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Are psychosocial variables, sleep characteristics or central pain processing prognostic factors for outcome following rotator cuff repair? A protocol for a prospective longitudinal cohort study

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ABSTRACT

Introduction Prognosis following surgical rotator cuff repair (RCR) is often established through the assessment of non-modifiable biomedical factors such as tear size. This understates the complex nature of recovery following RCR. There is a need to identify modifiable psychosocial and sleep-related variables, and to find out whether changes in central pain processing influence prognosis after RCR. This will improve our knowledge on how to optimise recovery, using a holistic rehabilitation approach.

Methods and analysis This longitudinal study will analyse 141 participants undergoing usual care for first time RCR. Data will be collected 1–21 days preoperatively (T1), then 11–14 weeks (T2) and 12–14 months (T3) postoperatively. We will use mixed-effects linear regression to assess relationships between potential prognostic factors and our primary and secondary outcome measures—the Western Ontario Rotator Cuff Index; the Constant-Murley Score; the Subjective Shoulder Value; Maximal Pain (Numeric Rating Scale); and Quality of Life (European Quality of Life, 5 dimensions, 5 levels). Potential prognostic factors include: four psychosocial variables; pain catastrophising, perceived stress, injury perceptions and patients' expectations for RCR; sleep; and four factors related to central pain processing (central sensitisation inventory, temporal summation, cold hyperalgesia and pressure pain threshold). Intercorrelations will be assessed to determine the strength of relationships between all potential prognostic indicators.

Our aim is to explore whether modifiable psychosocial factors, sleep-related variables and altered central pain processing are associated with outcomes pre-RCR and post-RCR and to identify them as potential prognostic factors.

Ethics and dissemination The results of the study will be disseminated at conferences such as the European Pain Congress. One or more manuscripts will be published in a peer-reviewed SCI-ranked journal. Findings will be reported in accordance with the STROBE statement and PROGRESS framework. Ethical approval is granted by the Ethical commission of Canton of Zurich, Switzerland, No: ID_2018-02089

Trial registration number NCT04946149.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be the first study *adequately* powered to identify modifiable psychosocial factors as potential prognostic factors of outcome after rotator cuff repair (RCR).
⇒ This study will also be the first to assess the complex interplay of psychosocial factors, sleep-related variables and central pain processing measures as potential prognostic factors of outcome following RCR.
⇒ The prospective longitudinal study design includes three measurement points, starting preoperatively, at 12 weeks postoperative, and following up for 12 months post RCR.
⇒ The questionnaires for sleep and patients' expectations were translated to German for the purposes of this study. Therefore, their validity in our population (German-speakers) has yet to be validated.
⇒ Tear size is a known prognostic indicator of how well recovery will go following RCR. We will not account for tear size in our prognostic model which may bias our results.

INTRODUCTION

Prognostic factor research most often focuses on biomarkers, including biological, clinical or physiological factors. Prognostic factors help us predict the likely outcome of a patient undergoing a procedure, given the presence of certain behaviours or characteristics.[1] For patients undergoing rotator cuff repair (RCR) for shoulder pain, prognostic factors often include: patient's age; fatty infiltration into the rotator cuff muscles; quantified

tendon tear size or multiple tendon involvement; and the presence of a confirmed diabetes diagnosis.[2] These are all non-modifiable biomedical markers with established capability to predict worse outcomes for patients following RCR.[2]

Despite these biomarkers being recognised prognostic factors for RCR, we are still not able to fully predict who will recover successfully. A person's perception of shoulder pain is far more complex than structural changes in the rotator cuff (RC) tendons. More information is required to gain a comprehensive understanding of all factors that influence recovery.[3–7] Yet, the number of RC repairs in Europe and the USA continues to grow,[4 8–10] in spite of this lack of knowledge on the odds of success. Current evidence suggests satisfactory outcomes post RCR range from 38% to 95%. This means surgical repair is either very successful or potentially a large waste of resources.[11–14]

There is growing evidence that psychosocial factors impact persistent shoulder pain.[4 15–18] Factors such as: high distress; maladaptive beliefs;[17] the perception of high-demand at work; and a lack of social support[18] can influence whether persistent shoulder pain and disability occur. Patients with existing preoperative (RCR) psychological conditions like: depression and anxiety;[14] who exhibit pain catastrophising and kinesiophobia;[19] or suffer psychological distress[14 20] may demonstrate greater preoperative shoulder pain.[14 19] In the reverse, patients who anticipate a good recovery (positive expectations) post-RCR show independent and strong associations with satisfactory outcomes (good prognosis) for pain and disability measured 1 year post surgery.[11 12 21] Prior research on psychosocial factors post RCR has been restricted to: preoperative measures;[19] has lacked statistical power;[14 20] or has failed to investigate potential psychosocial prognostic factors altogether.[11 12 21]

Sleep disturbances are also highly prevalent (up to 89%) in patients undergoing RCR. Sleep disturbance has been attributed to the presence of shoulder pain.[22–24] RCR seems to reduce this interplay between shoulder pain and sleep disturbances as findings demonstrate an overall post RCR improvement of sleep quality.[14 25] Yet, 41% of patients with RCR still suffer from sleep disturbances at 24 months follow-up.[23] Investigations of sleep disturbances in relation to shoulder pain and RCR are incomplete with multiple factors affecting the relationship.[26]

Central pain processing (CPP) changes are measured via assessments for central sensitisation. Assessments of CPP are almost absent in studies of patients undergoing RCR.[15 16 27] Two trials[28 29] investigated the role of central sensitisation, measured with quantitative sensory testing (QST) on outcome (pain and disability) after different shoulder surgeries (RCR, superior labrum from anterior to posterior (SLAP) repair, shoulder arthroscopy (SA) and subacromial decompression). Both studies found small effects of CPP on postoperative outcomes. If a high amount of CPP was present preoperatively, it was related to a worse outcome 3 months postsubacromial decompression.[28] In contrast, if a small amount of CPP was present 3 months postoperatively (RCR, SLAP-Repair, SA) it was associated to better functioning at 6 months postsurgery.[29]

The existence of potential modifiable prognostic indicators related to psychosocial factors, sleep and CPP and their effects on, shoulder function, disability, pain, quality of life and satisfaction following RCR require further investigation.[4 19] Neither the local tissue pathology-pain model nor the growing knowledge about local biochemical changes in RC tendons sufficiently describe the relationship between tissue changes and patients' perceived shoulder pain.[3 5 15 30] Studying the relationship of psychosocial factors, sleep and CPP with RCR would improve our prognosis for outcomes post RCR. This holds the potential to improve treatment selection choices and reduce unnecessary surgical interventions.[3 4 16 20 31]

This study aims to answer the following questions:

1. Do psychosocial factors such as pain catastrophising, perceived stress, injury perceptions, patients' expectations of surgery, sleep-related variables and measures of CPP obtained pre RCR (baseline), influence baseline shoulder function, disability, pain and quality of life and their evolution over time (1 year post-surgery)?
2. How do potential prognostic factors such as psychosocial indicators, sleep-related variables and CPP intercorrelate at baseline and over time?

METHODS

Study design and setting

The longitudinal cohort study will be implemented and reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies[32] informed and completed by the framework 'prognosis research strategy' (PROGRESS).[1 33]

Data will be obtained in a single shoulder and elbow surgery unit in the clinic of orthopaedic surgery and traumatology in alliance with the institute of therapy and rehabilitation of the acute care hospital, canton hospital Winterthur, Switzerland.

The current research project will analyse data from three time points in the routine clinical management post-RCR: 1–21 days preoperatively (T1); 11–13 weeks postoperatively (T2); and 12–14 months postoperatively (T3). Data from July 2019 onwards will be considered. Data collection including 12 months follow-up is estimated to be complete in Summer 2022.

See tables 1 and 2 for overview of measurement points.

Participants

The population of interest includes adult patients undergoing elective RCR, for tears of traumatic and non-traumatic origin. To avoid selection bias, we will include data from consecutive patient consultations.

Eligibility criteria

Inclusion criteria

1. Adult men or women ≥18 years of age.

Table 1 Outcome measures

	Type/Mode	Psychometric properties/Clinimetrics	T1: Baseline 2–3 weeks pre RCR	T2: 12 weeks post RCR	T3: 12 months post RCR
Primary outcome measure					
Shoulder function, disability and disease-specific quality of life	**WORC**	Positive evidence for five psychometric properties: ► internal consistency, ► reliability, ► content validity, ► hypothesis testing and ► responsiveness.[44 45] German version showed satisfactory construct validity, internal consistency, test-retest reliability. No specific testing for responsiveness.[44]	x	x	x
Description	This 21-item self-reported questionnaire represents a shoulder function, disability and quality of life measure in rotator cuff pathology.[46] The WORC measures five dimensions (pain, sports/leisure, work, daily living, feelings) with 3–6 questions per domain, measured on a 100 mm VAS. Left endpoint equals 'no' and right endpoint equals 'extreme'. The total WORC score ranges from 0mm (best) to 2100mm (worst) (21 items × 100 mm). The MID is calculated at ≥300 mm.[47]				
Secondary outcome measures					
Shoulder function	**CMS**	Validated in different shoulder diseases and recommended for patients with rotator cuff and osteoarthritis due to highest responsiveness in these groups.[48] Reliability was moderately rated with ICCs >0.8. Results about content and structural validity seem to be lacking.[45]	x	– No strength measure	x
	SSV	High correlations to CMS, tested in diverse shoulder diseases.			
Description CMS	The CMS assesses shoulder function of which 35% are subjective variables (maximum pain intensity, work, sport/leisure, sleep, pain free height for light work), and 65% are objective variables (ROM and strength measure). A sum score of 100 represents perfect shoulder function, 0 represents no functionality.[45]				
Description SSV	The SSV is evaluated by one single standardised question: 'What is the overall percent value of your shoulder, if a completely normal shoulder represents 100%?'[48]				
Maximum pain	**NRS**	Reported to be sensitive to measure change of pain level on the 11-point scale. Minimal clinical important difference is found to be 30%–33% of pain reduction.[49]	x	x	x
Description	Patients are asked to indicate the maximum perceived shoulder pain felt in daily life on an NRS from 0 (no pain at all) to 10 (worst imaginable pain).[50]				
Quality of life	**EQ-5D-5L**	Adopted and tested in Germany among general population.[51]	x	x	x
Description	The research group EuroQol developed the EQ-5D-5L tool 'in order to provide a simple, generic measure of health for clinical and economic appraisal'. It contains five dimensions: mobility, self-care, usual activities, pain/discomfort and depression/anxiety and five levels ranging from no problems, slight problems, moderate problems, severe problems and extreme problems.[52]				
Postoperative satisfaction	**Satisfaction questionnaire for postsurgical status**	No validation of this questionnaire in German language available. Forward backward translation with native speakers and expert physiotherapists was best compromise.	–	–	x
Description	Self-rated questionnaire containing eight questions. Four questions cover current state of satisfaction, one question asks for quality of life improvement, two questions ask about repetition of surgery and recommendation for others and one question asks about timing of the surgery. The survey originates from total shoulder arthroplasty research[35] and is modified to RCR. It is clear and simple to administer.				

CMS, Constant-Murley Score; EQ-5D-5L, European Quality of Life, 5 Dimensions, 5 Levels; MID, minimal important difference; NRS, Numeric Rating Scale; RCR, rotator cuff repair; ROM, range of motion; SSV, Subjective Shoulder Value; VAS, Visual Analogue Scale; WORC, Western Ontario Rotator Cuff Index.

2. Scheduled for elective arthroscopic RCR.
3. First time RCR on the target shoulder.

Exclusion criteria

1. Changes of intraoperative procedure (eg, anything but RCR).
2. Re-repair of tendon.
3. No surgery.
4. No preoperative data available; for example, fast track patients with trauma.

Outcome measures and prognostic factors

Our outcome measures are consistent with those used in the existing literature. We consulted the guidelines from the OMERACT 2016 Shoulder Core Outcome Set Special Interest Group.[34]

Our dependant variables are the *primary outcome measure* Western Ontario Rotator Cuff Index (WORC) for disease-specific function, disability and quality of life. The *secondary outcome measures* are: Constant-Murley Score (CMS) and Subjective Shoulder Value (SSV) for shoulder

Table 2 Potential prognostic factors

	Type/Mode	Psychometric properties/Clinimetrics	T1: Baseline 2–3 weeks pre RCR	T2: 12–14 weeks post RCR	T3: 12–14 months post RCR
Potential prognostic factors					
Psychosocial factors					
1 Catastrophic thinking	**PCS**	German PCS showed same factor structure like original version and acceptable to good reproducibility.[53] Validated in patients with low back pain.	x	x	x
Description	The PCS assesses whether or not there is presence of catastrophic thinking about pain. Thirteen items entail aspects about different thoughts and feelings while experiencing pain. Items are scored on a 5-point Likert scale. Higher scores indicate more severe catastrophic thinking about pain. There is a total score and a score for three subscales (eg, helplessness, magnification and rumination).[54]				
2 Perceived distress	**PSS**	The German version showed good psychometric properties like validity and reliability in the general population.[55]	x	x	x
	The PSS-10 includes 10 questions and assesses the degree to which life has been experienced as unpredictable, uncontrollable and overloaded in the past months. The questions are answered by 'yes' (1) or 'no' (0). The questions are general in nature and therefore the usage for patients with shoulder pain undergoing RCR is reasonable.				
3 Perceptions about injury	**IPQ-R**	The clinimetric properties for musculoskeletal pain are reported to be sufficient.[56] For rotator cuff tears and rotator cuff repair, the word 'injury' seems to be more adequate, therefore we exchanged the word illness (German: Krankheit) with injury (German: Verletzung).	x	x	x
Description	Designed to assess the cognitive and emotional representations of illness/injury. The items are formed by experiences, provided information and interpretation of symptoms. The IPQ-R is not disease specific and may be used in any group of interest.[57] The questionnaire has nine dimensions of injury perception: (1) Timeline (acute/chronic), (2) Consequences, (3) Personal control, (4) Treatment control, (5) Injury coherence, (6) Timeline cyclical, (7) Emotional representations as well as (8) Identity and (9) Causes. We amalgamated dimensions (1) and (6) into 'timeline' and dimensions (3) and (4) into 'control' and end up with six subscales for illness perceptions and one for causes. Further it includes three domains.[58 59] The first domain is called illness identity, the second is called the beliefs domain and the third is labelled as the consequence domain.[60] The authors adjusted the questionnaire to the cohort and exchanged illness with injury. The 32 injury perceptions and 18 causes answers are captured on a 5-point Likert scale from 'strongly disagree' (1) to 'strongly agree' (5).				
4 Expectations	**Study designed, 6 Questions about expectations**	Lack of German-translated questionnaires in the field. Consequently, the research team formulated six questions based on literature including the study of the MODEMS.[12 35]	x	–	–
Description	Patients' expectations will be assessed using five questions: (1) expected shoulder function in percentage at 12 weeks post RCR, (2) expected shoulder function at 12 month postop, (3) expected symptom reduction in percentage at 12 weeks post RCR, (4) expected symptom reduction in percentage at 12 months post RCR, (5a) and (5b) open questions about driver for high (>80%) or low (<80%) expectations for shoulder function and symptom reduction.				
Sleep					
	Study designed, 4 Questions about sleep	Due to study feasibility, we formulated four questions. Because sleep assessments were not validated in German language, or too long to integrate.	x	x	x
Description	Four questions regarding 5) sleep quality, 6) sleep efficiency, 7) sleep disturbance, 8) number of awakenings per night. The first question is transformed from the PSQI, for sleep quality and is rated on a 4-point Likert Scale. The question 2 to 3 are formulated by suggestion from research[61] and adapted to shoulder pain by the first author.				
Central Pain Processing					
9 Self-reported symptoms of central Sensitisation	**CSI**	It is a high-quality measurement tool, with high construct validity and test-retest reliability. The defined cut-off point is at 40 points.[62] German version is to be validated by the research group among Laekemann. Signed contract for the usage of this version.	x	x	x

Continued

Table 2 Continued

	Type/Mode	Psychometric properties/Clinimetrics	T1: Baseline 2–3 weeks pre RCR	T2: 12–14 weeks post RCR	T3: 12–14 months post RCR
Description	The original English questionnaire was developed in 2011[63] to assess key symptoms in relation to CSS. It consists of two parts: Part A with 25 items relating to pain, psychosocial aspects, cognitive and functional aspects; and Part B with seven different CSSs, like restless legs, irritable bowel and multiple chemical sensitivities and three disorders like neck pain (whiplash), depression and anxiety or panic attacks.				
10 TS	**Frey hair filament, 10 g calibrated**	No factor analysis available for testing loading of TS for CPP. TS is a common method in research to measure CPP.[64]	x	x	x
Description	Locations for applications will be at two local and one remote site: (1) Local painful site: the most painful site of the shoulder is marked on the skin with a pen, indicated on a body chart and noted in the assessors' documents, to determine the site for repeated measures. (2) Local standardised site: at ipsilateral upper trapezius muscle at the midpoint between C7 spinous process and the acromion. (3) Remote site is standardised at the contralateral muscle belly of tibialis anterior at 5 cm distal to the tibial tuberosity and 2 cm laterally.[65] The patient is asked to rate the first touch on an NRS from 0 (no pain at all) to 10 (worst imaginable pain). Then the measurement is repeated once per second (1 Hz) for 30 s on a surface of maximum 1 cm^2,[50] The standardisation of the frequency is important, as wind-up of the C-fibres only arrives if the stimulus is provided at least once every 3 s (<0.33 Hz).[66] After the 30 s application, the patient is asked to rate the last touch on an NRS. The difference between the last and the first rating is calculated. Fifteen seconds after the test, patients need to rate any ongoing pain sensation on NRS again.[67] Patients will be advised that the method does not aim to measure pain tolerance[68] and a number should only be given if the sensation was burning, stabbing, pulling or gnawing.				
11 CH	**Ice pack**	No factor analysis available for testing loading of CH for CPP. CH is a common method in research to measure CPP.[64]	x	x	x
Description	CH is measured with a cold pack, kept in the deep freezer which is simulating ice cubes for the ice test.[69] Locations for applications will be at two local and two remote sites: (1) Local painful site: the most painful site of the shoulder is marked on the skin with a pen, indicated on a body chart and noted in the assessors' documents, to determine the site for repeated measures. (2) Local standardised site: at ipsilateral upper trapezius muscle at the midpoint between C7 spinous process and the acromion. (3) Remote site is standardised at the contralateral muscle belly of tibialis anterior at 5 cm distal to the tibial tuberosity and 2 cm laterally.[65] The cold application is kept for 10 s, and the patients will rate the experienced pain on a NRS from 0 (no pain at all) to 10 (worst imaginable pain).[69] Patients will be advised the measure does not aim for pain tolerance and their pain should be reported if a burning, stabbing, pulling or gnawing sensation is felt.[68]				
12 PPT	**Wagner Instruments**	No factor analysis available for testing loading of PPT for CPP. PPT is a common method in research to measure CPP.[64]	x	x	x
Description	PPT represents a static psychophysical test, which measures the point of pressure evolving into pain. Its report of large to nearly perfect reliability in neck pain patients, demonstrates its great potential as measurement tool also for the present cohort.[70] The measurements will be conducted by digital hand-held pressure algometer with a rubber tip of approximately 1 cm^2 (FPX 50, FORCE TEN by Wagner Instruments), increasing pressure will be given perpendicular to the skin.[71] Measurements are taken at five standardised sites. 1. Two cm caudal from the acromion at the muscle belly of middle deltoid, bilaterally. 2. At the muscle belly in middle of the upper trapezius, bilaterally. 3. At the contralateral muscle belly of tibialis anterior at 5 cm distal to the tibial tuberosity and 2 cm laterally, as remote site.[65] All measurements will be repeated once and the mean PPT in kilopascals per site will be calculated.				
13 Neuropathic pain differential diagnosis	**DN4**	The DN4 showed more sensitivity and specificity in preselected cohorts with respect of neuropathic pain detection, and it is strongly advised to obtain a thorough clinical assessment when diagnosing neuropathic pain.[72]	x	x	x
Description	Short and easy to administer assessment, which consists of a subjective part, including seven symptoms (patient-rated) and an objective part including three signs (physician-rated). The cut-off point is 4 points, the total of points is 10, indicating that neuropathic pain mechanisms may be involved.[72]				
14 Pain surface/ distribution	**Body chart**		x	x	x
Description	Patients report their pain location and pain distribution. The assessor is painting the body chart at the same time as the patient reports it. Calculation of pain surface (in percentage) will be analysed using the Margolis Bodychart scoring system.[73]				

Continued

Table 2 Continued

	Type/Mode	Psychometric properties/Clinimetrics	T1: Baseline 2–3 weeks pre RCR	T2: 12–14 weeks post RCR	T3: 12–14 months post RCR
Additional prognostic factors					
15 Age	Date of birth		x	–	–
16 Sex	Female/male/other		x	–	–
17 Cause of tear	Traumatic vs non-traumatic		x	–	–
18 BMI	kg and cm		x	–	–

BMI, body mass index; CH, cold hyperalgesia; CPP, central pain processing; CSI, Central Sensitisation Inventory; CSSs, central sensitivity symptoms; DN4, Douleur Neuropathique 4; IPQ-R, Injury Perception Questionnaire-Revised; MODEMS, Musculoskeletal Outcomes Data Evaluation and Management System; NRS, Numeric Rating Scale; PCS, Pain Catastrophising Scale; PPT, pressure pain threshold; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; RCR, rotator cuff repair; TS, temporal summation.

function; maximum pain over the last 7 days on Numeric Rating Scale (NRS); European Quality of Life, 5 dimensions, 5 levels (EQ-5D-5L) for quality of life and health status; and a satisfaction measure developed by Swarup *et al*.[35]

A detailed description and overview about primary and secondary outcome measures and their psychometric properties is presented below in table 1.

Potential prognostic factors for postoperative outcome are:

I. psychosocial factor
   1. spain catastrophising,
   2. perceived stress,
   3. injury perceptions,
   4. patients' expectations for RCR

II. sleep-related variables
   5. sleep quality
   6. sleep efficiency
   7. sleep disturbance since when
   8. No of awakenings per night

III. measures of CPP
   9. the central sensitisation inventory (CSI) to assess self-reported somatic and emotional complaints associated to CPP
   10. temporal summation (TS)
   11. cold hyperalgesia (CH)
   12. pressure pain threshold (PPT)
   13. the Douleur Neuropathique-four assessment (DN4) to detect the possible presence of neuropathic pain and
   14. pain surface/distribution on the body chart

Further factors include patient-related characteristics such as; demographics: (15) age and (16) sex; clinical variables (17) trauma vs non-traumatic tendon tear; and health status such as (18) body mass index. These characteristics are all handled as potential prognostic factors to ensure a correct estimation of our primary prognostic factors.

Table 2 presents an overview of the potential prognostic factors including a detailed description of all measurement tools and test methodology.

Four (AS, JW, QdG, FM) experienced and trained (by the first author AS) shoulder specialists and physiotherapists will perform all the measurements (CMS, QST, SSV, NRS pain). To support the training, all participant assessment files will incorporate detailed descriptions with respect to how the assessor should formulate questions and offer answer suggestions.

Statistical methods and analysis

Statistical analyses will be performed using SAS (SAS V.9.4, SAS Institute Inc, Cary, North Carolina, USA). Level of significance is set at p=0.05. Measurements will take place at three time points in the perioperative management, as described above (T1=at baseline 2–3 weeks prior to RCR, T2=at 12 weeks post RCR and T3=at 12 months post RCR as follow-up).

The primary outcome (WORC) will be modelled using mixed-effects linear regression models for repeated (longitudinal) measures, using an unstructured covariance matrix. Dependent variables are the primary and secondary outcomes. Continuous secondary outcomes will be assessed in a similar way to the primary outcome. The models will be developed by stepwise reduction of the a priori determined potential prognostic factors (eg, psychosocial factors, sleep and CPP). A prognostic factor will be retained in the model if it has a significant effect on the initial outcome or on the outcome over time, or if the fit statistics (Deviance, AIC, BIC and R^2) of the model improves after inclusion of the variable, in order to increase the precision of the fixed-effects estimates.[36–38] This means that a prognostic factor may be retained in the final model, even if it is not significant (p>0.05), to ensure correct estimation of other (significant) prognostic factors.

Descriptive statistics will be performed for comorbidities such as obesity, diabetes and depression; for insurance status (healthcare vs accident insurance); and current profession.

Sample size

We will use a linear mixed-effects regression model for repeated measures. This will have a power of 90% to identify prognostic factors of both interindividual baseline differences in WORC score and a change in WORC score over time that are considered clinically relevant (we assume a SD of 300 points at baseline and a decline in WORC score of at least 15% over time on average),[39] at a confidence level Alpha=0.05 (two-tailed). The required total sample size was calculated to be 125 subjects (R, Edland package).[40 41] To account for an expected attrition rate of 12.5%, the final sample size was set at 141 participants.

The power is set at 90% to minimise the chance of making a type II error.

It is especially difficult to determine a correct sample size for a longitudinal exploratory study, as the final mixed model is likely to contain complex variance and correlation patterns that are not known beforehand. Therefore, we plan an interim analysis after the inclusion of the first 80 participants, to assess the drop-out rate, the achieved power and the potential futility of the a priori selected prognostic factors. Mixed models do not require complete datasets to produce accurate results, through correct specification of the likelihood function.[37]

Data security and management

Data generation, transmission, storage and analysis within this project strictly follow Swiss legal requirements for data protection. The electronic data capture software REDCap[42 43] will be used for data processing and management. REDCap was developed by an informatics core at Vanderbilt University in 2004, with ongoing support from US National Center for Research Resources (NCRR) and US National Institute of Health (NIH), grants NIH/NCATS UL1 TR000445. REDCap was specifically developed around HIPAA security guidelines and is Good Clinical Practice-compliant and fulfils the regulatory requirements regarding the collection of patient data in clinical trials or non-interventional studies and patient registries and the EU data protections laws. Appropriate coded identification (eg, pseudonymisation) is used in order to enter subject data into the database. The coding list of target data is saved in a secured folder on the hospital's server. Only the project leader, study nurses and principal investigator have access to it. Between the members of the research team only coded and deidentified data will be shared. Safe handling of the coded data will be covered by the software REDCap.

Study monitoring

An audit trail and history of data transmission are provided by REDCap. The steering committee of the research project will oversee all aspects of design, delivery, quality assurance and data analysis according to good clinical practice and local legislation.

Ethics

The study follows the principles of the Helsinki Declaration. Only data of patients who gave general consent to the hospital or informed written consent to the project will be considered for analysis. Ethical approval was received in January 2019 (ID 201802089) by the Ethical Committee of the Canton of Zurich, Switzerland.

Dissemination of results

The research team is committed to full disclosure of the results of the study. The results of the study will be disseminated for research purpose at different conferences and as published articles in peer-reviewed journals. Findings will be reported in accordance to the STROBE statement and we aim to publish in high impact journals.

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Contributors AS is the project leader, who receives support from FS and MMee with respect to topic-selection and study design. TS controls the statistical model and will support statistical data analysis. MMer and PB contributed to the protocol through critical review and intellectual content. DG and MP support the feasibility of the study and access to clinical data through the physiotherapy and orthopaedic clinic at Canton Hospital Winterthur. DG and MP also support data security by providing REDCap software. All authors gave final approval for publication of the present protocol version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

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