Title (clinicaltrial.gov): Exercise Into Pain in Chronic Rotator Cuff Related Shoulder Pain: a Prospective Single-Group Feasibility Study

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Description of this document:

This research proposal was approved on 6/11/2020 by the expert panel on Medical Sciences from the Flemish Research Council (FWO). It is described in pages 2-14 of this document.

Afterwards a progress report was submitted on 11/5/2022 to FWO and then positively re-evaluated. It is described in pages 15-18.

Ethical approval for the original protocol had been already obtained from the Ethical Committee of the University Hospital of Antwerp (ref:B300201837376) on 10/09/2018 and four subsequent amendments have been approved during the PhD project.

Rationale And Positioning With Regard To The State-Of-The-Art

Shoulder pain is the third most common musculoskeletal disorder, with lifetime prevalence ranging from 10% to 67% [1,2] and high reoccurrence rate of 41% after 1 year from the initial presentation [3]. The socio-economic burden of shoulder pain is mainly due to sick leave, representing 84% of the total cost per patient in a Swedish cost-of-illness study. On the other hand, the mean healthcare cost is 326 euros per patient with physiotherapy accounting for 60%[4]. Currently, non-operative management in form of physiotherapist-led exercises is the primary choice of treatment [5] and subacromial shoulder pain (SSP) is the most commonly diagnosed shoulder complaint [6]. However, it is not clear which are the best types of exercise, and in particular if pain should be elicited or avoided during exercise [7,8]. In the current framework of the concept "hurt not equalling harm" [9], we propose that the therapeutic modality of "exercising into discomfort" has strong benefit in the treatment of SSP. Numerous studies have been conducted on SSP but none has investigated the specific role of exercising into discomfort on shoulder pain and functionality. Therefore, **the main aim of the current proposal is to investigate the effectiveness of exercising into discomfort** in order to achieve faster and superior benefits in pain and function. Patients and physiotherapists will be the first beneficiaries of this project: reconceptualising the role of pain in exercise therapy will improve the conservative treatment in SSP, leading to postpone or even avoid surgery and reducing the high recurrence rate and healthcare costs. If successful, this can be proposed in the future for the management of other chronic tendinopathies.

Previous studies have clearly shown that shoulder **exercises are the preferred first choice of treatment for patients with SSP** [5,10-13]. National guidelines recommend active rehabilitation strategies for at least three months and limited use of glucocorticoid injection [14,15]. Numerous systematic reviews have been conducted on different modalities of exercise therapy in terms on specific muscle-activation (scapular-focused approach [16]), type of contractions (eccentric exercises [17]) or training modalities (such as stabilization or proprioception [18]), but no strong recommendations on the superiority of one approach to another can be drawn[18]. A review of systematic reviews suggested that loaded exercises and higher doses could provide superior benefits [19]. Another recent systematic review [9] advocated that exercising into discomfort in general musculoskeletal chronic pain could facilitate the reconceptualization of pain by addressing fear avoidance, self-efficacy and catastrophizing beliefs within a framework of "hurt not equalling harm" [9]. The rationale behind this approach lies on the analgesic effect of exercise as a form of endogenous pain modulation, which increases the pain threshold and reduces the pain intensity ratings through endogenous opioids and endocannabinoid mechanisms, occurring at peripheral, spinal and/or central sites [20]. Moreover, exercising a de-conditioned tissue allows the central nervous system (CNS) to reprocess the perceived painful stimuli into a new positive perception so the painful movement can be reintroduced progressively [21,22].

The experience of discomfort during training is already well-documented in the rehabilitation of lower limb tendinopathies: significant improvements were reported in RCTs where the progression and load of exercises were individually prescribed using the pain monitoring system (through the Visual Analogue Scale, VAS or Numeric Pain Rating Scale NPRS) for both patellofemoral pain [23] and Achilles tendinopathies [24]. Similarly, in shoulder rehabilitation research, promising results were found in an RCT comparing specific (loaded) exercises versus non-specific exercises in patients with subacromial impingement syndrome [25]. The authors reported a reduced need for surgery at 1 and 5 years of follow-up [25,26], and a significantly greater improvement of pain and shoulder function in the specific exercise group, in whom the pain monitoring model was used to score the individual resistance for each patient. However, in all previous studies pain during exercises was never exceeding 5/10 on VAS scale[23-25,27], even in studies which claim to test a painful strategy versus a non-painful one [28]. Hence, the role played by pain during exercise is not clear and since different exercises are equally clinically successful, it is more important to give individualized loaded exercises instead of one-size fits all programs, whatever the concept is (motor control, eccentric exercises, scapular exercises). Despite the potential of

resistance training**, it remains uncertain what dose of resistance should be given and whether the patient will benefit from having some discomfort/pain during the training or not.** [7] Therefore, the first objective of this project is to test **the effectiveness of exercising into discomfort in a strength training program on pain and function.**

The uncertainty in the best-evidence practice is also due to the multifactorial aetiology of SSP. The major hypothesis is that a reduction of the space between the acromion and the glenohumeral joint, the so-called subacromial space, causes an encroachment of the soft tissues during arm elevation, often referred to as "shoulder impingement" [6,15,29]. The subacromial tissues mainly involved are the rotator cuff (RC) tendons, [29] encountering degeneration and inflammation [6,30]. However, this anatomical "impingement" theory does not sufficiently explain the pathophysiology [15], which in fact displays a multifactorial aetiology[31,32]. Both intrinsic and extrinsic mechanisms are involved in SSP; the former in terms of degeneration of the tendon itself [31], the latter in terms of compression of the RC tendons. Intrinsic factors are linked to tendon degeneration, due to the natural process of aging, altered biology, genetic predisposition and tendon mechanical properties [31,32]. Extrinsic factors originate externally from the RC tendons and include anatomical variants of the acromion, alterations of humeral or scapular kinematics (named scapular dyskinesis), muscle imbalance, postural deviations and soft tissue tightness. In particular, **scapular dyskinesis is a key component** in the production of symptoms in SSP, in association with muscle imbalance or inadequate activation patterns (i.e. decreased activity of the serratus anterior and lower trapezius, and overactivation of the upper trapezius) [33]. However, the presence of scapular dyskinesis is not always associated with changes in shoulder symptoms and function during and after the rehabilitation. Therefore, **the second objective is to investigate whether improvements in shoulder pain, function and quality of life is positively related with reduced presence of scapular dyskinesis.**

In this context, ultrasound (US) imaging has the potential to quantify the changes in the subacromial space and in the tendon structures during the rehabilitation process. US is able to characterize tissue using high-frequency sound waves, which is typically between 5 and 12 MHz in the musculoskeletal field [34]. It has numerous advantages: it is non-invasive and non-radiating compared to radiography or computed tomography (CT) scan, cheaper and with higher image resolution than Magnetic Resonance Imaging (MRI), and available also as portable device [34,35]. On the other hand, it is highly operator-dependent and artifacts on the US image, such as anisotropy in tendon examination, can easily be encountered [36]. Nevertheless, a standardized procedure and a thorough training can minimize these pitfalls [37,38]. The subacromial space can be measured by US imaging as the articular distance between the acromion and the humeral head, called the acromiohumeral distance (AHD) [37-39]. This measurement has shown to be reliable and sensitive [30,37,40]. US can also detect tendon thickening, which is a sign of tendinopathy[37]. Numerous studies have specifically analysed the supraspinatus tendon thickness (STT), as this is the RC tendon mostly involved in SSP [40,41]. Although contrasting results have been found regarding differences in the STT between symptomatic and asymptomatic participants [37,38,41,42], it is possible that thicker tendons are more apparent in early stages of SSP and thinner in later stages [31]. In contrast, a systematic review concluded that RC abnormalities, such as degeneration or thinning, occur equally in symptomatic and asymptomatic populations, suggesting that these changes are part of the normal aging process [43]. Moreover, the interplay between STT and subacromial space was recently described as an occupation ratio, which represents the proportion of the subacromial space occupied by STT [41]. This ratio was higher in patients with SSP, showing that STT occupied a greater percentage of the subacromial space. However, until present **the mechanistic role of the subacromial space and its relationship with RC tendons thickness has not been studied in relation to the recovery process of SSP**. This could however provide useful knowledge on the working mechanisms of SSP therapy. Therefore, the **third objective is to examine the effects of exercising into discomfort on changes in subacromial space (quantified as acromiohumeral distance –AHD-) and tendon structures measured by US imaging in SSP patients.** As such, unravelling the factors contributing to the SSP recovery process will help clinicians to better steer their therapy and adapt therapeutic parameters during physiotherapy.

The relationship between clinical symptoms and tendon structural changes/subacromial space is a matter of great debate. Contrasting results are present in the literature regarding the relationship between subacromial space (measured as AHD) and functional improvement, with some studies showing a strong correlation [30] and others suggesting the opposite [44]. However, the relationships between AHD and functional improvements during and after treatment has not been largely explored and it warrants further investigations [45]. Concerning the association between STT and clinical outcomes, increased STT has been linked to decreased muscle strength and palpable tenderness [42], making it a reproducible parameter of tendon state during the rehabilitation process. In daily general practice, combining clinical information with US findings could aid the prescription of tailored exercises for SSP patients, leading to improved patient outcomes. **Therefore, in the fourth objective this study will elucidate the relationship between US findings and clinical symptoms during and after 'exercising into discomfort'.**

In summary, although physiotherapy offers promising results in the recovery of SSP, it is still not clear which type of exercise provides the best outcome and whether the patient should feel discomfort during the performance of an exercise, or pain should be avoided. This project aims to provide clinical evidence for the 'exercise into discomfort' approach, which can influence the entire concept of the management of SSP, contributing to the development of the best evidence-based practice in physiotherapy and reducing the relative healthcare costs of SSP. If this concept is proven to be successful, it confirms how the body's analgesic system is able to tackle its own pain similarly to other chronic pathologies such as patellofemoral pain or low back pain. This project will rely on both clinical outcomes (pain, function, scapular dyskinesis) and objective measures of subacromial space and RC tendon changes acquired with US. In this way, we will be able to track the evolution of subjective and objective changes happening during and after the rehabilitation process and how the presence of pain/discomfort during exercise influences them.

Scientific Research Objectives

The primary aim of this project is to provide proof-of-concept for the clinical effectiveness of the "exercising into discomfort" approach in patients with SSP. In the first three objectives, the focus will be on its effect on shoulder pain and functionality (patient-reported outcomes, objective 1), on scapular dyskinesis (objective 2), subacromial space, and the tendon structures (objective 3) during and after 3 months of exercise therapy in patients with SSP. In the fourth objective, the relationship between patient reported outcomes and the US measurements during the treatment course will be explored. Two groups will be compared in a randomized controlled trial (RCT): an intervention group "exercising into discomfort" (G1) and a control group "exercising without discomfort" (G2). The time points of assessment will be prior to the treatment at baseline (T0), at 6 weeks during treatment (T1), end of treatment at 12 weeks (T2), and follow up at 26 weeks (T3).

OBJECTIVE 1	**To investigate the effectiveness of exercising into discomfort during a strength training program in the treatment of SSP on self-reported shoulder pain and function**
Methods	Double Blind Randomized Controlled Trial comparing 2 groups (G1 versus G2), with SPADI (Shoulder Pain and Disability Index, a valid and reliable patient-reported outcome measure of pain and disability [46]) as primary outcome. A "high pain monitoring model" will be used to monitor pain during and 1 hour after every exercise in G1 (see "intervention" in methodology).
Hypothesis	In G1 SPADI will be reduced more than in G2.
Novelty/ Relevance	If successful, the results of this study will lead to a reconceptualization of exercises in SSP, allowing pain (defined as discomfort sensation) to be an essential component and not a barrier in the physiotherapy treatment.

OBJECTIVE 2	To investigate whether improvements in shoulder pain, function and quality of life is positively related with reduced presence of scapular dyskinesis
Methods	Scapular dyskinesis will be registered by visual observation at rest and during movements (abduction and flexion) and its effects on pain will be tested by scapular assistance test and scapular retraction test
Hypothesis	Scapular dyskinesis will decrease more in G1, in relation to the increase in strength and coordination of the scapulothoracic and scapulohumeral muscles.
Novelty/ relevance	Although the scapular control will be integrated in the exercises in both groups from the first session, we expect a greater improvement in G1 thanks to both increased muscle strength and regained self-efficacy in movement performance. Therefore, it is relevant to register how scapular dyskinesis is evolving during treatment in order to understand when and in which subgroups of patients it is contributing to symptoms of SSP.

OBJECTIVE 3	To investigate the effects of exercising into discomfort on changes in subacromial space (quantified as acromiohumeral distance AHD) and tendon structures measured by US imaging in SSP patients
Methods	Analysis of the secondary outcomes (subacromial space and tendon structure changes measured by US imaging) of the RCT conducted in objective 1
Hypothesis	In both groups there will be an increase in the subacromial space and decrease in STT. These changes will be more evident in G1
Novelty/ Relevance	The lack of understanding of tendon structural changes in "exercising into discomfort" in patients with SSP contributes to the inadequate management of this pathology. Information on such parameters will provide insights into the mechanisms behind this modality of exercise therapy during and after the end of the treatment. Moreover, this study aims to clarify the role of the subacromial space as a valuable indicator of SSP recovery. To the best of our knowledge, this is the first time that tendon structures are monitored during the treatment other than before and after rehabilitation (assessment at T2).

OBJECTIVE 4	To examine whether improvement in shoulder pain, function and quality of life is associated with changes in the subacromial space and tendon structures as measured by US imaging
Methods	Analysis of possible association between parameters measured by US (subacromial space, RC tendon thickness) and clinical symptoms (self-reported shoulder pain, questionnaires on functionality and quality of life) at T0, T1, T2, T3 in the RCT
Hypothesis	There will be a significant correlation between US imaging parameters and clinical symptoms
Novelty/ Relevance	There is contrasting evidence in the literature regarding the association between subacromial space and clinical symptoms. This study will elucidate this question and further enhance the knowledge regarding other significant tendon changes (i.e. combining AHD and RC thickness in the occupational ratio) during and after exercising into discomfort, laying the groundwork for future prognostic studies.

This project proposal is organized as a collaboration with other partner universities, relying on different expertise: Prof. Filip Struyf (University of Antwerp, Belgium) will be the main promotor of the PhD student and he is currently the world leading expert on shoulder pain (http://expertscape.com/ex/shoulder+pain); Prof. Luque-Suarez Alejandro (University of Malaga, Spain) will give guidance in the US training together with Santiago Navarro-Ledesma, who obtained a joint PhD degree (Malaga – Antwerp) on the use of US in rehabilitation for shoulder pain; Prof. Juul-

Kirstensen Birgit (University of Southern Denmark), expert on exercise therapy in shoulder pain and Dr. Lennard Voogt (University College Rotterdam) expert on assessment and management of chronic musculoskeletal pain. They wrote the initial project for the grant at the University of Antwerp together and they gave and will give continuous assistance during all the phases of the project (definition of the intervention, feasibility study, reliability study on US measures, RCT).

Research methodology and work plan

WP1: Preparation of the trial

In the previous academic year 2018/2019 the PhD student focused on the preparation of the trial, which included different tasks reported in the work plan in Table 1 (page 10).

Literature review and survey on current physiotherapy practice

The first task was to develop an intervention protocol for the modality "exercise into discomfort". In order to achieve this goal, a literature review on exercise therapy in SSP is being conducted. The PhD student collaborated also in a survey on current physiotherapy practice in Belgium and the Netherlands, which has been recently published in peer-reviewed journal (Task 1.1, work package WP1,Table 1). With this background information, the PhD student together with the research team designed the intervention (Task 1.2, WP1) during the academic year 2018/2019. After ethical approval, the successful recruitment of physiotherapists for the feasibility study started.

Feasibility study

In the recruited private practice, the feasibility study is now ongoing (Task 1.3, WP1). It includes 12 patients, which will allow to test 80% of compliance rate, ranging between 0.78 and 0.84 within a 95% of confidence interval. This number was obtained with the "Score method incorporating continuity correction" reported by Newcombe et al. [47]

The feasibility study aims to: 1) test a high-pain monitoring model (which is the intervention applied in G1 -"exercise into discomfort"-) and the rate of adherence to this modality, 2) test the rate of recruitment at this private practice, 3) verify adverse effects 4) test the practicability of delivering clinical questionnaires via online survey Qualtrics, 5) provide an indication of the time needed to collect the data.

The high pain monitoring model is based on the pain monitoring model which has been previously used in many studies[23,24,48,49]. The difference is that the pain during exercise is higher than in the previous studies until the 9th week, with certain caveats: 1) during the exercises, the patient should feel discomfort/pain exceeding the pain at rest, ranging between 4 and 7 on NPRS (Numeric Pain Rating Scale). During the last set of 10/15 repetitions pain should not exceed 7; 2) Discomfort/pain should return to baseline level after 1 hour; 3) Discomfort/pain should not increase from day to day. In the last phase of the treatment (between 9th and 12th week) the pain during exercise ranges between 0 and 2 on NPRS, in order to allow the patient to focus on more proprioceptive and sport/work related tasks. A preliminary analysis of the data on 6 patients at the 6-week follow-up showed that all the subjects attended at least 4/6 physiotherapy sessions and they were all adherent to the home exercise (at least 10/11 home exercises completed) except one patient. Two patients experienced a slight increase (1 point on NPRS) in the level of pain after the physiotherapy or home exercise in the first three weeks. Discussing with both physiotherapists and patients, this was related to an increased level of sport in the same period or due to additional treatment of the posterior capsule, which can provoke initially some pain. The physiotherapist adapted the exercise and from the 4th week onwards the pain decreased to initial levels after 1 hour of exercise. Moreover, it emerged that a measurement of the pain after 1day was necessary to evaluate the evolution of the pain after painful exercises. This will be added in the design of the RCT and it is also in line with the recent recommendation for evaluating pain during and after exercises[50].

The rate of recruitment at this private practice was 5 patients per month, which means we will be able to recruit 60 patients for the RCT at this practice in 1 year (WP2), thereby minimizing the recruitment risk inherent to RCTs. Two physiotherapists conducted an initial screening at the first visit based on the history taking, which allowed to exclude 37 patients. If considered eligible, the patients underwent to a second screening phase led by the PhD student: only 3 patients were excluded at this time point. The estimated time for the screening is 30 minutes while 1 hour is necessary for the rest of the measurements. Qualtrics proofed to be a practical modality of taking clinical questionnaires because no data were lost, and the patients who did not filled in the questionnaire within 2 days were sent a reminder.

Ultrasound measures

In May 2019 the US machine was bought with the budget of the doctoral grant. In August 2019 the PhD student followed a training on US imaging during a research stay of 4 days under the supervision of the US expert Santiago Navarro Ledesma at the partner University of Malaga (Task 1.4, WP1). In February 2020 this researcher came to Antwerp for a 2-week period to conduct an inter-reliability study on the US parameters previously decided and discussed during the research stay. This part of the project is currently in the phase of data analysis. This will allow to validate the skills of the PhD student as novice sonographer and to decide which US measures are valid and reliable to be part of the second phase (RCT, WP2). The US measures are described in WP2, under "Outcomes measures".

Ethical approval and fine-tune protocol

Ethical approval for the original protocol has been already obtained from the Ethical Committee of the University of Antwerp. The reliability study and feasibility study have been added and approved by submitting two amendments. The whole protocol will be analysed and modified based on the feedback of the physiotherapists and the patients. A revision of the protocol after the feasibility study will be critically analysed together with the rest of the research team in April 2020 during one or more Skype meetings and, if necessary, also submitted as amendment to the Ethical Committee.

WP2: Randomized controlled trial

Design

This study will be conducted as an experimental randomized, controlled, double-blind trial (RCT) in one physiotherapy practice in Belgium. The patients with SSP will be randomized into one of 2 groups (concealed, permuted block randomization of 2,4,6 size using randomisation.com), being either exercising into discomfort (G1) or exercising with slight/no discomfort (G2).

All training sessions will be applied for 12 weeks, three times weekly. The time points of assessment will be: before the start of the treatment (T0), at 6 weeks (T1), 12 weeks (T2), 26 weeks (T3). All participating patients will follow the flowchart illustrated in Figure 1.

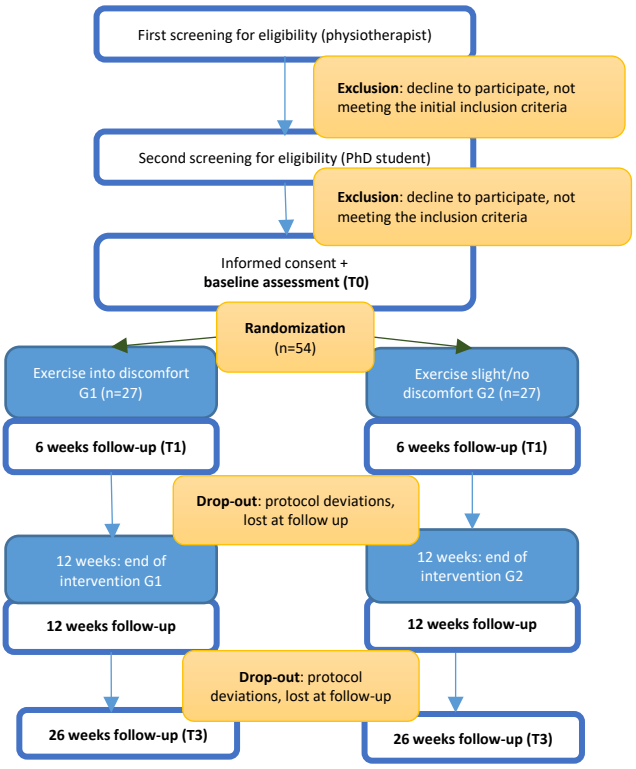

Figure 1 Flow chart

Sample size

The sample size calculation was made using the Edland method, R package longpower 1.0-11[51], based on the following data: 8% points as smallest clinically important difference in SPADI [52], 15% of estimated drop-out (as mean of dropout rates from previous studies [53-55]) and 30% for adjustment

for non-linearity of the data (since there is usually a higher decrease in SPADI in the first 3 months compared to 6 months). Considering a mixed regression model for repeated measures and using a moderate effect size (corresponding to 8% as smallest clinically relevant difference), confidence level at 5%, and power at 90%, the required total sample size is **54 subjects**, taking into account 15% drop-out rate**.** The variance of the residuals cannot be estimated from previous studies, but it has a very limited effect on the sample size. It does not change the result of the power calculation, and therefore it is not included in this analysis.

Physiotherapist and patient recruitment

The physiotherapists participating in the feasibility study agreed in taking part to the second phase of the project (Task 2.1, WP2). They will perform a standardized initial screening of all patients referred with SSP diagnosis. The rate of recruitment estimated in feasibility study will allow us to recruit 54 patients in 1 year time, between April 2020 and April 2021. The last measurement of the last patient should be in October 2021 (6 months follow-up, Task 2.3, WP2). Following the successful procedure developed in the feasibility study, the patient will be screened in two phases: first by the physiotherapist and, if they are willing to participate, secondly by the PhD student at a separate visit.

The **inclusion criteria** are: 1) patients aged 18-65 years old; 2) referred to non-operative physiotherapy treatment due to shoulder pain; 3) shoulder pain for at least three months' duration prior to enrolment; 4) at least three of the following positive provocative shoulder tests: Neer test, Hawkins-Kennedy test, Jobe test, painful arc, external rotation resistance test [56].

The **exclusion criteria** are: 1) resting pain more than 2/10 on VAS scale; 2) bilateral shoulder pain; 3) history of shoulder surgery, fracture or dislocation; 4) clinically (positive drop-arm test, external or internal rotation lag test) and/or previous ultrasonography examination confirming the presence of full-thickness rotator cuff tear or calcifications larger than 5mm [57]; 5) evidence of adhesive capsulitis; 6) corticoid injections 6 weeks prior to the study. Further exclusion criteria are: history of cervical or thoracic spine surgery, primary complaint of spinal pain or signs of CNS involvement or signs of cervical nerve root involvement; presence of competing pathologies (inflammatory arthritis, neurological disorders, fibromyalgia, malignancy, psychiatric illness, etc.); primary diagnosis of acromioclavicular pathology, shoulder instability. Furthermore, patients will be excluded if they have a radiologically confirmed fracture, pregnancy or inability to understand spoken and written Dutch.

Intervention

It corresponds to "Task 2.2", WP2 in Table 1 (page 10). Every physiotherapy session lasts 30 minutes and it includes 20 minutes of exercise therapy based on 4 strengthening exercises and 10 minutes of manual therapy (focusing on the release of posterior capsule). The manual therapy will be applied to all the patients without distinction to the two groups. The exercise therapy will be the distinct element between the two groups: group 1 (G1, exercising into discomfort) will execute exercises with pain intensity from 4/10 to maximum 7/10 on a NPRS scale, while group 2 (G2, exercising with slight/no discomfort) will execute not/slightly-painful exercises with pain intensity inferior to 2/10. These limits are set in order to ensure a clear difference in pain intensity between the two groups and a preliminary analysis of the feasibility study showed it was possible for the patient in G1 to train between 4 and 7/10 following the high-pain monitoring model. The pain level in G1 will decrease to 0-2 at 9th week so the patients can focus on more proprioceptive or sport/work related tasks. The exercises are individually prescribed and each patient will have 4 personalized strengthening exercises, with one focusing on the painful direction (which is usually abduction, flexion or external rotation) and the rest of exercises will elicit pain but not in the painful direction (for example, closed kinetic chain exercises or exercises with elastic bands). The aim in both groups is to gain strength in both scapulothoracic and scapulohumeral muscles, re-balancing the force couples in the shoulder joint during specific movements (i.e. re-train arm elevation in which a lower activity of serratus anterior and overactivation of the upper trapezius is present), without isolating one muscle during the exercise. Scapula stabilization exercises will be integrated with rotator cuff strengthening in one exercise (i.e. closed kinetic chain as push-up) from the first session, since recent studies showed that the order of exercise

(scapular and then RC exercises or vice versa) was not affecting significantly the clinical outcomes[58]. Our hypothesis is that a painful shoulder program focusing on strengthening exercises, with certain caveats, will load the shoulder muscles allowing a better and possibly faster recovery.

The choice of the research team to not choose a particular and specific sets of exercises was motivated by two main reasons: 1) allow the physiotherapist to prescribe individualized exercises and 2) let the physiotherapist progress the exercise based on patient's needs (sport, work-related activities) and to adapt it on the load provoking pain. In both groups, lifestyle advice, ergonomics corrections, pain education regarding the subacromial shoulder pain will be provided, in line with current physiotherapy practice in Belgium[59]. We believe that this approach of "exercising into discomfort" can give a different insight in the treatment of SSP but it will remain well-integrated in the current physiotherapy practice.

Outcome measures

All outcomes will be measured at baseline (T0) and 6 (T1), 12 (T2), 26 (T3) weeks and the assessors will be blinded to group allocation. The **primary outcome** is the **difference in mean change between groups from T0 to T1, T2 (12 weeks, end of the treatment), and T3 (26 weeks, follow-up)** in the patient self-reported outcome score **Shoulder Pain and Disability Index (SPADI)**. This questionnaire is a patient-reported outcome measure (PROM) with high test–retest reliability and construct validity [46] and is available and validated in Dutch [46].

Secondary outcomes are registered for each patient at the same time points as the primary outcome, except for the Global Perceived Effect Score, which will be assessed after 1st treatment and then at 6 and 12 weeks. The secondary outcomes are:

Scapular dyskinesis: The procedure we will use is based on the procedures described by Tate et al. [60] and Struyf et al. [61]. Scapular position will be observed at rest and during active loaded and unloaded humeral motion in a frontal and sagittal plane. The effect of scapular correction will be tested by means of the modified scapular assistance test and scapular retraction test [61,62]. Reduction of pain during these tests compared with non-assistance during the same tests confirms scapular involvement in the shoulder complaints.

Subacromial space: Acromiohumeral distance (AHD) is a US measurement used to quantify the subacromial space. It is defined as the shortest linear distance between the most inferior aspect of the acromion and the humeral head [30]. AHD is measured at 0 and 60 degrees of active shoulder elevation in the scapular plane, following the procedure of measurement indicated by Navarro-Ledesma et al [39]. It has already been used to evaluate different populations, such as healthy volunteers [39] and patients with shoulder pain [30,37].

Tendon changes: Tendon structural changes (limited to RC thickness and long biceps) will be evaluated using US device and following international guidelines [37,41,44,63]. STT will be also computed as percentage of subacromial space, known as the occupation ratio (using the formula [(STT/AHD)*100] [41].

Shoulder strength and Range of Motion (ROM): Shoulder strength is measured as isometric strength measurements with handheld dynamometer (IsoForce Dynometer EVO2; Medical Device Solutions AG) in abduction external rotation and scapular plane elevation. ROM in active and passive abduction and external/internal rotation will be determined with a goniometer (HALO digital goniometer; HALO, Medical Devices). These devices are already available at the University of Antwerp.

Shoulder related Quality of Life: Health-related Quality of Life index and Health-related Quality of Life VAS, measured with the EQ-5D-5L [64].

Adherence: The pain and the amount of exercise performed will be recorded in an exercise and pain diary. The participants will be asked to complete a pain diary, reporting pain on the VAS scale before and 1 hour and 1 day after each training session as well as the home training. Adherence will be analysed in terms of compliance with self-reported exercise diary: good compliance is defined by attendance of 6/9 supervised sessions and 80% of 27 home exercises.

Fear of pain questionnaire-9 and Fear-Avoidance Beliefs Questionnaire (FABQ): these outcomes allow qualitative analysis of which patient characteristics (i.e. high level of anxiety and fear associated with pain) undermine compliance in case low adherence is observed. These questionnaires are both psychometrically sound and validated in Dutch [65-67].

Other relevant outcomes: Patients fill out the global perceived effectiveness (GPE) rating (1-much worse, 2-slightly worse, 3-no change, 4-slightly better, 5-much better) after the first session, at 6 and 12 weeks [68].

WP3: Data analysis

Statistical analyses will be performed using JMP ®Pro 14.0.0 (SAS Institute Inc., Cary, NC, USA) . Level of significance is set at p= 0.05. Appropriate descriptive statistics will be performed.

OBJECTIVE 1,2,3: A mixed regression model for repeated measures will be used to assess both the evolution of SPADI (pain and function), strength, ROM and US parameters within persons from baseline (T0) over time (T1, T2, T3) and the differences in evolution between subjects. Potential confounders are: age, gender, BMI, previous corticosteroid injections, severity of initial symptoms. They will be measured during the history taking at the first assessment and added into the mixed regression model as co-variants. If for a certain variable the percentage of missingness will be more than 15%, multiple imputation for missed observation will be used. There are three assumptions for the mixed regression model: change over time, a sensible measure for time (multiple time points of measure), normality of residuals (it will be checked using a Shapiro-Wilk test). If these residuals are not normally distributed, an appropriate transformation will be performed first. Therefore, this model best fits the longitudinal design of the RCT. **OBJECTIVE 4**: correlation analysis between tendon structures and clinical symptoms using the correlation for pairs of continuous variables in JMP.

Work Plan

Table 1 shows the overall timeline of this four-year project, including the following four work packages (WP): the preparation of the trial (WP1), the RCT (WP2), data analysis (WP3), finalizing PhD (WP4). The main 4 milestones are: fine-tune protocol after feasibility study (M1), end of patients recruitment (M2), end of data analysis (M3), submission and correction of relevant publications (M4).

	Year	2019				2020				2021				2022				2023			
	Quarter	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*
WP1: preparation of the trial																					
Task 1.1	Systematic review in exercise in SSP, survey on physiotherapy practice in SSP																				
Task 1.2	Development of intervention protocol																				
Task 1.3	Feasibility study																				
Task 1.4	US training, US reliability study																				
Task 1.5	Fine-tune protocol, ethical approval																				
WP2: RCT																					
Task 2.1	Baseline measurements T0 (0w)																				
Task 2.2	Intervention – T1(6w), T2 (12w)																				
Task 2.3	Follow up – T3 (26w)																				
WP3: Data analysis																					
Task 2.1	Data analysis for Objectives 1,2,3,4 (T0,T1,T2)																				
Task 2.2	Data analysis for Objectives 1,2,3,4 (T3)																				
WP4: Finalising PhD																					
Task 4.1	Writing articles (systematic review, feasibility study, protocol RCT, RCT)																				
Task 4.2	writing PhD thesis																				
Task 4.3	Submission and defence																				
Milestones								M1				M2				M3				M4	

Table 1 Timeline of 4-year project. WP=Work packages, T0=baseline, T1=6weeks, T2=12weeks, T3=26weeks

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Specify the progress of your PhD project.
If you deviate from the approved application please describe and motivate.

Table 1 shows the overall timeline, including the following five work packages (WP): the preparation of the trial (WP1), the RCT (WP2), data analysis (WP3), writing articles and finalizing PhD (WP5). The main 4 milestones are: fine-tune protocol after feasibility study (M1), end of patient's recruitment (M2), end of data analysis for RCT (M3), writing PhD dissertation (M4). The project was financed by the University of Antwerp from 1/10/2018 to 30/10/2020 and by the FWO from 1/11/2020 to 31/10/2022. The timeline has been adapted and it is based on recruitment rate for the RCT of the last two years, impacted by the Covid-19 pandemic. Changes compared to the initial FWO project are described in detail below.

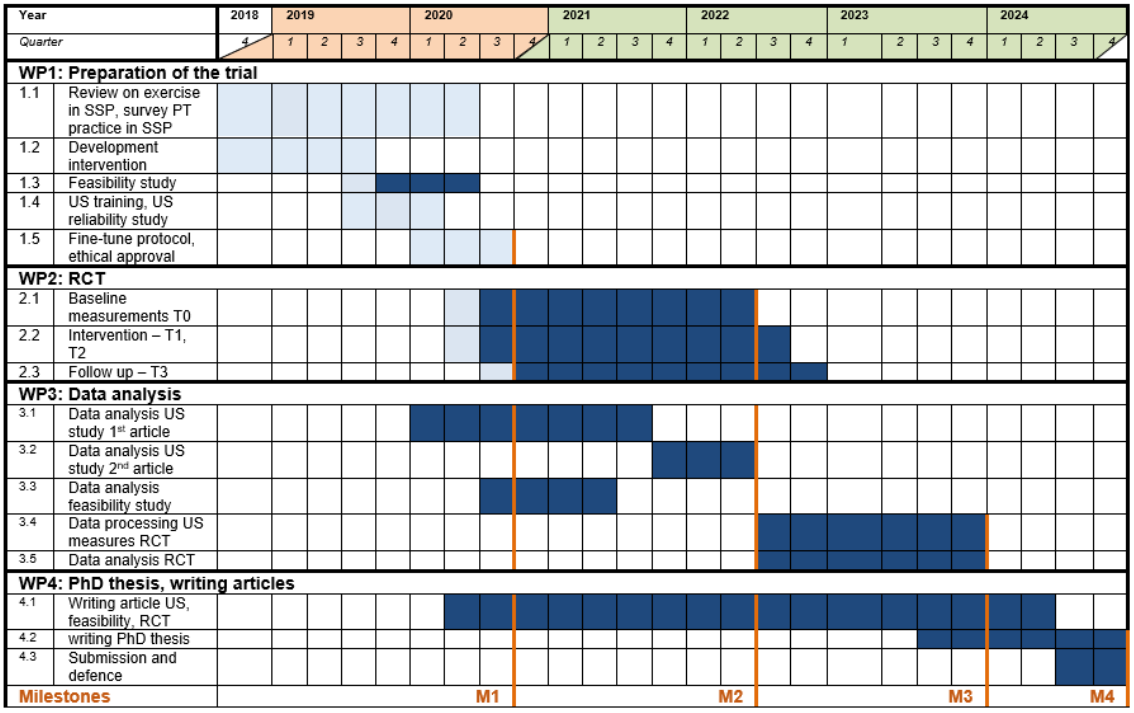

***Table 1 Timeline**. The years in orange indicate the funding from DOCPRO (University of Antwerp) and the years in green indicate the funding from FWO. Abbreviations: M=Milestone, PT=physiotherapy, RCT=Randomized Controlled Trial, SSP=Subacromial Shoulder Pain, T0=baseline, T1=9weeks, T2=12weeks, T3=26weeks, US=Ultrasound, WP=Work package. The initial timeline proposed in the FWO project is in light blue, adaptations to the timeline are indicated in dark blue.*

WP1: Preparation of the trial

Development of the intervention for the RCT (WP1: 1.1, 1,2): Aim: develop the intervention protocol for the RCT based on the most recent literature about exercises in subacromial shoulder pain. The intervention protocol was developed by October 2019. Moreover, a survey on current physiotherapy practice in Belgium and the Netherlands was published to serve as a starting point for the intervention (co-authorship, see Publication list). *Status*: completed according to the plan.

US training and US reliability study (WP1: 1.4): Aim: validate the skills of the PhD student as novice sonographer. In August 2019 the PhD student followed a US training during a 4-days research stay supervised by the US expert Santiago Navarro Ledesma. In February 2020 the US expert came to Antwerp for a 2-week period to conduct an inter-reliability study on the US parameters previously decided and discussed during the research stay. *Status*: completed according to the plan.

The research stay proposed in the first FWO project in Denmark in September 2020 on the use of the sonoelastography, which is an US feature detecting differences in the elasticity of the soft tissues, was not conducted. It was not possible to measure this feature with the available US machine and the PhD student acquired the necessary US skills already in the reliability study phase performed in February 2020 for the relevant measures for the RCT.

Feasibility study and fine-tune the protocol (WP1, 1.3 1.5): Aim: a feasibility study on exercise into discomfort was performed from November 2019 to May 2020. *Status*: completed (start delayed compared to FWO initial project, from Q3-2019 to Q4-2019). A critical revision of the protocol for the RCT was performed after the feasibility study, as mentioned in the FWO application. Some changes were necessary to the protocol. **1) Changes to the intervention in the RCT:** the intervention in the RCT changed from 4 exercises into discomfort between 4-7 on a Numeric Pain Rating Scale (NPRS, scale 0-10) proposed in the initial FWO application to 1 exercise into discomfort and the 3 remaining exercises performed with no/minimal pain. This modification was necessary after a thorough analysis of the feasibility study and discussion with the physiotherapists and the research team. If this single painful exercise was not provocative anymore (4-7 on NPRS) before 9 weeks, a rate of perceived exertion (Borg Scale) was used instead of the NPRS. In this way, the exercises could be between 4 (somewhat hard) and 7 (very hard) representing more the subjective effort during the exercise than the pain provoked during the exercises. Although this modification could potentially change the comparison between a painful vs. non-painful exercise program, this final decision was taken together with the research team in order to compensate possible deviations from the protocol in the future RCT. **2) Impact of Covid-19 on feasibility study:** patients stopped to go to the physiotherapists from March to May 2020 but they continued to exercise at home. Questionnaire were sent online via Qualtrics, therefore subjective data were not lost. Objective measures (i.e. strength and US measures) were lost for 7 patients at follow-up of 6 and/or 12 weeks but available data for patients who went at least 7 out of 9 sessions to the physiotherapists were analysed in order to adjust the protocol for the RCT. **Milestone 1** (ethical approval on amendments to the protocol and fine-tune the protocol for the RCT): completed according to the plan.

WP2: RCT

The RCT started in July 2020 and is still on going. In the initial FWO application the aim was to start the recruitment in April 2020 and to complete it by April 2021, with the final follow up in October 2021 (6 month after baseline assessment). A **change to the timeline and sample size** was necessary because of the low recruitment rate during the pandemic of Covid-19. The recruitment rate during the feasibility study before the pandemic (November 2019-February 2020) was 4-5patients/month. The recruitment rate during the RCT was: 2.6 patients/month during the first year (July 2020-July 2021) and then 1.2 patient/month in the following 6 months (August 2021-January 2022). Fifty-four patients were included in the initial sample size calculation, estimating 15% of drop-out, power=90% and minimal clinically important difference (MCID)=8 points on the primary outcome SPADI. We planned to recruit patients until May 2022, aiming to 44 patients, with the last follow up measure in November 2022. Forty-four patients will still allow to have a well-powered study (85%) with MCID=10 points, which is considered in the range 8-13 points of the MCID in SPADI (Roy JS, MacDermid JC, Woodhouse LJ. Measuring shoulder function: a systematic review of four questionnaires. Arthritis Rheum. 2009;61(5):623-32). The extended time for data analysis in 2023 will allow the PhD student to conduct a thorough data analysis of objective and subjective data (see "Data analysis for 2nd term"). *Status*: 42 patients were recruited by the end of April 2022.

WP3: Data analysis

US measure	Intra-rater reliability, ICC (95%CI)
AHD	0.97 (0.93-0.99)
SSP	0.87 (0.71-0.94)
AHD60	0.85 (0.69-0.93)
~~**AHD60w**~~	~~0.77 (0.52-0.90)~~
CHD0	0.93 (0.86; 0.97)
LHB	0.90 (0.78; 0.96)
SCP	0.92 (0.83; 0.97)
CHD60	0.91 (0.81; 0.96)
~~**CHD60w**~~	~~0.88 (0.76; 0.95)~~

***Table 2 - US measures**. ICC: 2-way mixed model, absolute agreement (average measures). Abbreviations: AHD= Acromiohumeral Distance, AHD60= Acromiohumeral Distance at 60°; AHD60w= Acromiohumeral Distance at 60° with free weight; CHD= Coracohumeral Distance, CHD60= Coracohumeral Distance at 60°; CHD60w= Coracohumeral Distance at 60° with free weight; LHB= Long Head of Biceps tendon; SCP= Subscapularis tendon, SSP= Supraspinatus tendon.*

Data analysis 1st,2nd US articles (WP3, 3.1 and 3.2): *Status*: data analysis completed. The time necessary for data analysis for the US measures was added to the timeline. *Main results*: inter-rater reliability was calculated in the reliability study performed in February 2020 with the US expert Santiago Navarro Ledesma. Inter-rater reliability varied largely from poor to good between two examiners with different US experience (novice VS expert examiner). However, since the only US examiner for the RCT is the PhD student, the data for the intra-rater reliability of the PhD student were considered relevant in order to proceed to the US measures in the RCT. The intra-rater reliability of the PhD student can be found in Table 2. The ICC values for the PhD student are ranging from good to excellent (0.85-0.97). The measures with weights (AHD60w and CHD60w) were excluded in the final protocol in the RCT because of time limitations in the measurement protocol and also because the patients could not hold the weight assigned for the whole testing period.

The first manuscript resulting from this reliability phase was: "Subacromial space measured by ultrasound imaging in asymptomatic subjects and patients with subacromial shoulder pain: an inter-rater reliability study"; authors: Claudia Cavaggion, Santiago Navarro-Ledesma, Alejandro Luque-Suarez, Birgit Juul-Kristensen, Lennard Voogt, Filip Struyf; journal: Physiotherapy Theory and Practice (IF2020=2.28, Q3 Rehabilitation), **Manuscript 1**. The data analysis for the second manuscript has been completed and the manuscript will be submitted by June 2022 (see **Manuscript 2**).

Data analysis of feasibility study (WP3, 3.3): *Status*: data analysis completed. The time necessary for data analysis for the feasibility study was added to the timeline. The manuscript has been recently submitted (see **Manuscript 3**).

Updated research approach and work plan for the 2nd term.

Update, elaborate and motivate the planned course of activities for the 2nd term. You might use a table or graphic representation (timing work packages, milestones, critical path).

WP2 RCT: End of patient recruitment and data collection

As previously mentioned, we changed the timeline compared to the initial FWO proposal, based on the current recruitment rate impacted by the Covid-19 pandemic. The end of patient recruitment will be in May 2022 (**Milestone 2**) and the last follow up will be in November 2022. The adaptations are indicated in dark blue in Table 1. *Status*: data collection.

WP3: Data analysis

Data analysis of the RCT (WP3, 3.4 and 3.5): demographics and other objective measures (strength, range of motion, scapular dyskinesis, data from the US machine) will be processed already from June 2022, but the data concerning the randomization process of two groups will be unblinded only at the end of the trial in November 2022. Related manuscripts: see **Manuscript 4 and 5**. The end of the data analysis will be **Milestone 3.** *Status:* Milestone 3 has been delayed from Q2 2022 (initial FWO project) to Q4 2023. This delay is due to a decrease in patient recruitment caused by the pandemic of Covid-19. However, thanks to the extension of the FWO scholarship, there will be sufficient time to recruit all patients and to conduct a thorough data analysis for both objective and subjective measures.

WP4: Articles, PhD thesis

- **Manuscript 2**: "Reliability of coracohumeral distance and subcoracoid tendons in subacromial pain syndrome" Claudia Cavaggion, Santiago Navarro-Ledesma, Birgit Juul-Kristensen, Alejandro Luque-Suarez, Lennard Voogt, Filip Struyf.
- **Manuscript 3:** "Exercise into pain in chronic rotator cuff related shoulder pain: a feasibility trial"
- **Manuscript 4:** "The effect of exercise into pain in chronic rotator cuff related shoulder pain: a randomized controlled trial"
- **Manuscript 5**: "The effect of exercise into pain in subacromial shoulder pain on subacromial and subcoracoid spaces"

PhD Thesis (Milestone 4): "The effect of exercise into discomfort on clinical outcomes and ultrasound imaging parameters in patients with subacromial shoulder pain". The submission will be 4 months before the defence, and the defence will be within the FWO term.