Electrical muscle stimulation for the treatment of functional posterior shoulder instability – A randomized multicentric study

Clinical Study Protocol

Short Title: EMS Study

Study Type:	Prospective randomized controlled trial
Principal Investigator:	PD Dr.med.univ. Philipp Moroder Center for Musculoskeletal Surgery (CMSC) Charité University Hospital Berlin Augustenburgerplatz 1, 14193 Berlin, Germany Email: philipp.moroder@charite.de
Protocol Version and Date:	4.0 08.04.2020

STUDY SYNOPSIS

Sponsor	PD Dr. Philipp Moroder, Charité Berlin
Sponsor - Representative	Prof. Dr. Laurent Audigé
Study Title:	Electrical muscle stimulation for the treatment of functional posterior shoulder instability – A randomized multicentric feasibility study
Trial registration:	http://www.isrctn.com/ISRCTN10085480
Background and Rationale:	Functional posterior shoulder instability (FPSI) is a force imbalance of stabilizing shoulder muscles which mainly affects teenagers and young adults with severe implications on shoulder function. Severily restricted shoulder function and symptoms such as pain, loss in range of motion due to weakness or blockage that inhibits any further movement as well as a strong feeling of instability are reported by the affected patients. Even though surgical treatment is effective in structural posterior shoulder instability, patients suffering from FPSI should not be treated surgically since it often does not lead to the desired stabilization of the shoulder joint but instead to severe pain, movement restriction, as well as early glenohumeral degenerative changes. Current gold-standard treatment consists of physiotherapy including core exercises, coordination training, strengthening exercises as well as training with biofeedback. However, conventional physiotherapy as well as muscle training therapy is also often ineffective. In a multicentric prospective randomized controlled trial we would like to objectively assess a promising new EMS (Electrical muscle stimulation)-based treatment concept which was evaluated at our institution in a prospective pilot trial involving 24 cases with previously unsuccessful conventional physiotherapy treatment of FPSI.
Objective(s):	The primary objective is to demonstrate that the EMS based therapy shows a better clinical effect than the convential state-of-the art physiotherapy treatment of functional posterior shoulder instability.
Outcome(s):	Primary Parameter: - WOSI (Western Ontario Shoulder Instability Index) Secondary Parameter: - SSV (Subjective Shoulder Value) - ROM - Strength measurement (Flexion/Abduction/Rotation) - Impairment of daily activities - Sports impairment - Pain level - Satisfaction level with treatment
Study design:	Prospective, randomized, controlled, optional crossover study

Inclusion / Exclusion criteria:	Key inclusion criteria: - Non-controllable positional functional posterior shoulder instability Key exclusion criteria: - < 14 years - multidirectional instability - static posterior instability/migration - connective tissue disease - degenerative joint disease - structural defects visible on pre-treatment MRI o Any acquired glenoid bone defect o Glenoid dysplasia with more than 10° of retroversion (of cartilagineous surface) according to Imhoff et al.[7] o Convex cartilagineous glenoid articular surface o Static posterior glenohumeral decentering >55% according to Walch et al.[18] o Degenerative changes (any visible cartilage damage or OA) - neurological disorder or nerve injury - existing pain syndrome (defined by pain at rest or during motion which is not caused by dislocation but impedes physiotherapeutic training and/or EMS) - non-tolerance of EMS treatment (e.g. cardiac pacemaker) - previous participation in a pathology-specific standardized EMS or physiotherapy protocol
Measurements and procedures:	Follow-up per patient (time after start of the treatment): Baseline (Inclusion), 0 weeks (Start treatment), 6 weeks, 3 months, 6 months and 12 months Duration of intervention per patient: 6 weeks
Study Product / Intervention:	Experimental intervention: electrical muscle stimulation based therapy protocol
Control Intervention (if applicable):	Control intervention: conventional state-of-the art physiotherapy protocol
Number of Participants with Rationale:	There will be a total of 88 patients included. Rationale: See Statistical Considerations
Study Duration:	30 months
Study Schedule:	01/20 First-Participant-In (planned) 07/22 Last-Participant-Out (planned)

Study Centre(s):	It is a multicentric, multi-national study. N=6 clinics Clinics: - Charitè University Hospital, Berlin, Germany (Leadclinic) - ATOS Clinic, Munich, Germany - Hannover Medical School (MHH) – DIAKOVERE Annastift – Department of Orthopaedic Surgery, Hannover, Germany - St. Vincentius Clinic, Karlsruhe, Germany - University Hospital Düsseldorf, Department of Orthopaedics and Trauma Surgery, Düsseldorf, Germany - Schulthess Clinic, Zurich, Switzerland
Statistical Considerations:	Sample Size: The calculated sample size for a power of 80%, an alpha error probability of 5%, and an estimated effect size of 0,8 is 52. The effect size was calculated according to Cohen by dividing the minimally clinically important difference of the WOSI (10,4%) by the expected standard deviation of the WOSI among the study participants (13%) based on the pilot trial results. When accounting for an expected drop-out rate of approximately 20% due to non-compliance or loss to follow-up 66 patients need to be assigned to the trial. Due to the strict exclusion criteria with an expected exclusion rate of 25% approximately 88 patients need to be assessed for eligibility. In the pilot trial the adherence rate to the EMS treatment was 88%. A similar compliance rate is expected for both intervention groups of the proposed project. The rate of loss to follow-up is expected to be low considering the short follow-up period until reaching the primary endpoint at time-point T2 (3 months after the beginning/6 weeks after the end of the intervention). The expected combined drop-out rate due to lack of compliance with treatment or loss to follow-up is 20%. <u>Primary Analysis</u> The analysis of the primary outcome parameter (WOSI at 3 months) will be performed using an independent sample T-Test or linear regression with WOSI as the dependent variable and treatment intervention and baseline factor(s) as the independent variable depending on the need for statistical adjustment. The strength of effect will be presented as the mean group difference along with its 95% confidence interval. A random-effect model will be used to account for center effect. <u>Secondary Analyses</u> All secondary analyses will be explorative. Secondary outcome variables will be analyzed using univariable random-effect logistic (categorical variables) or linear (continuous variables) regression. Multivariable regression will be conducted depending on the need for adjustment of baseline prognostic factors. Significance level is set to 0.05.

GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

STUDY SCHEDULE

Table 1: Schedule of examination time points and data collection (mo = months, w = weeks)

			Follow-up time points and window[1]					
	Screen Visit	Intervention	0 w	6 w (± 1w)	3 mo (±1w)	4.5* mo (±1w)	6 mo (±2w)	12 mo (± 2w)
Inclusion/Exclusion	x							
Consent/Randomization	x							
Demographics	x							
Video	x			x	x	x	x	x
Pathology History	x							
Western Ontario Shoulder Instability Index (WOSI)	x		x	x	x	x	x	x
Subjective Shoulder Value (SSV)	x		x	x	x	x	x	x
Clinical Examination (Strength/ROM)	x		x	x	x	x	x	x
Impairment of daily activities	x		x	x	x	x	x	x
Sports impairment	x		x	x	x	x	x	x
Pain level	x		x	x	x	x	x	x
Satisfaction level with treatment	x		x	x	x	x	x	x
Adverse Events / Complications		x	x	x	x	x	x	x

* = only if crossover has been made

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

PD Dr. Philipp Moroder, Centrum für Muskuloskeletale Chirurgie (CMSC), Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin,

E-Mail: philipp.moroder@charite.de

1.2 Sponsor-Representative / Statistician ("Biostatistician")

Prof Dr. Laurent Audigé, Head of Teaching, Research and Development, Lengghalde 2, 8008 Zürich, Schweiz

Tel: +41 44 385 75 80; E-Mail: laurent.audige@kws.ch

1.3 Involved clinics

Charitè University Hospital, Berlin, Germany

(PI: PD Dr. Philipp Moroder)

ATOS Clinic, Munich, Germany

(PI: PD Dr. Mark Tauber)

Hannover Medical School (MHH) – DIAKOVERE Annastift – Department of Orthopaedic Surgery, Hannover, Germany

(PI: Dr. Marc Frederic Pastor)

St. Vincentius Clinic, Karlsruhe, Germany

(PI: Dr. Christian Gerhardt)

University Hospital Düsseldorf, Department of Orthopaedics and Trauma Surgery, Düsseldorf, Germany

Schoen Clinic Düsseldorf, Germany

(PI: PD Dr. Thilo Patzer)

Schulthess Clinic, Zurich, Switzerland

(PI: Prof. Dr. Laurent Audigé)

2. ETHICAL AND REGULATORY ASPECTS

2.1 Study registration

The study has been registered in the ISRCTN registry, a clinical trial registry recognised by WHO and ICMJE: http://www.isrctn.com/ISRCTN10085480

2.2 Competent Ethics Committee (CEC)

Each investigator has to seek the approval from the CEC for the conduction of the clinical study

The reporting duties (all changes in the research activity and all unanticipated problems involving risks to humans; including in case of planned or premature study end and the final report) will be followed as written in the applicable law.

No changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end.

2.3 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the European Regulation on medical devices 2017/745 and the ISO Norm 14155 and ISO 14971, and the national regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.4 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study.

The participants get enough time (min 24h) whether to participate or not.

The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) at the same time as the participant sign, and it will be retained as part of the study records.

2.5 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further

ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

2.6 Early termination of the study

The Sponsor may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.7 Protocol amendments

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

The PI or his designee has the responsibility to amend the protocol or to provide suggestions for a protocol amendment. He is also responsible to communicate these modification to its competent persons.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Functional posterior shoulder instability (FPSI) is a force imbalance of stabilizing shoulder muscles which mainly affects teenagers and young adults with severe implications on shoulder function. Patients with FPSI suffer from repetitive posterior dislocations every time the shoulder passes a particular phase of movement in the mid-range of motion. Severily restricted shoulder function and symptoms such as pain, loss in range of motion due to weakness or blockage that inhibits any further movement as well as a strong feeling of instability are reported by the affected patients. Extreme limitations during daily and sporting activities as well as the “freakish looking dislocations” can lead to stigmatization among peers and emotional stress for the affected patients.[14] The estimated prevalence of this often under- and misdiagnosed pathology is around 0.05% of the population[5] and might be even higher according to more recent studies.[12] Even though surgical treatment is effective in structural posterior shoulder instability, patients suffering from FPSI should not be treated surgically since it often does not lead to the desired stabilization of the shoulder joint but instead to severe pain, movement restriction, as well as early glenohumeral degenerative changes.[3; 6; 9; 11; 17] Current gold-standard treatment consists of physiotherapy including core exercises, coordination training, strengthening exercises as well as training with biofeedback.[8; 17] However, conventional physiotherapy as well as muscle training therapy is also often ineffective. In daily clinical practice patients affected by FPSI typically visit several shoulder specialists and physiotherapists and after years of unsuccessful conservative treatment finally undergo a salvage surgical stabilization attempt with often worse outcome than before.[14] A skillful neglect has been proposed as the alternative treatment option as symptoms may regress after several years. [6; 11] However, this waiting approach seems not applicable in clinical practice since the affected patients are young and suffer extensively

from their functional restrictions and their social implications. The ineffectiveness of available treatment options and the helplessness of shoulder specialists confronted with this pathology even led to the dismissal of FPSI as attention seeking behavior or even psychiatric condition in the past[4] which further increased the disease burden and social stigmatization of the patients suffering from FPSI.

In a multicentric prospective randomized controlled trial we would like to objectively assess a promising new EMS-based treatment concept which was evaluated at our institution in a prospective pilot trial involving 24 cases with previously unsuccessful conventional physiotherapy treatment of FPSI.[13] For the patients themselves this new treatment concept potentially could represent a true „game-changer" that might free them of the burden of FPSI.

For the examined pathology there is no guideline regarding recommended outcome measurements or core outcome sets. The Western Ontario Shoulder Instability Index (WOSI) which is a shoulder instability-specific subjective outcome measurement with proven high validity, reliability, and responsiveness[10] recommended for the evaluation of shoulder instability[15] will serve as main outcome measurement. The WOSI covers four categories: physical symptoms (10 items); sports, recreation, and work (4 items); lifestyle (4 items); and emotions (3 items). The reason to choose a subjective outcome measurement is the fact that 1) the patients' own perception of their shoulder function is a key factor to determine the success of treatment,[16] 2) a comprehensive, valid, and reliable objective clinical or radiographic outcome measurement in this highly-dynamic pathology is not obtainable, and 3) objective clinical outcome measurements might slightly vary between participating centers despite standardization. Secondary outcome measures of the proposed trial include the Subjective Shoulder Value (SSV), impairment of daily activities, sports Impairment, pain level, satisfaction level with treatment, range of motion, and strength. Data collection will include questionnaires independently completed by the patients for subjective outcome measures and standardized clinical examinations by physicians for objective outcome measurements.

3.2 Clinical Evidence to Date

In a recent prospective pilot trial performed at our institution, 24 cases with unsuccessful treatment of positional functional posterior shoulder instability were enrolled in a new functional treatment concept involving electric muscle stimulation (EMS) therapy. In this negative-selection of patients, where previous treatment including conventional physiotherapy for at least three months with or without additional surgical stabilization attempts had failed, an improvement in subjective and objective outcome parameters was achieved and stability was reobtained in most patients within 3-6 weeks of treatment.

3.3 Rationale for the intended treatment

A continuous and iterative improvement process of the EMS treatment protocol under investigation was completed during the recently accomplished prospective pilot trial based on the patients' objective and subjective response as well as adherence to the prescribed therapy plan. The amount of physiotherapy session or EMS treatments is based on a typical amount of physiotherapy sessions a patient undergoes for treatment of shoulder instability.

3.4 Explanation for choice of comparator (or placebo)

Pathology-targeted physiotherapy is the current treatment standard of FPSI and will serve as the control intervention in the proposed trial. All involved centers specified and agreed on a standardized exercise protocol for the control intervention during a Delphi survey. The control intervention will have the same exercises, duration, intervals, and instructing physiotherapist (at each center) as the experimental intervention. An optional bi-directional cross-over into the other intervention group (experimental or control) is possible after follow-up examination at the time-point T2 (3 months after the beginning/6 weeks after the end of the intervention)

in the case of subjectively unsatisfying result despite completion of the originally assigned intervention.

3.5 Risks / Benefits

No adverse events were recorded in any of the 24 cases involved in the pilot trial (carried out at Charitè University Hospital, Berlin, Germany). In this pilot trial 24 cases with unsuccessful treatment of FPSI were enrolled in a new functional treatment concept involving electric muscle stimulation (EMS) therapy. In this negative-selection of patients where previous treatment including conventional physiotherapy for at least three months with or without additional surgical stabilization attempts had failed an improvement in subjective and objective outcome parameters could be achieved and stability was reobtained in most patients within 3-6 weeks of treatment.[13]

3.6 Justification of choice of study population

All patients with FPSI will be included in this study irrespective of age, gender, degree of hyperlaxity, or duration of symptoms. Exclusion criteria focus on structural anomalies (static posterior migration, connective tissue diseases, degenerative joint diseases, structural defects) and other pathologies (multidirectional instability, neurological disorder or nerve injuries, existing pain syndrome, medical contraindication to EMS treatment) hindering, impeding, or prohibiting the complete administration of the control or experimental intervention. Additionally, patients with previous participation in a pathology-targeted standardized EMS or physiotherapy protocol are excluded in order to avoid patient's potential unwillingness to participate in or preformed mindset towards an intervention that they previously tried already without success. This combination of inclusion and exclusion criteria seems adequate to create a homogeneous group of study participants that still represents the typical characteristics of the majority of patients suffering from FPSI.

4. STUDY OBJECTIVES

4.1 Overall Objective

If the null-hypothesis can be rejected and the results of the new therapy concept show more effectiveness than the current treatment standard a much needed step-forward in the treatment of patients with FPSI will be achieved and likely lead to a complete change in the current treatment paradigms for this challenging pathology.

4.2 Primary Objective

This study wants to show that a certain therapy for FPSI leads to a better WOSI Score.

4.3 Secondary Objectives

This study wants to show that a certain therapy with FPSI leads to a better SSV, ROM respectively higher “satisfaction level with the treatment” and strength (abduction, flexion, rotation). Also the other secondary objectives like “impairment of daily activities”, “impairment of the job”, “sports impairment” and pain level should be decreased after a FPSI therapy.

4.4 Safety Objectives

Not applicable.

5. STUDY OUTCOMES

5.1 Primary Outcome

For the examined pathology there is no guideline regarding recommended outcome measurements or core outcome sets. The Western Ontario Shoulder Instability Index (WOSI) which is a shoulder instability-specific subjective outcome measurement with proven high validity, reliability, and responsiveness[10] recommended for the evaluation of shoulder instability[15] will serve as main outcome measurement. The WOSI covers four categories: physical symptoms (10 items); sports, recreation, and work (4 items); lifestyle (4 items); and emotions (3 items). The reason to choose a subjective outcome measurement is the fact that 1) the patients' own perception of their shoulder function is a key factor to determine the success of treatment,[16] 2) a comprehensive, valid, and reliable objective clinical or radiographic outcome measurement in this highly-dynamic pathology is not obtainable, and 3) objective clinical outcome measurements might slightly vary between participating centers despite standardization.

5.2 Secondary Outcomes

SSV: The Subjective Shoulder Value (SSV) is based on a single question that is answered subjectively the patients. The English formulation of this question is: "What is the overall percent value of your shoulder if a completely normal shoulder represents 100%?"[1]

ROM
The following active and passive range of motion parameters will be documented:

Abduction

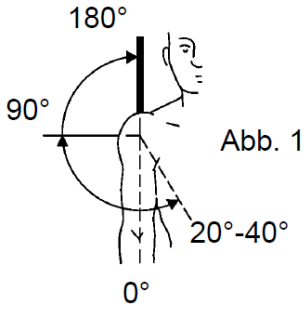


Abb. 1

Elevation (flexion)

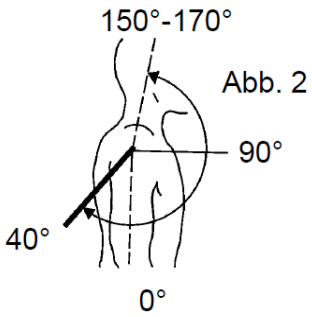


Abb. 2

External rotation by 0°

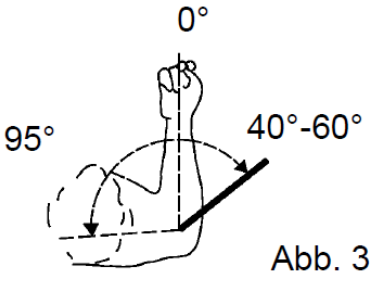


Abb. 3

External-internal rotation by 90°

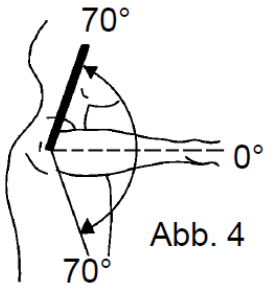


Abb. 4

Strength:

Abduction strength: The abduction strength (kg) is measured by 90° abduction in both shoulders (i.e. measured also for the opposite shoulder) using a spring balance (e.g. Pesola AG, Baar, Switzerland). The test is done with the patients standing. The arm should be abducted 90 degrees in scapula plane with the thumb showing upward. Only one measurement is performed.

Flexion strength: The flexion strength (kg) is measured by 90° flexion in both shoulders (i.e. measured also for the opposite shoulder) using a spring balance (e.g. Pesola AG, Baar, Switzerland). The test is done with the patients standing with thumb showing upward.

External rotation strength: The external rotation strength (kg) is measured with the arm in neutral rotation and the elbow flexed 90° in both shoulders (i.e. measured also for the opposite shoulder) using a spring balance (e.g. Pesola AG, Baar, Switzerland). The test is done with the patients standing with thumb showing upward.

Internal rotation strength: The internal rotation strength (kg) is measured with the arm in neutral rotation and the elbow flexed 90° in both shoulders (i.e. measured also for the opposite shoulder) using a spring balance (e.g. Pesola AG, Baar, Switzerland). The test is done with the patients standing with thumb showing upward.

Pain Level:

The pain level will be assessed with NRS (0 = no pain, 10 = worst pain).

Questions about impairment:

The patient will be asked about the impairment in daily activities, in the job and in sports activities (0% = no impairment, 100% = total restriction; 20% steps).

Satisfaction:

The patient will be asked about the level of satisfaction of the treatment (0% = not at all, 100% = complete satisfaction)

Characteristic of the subluxations

The patients will be asked about the subluxations events (e.g. first time, which movements) and previous treatments (e.g. surgery, physiotherapy).

5.3 Safety Outcomes

Based on the complication-free pilot trial, no adverse events are pre-specified but continuous recording of unexpected adverse events will be executed in both treatment arms. In the case that adverse events are recorded, the independent expert group and ethical committee supervising the trial will be informed and may decide whether the trial can be continued or must be stopped.

6. STUDY DESIGN

6.1 General study design and justification of design

This is a multicentric, prospective, randomized and optional crossover study.

There will be an intervention period of 6 weeks and afterwards a follow up time of totally 12 months. After 3 months the primary endpoint (WOSI) will be measured. Afterwards the mentioned optional cross-over in the other group is allowed in the case of subjectively unsatisfying result despite completion of the originally assigned intervention. This approach ensures that the primary endpoint still can be obtained and only secondary endpoints will be jeopardized if an unexpected high rate of cross-over from one intervention group to the other occurs.

6.2 Methods of minimising bias

The strict inclusion and exclusion criteria create a homogeneous group of study participants. After a patient has decided to enter the study and provided written informed consent, he/she will be randomized in one of the two treatment groups (allocation ratio 1:1) (details: see 6.2.1).

The multicentric design will introduce variation in expertise of persons executing the interventions, however all interventions in all centers are completed based on pre-defined standardized protocols. We will also adjust the statistical analyses for clustering of patients within centers. Analysis will therefore include measured effect differences between centers.

Furthermore the multicentric design helps to diminish the risk of confirmation bias since the experimental intervention was developed by one of the participating trial centers where the experimental intervention is likely to unwittingly be favoured. This trial setting allows to objectively predict if the study results can be generally reproduced if the study protocols are applied in other institutions.

Since the main outcome measurement is a subjective score, blinding of the examiner is not necessary. Blinding of the patients themselves is not possible due to the nature of experimental and control intervention. This circumstance can potentially introduce a confirmation bias from the patients' side. However, according to the trial design, all patients with previous participation in a pathology-targeted standardized EMS or physiotherapy protocol are excluded which reduces the risk for a pre-conditioned mindset in patients.

6.2.1 Randomisation

A randomization sequence will be generated electronically using Stata (StataCorp LP, Texas USA) separately for each participating centers for up to X patients and loaded within an online study database in REDCap[2] (Research Electronic Data Capture) for automatic concealed allocation. Block-randomization with blocks of 2 and 4 will be used to minimize the risk of unequal group sizes. The randomization process allows to divide the study participants into two cohorts of comparable characteristics. We will compare these cohorts with regards to potential confounding factors before the outcome analyses and adjust statistically for any observed imbalance as appropriate.

7. STUDY POPULATION

7.1 Eligibility criteria

All patients with FPSI will be included in this study irrespective of age, gender, degree of hyperlaxity, or duration of symptoms. Exclusion criteria focus on structural anomalies (static posterior migration, connective tissue diseases, degenerative joint diseases, structural defects) and other pathologies (multidirectional instability, neurological disorder or nerve injuries, existing pain syndrome, medical contraindication to EMS treatment) hindering, impeding, or prohibiting the complete administration of the control or experimental intervention. Additionally, patients with previous participation in a pathology-targeted standardized EMS or physiotherapy protocol are excluded in order to avoid patient's potential unwillingness to participate in or preformed mindset towards an intervention that they previously tried already without success. This combination of inclusion and exclusion criteria seems adequate to create a homogeneous group of study participants that still represents the typical characteristics of the majority of patients suffering from FPSI.

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Non-controllable positional functional posterior shoulder instability
- Informed Consent as documented by signature

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- multidirectional instability
- static posterior instability/migration
- connective tissue disease
- degenerative joint disease
- structural defects visible on pre-treatment MRI
    - Any acquired glenoid bone defect
    - Glenoid dysplasia with more than 10° of retroversion (of cartilagineous surface) according to Imhoff et al.[7]
    - Convex cartilagineous glenoid articular surface
    - Static posterior glenohumeral decentering >55% according to Walch et al.[18]
    - Degenerative changes (any visible cartilage damage or OA)
- neurological disorder or nerve injury
- existing pain syndrome (defined by pain at rest or during motion which is not caused by dislocation but impedes physiotherapeutic training and/or EMS)
- non-tolerance of EMS treatment (e.g. cardiac pacemaker)
- previous participation in a pathology-specific standardized EMS or physiotherapy protocol for the affected shoulder
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant,
- Enrolment of the investigator, his/her family members, employees and other dependent persons

7.2 Recruitment and screening

The estimated prevalence of functional shoulder instability is approximately 0.05% of the population[5]. More precise numbers are not available in the literature. In our pilot trial we treated over 20 cases suffering from FPSI within a one-year timespan at our referral center for shoulder pathologies. All centers included in the proposed project have a similarly large access to potential study participants. Therefore, a sufficient access to the potential study population is available to make recruitment of the planned number of patients within the pre-defined time period likely. Moreover, the observed acceptance rate of the patients to

participate in a standardized training protocol both, with or without EMS, was very high in the pilot trial. Therefore, the willingness to participate in a randomized trial is expected to be substantial as well, especially considering the offered optional bi-directional cross-over design making both types of intervention accessible for the patients.
During the pilot trial many patients expressed the desire to make this new form of treatment available more close to their home which led us to the decision to turn the proposed project into a multicentric trial involving not only some of the largest shoulder centers in German speaking countries but also considering strategical geographical locations. This should help to reduce time-comsuming travel and costly hotel stays for the patients and their parents and thus facilitate recruitment.

7.3 Criteria for withdrawal / discontinuation of participants

Each patient has the right to withdraw from the study at any time without prejudice. If a subject withdraws from the study, the reason(s) will be stated. Patients who withdraw from the study will not be replaced.

Patient's participation in the study will start by signing and returning the informed consent to the PI or project coordinator. They may end participation prematurely for one of the following reasons: voluntary withdrawal, illness or other event (e.g. complication, trauma event, travel, …) that prevents further participation in the study and death.

8. STUDY INTERVENTION

8.1 Experimental Intervention (treatment)

The experimental intervention consists of pathology-targeted physiotherapy exercises with simultaneous EMS stimulation which was developed and tested in a pilot trial involving patients without previous treatment success. Electric stimulation targets the external rotators and scapula retractors and consists of rectangular symmetrically compensated alternate current with a frequency of 30Hz and varying intensity. The training involves a combination of pre-defined pathology-targeted exercises with increasing difficulty and intensity. The intervention will include 18 one-hour trainings evenly distributed over a time period of 6 weeks and will be administered by the same physiotherapist at each participating center based on a standardized protocol.

8.2 Control Intervention (standard therapy)

The control intervention consists of the current treatment standard for FPSI, namely pathology-targeted physiotherapy with exercises that were further specified during a Delphi survey. The control intervention will have the same exercises, duration, intervals, and instructing physiotherapist (at each center) as the experimental intervention.

8.3 Crossover

An optional bi-directional cross-over into the other intervention group (experimental or control) is possible after follow-up examination at the time-point T2 (3 months after the beginning/6 weeks after the end of the intervention) in the case of subjectively unsatisfying result despite completion of the originally assigned intervention.

8.4 Compliance with study intervention

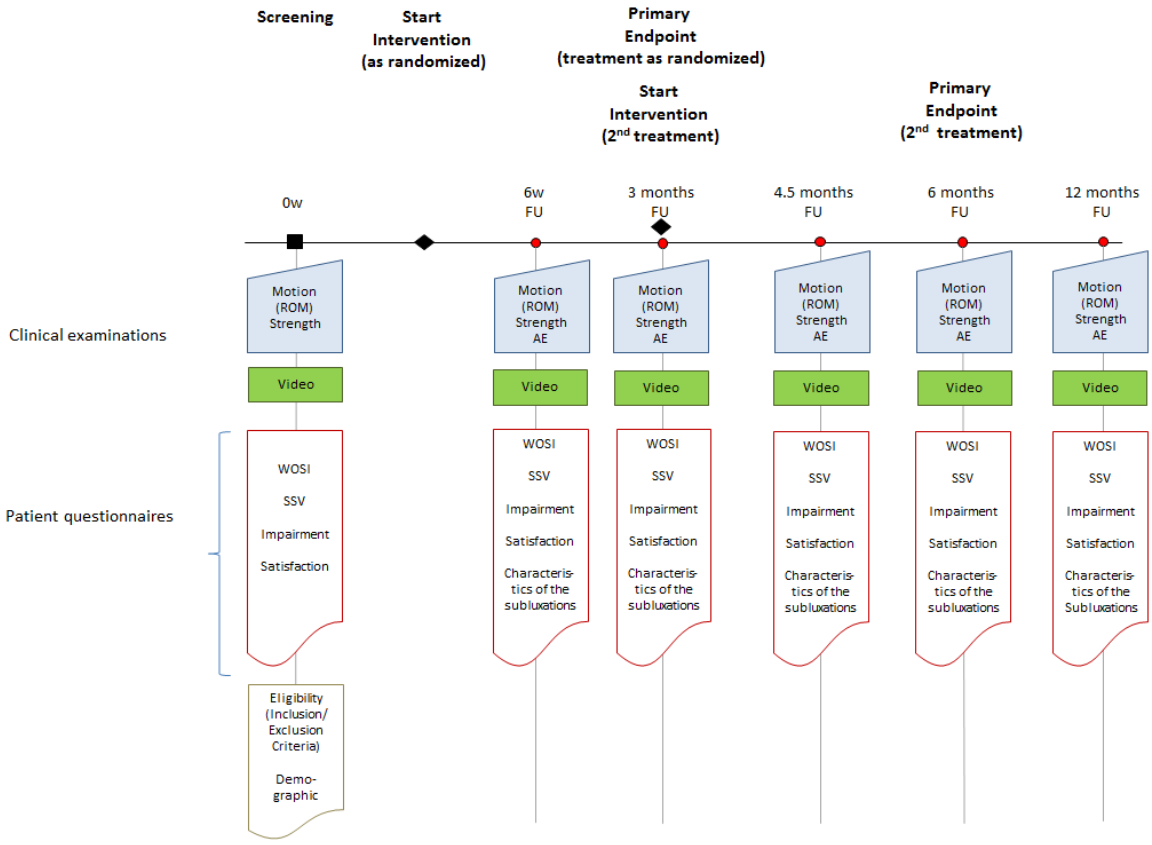
The intervention (EMS or physiotherapy) will be logged in the REDCap database to ensure that the patient got the correct intervention. There are no reasons to withdrawn a patient from the study. The patient can drop-out any time from the study. The PI is in charge to collect as much data as possible from withdrawn patients (e.g. telephone call, Email); patients who withdraw from the study will not be examined.

Withdrawn patients will not be replaced.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

After the patient signed the informed consent they will be allocated in the EMS treatment group or control group by a block randomization procedure.



Each patient (treatment and control group) get a one hour training lesson three times per week during the intervention period of 6 weeks .

The primary endpoint will be measured 3 months after the intervention period has been finished. Afterwards the mentioned optional cross-over in the other group is allowed in the case of subjectively unsatisfying result despite completion of the originally assigned intervention. In this case the study will get one appointment more (4.5 months after patient has been included).

The next time points will be 6 and 12 months after therapy finished.

There will be a measurement of the ROM and different strength parameters at each follow-up appointment (time needed: 30min). Additionally there will be a questionnaire to fill out by the patients to get the subjective parameters (time needed. 30min). Furthermore there will be recorded video from the patient (anonymized; from the backside) to visualize the movement pattern. Optional the patient can hand over a video from his main sport activity (anonymized) to the study coordinator. Both videos will upload into the data base for quality evaluation.

9.2 Procedures at each visit

9.2.1 Screening day/Baseline:

- Screening of the eligibility of the patients
- Collection of demographic data
- Recording of baseline data
    - Subjective data (Questionnaires)
    - Clinical Examination (ROM and strength measurement)
    - Anonymized video

9.2.2 Intervention visit 1 - 18

Intervention Visits 1 -18 (3 per week; 6 weeks)

- Execution of
    - 1h Intervention: EMS Therapy
    - 1h Control: Physiotherapy
- Acquisition of AEs

9.2.3 FollowUp Visits (6 weeks, 3 months, 4.5 months, 6 months, 12 months)

- Recording of follow-Up data
    - Subjective data (Questionnaires)
    - Clinical Examination (ROM and strength measurement)
    - Video
- Acquisition of AEs

10. STATISTICAL METHODS

10.1 Hypothesis

Null-Hypothesis:

Electrical muscle stimulation (EMS) based therapy has the same clinical effect as conventional state-of-the art physiotherapy treatment for functional posterior shoulder instability measured by the primary outcome parameter (WOSI Score).

Alternative-Hypothesis:

Electrical muscle stimulation (EMS) based therapy has a better clinical effect as conventional state-of-the art physiotherapy treatment for functional posterior shoulder instability measured by the primary outcome parameter (WOSI Score; MCID Delta > 10,4%).

10.2 Determination of Sample Size

The calculated sample size for a power of 80%, an alpha error probability of 5%, and an estimated effect size of 0,8 is 52. The effect size was calculated according to Cohen by dividing the minimally clinically important difference of the WOSI (10,4%) by the expected standard deviation of the WOSI among the study participants (13%) based on the pilot trial results. The software used to calculate the sample size was G*Power (HHU Duesseldorf, Duesseldorf, Germany). When accounting for an expected drop-out rate of approximately 20% due to non-compliance or loss to follow-up 66 patients need to be assigned to the trial. Due to the strict exclusion criteria with an expected exclusion rate of 25% approximately 88 patients need to be assessed for eligibility.

10.3 Planned Analyses

10.3.1 Datasets to be analysed, analysis populations

All patients meeting inclusion/exclusion criteria and randomized will be included in the analysis. The efficacy analysis will be performed first on an 'intention-to-treat' (ITT) basis followed by on a 'per-protocol' (PP) basis (definitions provided below).

- The intention-to-treat population (ITT) is based on the initial treatment allocation.
- The per-protocol population (PP) is based on the treatment the patients actually received according to the protocol

An overview of the number of patients enrolled in the study will be presented in a flow chart that will indicate the eligibility for the various analysis populations.

All recorded and derived variables will be presented according to the categories of treatment group and examination time points using appropriate descriptive summary tables. Adverse events with onset after initiation of the study treatment will be displayed in summary tables.

Baseline characteristics will be compared between the treatment groups by means of descriptive statistics and standardized differences. Prognostic factors suspected to be unbalanced between the groups will be taken into account during the analyses.

10.3.2 Primary Analysis

The analysis of the primary outcome parameter (WOSI at 3 months) will be performed using an independent sample T-Test or linear regression with WOSI as the dependent variable and treatment intervention and baseline factor(s) as the independent variable depending on the need for statistical adjustment. The strength of effect will be presented as the mean group difference along with its 95% confidence interval. A random-effect model will be used to account for center effect.

10.3.3 Secondary Analyses

All secondary analyses will be explorative. Secondary outcome variables will be analyzed using univariable random-effect logistic (categorical variables) or linear (continuous variables) regression. Multivariable regression will be conducted depending on the need for adjustment of baseline prognostic factors. Significance level is set to 0.05.

10.3.3.1 Safety analysis

Based on the complication-free pilot trial, no adverse events are pre-specified but continuous recording of unexpected adverse events will be executed in both treatment arms. In the case that adverse events are recorded, the independent expert group and ethical committee supervising the trial will be informed and may decide whether the trial can be continued or must be stopped.

10.4 Handling of missing data and drop-outs

Missing data will be monitored closely and queries generated back to the responsible study site for completion as much as possible.

Missing values due to lack of compliance or patient dropout from the study should remain within the expected minimum. Nonetheless, data analysis will be completed with and without missing data imputation to assess the robustness of the results.

11. QUALITY ASSURANCE AND CONTROL

11.1 Data handling and record keeping / archiving

11.1.1 Case Report Forms

Source data includes all information in original records, observations, or other activities necessary for the reconstruction and evaluation of the documentation process for this study. Samples of source data include, but are not limited to, medical history information, demographics, informed consent, patient identification number, questionnaire responses and outcome scores.

Source data are entered by the study staff, physicians and patients either on paper CRF / source worksheets (WS) or electronically into eCRFs web-based Electronic Data Capture system (REDCap) [2]. Patients are invited to enter study questionnaires electronically, either on a tablet computer at the clinic or from home after invitation by email with an electronic link to the relevant eCRF. Alternatively they will complete paper-based CRFs.

In addition, selected patient demographics and surgical parameters may be imported into REDCap from the patient information system as requested by respective study sites.

11.1.2 Record keeping / archiving

All materials pertaining to the study, including completed WSs and paper CRFs, will documented into a Trial Master File by the study coordinator, sorted and kept in closed archives at the Research and Development Department of the Schulthess clinic.

Each study site will maintain a study Investigator Site File (ISF) to document local study procedures. All study data must be archived for a minimum of 15 years after study termination or premature termination of the clinical trial.

11.1.3 Imaging data

Imaging data of the participants will be collected and stored at each study center locally as part of the clinical routine when screening the eligibility of the patients. In the final monitoring process, all collected imaging data will be evaluated at each study center and exported as pseudonymized data.

11.2 Data management

11.2.1 Data Management System

Study data will stored into the REDCap web-based Electronic Data Capture system [2] that is hosted on a dedicated server maintained by the IT department at the Schulthess clinic.

New software releases are installed after being tested by an IT support person, according to a check list of tasks that the system should perform successfully.

11.2.2 Data security, access and back-up

The REDCap study database is password protected and only accessible to dedicated personnel after signing a confidentiality form. Data exported from REDCap for the analyses are saved into a dedicated server only accessible to designated researchers.

Data security and confidentiality rules of the Schulthess clinic applies to all involved personnel.

The IT department of the Schulthess clinic is responsible and perform back-up procedures of all collected and transformed data according to internal rules.

11.2.3 Analysis and archiving

Study data is exported from the REDCap data management system in csv text file format before being imported into Stata software (StataCorp LP, Texas USA) for statistical analyses.

For archiving see section 12.1.3.

11.2.4 Electronic and central data validation

At the time of data entry into the paper-based clinical report form (CRF), working sheets or electronic clinical report form (eCRF) the responsible person checks the completeness and consistency of the collected data. The utilized electronic data capture system (eDCS) (REDCap[2]) allows minimizing data entry error by development of branching logics and on-line data checks (e.g. range checks).

The statistician performs data quality control per query as appropriate to ensure the quality and integrity of the data. All queries related to a specific analysis are resolved before the final analyses can be performed. Variables required for the analyses are transformed or created after data transfer into Stata and saved in the final analysis dataset.

Data centralization and statistical analysis procedures are fully documented by the Stata programming files.

11.3 Monitoring

Study monitoring will be described in a monitoring manual. Each site will be visited at least twice, i.e. for an initiation visit (kick-off meeting) before recruiting the first patient and for a closure visit after the last patient follow-up. This will ensure understanding and standardization of study procedures as well as the integrity of the recorded data. Onsite monitoring visits will be performed only if deemed necessary for the success of the study. Project monitoring visit or closure will involve validating a defined random sample of source documents, as well as checking the appropriate management and maintenance of essential documents. This will be performed by the designated study coordinator.

The local study coordinator on each study site will check the data entered in the CRF or eCRF for each individual case with regard to completeness, plausibility and consistency. Original paper CRFs are to be regarded as documentary evidence. All entries must be made accordingly, and any alteration must be entered as an addition with explanatory note, date and signature. Electronic data entry will be performed on each study site and sites will have access only to their own case data.

The main study coordinator and project statistician will have access to all study data. They will perform regular data checks and generate queries back to the responsible site for clarification and data correction as appropriate. The investigators agree to allow the study coordinator direct access to all relevant documents and to allocate his/her time and the time of his/her staff to discuss findings and any relevant issues. This will include ensuring all data entry into the eDCS is complete and consistent with all enrolled subjects. Inconsistencies will be resolved throughout the study.

The statistician performs data quality control per query as appropriate to ensure the quality and integrity of the data. All queries related to a specific analysis are resolved before the final analyses can be performed. Variables required for the analyses are transformed or created after data transfer into Stata and saved in the final analysis dataset. Data centralization and statistical analysis procedures are fully documented by the Stata programming files.

11.4 Audits and Inspections

There is no plan for auditing the study, nevertheless the study documentation and especially the source data/documents are accessible to auditors/inspectors (panel of independent

international experts) and questions will be answered during possible inspections. In this process, all involved parties must keep the patient data strictly confidential.

11.5 Confidentiality, Data Protection

During this study, medical information from included patients will be treated in strict confidence and shall not be disclosed to third parties. Confidentiality will be ensured through anonymization of the clinical results in the scientific presentations and publications. The patient identification will be known only at respective study site by authorized personnel who are bound to confidentiality.

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections. Access to REDCap will be allowed only to the study team, and analyses files will accessible by the study team on the dedicated server at the Research and Development Department.

12. PUBLICATION AND DISSEMINATION POLICY

The results of the trial will be presented in a manuscript according to the CONSORT guidelines and published in a peer-reviewed journal. To ensure general availability, the publication will be made open-access. To improve dissemination and visibility the trial results will be presented at national and international shoulder conferences.

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