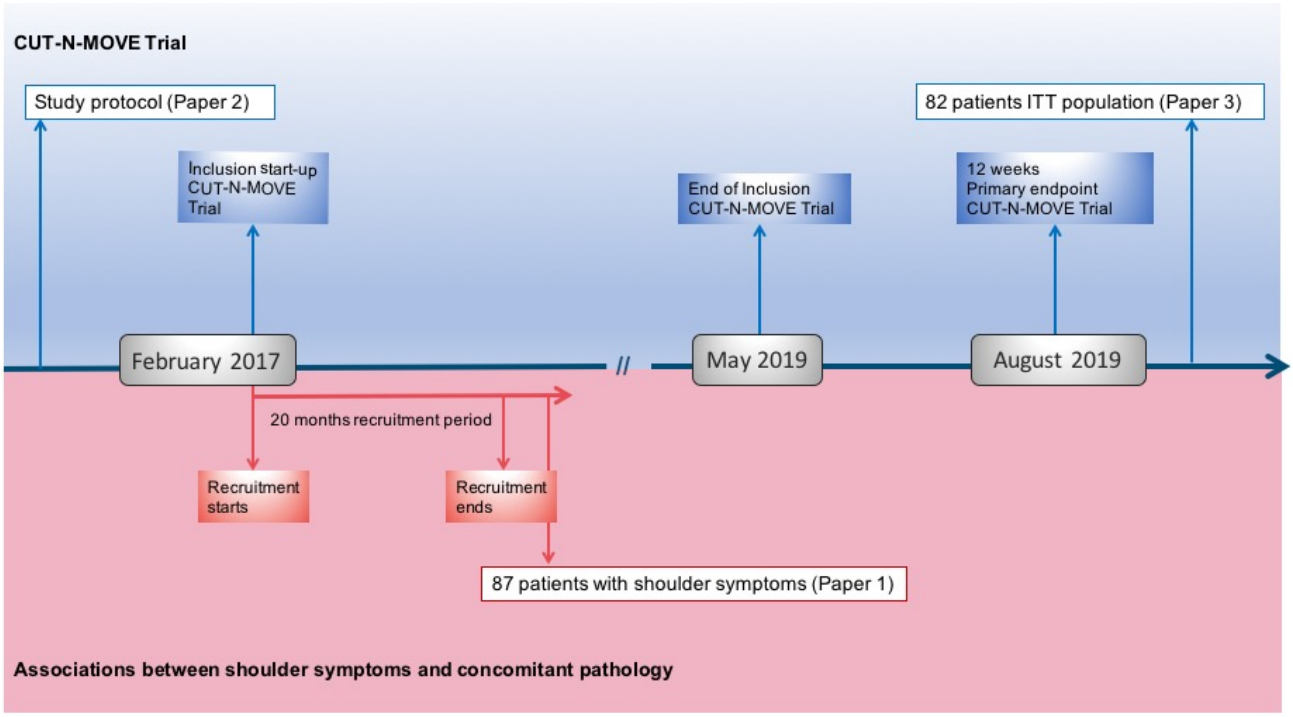


Figure 10. Overview of timing of studies and included number of populations

Ethics

The Paper 1 (Associations-study) used data collected as part of the RCT-study (including obtaining surgery information) and did therefore not require additional approval by committee on biomedical research ethics or informed consent.

The Paper 2 & 3 (RCT-study) was approved by Health Research Study Board for the Capital Region Denmark (H-16033995) on the 18 October 2016 and by the Danish Data Protection Agency (2012-58-0004) on the 15 February 2017, and the study was registered in Clinical Trial (www.clinicaltrials.gov, NCT02969135) on the 15 November 2016. The study was conducted in accordance with Danish law, the local research ethics committee requirements and the principles of

the Declaration of Helsinki (91). Informed consent was obtained from all patients. All data was handled in confidence according to the Danish Data Protection Act.

Study design

Paper 1

Paper 1 was a cross-sectional study (92), and as illustrated in Figure 10 it was a secondary analysis of data collected as part of the RCT-study (93).

Paper 2 & 3

The study was designed as a multicenter, randomized, controlled, outcome assessor blinded, superiority trial, called CUT-N-MOVE, with a two-group parallel design comparing a progressive rehabilitation (PR) strategy with usual care (UC). Primary endpoint was 12-week post intervention. Paper 2 describes details on the trial protocol (93).

The protocol conforms to the recommendations of the Enhancing the Quality and Transparency Of health Research (EQUATOR) network (94) using the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist, the Consolidating Standards of Reporting Trials (CONSORT) statement (93, 95), the two checklist for reporting aspects of the exercise interventions: the Template for Intervention Description and Replication (TIDieR) (96), and the Consensus on Exercise Reporting Template (CERT) (97).

Participants, settings and data collection

Paper 1

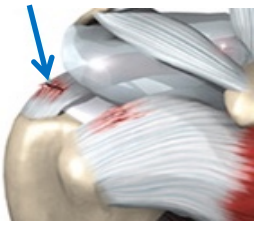
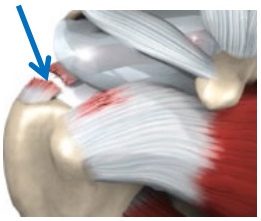
Data was collected from participants that met the preoperative inclusion in the RCT-study, and with an arthroscopically verified partial or full thickness supraspinatus tear. Eligibility criteria for patients in paper 1 are listed in Table 1. The recruitment period was the first 20 months of inclusion for the RCT (Figure 10).

Paper 2 & 3

Between March 2017 and May 2019 participants were recruited from two Orthopedic Departments in the Capital Region of Denmark; the Section for Sports Traumatology, Department of Orthopedic

Surgery Copenhagen University Hospital, Bispebjerg and Frederiksberg and from The Shoulder-Elbow Unit, Copenhagen University Hospital, Herlev and Gentofte. Eligibility criteria for patients are listed in Table 1. To include a less heterogenous population and to strictly follow the national guidelines we decided to only include patients with full thickness supraspinatus tear in the RCT-study.

Table 1 Eligibility criteria for patients included in Paper 1, 2 & 3

	Inclusion criteria Paper 1	Inclusion criteria Paper 2 & 3
Anamnesis	Women and men above 18 years with no previous shoulder symptoms who experienced a traumatic event defined by "a sudden onset of symptoms and signs following the specific traumatic event" generating suspicion of a full thickness supraspinatus tear Scheduled for surgical RC repair	Women and men above 18 years with no previous shoulder symptoms who experienced a traumatic event defined by "a sudden onset of symptoms and signs following the specific traumatic event" generating suspicion of a full thickness supraspinatus tear Scheduled for surgical RC repair (The trauma could comprise a forced abduction and external rotation; mitigate for a fall; a fall on the outstretched arm; a pull in the arm or a shoulder luxation)
Clinical examination	Present with reduced arm elevation strength and pain Further generating suspicion of a full thickness supraspinatus tear	Present with reduced arm elevation strength and pain Further generating suspicion of a full thickness supraspinatus tear
Radiological examination	Ultrasound or MRI verified full thickness supraspinatus tear	Ultrasound or MRI verified full thickness supraspinatus tear
Surgery	*Verified partial or full thickness supraspinatus* tear* 	*Verified full thickness supraspinatus tear** 
	Exclusion criteria Paper !	**Exclusion criteria Paper 2 & 3**
Anamnesis	No history of trauma Prior shoulder surgery (incl. ipsilateral gleno-humeral joint, AC-joint, thoraco-scapular joint) Glenohumeral osteoarthritis (OA), rheumatoid arthritis or periarthrosis Inability to speak or read Danish	No history of trauma Prior shoulder surgery (incl. ipsilateral gleno-humeral joint, AC-joint, thoraco-scapular joint) Glenohumeral osteoarthritis (OA), rheumatoid arthritis or periarthrosis Inability to speak or read Danish *Inability to perform the physical training**
Surgery	Isolated teres minor or subscapularis tear	Isolated teres minor or subscapularis tear *Not repairable supraspinatus tear** *Partial thickness/ width tear**

*Criteria written in Italic style marked * illustrates differences in in-/exclusion criteria between groups*

Procedure

Paper 1, 2 & 3

Orthopaedic surgeons performed the initial screening and referred patients awaiting surgery to the principal investigator, who performed the final eligibility assessment, provided the patient with detailed information about the study and asked for consent to participate in the study. After obtaining written consent the primary investigator (or two outcome assessors) performed all baseline and follow-up assessments. Before starting the data collection, the assessors and the primary investigator decided on a consensus standard for collection and recording of all outcome variables. Paper 1 only includes data from baseline measurements and information from the surgery, while Paper 2 is the scientific documentation for the RCT-study in Paper 3, and Paper 3 includes data on baseline as well as follow up measurements. Demographic characteristics and patient reported shoulder pain and disability were collected at baseline.

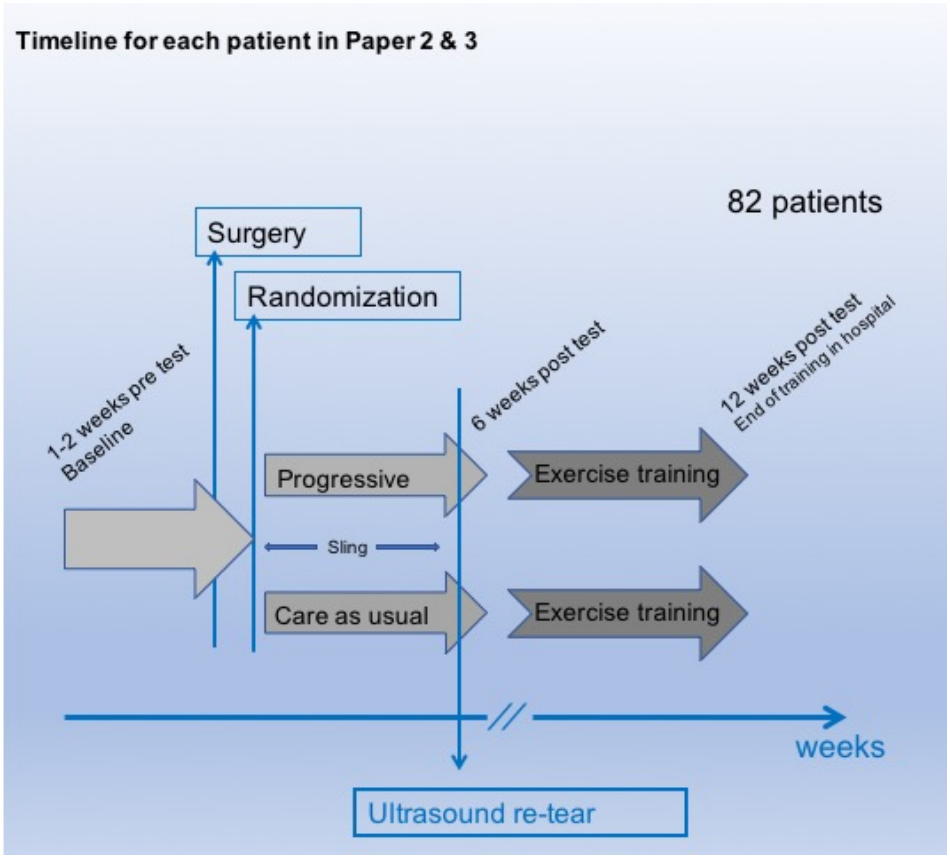


Figure 11 Timeline for each patient in Paper 2 & 3

After the operation the orthopaedic surgeon described the structural pathologies or concomitant injuries of the shoulder identified during arthroscopy using a prespecified list (defined by surgeons).

Patient reported outcomes and information from surgery reports were collected using the Procordo Research Platform, which is an electronic online Data Trial Management System (DTMS) (www.procordo.com).

The procedure during each outcome assessment was similar: The patients answered the questions about pain and disability in a web-based survey form, and the objective assessments were performed whereupon the outcome assessor manually entered data from the objective assessments (Figure 6). After the operation the orthopedic surgeon further provided information to verify a repairable total/full-thickness supraspinatus tendon tear (Paper 3), and participants were finally included in the RCT and electronically randomized as depicted in Figure 11.

Postoperative rehabilitation interventions

Paper 2

Based on a systematic review of the literature and workshops with clinical physiotherapists, a postoperative rehabilitation (exercise therapy) intervention was designed to address patients with surgically repaired RC-tears.

A systematic review of the literature was performed searching the following databases electronically up to December 2015: PubMed/ MEDLINE, EMBASE, CINAHL and Pedro. The following MeSH terms and key words were used: shoulder pain, shoulder, immobilization, postoperative, remobilization, repair, rehabilitation, physiotherapy, physical therapy modalities, physical therapy, exercise, training, surgery, arthroscopy, strain, sprain, rupture, lesion, tear(s), supraspinatus tendon(s), tendon(s) and rotator cuff, rotator, cuff, clinical trial, randomized controlled trial, randomised controlled trial, systematic review. Data on study demographics, methodology and features of exercise protocols were extracted and placed in table form separately for clinical trials, systematic reviews and electromyographic analyses of shoulder muscle activities respectively.

The principal investigator collaborated with two clinical physiotherapists specialized in orthopedic shoulder rehabilitation and neuromuscular training aspects in the development of the exercise therapy intervention. Physiotherapists from the other University Hospital (Herlev-Gentofte) were invited to participate in a series of four workshops (February to November 2016). At the first workshop, the panel members were, by the principal investigator, presented with an overview of the best evidence from reviewing the literature including eight systematic reviews published in 2014 and 2015 and components of previous exercise protocols (Paper 2, additional file 1). Input from the

panel of clinicians (expert panel) was collected by the principal investigator and a group consensus technique with feedback between the workshops was completed (98). A detailed record of each step was sent out to the panel members before each workshop summarizing the two protocols (PR and UC) focusing on an intentional discrepancy between interventions for use in the RCT-study. The principal investigator synthesized the results from the workshops into a standardized rehabilitation intervention. The two standardized rehabilitation interventions were reviewed and approved by an orthopedic surgeon (MK) and subsequently presented to a group of patients in the process of rehabilitation following RC-tear, and their feedback resulted in small adjustments. Finally, the detailed and illustrated manual for physiotherapists was developed including criteria for the two separate protocol-progressions depicted in dotsheets for both on-site and home training (Figure 12 & 13) and (Paper 2, additional file 1 and 2). In addition, a home training exercise pamphlet including logbook for the patients was compiled.

The rehabilitation intervention included shoulder-specific exercises progressed through different phases as defined by levels of shoulder function, as described in the introduction (93). Examples of progression of flexion, external rotation, and scapula -exercises are depicted in Figure 14. The comprehensive detailed descriptions of all on-site and home exercises are found in Paper 2, additional file 1 and 2.

Paper 2 & 3

The 12-weeks postoperative interventions were conducted at the local physiotherapy departments by 10 physiotherapists trained in orthopaedic rehabilitation. An overview of the differences in the postoperative interventions is illustrated in Table 2. The PR group started loading (assisted active range of motion (AAROM) and active range of motion (AROM)) at week 2 (Figure 12), while this was introduced in the UC group at week 6 (Figure 13). The PR group attended individual physiotherapist-supervised exercise therapy three times weekly, supplemented with recommended daily home exercises (week 2, 3, 4 and 5), and the UC group attended individual physiotherapist-supervised exercise therapy once a week supplemented by recommended daily home exercises (week 2, 3, 4 and 5). From week 6 to 12 both groups received the same type of physiotherapist-supervised exercise therapy twice a week (individually or in small groups) next to the recommended unsupervised daily home exercises (Table 2). Thus, from week 2 to week 6, there was a difference between the interventions (PR and UC) and therefore the first postoperative outcome assessments (post test) were performed 6 weeks post-surgery, one week after sling

removal. Moreover, the second postoperative outcome assessments (primary and additional outcomes) were performed 12 weeks post-surgery since that was also the end of the 12-weeks postoperative interventions (Figure 11).

Table 2 Overview of the differences in postoperative intervention in RCT-study (Paper 2 & 3)

Progressive rehabilitation (PR)		Usual care (UC)	
Week		Week	
1- 5	Immobilization 2 weeks in fixed sling followed by 3 weeks in non-fixed sling	1-5	Immobilization 2 weeks in fixed sling followed by 3 weeks in non-fixed sling
2- 5	Physiotherapist guided PROM exercises PROM Restrictions: ABD + FLEX: None IR < 90 degrees in neutral ER < 45 degrees in neutral	2- 5	Physiotherapist guided PROM exercises PROM Restrictions: ABD + FLEX: None IR < 90 degrees in neutral ER < 45 degrees in neutral
2	Close-chain AAROM and AROM exercises AAROM and AROM Restrictions: ABD + FLEX < 90 degrees IR < 90 degrees in neutral ER = 0 degrees in neutral		
3- 5	Close-chain AAROM and AROM exercises AAROM and AROM Restrictions: ABD + FLEX < 90 degrees IR < 90 degrees in neutral ER < 45 degrees in neutral		
6-12	Therapist-supervised AROM (FLEX, ABD, EXT, ER and IR) with gradually (individually) increased loading and progression from close-chain to open-chain exercises.		
12-20	Continuation of rehabilitation in the community		

PR, progressive rehabilitation; UC, usual care; ROM, range of motion; PROM, passive range of motion; ABD, abduction; FLEX, flexion; IR, Internal rotation; ER, external rotation; AAROM, assisted active range of motion; AROM, active range of motion; EXT, extension.

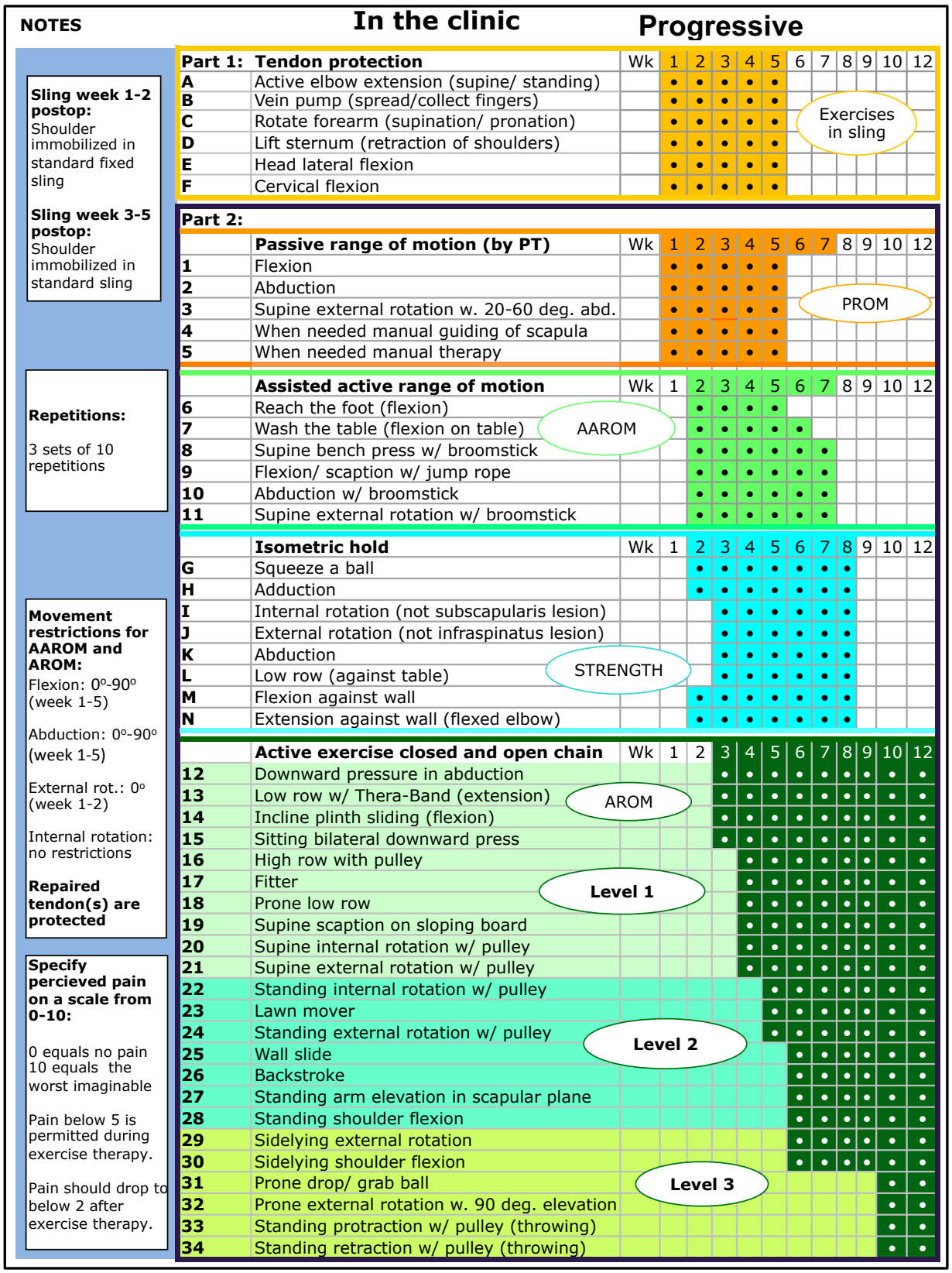


Figure 12. Dotsheet showing progression in PR group. ROM, range of motion; PROM, passive range of motion; ABD, abduction; FLEX, flexion; IR, Internal rotation; ER, external rotation; AAROM, assisted active range of motion; AROM, active range of motion; EXT, extension; Wk, postoperative week; w/, with

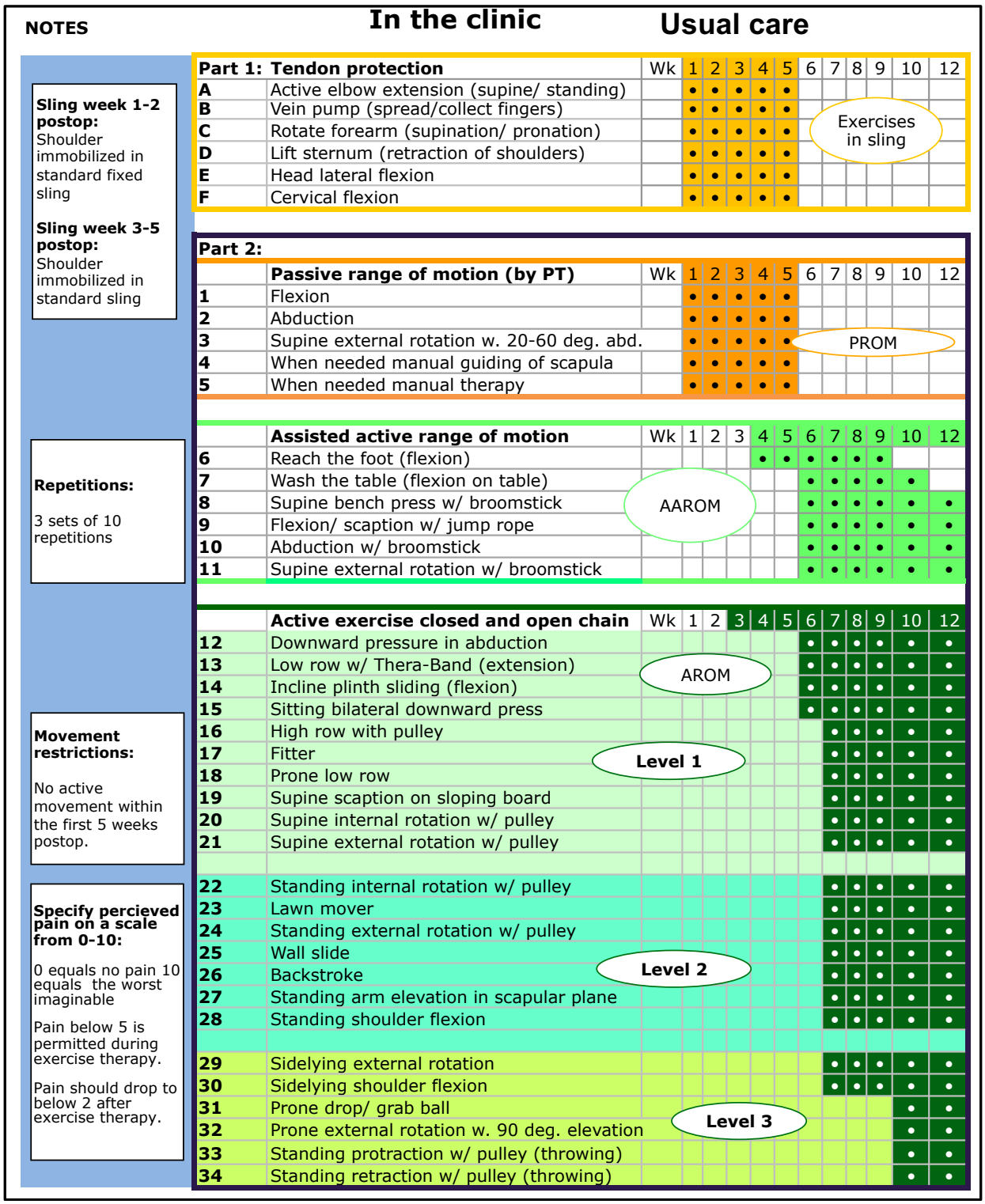


Figure 13. Dotsheet showing progression in UC group. ROM, range of motion; PROM, passive range of motion; ABD, abduction; FLEX, flexion; IR, Internal rotation; ER, external rotation; AAROM, assisted active range of motion; AROM, active range of motion; EXT, extension; Wk, postoperative week; w/, with

Figure 14. Examples of progression of flexion, external rotation, and scapula -exercises as described in the dotsheets.

The therapists adjusted exercise intensity as determined by the patient's ability to complete 3 sets of 10 repetitions for a given exercise without exacerbating pain. This means that for all exercises pain

above 5 on NPRS (from 0 to 10) should not be provoked during exercises. The exercise therapy continuously determined and applied the load for 20 repetitions maximum (RM), with progression from ½ kg to 3–4 kg during the 12 weeks. Each exercise was guided with focus on correct performance and movement quality (direction, speed, posture and coordination) with sufficient rest between sets to allow for recovery. It was recommended to increase the load by 2–10% when the patient was able to perform the current workload properly and with 1–2 repetitions more than the required number of 10 repetitions (Paper 2, additional file 2).

Compliance

Intervention compliance and attendance within the 12 weeks were recorded in exercise logbooks for both groups. In the exercise logbooks, the patients were asked to report completed home-based exercise sessions and reasons for non-completed sessions (pain or other reasons). Supervision of the subsequent home exercises at the commencement of every on-site session was performed to facilitate program adherence. Reinforcement techniques were used with the physiotherapist giving positive feedback and appraising/commending patients for their efforts. Satisfactory intervention compliance was defined as having attended at least 75% of the scheduled rehabilitation programs, both at on-site supervised sessions or un-supervised (home-based) sessions, as individually tailored by the physiotherapist.

Outcomes

For an overview of outcomes in the studies, see Table 3.

Paper 1

As illustrated in the first box in Figure 15, shoulder pain was assessed using Numeric Pain Rating Scale (NPRS) with the question "How do you perceive your worst/maximum pain during the past 24 hours?" (99). As a measure of shoulder disability, we used the WORCPhysical (35) (Table 3). WORC is a self-administered questionnaire developed to measure pain, functional activity level and health related quality of life in patients with RC disease (Table 3) (35). WORC consists of 21 items in 5 subdomains, however in this paper we used only WORCPhysical which includes 6 items each scored on 100 mm VAS scale and summed up to a total raw score of maximally 600 with higher score indicating worse physical symptoms. It was further converted into a percentage score ranging

from 0 (worst possible) to 100 (best possible) (35, 100). The Danish cross-culturally translated, reliable and responsive version that was found valid in RC patients was used (37).

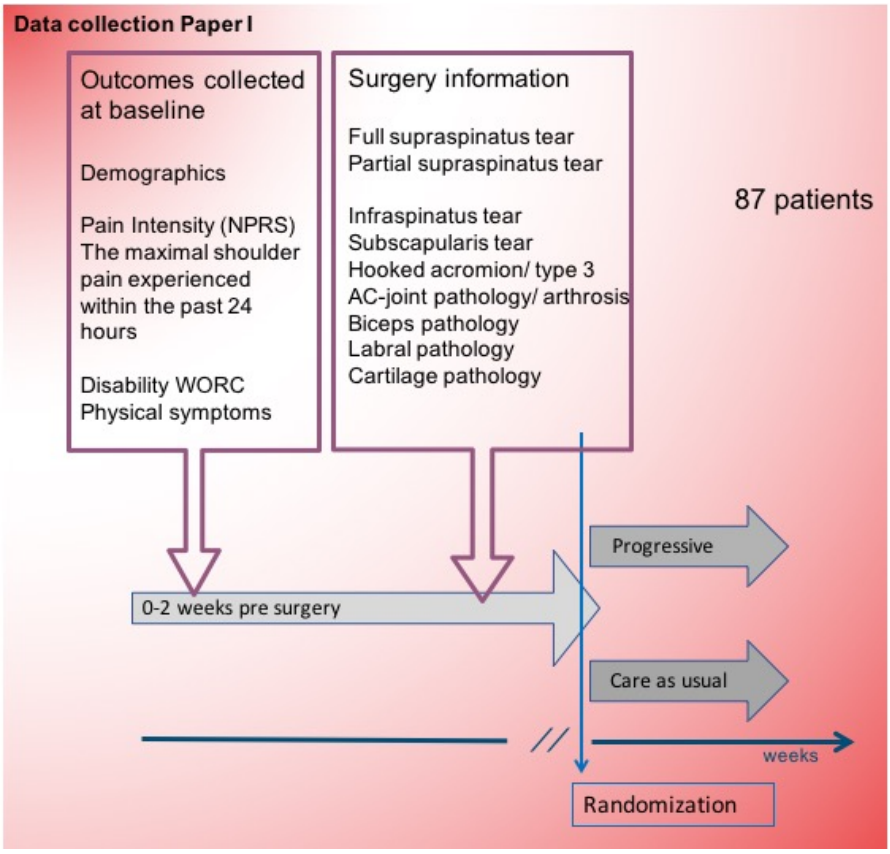


Figure 15 Overview of data collection for Paper 1

As illustrated in the second box in Figure 15, the orthopaedic surgeon described the structural pathologies or concomitant injuries of the shoulder identified during arthroscopy using a prespecified list. The list included a categorization of partial supraspinatus tear or full thickness supraspinatus tear, infraspinatus tear, subscapularis tear, hooked acromion (type 3), AC-joint osteoarthritis and biceps tendon pathology (long head of biceps tear/ partial tear/ tendinosis), labral tear and cartilage lesion.

Paper 2

Primary outcome

When preparing and designing the protocol for the RCT-study we found it imperative to use a valid and reliable disease specific patient reported questionnaire responsive to the change in the specific group of postoperative RC patients and therefore WORC was selected (Paper 2) (35, 100). The

WORC has excellent reliability with intra class correlation (ICC) between 0.84 and 0.99 (101, 102). Specifically, WORCPhysical was selected as primary outcome because it has shown the highest reliability (Paper 2) (38, 102).

Paper 3

As previously mentioned, WORC consists of 21 items in 5 subdomains: physical symptoms (6 items), sports and recreation (4 items), work (4 items), lifestyle (4 items) and emotions (3 items). Each question is scored on 100 mm VAS scale and summed to a total score of maximally 2100, with 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 (35, 100). The minimal clinical important difference (MCID) for WORC Total is 11.7%-points (35). Also in the RCT-study the Danish cross-culturally translated, reliable and responsive version was used (37).

Table 3 Overview of primary and secondary outcomes and assessment visits

	Study I		Study II & III			
Visit	Baseline	Surgery	Baseline	Surgery	Week 6	Week 12
Day	-7 ±7	1	-7 ±7	1	40 ±3	84 ±5
Informed consent	●		●			
Surgery information[§§]		●		●		
Randomization				●		
WORC physical symptoms subdomain	●		●		●	primary
WORC other subdomains and total			●		●	●
DASH			●		●	●
GRS					●	●
NPRS (at rest)			●		●	●
NPRS (during general activity/ function)			●		●	●
NPRS (during the past 24 hours)	●		●		●	●
ROM			●		●	●
Strength (MVC)			●			●
Return to work						●
Tendon re-tear					●	

WORC, Western Ontario Rotator Cuff Index; DASH, Disabilities Arm, Shoulder and Hand questionnaire; MRI, magnetic resonance imaging; GRS, Global Rating Scale; NPRS, numeric pain rating scale; ROM, range of motion; US, ultrasound. [§§]partial supraspinatus tear or full thickness supraspinatus tear, infraspinatus tear, subscapularis tear, hooked acromion, AC-joint osteoarthritis and biceps tendon pathology, labral tear and cartilage lesion.

<u>Secondary patient-reported outcomes</u>

Secondary outcomes were change in WORC scores at week 6. Additionally, secondary patient reported outcomes measured at week 6 and 12 included change in patient reported outcomes using the semi-generic upper extremity questionnaire Disability Arm Shoulder Hand (DASH) with MCID

of 11.7%-points (36, 39); Patient Global Rating Scale (GRS) to get a general impression of recovery from baseline to respectively 6 and 12 weeks postoperatively (103, 104), and NPRS where patients were asked about perceived pain at rest, during general activity/ function and as in Paper 1 'How do you perceive your worst/maximum pain during the past 24 hours?' (99, 105). The minimal clinical important difference (MCID) for NPRS is 2%-points (99).

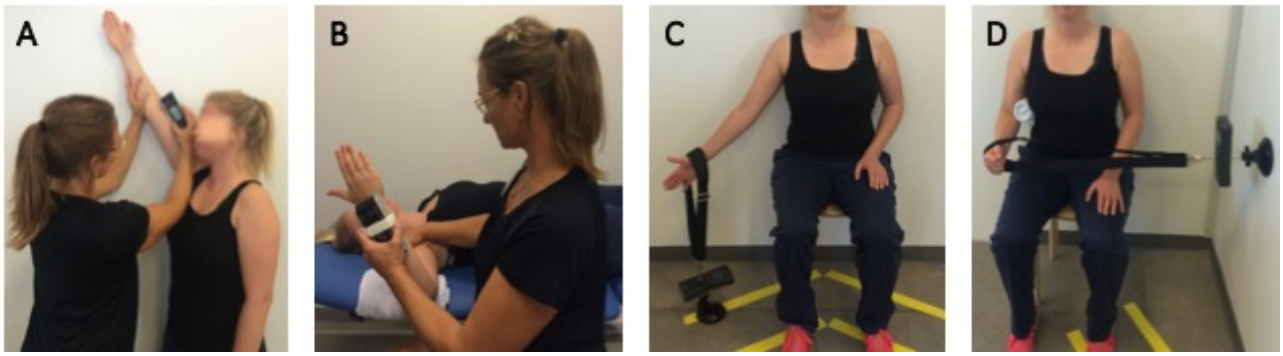


Figure 10. A illustrates test of passive shoulder elevation range of motion, B illustrates test of passive external shoulder rotation range of motion, C illustrates test of MVC 45 degrees scaption, D illustrates test of MVC external rotation

Secondary objective outcomes

Secondary objective outcomes included change in active and passive shoulder elevation ROM in the scapular plane (standing) (Figure 10, A); external shoulder rotation (Figure 10, B) and internal shoulder rotation (in 90° abduction when supine) (106, 107), as measured by Digital Inclinometer (table 3). Maximum isometric voluntary contraction (MVC) of shoulder elevation in the scapular plane (Figure 10, C) and external (Figure 10, D) and internal rotation (sitting) (106, 108, 109) is measured by IsoForce EVO2 dynamometer (only at baseline and week 12).
Registered demographic data included age, gender, tendon(s) involved, dominant side affected, employment, patient-reported number of sick days from work. Tendon retear was assessed by radiologist or sports medicine doctor at 6 weeks postoperative using US (Hitachi Ascendus ultrasound scanner).

Sample Size and Power Calculations

Paper 1

No sample size calculation was conducted due to the exploratory nature of this study, and for pragmatic reasons, the recruitment period was only the first 20 months of inclusion for the RCT.

Paper 2

The sample size was calculated to test the superiority of PR over UC in the assessment of the change in the WORC Physical symptoms subdomain (WORCPhysical) at postoperative week 12 (primary outcome) (110). A total of 41 patients was required per group to establish a clinically significant mean difference of 12 points, with a common standard deviation of 20 (0-100 scale) (111), and with 80% power and a significance level of 5%. To account for dropouts (max 20%), we planned to include a total of 50 per group.

Paper 3

As stated above, the plan was to include a total of 50 per group, however, as there were no dropouts the recruitment period was stopped when the required sample size for the RCT with 12 weeks follow up was reached (2 times 41 patients).

Randomization and Allocation Concealment

Paper 2

When designing a high quality RCT-study the randomization-process is imperative. Assigning interventions (treatment arms) to trial participants is a crucial aspect of a clinical trial design and a random assignment method (randomization) is preferred. It eliminates selection bias by balancing both known and unknown predictors, and it permits using a probability theory to express the possibility that any between group difference at baseline simply reflects chance, and it facilitates the blinding of treatment arms to the outcome assessors, investigators, and in some cases participants (95). We therefore made sure that we implemented an unpredictable allocation sequence with concealment using Procordo Research Platform.

Paper 3

Participants were randomized (1:1) to receive either PR or UC. To control for potential imbalance in the randomization, stratification (age, gender and center) and blocking were employed. Randomization to one of two treatment arms was computer-generated based upon permuted random blocks of variable size (3 to 6 in each block) using the Procordo Research Platform. Randomization was performed after baseline tests and surgery, and allocation (based on the randomization) was performed by a person otherwise not included in the current project.

Blinding

Paper 2

When planning a high quality RCT-study the blinding-process is important to minimize performance and ascertainment bias (95). The present RCT-study was an "open-label" trial and therefore the physiotherapists delivering the interventions and the patients were not blinded to treatment allocation. It is challenging to blind the participants (and physiotherapists) performing a training intervention. However, blinding and equipoise was rigorously maintained by emphasizing to the patients that each training protocol (PR and UC) was safe and that it was developed based on best available evidence, and patients were informed that 2 strategies were compared, and they were blinded to study hypotheses.

Further, the physiotherapists delivering the interventions and the patients were instructed to withhold information about the assigned intervention and not reveal allocation to the outcome assessors or investigators.

Paper 3

Baseline examinations were performed before group allocation. To reduce bias all post-examinations were performed blinded to group allocation by the principal investigator or two physiotherapists trained as outcome assessors.

Statistics

Paper 1

The study population was described with mean, minimum, and maximum percentage and SD for continuous data. Full thickness and partial thickness supraspinatus tears were merged into one supraspinatus tear- variable (dependent variable). To analyze whether the total number of concomitant structural pathologies (counts; continuous variable) was associated with pre-operative patient-reported measures, a standardized linear regression analysis was performed with the patient-reported measures (NPRS/WORCPhysical) as dependent variables and number of concomitant pathologies as predictor/independent variable (analysis 1). We grouped the participants according to the extent of concomitant pathologies into 3 a priory defined categories: A) isolated supraspinatus tear (i.e. no concomitant pathology); B) supraspinatus tear with one concomitant pathology and C) supraspinatus tear with two or more concomitant pathologies. Differences between these groups of

participants in patient symptoms were analyzed using analysis of covariance (ANCOVA) adjusted for age, sex, BMI and hand dominance with post-hoc Bonferroni comparisons (analysis 2). To analyze whether one particular pathology in combination with the supraspinatus tear (total or partial) was associated with patient symptoms, linear regression analyses were performed with patient symptoms as dependent variables and the presence of each of the structural pathologies as predictors. We tested the association between patient symptoms and supraspinatus tear by adding each of the structural pathological variables stepwise into the full model (all variables) (analysis 3). General patient characteristics (e.g. age, sex, BMI & hand dominance) (19) were considered covariates and the analyses were repeated with adjustment for these. The level of significance was set to 5% (p=0.05) and all analyses were performed in IBM Corp. SPSS Statistics version 25 (Armonk, New York, United States).

Paper 2

To conform to contemporary guidelines we included all randomized patients in the 'intention-to-treat' (ITT) analyses (95, 112). ITT population was defined as all randomized participants irrespective of compliance or withdrawals (retained in the group to which they were allocated) (112). Patients were considered randomized as soon as the training group was assigned according to the allocation sequence. The ITT analyses were performed blinded to group allocation (112) and before group allocation was unblinded, consensus agreement on interpretation of the primary outcome was signed by all authors (113). All data analyses were planned to be carried out according to a pre-established analysis plan (114) and data presented for the difference between groups with 95%CI (115). For further details regarding the preparation of the statistical part of the RCT-study see the Paper 2 and the section below.

Paper 3

The primary analysis was performed as an assessment of the between-group difference in changed WORCPhysical score after 12 weeks in the Intention-To-Treat (ITT) population (114).
Missing follow up data was imputed using baseline observation carried forward (BOCF). As described the Per-protocol (PP) population was defined as the as-observed population participants that had attended at least 75% of the scheduled rehabilitation appointments (93). Sensitivity analyses were performed for detecting differences in demographics and baseline data 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. Baseline data were defined as all measurements performed at the baseline visit.

The primary analysis of the WORCPhysical was performed by a repeated measures analysis of covariance (ANCOVA) on change in WORCPhysical as dependent variable, with a factor for group (2 levels), a factor for time (2 levels; 6 and 12 weeks), and adjustment for WORCPhysical value at baseline as independent variables and confounders (age, gender and center). Secondary outcome measures were analysed with ANCOVA for the continuous outcome measures (pain, patient reported outcomes, strength, ROM) as dependent variables (individually/one at a time), with the same independent variables and confounders as in the analyses of the primary outcome.

An external statistical consultant performed the analyses on the primary outcome blinded. All statistical tests were two-sided with $p < .05$ considered statistically significant (using 95% CI). All data analyses were carried out according to the pre-established analysis plan (114) and performed by the IBM SPSS Statistics Version 25.0 software (SPSS Inc., Chicago, IL).

Summary of results

Paper 1

Table 4 Demographic and pathological characteristics (n= 87) for participants with supraspinatus tear

Characteristics	Distribution
Age in years, mean	60
Male, n (%)	52 (60 %)
Height in cm, mean	174
Weight in kg, mean	82
BMI in kg/m^2, mean	27
Dominant side affected, n (%)	58 (67 %)
WORC Physical, %	50.1
Pain Intensity (NPRS 0-10)	6.95
Structural pathology found at arthroscopy	
Full supraspinatus tear, n (%)	69 (79 %)
Partial supraspinatus tear, n (%)	18 (21 %)
Infraspinatus tear, n (%)	26 (30 %)
Subscapularis tear, n (%)	15 (17 %)
Hooked acromion, n (%)	58 (67 %)
AC-joint arthrosis, n (%)	15 (17 %)
Biceps tendon pathology, n (%)	27 (31 %)
Cartilage lesions, n (%)	3 (3 %)
Labral pathology, n (%)	2 (2 %)

BMI, Body Mass Index; WORC Physical, Western Ontario Rotator Cuff Index (physical symptoms subdomain); NPRS, Numeric Pain Rating Scale (worst pain past 24 hours); SD, Standard Deviation

In total, 87 participants were included in the study. Sixty percent of the participants were males and the average age was 60 years (ranging from 39-79). Seventy-nine percent of the participants had a full-thickness supraspinatus tear, and 21% had a partial-thickness supraspinatus tear (Table 4). The prevalence of concomitant structural pathology was 91% (Table 4). The most frequent concomitant structural pathology was a hooked acromion/type 3 (67%) and biceps pathology (31%) and the most frequent additional tendon pathology was an infraspinatus tear (30%) (Table 4). As depicted in Figure 11 the participants most frequently had one (37%) (the orange area) or two (35%) (the grey area) concomitant pathologies besides the supraspinatus tear. The dark blue area represents the small group with no concomitant pathology which include 8 patients (Figure 11). The most common combination of concomitant pathologies was hooked acromion (67%) in combination with infraspinatus tear (28% of the 67%). As the prevalences of cartilage and labrum pathologies were only 3% and 2%, respectively, these pathologies were not included in the linear regression analyses.

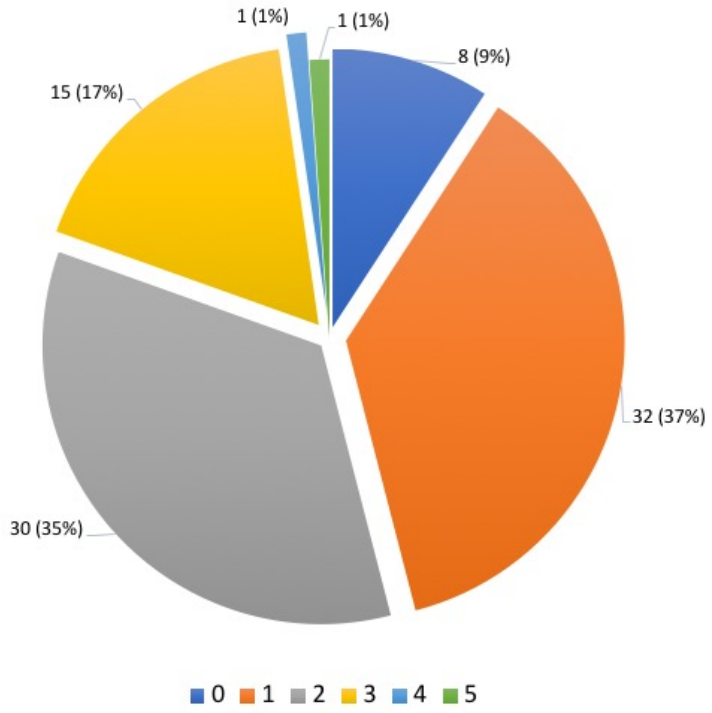


Figure 11 The frequency of number of concomitant pathologies.

No statistically significant association was found between number of structural shoulder pathologies and preoperative patient symptoms in the standardized linear regression analysis (Table 5).

Neither did ANCOVA (adjusted for age, sex, BMI and hand dominance) yield any statistically significant association between the number of structural shoulder pathology (3-level category) and preoperative patient symptoms (Table 6).

Table 5 Total number of concomitant structural pathologies association (crude and adjusted) with patient-reported symptoms (WORCPhysical and NPRS for pain intensity) for supraspinatus tear (analysis 1)

	Number of structural pathologies					
Symptoms	Crude B estimate			Adjusted B estimate*		
	Partial R^2	B(95% CI)	p value	Partial R^2	B(95% CI)	p value
WORC Physical	0.003	-1.134 (-5.956; 3.687)	0.641	0.027	-0.813 (-6.040; 4.414)	0.847
Pain intensity	0.001	-0.076 (-0.615; 0.464)	0.781	0.086	-0.198 (-0.766; 0.369)	0.251

* Adjusted for age, sex, BMI & dominance. WORC Physical, Western Ontario Rotator Cuff Index (physical symptoms subdomain); NPRS, Numeric Pain Rating Scale (worst pain last 24 hours); B, Regression coefficient; 95% CI, 95% confidence interval; p, p value.
Partial R^2 is the proportion of the variance in the dependent variable explained by the independent variable (each number of concomitant pathology added). B is the slope of the regression line.

Table 6 The influence of group characteristics on patient-reported symptoms (WORCPhysical and NPRS for pain intensity) with 3-level category scale for supraspinatus tear (analysis 2)

	Number of structural pathologies*			
Symptoms	A (Isolated) n = 8	B (+1) n = 32	C (+ ≥ 2) n = 47	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	p value
WORC Physical	55.4 (37.6; 73.2)	49.0 (40.2; 57.9)	47.6 (40.9; 54.4)	0.721
Pain intensity	7.9 (5.9; 9.8)	6.8 (5.8; 7.7)	6.9 (6.2; 7.6)	0.588

* Adjusted for age, sex BMI & dominance. A, isolated supraspinatus tear; B, supraspinatus tear with one concomitant pathology; C, supraspinatus tear with two or more concomitant pathologies; 95% CI, 95% confidence interval; WORCPhysical, Western Ontario Rotator Cuff Index (physical symptoms subdomain); NPRS, Numeric Pain Rating Scale (worst pain past 24 hours); p, p value

In the third analysis we found that no single pathology in combination with the supraspinatus tear was associated with worse patients' symptoms (Table 7). We did see an association of infraspinatus involvement and increased disability on WORCPhysical in both the crude univariate and multivariable regression analyses (not displayed). However, this association was not statistically significant when adjusting for possible confounders in the adjusted multivariable model (Table 7).

Table 7 Linear regression (adjusted) of each concomitant structural pathology with patient-reported symptoms (WORC physical dimension and NPRS for pain intensity) for supraspinatus tear (analysis 3)

PROM			Adjusted multivariable model[§§]	
WORC Physical	Pathology	R^2 0.098	B (95% CI)	p
	Infraspinatus tear		-9.165 (-20.524; 2.194)	0.112
	Subscapularis tear		9.298 (-2.913; 21.508)	0.133
	Hooked acromion		0.597 (-10.848; 12.043)	0.917
	AC-joint arthrosis		3.852 (-10.803; 18.507)	0.602
	Biceps tendon		-3.738 (-15.348; 7.872)	0.523
Pain intensity	Pathology	R^2 0.105	B (95% CI)	p
	Infraspinatus tear		-0.355 (-1.623; 0.914)	0.579
	Subscapularis tear		0.588 (-0.775; 1.952)	0.392
	Hooked acromion		-0.028 (-1.307; 1.250)	0.965
	AC-joint arthrosis		-0.448 (-2.085; 1.188)	0.586
	Biceps tendon		-0.662 (-1.958; 0.634)	0.312

[§§]Adjusted for age, sex, BMI & dominance. WORCPhysical, Western Ontario Rotator Cuff Index (physical symptoms subdomain); NPRS, Numeric Pain Rating Scale (worst pain past 24 hours); B, Regression coefficient; 95% CI, 95% confidence interval; p, p value. R^2 is the proportion of the variance in the dependent variable explained by the independent variable. B is the slope of the regression line.

Paper 2 & 3 (RCT-study)

Between March 2017 and May 2019, a total of 326 patients from two orthopedic departments were screened for eligibility. Of these, 126 patients fulfilled the preoperative eligibility criteria and signed informed consent to participate. Forty-four participants did not meet postoperative inclusion criteria and were excluded (Figure 12). Thus 82 participants with a traumatic based repairable full-thickness RC tear fulfilled the final postoperative eligibility criteria (62 of these were also included in Paper 1). The 82 constituted the ITT population; 41 patients were randomized to PR and 41 to UC (Figure 12). The two groups were comparable at baseline with respect to demographics and surgical characteristics, with no group difference in number of dropouts (Table 8 and Figure 12).

The PP population consisted of 53 patients (25 PR; 28 UC). There was no between-group difference in number of compliers, and demographics, and clinical characteristics of the PP were comparable with the ITT population (Paper 3, additional file 1).

Table 8 Demographics and baseline data for PR and UC groups. Data are reported for each group as the total with Mean ± SD, n (%). Intention-to-treat population.

Characteristics	PR Group (n=41)	UC Group (n=41)
Age in years, mean (SD)	59 (8.6)	61 (8.0)
Male, n (%)	29 (70.7%)	25 (61.0%)
Height in cm, mean (SD)	177 (8.7)	176 (10.0)
Weight in kg, mean (SD)	89 (19.4)	86 (21.1)
BMI in kg/m^2, mean (SD)	28.2 (5.2)	27.8 (5.0)
Side (right/ left)	(28/13)	(25/16)
Dominant side affected, n (%)	27 (65.9%)	27 (65.9%)
Employment		
Manual labour, n (%)	13 (31.7%)	19 (46.3%)
Office work, n (%)	9 (22.0%)	9 (22.0%)
Retired, n (%)	19 (46.3%)	13 (31.7%)
Number of sick days, mean (SD)	70 (60.8)	60 (51.7)
Injured tendons		
Patients with 1 tendon tear n (%)	29 (70.7%)	22 (53.7%)
Patients with 2 tendon tears n (%)	10 (24.4%)	16 (39.0%)
Patients with 3 tendon tears n (%)	2 (4.9%)	3 (7.3%)
Supraspinatus involved, n (%)	41 (100%)	41 (100%)
Infraspinatus involved, n (%)	11 (26%)	15 (36.6%)
Subscapularis involved, n (%)	3 (7.3%)	7 (17.1%)
Primary Outcome		
WORC Physical % (SD) (0-100 (best) %)	54.0 (19.6)	49.3 (18.2)
Secondary Patient Reported Outcomes		
WORC Sports and recreation % (SD)	35.5 (24.7)	28.6 (21.3)
WORC Work % (SD)	27.4 (20.2)	22.6 (19.8)
WORC Lifestyle % (SD)	41.2 (26.7)	39.9 (23.7)
WORC Emotions % (SD)	41.7 (25.6)	43.0 (29.7)
WORC Total % (SD)	41.2 (18.5)	37.6 (17.8)
DASH (0-100 (most disabled) %)		
Total % (SD)	43.39 (18.4)	44.73 (14.6)
Work % (SD) ‡	45.0 (32.5)	45.0 (32.3)
Leisure time/ Hobby % (SD) ‡‡	72.5 (27.5)	74.0 (25.8)
NPRS, mean (SD) (0-10)		
At rest	3.9 (2.6)	4.0 (2.6)
During activity	6.0 (2.7)	6.7 (2.5)
Worst (past 24 hours)	6.8 (2.6)	7.2 (2.1)

PR, progressive; UC, usual care; WORC, Western Ontario Rotator Cuff Index; DASH, Disability Arm Shoulder Hand; NPRS, Numeric Pain Rating Scale; cm, centimeter. ‡ Optional module (voluntarily if answered) – n=25 for PR and n=30 for UC. ‡‡ Optional module (voluntarily if answered) – n=15 for PR and n=19 for UC.

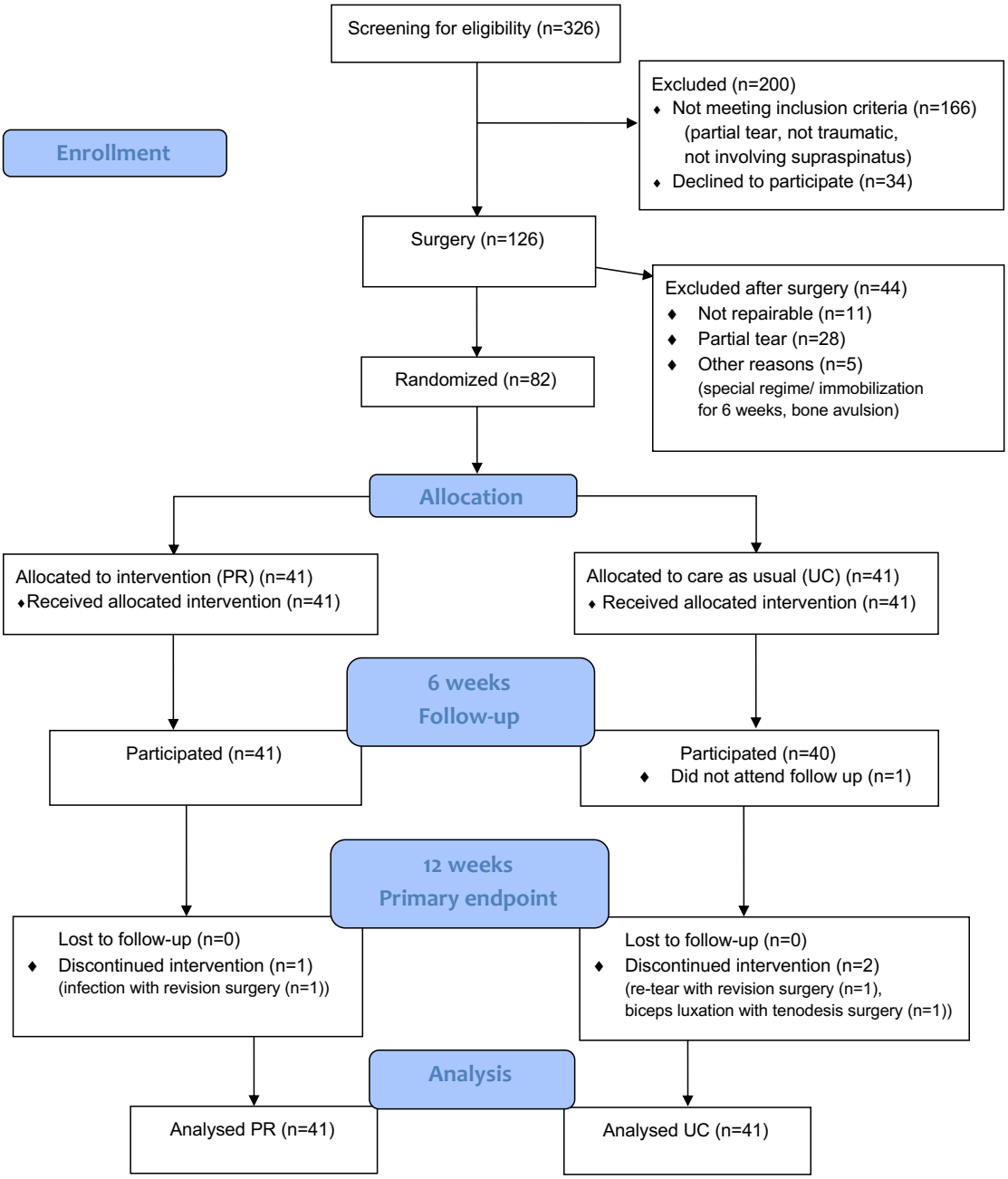


Figure 12. Flowchart of patients with traumatic rotator cuff tears in the CUT-N-MOVE trial intention-to-treat (ITT) population. All patients receive allocated intervention meaning that a total of 82 patients (PR, n = 41, 100%; UC, n = 41, 100%) constituted the "as observed" population for the primary outcome. Three patients experienced adverse events; one re-tear required revision surgery (UC, n = 1), one patient developed infection reguiring revision surgery (PR, n = 1), and one patient developed a biceps medial luxation managed by tenodesis surgery (UC, n = 1). PR, progressive group; UC, usual care group.

Efficacy Analysis

For the primary outcome at week 12 there was no significant group difference in change from baseline in WORCPhysical score (adjusted for age, sex and center), with mean group difference of 0.8 points (95% CI, -6.4 to 7.9; p = 0.834) (Table 22). At week 6 the mean group difference of change from baseline in WORCPhysical was 2.8 points (95% CI, -4.1 to 9.7; p = 0.42) (Paper 3,

Table 2). Furthermore, no significant between-group differences were found in the secondary outcomes (DASH, pain, ROM, and strength) at 6 and 12 weeks. An exception was the change from baseline in active scaption ROM at 6 weeks of 13.8° (95% CI, 0.2 to 27.4; p = 0.046) in favor of the PR group (Paper 3, Table 2), which did not stay significant at 12 weeks (Table 9). Both groups had significantly and clinically relevant improvements over time in WORC, DASH, pain, ROM, and strength (Figure 12).

The sensitivity analyses on the PP population (PR 25; vs UC 28) showed no group difference in compliance, and the PP population did not differ from the ITT population. The efficacy results of the PP analyses confirmed the ITT results (Paper 3, additional file 2).

Table 9. Changes from baseline to 6 and 12 weeks postoperatively for primary and secondary outcomes for PR and UC in the Intention-to-treat population

	Within group change		Adjusted a)	
	PR (n=41) mean change (SE)	UC (n=41) mean change (SE)	Between-Group difference on mean change (95% CI)	p-value
Primary Outcome				
WORC Physical symptoms	19.0 (2.5)	18.2 (2.5)	0.8 (-6.4-7.9)	0.834
Secondary Outcomes				
WORC Sports and recreation	11.5 (2.8)	10.1 (2.8)	1.4 (-6.5-9.3)	0.723
WORC Work	16.6 (3.0)	19.2 (3.0)	-2.7 (-5.9-11.1)	0.541
WORC Lifestyle	22.5 (3.2)	25.6 (3.2)	-3.1 (-6.1-12.2)	0.508
WORC Emotions	20.1 (3.6)	23.0 (3.6)	-2.9 (-7.2-13.0)	0.568
WORC Total	17.7 (2.3)	19.2 (2.3)	-1.5 (-5.0-8.0)	0.650
DASH Total	-8.3 (2.8)	-3.4 (2.8)	-5.0 (-12.9-3.0)	0.212
Work ‡	-9.6 (6.7)	-7.1 (5.4)	-2.5 (-20.9-15.9)	0.782
Leisure time/ Hobby ‡‡	3.5 (9.3)	-12.0 (6.4)	15.5 (-9.4-40.4)	0.204
NPRS At rest	-2.7 (0.2)	-3.1 (0.2)	-0.4 (-0.1-0.9)	0.108
NPRS During activity	-3.1 (0.3)	-3.9 (0.3)	0.8 (0.0-1.6)	0.060
NPRS Worst (past 24 hours)	-3.0 (0.4)	-3.5 (0.4)	0.6 (-0.5-1.6)	0.290
GRS Improved (score 1-7) n (%)	30 (73%)	25 (61%)	12 (-36.8-9.2)	0.240
ROM (°)				
Scaption passive	7.0 (3.0)	3.2 (3.0)	3.8 (-4.6-12.2)	0.372
Scaption active	21.1 (4.3)	12.0 (4.2)	9.1 (-2.9-21.1)	0.136
External rotation passive	1.5 (3.0)	1.7 (3.0)	-0.2 (-8.7-8.3)	0.966
External rotation active	0.1 (2.8)	1.4 (2.8)	1.3 (-9.2-6.6)	0.744
Internal rotation passive	-2.5 (1.6)	0.6 (1.6)	-3.1 (-7.7-1.6)	0.190
Internal rotation active	-1.0 (1.7)	2.4 (1.7)	-3.5 (-8.3-1.4)	0.162
Strength (MVC) (Nm)				
Scaption	7.4 (4.3)	14.3 (4.2)	-6.9 (-18.9-5.2)	0.259
External rotation	15.4 (3.2)	10.7 (3.1)	4.7 (-4.2-14.0)	0.293
Internal rotation	6.7 (5.0)	11.9 (4.9)	-5.2 (-19.2-8.8)	0.462

a) Adjusted for baseline values, age, sex and center. PR, progressive; UC, usual care; WORC, Western Ontario Rotator Cuff Index; DASH, Disability Arm Shoulder Hand; NPRS, Numeric Pain Rating Scale; GRS, Global Rating Scale (ranging from -7 to 7; percieved improvement ranging from 1-7); °, degrees; MVC, Maximum isometric voluntary contraction; 95%CI, 95% Confidence Intervals. ‡ Optional module (voluntarily if answered) – n=25 for PR and n=30 for UC. ‡‡ Optional module (voluntarily if answered) – n=15 for PR and n=19 for UC.

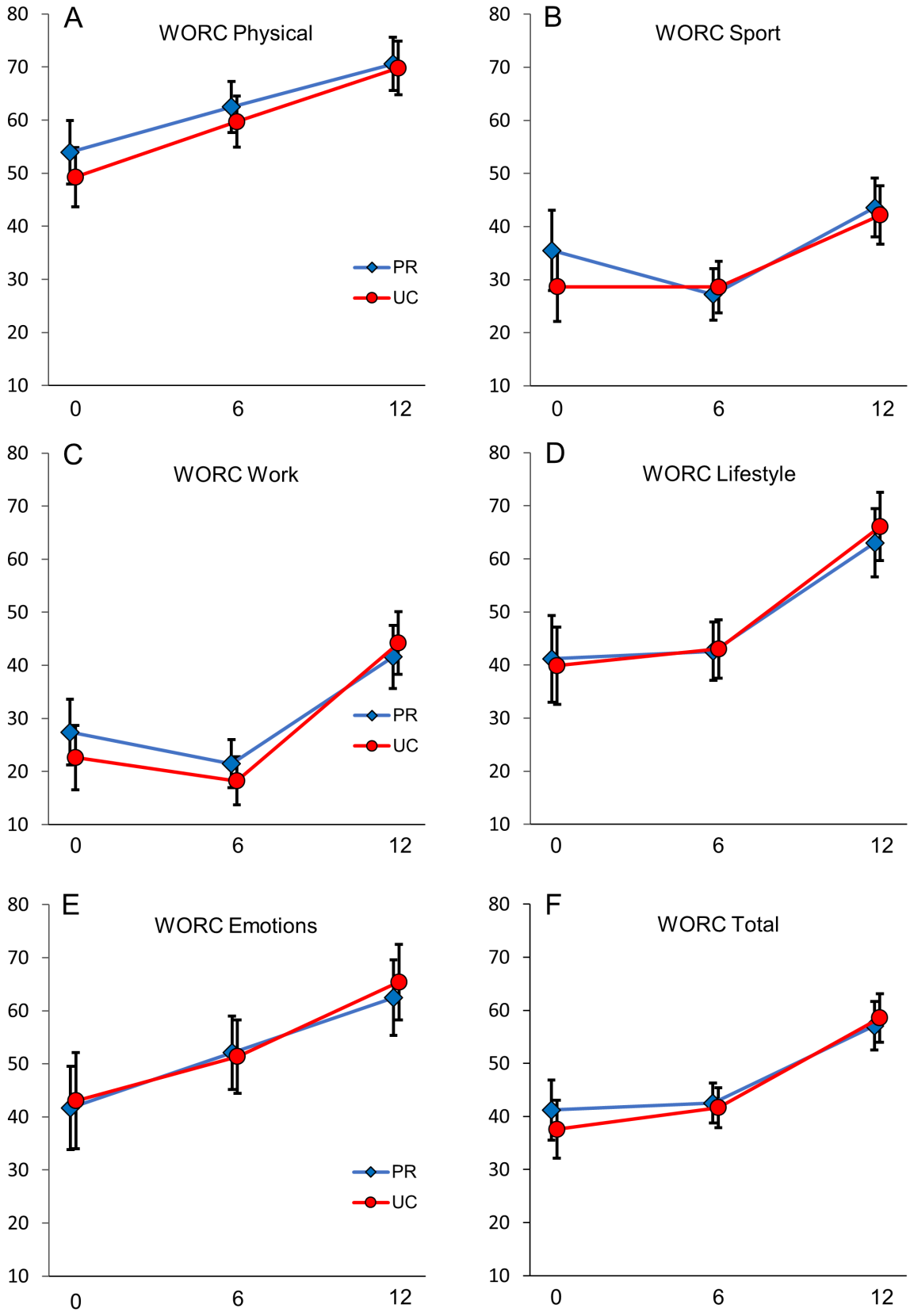


Figure 12. WORC at baseline, 6 and 12 weeks postoperative for the patients in the CUT-N-MOVE trial. The graphs illustrate the results from the Intention-To-Treat population with datapoints representing means and error bars indicate 95% CI´s. WORC, Western Ontario Rotator Cuff Index; PR, progressive group; UC, usual care group.

Re-tears and Adverse Events

Totally, there were 9 re-tears registred by US at 6 weeks postoperatively (11%) (PR=6 (15%); UC=3 (7 %); p= 0.295). One of the re-tears (UC) required revision surgery. One participant (PR) developed infection requiring revision surgery, and one participant (UC) developed a biceps medial luxation managed by tenodesis surgery (Figure 1).

General discussion

Main findings

Paper 1

In this cross-sectional study we found that the preoperative self-reported pain and disability in patients scheduled for RC surgery, were not associated with pathology of infraspinatus, subscapularis or other structural joint pathologies in concomitance with the supraspinatus tear, neither in terms of number of pathologies nor type of pathology (Paper 1). This indicates that concomitant structural pathology adds only little to the physical disability and pain perceived by patients with a traumatic supraspinatus tear.

Paper 2

Based on a review of the existing literature, extraction of components of previous exercise interventions and input from clinical PT´s and shoulder patients, we designed a progressive physiotherapy exercise intervention including active loading targeting postoperative RC patients (Paper 2). The details of the PR and the UC were presented as part of the study protocol in paper 2 which is a transparently described protocol including a rigorous methodological design to measure treatment effect.

Paper 3

Patients performing PR did not improve more on WORCPhysical than patients performing UC at 6 and 12 weeks following surgical RC repair. Thus, UC was as effective as PR when measured on self-reported physical function. In addition, no differences between groups were found in the secondary outcomes (DASH, pain, ROM, and strength) at 6 and 12 weeks. Our study further showed that both PR and the traditional UC improved significantly and at a clinically relevant level.

Explanation of results and comparison with findings from other studies

Paper 1

It is common to consider the occurrence of concomitant shoulder pathologies in patients with RC tears as an indicator of the severity of the condition in surgical decision making, and recent studies have increased the awareness of such pathologies (23, 26). However, our results are in line with some of the earlier findings (29, 30, 116). These studies showed no association between tear size

and symptoms (30, 116) or between patient-reported pain and disability and tear size, fatty infiltration, tendon retraction, and muscle atrophy in patients with RC tears undergoing operative and nonoperative treatment (29). It is anticipated that other factors such as mental health, sex, and age may also be associated with pain and function in these patients (29). Conversely, in longitudinal studies symptoms correlated with tear size (117, 118), which was further confirmed narratively by a recent comprehensive systematic review examining the relationship between imaging features and shoulder symptoms (23). However, inconsistent results have been reported regarding the relationship between individual imaging-detected shoulder pathologies and symptoms in patients with RC tears (23).

Perception of pain and disability

A possible explanation for the lack of association found in our study may be that several factors other than the supraspinatus tear and the concomitant structural pathology investigated in the present study may influence shoulder pain and disability. For example, the presence of subacromial bursitis has been found to significantly increase shoulder pain (31), as nociceptors in the bursa may be activated as a result of tissue damage and inflammation in patients with supraspinatus tears (119). In addition, increased pressure on the coracoacromial ligament due to anterosuperior migration of the humeral head may also induce pain (120). Pain may also be related to labral pathology or cartilage lesions caused by the trauma (26, 121), however, in the present study the prevalence of these pathologies was too low to be included in the analysis.

Also, perhaps the explanation for no association could be that the pain perceptions from different structures may merge and give a uniform pain experience, and consequently patients or instruments used to quantify shoulder symptoms may simply not manage to distinguish between the symptoms from different pathologies. The complexity in symptoms and the unclear relationship with structural involvement has been investigated in other patient groups. For instance, no relevant association was found between structural knee pathology and self-reported pain and function prior to arthroscopic meniscal surgery (122).

Paper 2 & 3

Loading paradigm

The absence of difference between the two interventions may relate to the loading paradigm of the interventions. While our PR group performed an exercise program with early supervised active exercise therapy three times a week from day 8 (and home exercises the remaining four days a week), the UC group performed an exercise program with early supervised passive exercise therapy once a week starting from day 8 (plus home exercises the remaining six days a week).

Focusing on the loading of the exercise intervention, our intervention was based on evidence of tendon healing from basic science, including cadaver and animal studies on biomechanical and biological tendon healing capacity suggesting performance of continuous passive ROM exercises already during the early postoperative period (71). Further, loading the collagen increases tendon healing (57), thus based on biomechanical studies it has been anticipated to generate optimal tendon healing via controlled and gradually increased loading from passive to active exercises and with frequent resting periods (83). Although loading is important for optimal tendon healing (57), to our knowledge, only two RCT-studies (84, 123) and two prospective randomized pilot studies (85, 124) have focused on the loading of the exercise intervention, and the results are diverging. In line with the current results two of the studies found no difference in self-reported function (WORC, Constant Murley and Pain), AROM, and muscle strength between early active loading and delayed active loading (85, 123). In contrast, the other two studies found superior short term effects of early active loading vs delayed active loading, on self-reported function (DASH and Constant Murley and pain) (84, 124). Further, none of the four studies reported any increased re-tear rate in the intervention group (84, 85, 123, 124).

The remaining of the previous studies concerning postoperative rehabilitation have focused on timing of the exercise intervention (and not loading), which hampers comparison with the present study. Their exercise intervention were designed in an effort to protect the repaired tissue, promote healing, and prevent stiffness, and they have typically compared an early passive ROM intervention versus a 6 weeks delayed intervention (69, 70, 77, 78, 125).

Heterogeneity

The few existing and abovementioned primary studies published on the optimum time period for postoperative rehabilitation following RC repair vary, to a large extent, in timing and loading which

hampers overall comparison between studies (82). An example is the timeframes and thereby categorization of early intervention varying from day 2 to day 28 post-surgery, and in the delayed intervention varying from day 28 to day 56, with some of the studies not specifying the content of intervention groups, as also recently reported in an overview of systematic reviews on this area (82).

Evidence gap

As further support for the lack of primary studies, a large amount (n=15) of systematic reviews of varying quality have been completed within the past 5 years on almost the same few primary studies, showing in an attempt and desire to summarize the available evidence on postoperative rehabilitation following RC repair. Regarding early passive ROM, the latest review concluded that early passive ROM intervention may be beneficial, particularly for small and medium tears without compromising repair integrity; however, more studies with higher quality are required, especially for patients with large tears (73, 82). In contrast to the current study showing an overall re-tear rate of 11% with no group difference and on previous primary studies on early active loading (84, 123), the only existing systematic review focusing on tendon healing and early active loading, concluded that active ROM was associated with increased risk of a structural defect for small (< 3 centimetres) and large (> 3 centimetres) RC tears. However, that review only included two smaller primary studies (87). Unfortunately, this massive production of systematic reviews and meta-analyses may often be redundant, misleading, or even serving conflicted interests (126) and consequently appear incomprehensible instead of clarifying the evidence.

Repair integrity

The present study showed an overall re-tear rate of 11%, with no statistically significant group difference similar to previous studies (68-70, 77, 78, 84, 123). However, the study was not powered to detect differences in re-tear rate and comparison between studies is difficult, since the evaluation of repair integrity and thus the time course of healing or failure varies from 6 weeks to one year postoperative. Reporting repair integrity is important since timing and loading aspects of postoperative rehabilitation may influence the RC healing just as tear size and repair method (127), and it is anticipated that a healed RC repair results in a superior outcome for the patients compared with a non-healed repair (128).

Natural tendon healing

It is possible that the difference in intervention loading between the groups was insufficient to substantially influence/ overrule the natural healing process following surgical repair (55-57, 65, 83). Furthermore, since the surgical repair and postoperative physiotherapy is an integrated package for patients with RC tears it seems difficult to differentiate between effects of surgery and postoperative physiotherapy rehabilitation. It would require a third arm in the RCT with no exercises to investigate the natural healing process alone, however this was not possible for ethical reasons.

Methodological considerations

Paper 2 & 3

Outcome measures

In the current study, WORCPhysical was selected as primary outcome to be as specific as possible in relation to the selected population. In contrast, the two aforementioned studies focusing on loading that did find a superior short term effect of increased loading used other self-reported outcomes, such as DASH (84) which is a semi-generic upper extremity questionnaire and Constant Murley (124) which is a mixed subjective and objective score. However, in line with the current study results, the only previous RCT-study focusing on loading that did use WORC as a primary outcome measure also found no difference between groups (123). WORCPhysical (one subdimension of five in WORC Total) may not fully cover all self-perceived improvements, however, we also included additional subdomains as secondary outcomes. These found no difference between groups in the remaining subdomains (sports and recreation, work, lifestyle, and emotions) and in WORC Total. This is in line with the one previous study also reporting WORC Total with no group difference (123). Additionally, our results on the secondary self-reported outcomes DASH and NPRS also showed no group difference which further supports our results of the primary outcome.

Included population

Compared with other studies using populations of non-traumatic/ traumatic and partial/ full-thickness tear (68-70, 77, 78, 84, 123), the present population of traumatic full-thickness tears of one to three tendons may have had more severe or extensive damage (13, 30). This may have

resulted in difficulties in completing the progressive PR intervention (93) and thereby affected compliance or adherence to the PR-protocol. However, compliance calculation showed no difference between the current groups. In contrast to our study, all aforementioned previous RCT-studies (68-70, 77, 78, 84, 123) failed to document patient compliance or adherence to protocols which entirely hampers comparisons.

Recruitment challenges affecting project inclusion rate

We experienced major recruitment challenges partly caused by the Capital Region´s implementation of a new electronic health platform (the Epic System) (in Danish 'Sundhedsplatformen'), and partly caused by the relocation of The Shoulder-Elbow Unit from the Herlev location to the Gentofte location. Two months after recruitment began the elective surgery in the Department of Orthopedic Surgery was reduced to 50% for 5 months which clearly reduced project inclusion rate. Eight months later the relocation of The Shoulder-Elbow Unit also considerably affected project inclusion rate.

Clinically relevant improvements

The similarity in efficacy between the groups with narrow confidence intervals and sensitivity analyses supporting the ITT-results imply equivalent efficacy. This was seen in the similar clinically relevant group improvements from baseline to 12 weeks postoperative in WORCPhysical (MCID 11.7) (35), of 19.0 (PR) and 18.2 (UC); WORC Total (MCID 11.7), 17.7 (PR) and 19.2 (UC); and pain (NPRS mean (at rest/ during activity/ worst) (MCID 2) (99), -2.9 (PR) and -3.5 (UC). This is further in line with the current patient perceived global effect outcome measure (Global Rating Scale), where 73% (PR) and 61% (UC) felt overall improvement from baseline to 12 weeks postoperative.

Limitations

Paper 1

Although our study is not longitudinal it provides cross sectional evidence that structural characteristics of RC tears and the most frequent concomitant structural pathologies are not associated with pain and disability. The cross-sectional study design also means that prognostic factors are not taken into consideration, but on the other hand we adjusted for possible confounders such as age, sex, BMI & hand dominance. Only eight patients had no concomitant pathology, which

precluded any meaningful subgroup analyses, however, it illustrates that traumatic events often result in impairment/damage of several structures of the shoulder. Some of the concomitant pathologies are likely to be prevalent at the time of injury (e.g. hooked acromion or AC-joint osteoarthritis) but these do not seem to contribute to the symptoms related to the traumatic supraspinatus tear as patients with previous shoulder symptoms were not included. Additionally, we cannot rule out that the RC tears were acute-on-chronic (i.e. progression of asymptomatic pre-existing tears) in this population with an average age of 60 years. Due to the pragmatic nature of the present study, 9 different surgeons described the specific pathology identified during surgery, which may lead to different classification of pathology despite guidelines.

Paper 2 & 3

Using an exercise diary for home-based exercises may be a pragmatic, however perhaps not the optimal approach, as the validity and reliability of the self-reported measures of adherence to unsupervised home-based exercises is not sufficiently investigated (129). Therefore, this could be regarded as a limitation because of potential reporting-bias. Both the home-based exercises and the supervised on-site exercise therapy were included in the compliance calculations for a given patient. Patients were considered compliant if above 75% of both the home-based and on-site exercise program. Nevertheless, since we do not believe that one group was less reliable in their reporting than the other group, and that compliance did not differ (PR: 61% and UC: 68%, PP population), it is not likely to have biased the data.

Another limitation is the lack of double blinding, affecting patient expectations differently, whether allocated to the intervention or control even though patients were blinded to the study hypothesis. As previously mentioned, the lack of a third group with no postoperative rehabilitation may have implied an effect of the natural healing on the effect measure. However, this effect remains unclear, as this was not part of the study purpose. An age-related effect could have influenced the data, but since age did not differ between groups, this is not recognized as a limitation.

Strengths

Paper 1

A strength of the Paper 1 is the uniform group of traumatic supraspinatus tear patients. Another strength is the use of patient-reported measures with reliable and valid psychometric properties.

Also, the recording of pathologies was performed during surgery, which is considered a gold standard for diagnostics and superior to imaging such as MRI and US.

Paper 2

A major strength is that the protocol conforms to the recommendations of the Enhancing the Quality and Transparency Of health Research (EQUATOR) network (94) using the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist and the Consolidating Standards of Reporting Trials (CONSORT) statement (93, 95). Additionally, it is a strength that we used the TIDieR (96) checklist for reporting aspects of the exercise interventions. Also, Paper 2 complies to 16-item CERT (97) which provides useful guidance for clarifying information about the type of exercises, as well as exercise therapy details such as dosage, intensity, frequency, and whether or not supervision or individualization is required. Hopefully, this rigorous prepared and described protocol can be an inspiration for future intervention studies including transparency around predefining exercise intervention including progression.

Paper 3

The strengths are the rigorous methodological study design including blinding of examiners, publication of a statistical analysis plan prior to data handling, a blinded outcome analysis performed by an external statistician, publication of a consensus agreement on interpretation of the results prior to unblinding, and publication of a detailed study protocol including a standardized public exercise protocol for both intervention groups. Furthermore, the study had adequate power to detect clinically relevant improvements in disease-specific patient reported outcome measures (WORC and DASH). Another strength of the trial is that we measured compliance and adherence to both the supervised on-site and homebased exercises protocols and thereby were able to support ITT-results by sensitivity-analyses.

Generalizability

Paper 2 & 3

The randomization process stratified participants by age, sex, and center equally in the groups, resulting in high external validity, and thereby generalizable to most repairable traumatic full-thickness RC tears, along with a heterogenic socioeconomic population recruited from a large diverse urban area.

Conclusions

Paper 1

In the population of patients with traumatic RC tears we hypothesized that preoperative shoulder pain and disability were positively associated with the number of concomitant structural pathologies present in patients with a supraspinatus tear.

However, we found no association between the preoperative symptoms and concomitant structural pathologies and therefore the hypothesis of this study could not be confirmed. Our results suggest that a direct relationship between number of pathologies or type of pathology and preoperative shoulder symptoms is doubtful.

Paper 2 & 3

Further, on the basis of the limited evidence regarding the postoperative rehabilitation, we hypothesized that patients who received PR would benefit more with respect to improved shoulder function, pain reduction, and quality of life than those receiving UC. To test this we prepared and performed a rigorous RCT-study.

However, the hypothesis of this study could not be confirmed since patients performing PR did not improve more on WORCPhysical than patients performing UC at 6 and 12 weeks following surgical RC repair. Thus, UC was as effective as PR when measured on self-reported physical function. The secondary outcomes and sensitivity analyses supported this result. Our study further showed that both PR and the traditional UC improved significantly and at a clinically relevant level. Hereby, our results corroborate that initiating specific postoperative PR with functional activation of RC muscles entails no disadvantages compared with UC in terms of HRQoL, pain, ROM, strength, nor adverse events at 12 weeks follow up.

Perspectives and clinical implications

Paper 1

Lack/ absence of associations between preoperative shoulder symptoms and concomitant structural pathologies in patients with RC tears are important to keep in mind, when diagnosing shoulder pathology, making surgical decisions and in pre-operative information of the patients.
Also, the patients pain perception from different structures may merge and give the feeling of one consistent pain experience and the available instruments used to quantify shoulder symptoms may not be able to distinguish between specific structures. In a future study it would be interesting to separate partial and full-thickness supraspinatus tears, including tear size and type, as specifically the strength deficit may differ between the subgroups.

Paper 2 & 3

Our finding that initiating specific postoperative PR with functional activation of RC muscles entails no disadvantages compared with UC suggests that shared decision making between patients and therapists, based on preferences, can safely be performed to ensure improved clinical patient outcome. In line with the evidence based intervention in the present study current Clinical Guidelines (130, 131) now advocate commencement of active ROM exercises after an adequate period of passive ROM.

While successful arthroscopic RC repair requires accurate surgical techniques, it is also apparent that an individualized rehabilitation protocol supervised by skilled physiotherapists is equally important. As rehabilitation protocols often are based on clinical experience and expert opinions rather than scientific rationale, future research should be focused on more detailed time of loading and exercise quality in the progression through the overlapping rehabilitation periods. Further, long-term effects and potential health predictors are still to be investigated for the benefit of patients and tendon healing perspectives.

As seen from the current study surgery and postoperative training have positive effect on pain, function and quality of life. According to a recent prospective cohort study including 5 years follow-up, patient reported outcomes after surgical and nonsurgical treatments are not significantly different from each other (132). This may speculate whether training alone is just as effective as surgery or whether the natural tendon healing may overrule any intervention (nonsurgical or

surgical). Therefore, future Clinical Guidelines should provide evidence, based on high-quality research, regarding distinction between who should be offered training as first-line treatment, who will benefit from such training alone, and who will benefit from surgery including postoperative training.

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Appendices

Paper 1

Kjær BH, Juul-Kristensen B, Warming S, Magnusson SP, Krogsgaard MR, Boyle E, Henriksen M. Associations between shoulder symptoms and concomitant pathology in patients with traumatic supraspinatus tears. (submitted JSES).

Paper 2

Kjær BH, Magnusson SP, Warming S, Henriksen M, Krogsgaard MR, Juul-Kristensen B. Progressive early passive and active exercise therapy after surgical rotator cuff repair - study protocol for a randomized controlled trial (the CUT-N-MOVE trial). Trials. 2018 Sep 3;19(1):470. doi: 10.1186/s13063-018-2839-5.

- Additional file 1: Postoperative exercises for rotator cuff patients
- Additional file 2: Dotsheets explaining exercise therapy progression for PR and UC including unsupervised hometraining programme
- Additional file 3: SPIRIT checklist

Paper 3

Kjær BH, Magnusson SP, Henriksen M, Warming S, Boyle E, Krogsgaard MR, Al-Hamdani A, Juul-Kristensen B. Effects of 12 weeks of progressive early active exercise therapy after surgical rotator cuff repair – primary results from the randomized controlled CUT-N-MOVE trial (ready for submission in AJSM).

- Additional file: Per protocol analyses