Statistical Analysis Plan for the SINEX study: Three Months of Physical Therapist-supervised Neuromuscular Shoulder Exercise Program versus Standard Care for Patients with Traumatic Anterior Shoulder Dislocations

An Assessor-blinded Randomized Controlled Trial (The SINEX study)

Eshoj, Henrik; Rasmussen, Sten; Frich, Lars Henrik; Hvass, Inge; Christensen, Robin; Jensen, Steen Lund; Søndergaard, Jens; Søgaard, Karen; Juul-Kristensen, Birgit

Publication date:
2017

Document version
Publisher's PDF, also known as Version of record

Citation for pulished version (APA):
Eshoj, H., Rasmussen, S., Frich, L. H., Hvass, I., Christensen, R., Jensen, S. L., ... Juul-Kristensen, B. (2017). Statistical Analysis Plan for the SINEX study: Three Months of Physical Therapist-supervised Neuromuscular Shoulder Exercise Program versus Standard Care for Patients with Traumatic Anterior Shoulder Dislocations: An Assessor-blinded Randomized Controlled Trial (The SINEX study).

STATISTICAL ANALYSIS PLAN (SAP)

Three Months of Physical Therapist-supervised Neuromuscular Shoulder Exercise Program versus Standard Care for Patients with Traumatic Anterior Shoulder Dislocations: An Assessor-blinded Randomized Controlled Trial (The SINEX study)

Henrik Eshoj[1], Sten Rasmussen[2, 3], Lars Henrik Frich[4, 5], Inge Hvass[6], Robin Christensen[7], Steen Lund Jensen[3], Jens Søndergaard[8], Karen Søgaard[9] and Birgit Juul-Kristensen[9]

Affiliations:
[1] Quality of Life Research Center, Department of Hematology, Odense University Hospital, Odense, Denmark
[2] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[3] Orthopaedic Surgery Research Unit, Aalborg University Hospital, Aalborg, Denmark
[4] Department of Orthopaedics and Traumatology, Odense University Hospital, Odense, Denmark
[5] Department of Clinical Research, University of Southern Denmark, Odense Denmark
[6] Shoulder sector, Orthopedic Department, South-West Jutland Hospital, Esbjerg, Denmark
[7] Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark
[8] Research Unit of General Practice, University of Southern Denmark, Odense, Denmark
[9] Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

Statistical advisor: Robin Christensen (RC), Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

Statistical analyst: Eleanor Boyle (EA), Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

Database manager: Anne Marie Rosager (AMR), Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

Publication date: 10.10.2017
Citation for published version:
Henrik Eshoj[1], Sten Rasmussen[2], Lars Henrik Frich, Inge Hvass, Robin Christensen, Steen Lund Jensen, Jens Søndergaard, Karen Søgaard and Birgit Juul-Kristensen
Statistical Analysis plan (SAP): Three Months of Physical Therapist-supervised Neuromuscular Shoulder Exercise Program versus Standard Care for Patients with Traumatic Anterior Shoulder Dislocations: An Assessor-blinded Randomized Controlled Trial (The SINEX study).

TABLE OF CONTENTS

STUDY SYNOPSIS

Traumatic anterior shoulder dislocation (TASD) is a common injury [1] within young (<40 years of age) active individuals [2] and induce a high risk for recurrent anterior shoulder dislocation to evolve due to post-traumatic pathophysiological changes in the shoulder joint [3]. Recurrent anterior shoulder dislocation may have negative consequences for shoulder function, with joint stability being further compromised after every dislocation. Thus, patients are often limited in sports-related and social activities affecting their shoulder-related Quality of Life (QoL) [4-7]. Standard care consists of orthopedic manually treated shoulder reduction at emergency departments, followed by shoulder immobilization and, if provided, some kind of physiotherapy [8]. However, there is no evidence-based exercise program to prescribe for patients with TASD [3] and studies investigating non-surgical treatment for this patient group is low [9].

The current study will shed light on the effect of non-operative treatment for patients with trauma-initiated primary and subsequent recurrent anterior shoulder dislocation and provide foundation for non-operative treatment guidelines. Additionally, this trial will support evidence-based shared decision-making processes between physicians and patients in clinical practice, when patients seek orthopedic and/or physiotherapy treatment for a primary or recurrent anteriorly dislocated shoulder.

Ethical Trial registration: S-20140093

Clinicaltrial.gov registration: (NCT02371928)

STUDY OBJECTIVES AND OUTCOMES

The primary outcome, the Western Ontario Shoulder Instability Index (WOSI) [10], was obtained for all participants at baseline, four, and eight weeks, besides at follow-up at three months (12 weeks). The secondary outcomes were obtained from all participants at baseline and at follow-up after 3 months (12 weeks).
This study tests the hypothesis that patients with TASD treated with shoulder neuromuscular exercises (intervention, SINEX group) will experience and report larger improvements in shoulder related QoL, pain and function, respectively, than those treated with instructions on self-managed shoulder exercise program (control, Standard Care group).

The intervention (SINEX) group received: 12 weeks of individually physiotherapist-supervised exercise specifically targeting the rotator cuff and scapular muscles. Moreover, functional kinetic chain exercises are incorporated for progressing to more difficult levels, mimicking daily activities and improving the transferability of everyday activities. In total, seven exercises are included in the SINEX program and can be individually progressed from basic to elite level (A to G). Participants are instructed to perform each exercise at home as follows; exercises at basic levels (A to E) seven days a week and exercises at elite levels (F to G) three times a week. Participants are provided with online access to instructions and video recordings of each exercise and the accompanying levels of progression through the physiotherapy site www.digifys.com. Further, participants receive supervised physiotherapy sessions throughout the 12 weeks. The physiotherapists decide the

amount of supervision based upon movement control and capabilities of the individual patient.

The control (Standard Care) group received: one introductory supervised physiotherapy session on how to perform the 12-week self-managed training-based shoulder exercise program consisting of strengthening exercises for the rotator cuff and scapular muscles. Exercises are performed three times weekly with 10x2 repetitions for each exercise. Also, patients are provided a leaflet containing photos and descriptions of each exercise.

All methods are described in the protocol published by Eshoj et al. [11]. To meet the required sample size of patients with TASD, an adjusted power calculation was performed after publishing the protocol.

PRIMARY OBJECTIVE AND OUTCOME

The primary objective in this randomized controlled trial was to evaluate the efficacy and safety of a 12-week physiotherapist-supervised neuromuscular shoulder exercise (SINEX) program in comparison with 12-weeks of self-managed shoulder exercise program (standard care) in patients with TASD as measured by the primary outcome being the total score of (WOSI) questionnaire [10].
The primary endpoint was chosen based upon the fact that the primary effect measure is a patient reported shoulder-related QoL outcome and not, as in previous trials including patients with primary TASD, whether the shoulder re-dislocates or not. Further, WOSI-total is recommended as primary outcome when evaluating patient reported treatment effects in patients with shoulder instability [12] and is translated, reliable and valid for use in Danish shoulder instability patients [13]. WOSI covers 21 items, ranging from 0-2100 with higher scores representing worse QOL [10] (Table 1). Each item is scored from 0-100 on a visual analogue scale. WOSI holds four subscales/domains; Physical symptoms (10 items), Sport/recreation/Work (4 items), Lifestyle (4 items) and Emotions (4 items). Each of the WOSI subscales will be reported and analyzed as secondary outcomes.

SECONDARY OBJECTIVES AND OUTCOMES

The secondary objectives are to compare changes from baseline to the 12-weeks follow-up between the two treatment arms in a number of patient reported outcomes besides physical test measures. The secondary outcomes are to be used as support for the interpretation of the primary outcome. Also, these analyses can only be supportive, explanatory and/or hypothesis generating, which are why multiple comparisons are not deemed to be a problem.

THE PATIENT REPORTED OUTCOME MEASURES

1) The four subscales of the WOSI (with the level of no trouble equal to 0, accounting for all domains [10]): a. Physical symptoms (0-1000); b. Sport/recreation/work (0-400); c. Life-style (0-400); d. Emotions (0-300)

2) The Tampa Scale of Kinesiophobia (TKS) questionnaire ranging from 17-68 with 68 representing highest fear of movement and re-injury [14, 15] with scores equal to or above 37 representing high fear of movement and re-injury [14].

3) Pain intensity at rest, within the latest 24 hours and seven days, respectively, using the Numeric Pain Rating Scale (NPRS) ranging from 0-10 score with 10 representing worst imaginable pain [16]

4) Patient-rated important activity using the Pain Specific Function Scale (PSFS) scored at a NRS ranging from 0-10 with 10 indicating no problems in performing the activity [17].

5) Health related QoL using the EQ-5D´s Visual Analogue Scale (EQ-VAS) ranging from 0 to 100 with 0 representing lowest health-related quality of life.

6) Cost-effective analysis using the total score of the EuroQol-5D-5L (EQ-5D) ranging from -0.59 to 1 with -0.59 representing lowest scores [18].

THE PHYSICAL OBJECTIVE TESTS

1) Clinical evaluation of anterior shoulder instability using the clinical shoulder tests apprehension, relocation and surprise (positive, yes/no) [19], [20], [21].

2) The Constant-Murley Shoulder Score (CMS; 0-100 score, 100=best possible shoulder function [22] based on patient reported questions and objective physical test measures, consisting of shoulder range of movement (CMS-ROM) and isometric shoulder abduction strength (CMS-Strength).

3) Shoulder proprioception using a repositioning test with patients blindfolded, asked to actively reproduce different shoulder angles within low ranges (equal to 60±10 degrees) of shoulder flexion and abduction. The test is conducted by using a laser beam attached at the elbow pointing towards pre-specified targets using a target scale [11, 23].

SELF-REPORTED HISTORICAL INFORMATION COLLECTED AT THE 3 MONTHS FOLLOW UP

1) Number of visits to the general practitioner or secondary healthcare system
2) Number of new shoulder dislocation/subluxation events
3) Number of days sick listed from work and sport attributed to the actual shoulder injury
4) Number of referrals to or completed shoulder surgical procedures attributed to the actual shoulder injury

5) Global Perceived Effect (GPE) measures; evaluated using the question "*Compared to when this treatment first started, how would you describe your current shoulder problem?*'' (7 response categories ranging from very much worse to very much better)
6) *"If you had the choice, would you then consider having stabilizing shoulder surgery performed?"* (Yes/no?)

For further information on self-reported historical information, please see Table 4.

DESCRIPTIVE OUTCOMES AND ADHERENCE

Baseline descriptive outcomes are to be published separately by Eshoj and colleagues (proposed title: "Patients with primary or recurrent traumatic anterior shoulder dislocation have equally poor self-reported and measured shoulder function - a cross-sectional study") and are distributed by number of dislocations (primary versus recurrent up to five dislocations).

Adherence to the (intervention) SINEX program: registered by the treating physiotherapists as number of supervised sessions attended by the patient. For treatment-related variables adherence is classified in accordance with the following criteria:

- Satisfactory (as defined per protocol) adherence for the patients is 50% participation (at least seven supervised sessions out of 14 possible sessions), besides
- Completion of at least two thirds (66%) of the scheduled home-based exercises registered by use of training diary.

Adherence to the (control) Standard Care program: Completion of at least two thirds (66%) of the scheduled home-based exercises registered by use of training diary.

PRIMARY ENDPOINT

This study was designed as an exploratory superiority trial with two groups (SINEX and Standard Care) using the patient reported WOSI questionnaire as primary outcome. It was expected that the group allocated to SINEX improved 250 points more than the group allocated to standard care based on the primary outcome WOSI-total at the end point after 3 months. Thus, the primary endpoint is based upon the between group difference in change in the total WOSI score.

SECONDARY ENDPOINTS

The secondary endpoints will be analyzed for between group differences in change from baseline to the 3 months follow up. For sensitivity and exploratory purposes a per-protocol analysis, including those with good compliance, as defined above, will be performed.

STUDY DESIGN

This trial was a multi-center randomized (1:1), assessor-blinded, controlled clinical superiority trial with a paralleled group design investigating the efficacy and safety of SINEX versus standard care

for patients with TASD (see flowchart, Figure 1). Patient recruitment was conducted from three orthopedic shoulder units in The Region of Southern and Northern Denmark. Eligibility criteria were men and women aged 18-39 years with trauma initiated primary and subsequent recurrent anterior shoulder dislocation. All patients should comply with the following inclusion criteria: minimum one radiologic verified anterior shoulder dislocation, in addition to self-reported shoulder trouble within the latest week at the time of assessment for trial inclusion, e.g. reduced ability to perform specific shoulder movements during sports/leisure activity and/or work. Exclusion criteria were the following: humeral fracture and/or bony Bankart warranted for shoulder surgery, prior surgery in the affected shoulder joint, more than five anterior shoulder dislocations (verified by patient register or subjective evaluation), suspected competing diagnosis (e.g. rheumatoid arthritis, cancer, neurological disorders, fibromyalgia, schizophrenia, suicidal threatened, borderline personality disorder or obsessive compulsive disorder), sensory and motor deficits in neck and shoulder, pregnancy, inadequacy to write and speak Danish, besides not willing or able to attend 12 weeks of a physical therapist-supervised neuromuscular shoulder exercise program.

SAMPLE SIZE

With a mean baseline WOSI-total score expected to be 1100 points (range 0-2100, with 2100 as worst possible score) and a common standard deviation assumed to be 320 [24], a sample size of 36 participants per group was required to detect a statistical significant difference (significance level of 0.05, 90% power). To account for possible barriers, non-compliant patients and participants' lost-to-follow-up, a total sample size of 80 participants (40:40) was targeted.

DEVIATION FROM TRIAL REGISTRATION

According to trial registration at Clinicaltrials.gov (NCT02371928) a number of changes have been made. Due to difficulties with inclusion of patients it was decided by March 9th, 2016 to remove the inclusion criteria; Minimum two positive tests out of three clinical tests for anterior shoulder instability (apprehension, relocation and/or surprise).

Further, due to poor validity of the prone lying shoulder sensorimotor control measurements [25] this outcome was omitted from the current trial. Finally, when registering the trial, a power of 90% was targeted. This was to allow for difficulties in recruitment and to take dropouts or non-compliant participants into consideration. However, a priori, it was decided to close the recruitment of participants on March 31th, 2017 after a recruitment period of 24 months [11]. Unfortunately, only 56 patients were included at this time point. Though, despite not achieving the requested sample size of 80 patients, the results for the 56 patients included are reported since the outcome of this trial is of extreme importance since this is the first trial to compare the effect of two conservative treatment strategies for patients with anterior shoulder dislocation as is initiated by trauma.

RANDOMIZATION, ALLOCATION AND BLINDING PROCEDURES

Following baseline assessment patients were randomly assigned to either of the two exercise groups (SINEX vs. Standard Care). An independent biostatistician, with no involvement in the clinical care

of the patients, prepared a computer generated list of random numbers (1:1), packed at each trial site into sequentially numbered, opaque, concealed envelopes, stating which group every single individual was allocated to. A stratification technique was used based on injury status: (*i*) primary (first time) or (*ii*) recurrent (second–fifth) anterior shoulder dislocation. After randomization a research secretary, not involved in the outcome assessments, forwarded group assignments to a treating physiotherapist who contacted patients for scheduling an appointment for the first exercise instruction. Outcome assessors performing all outcome measurement were kept blinded according to treatment allocation and were also not involved in the treatment of patients.
Blinding of treatment allocation for patient and physiotherapists were not possible due to the design. To retain the blinding of the outcome assessors, patients were encouraged not to reveal their treatment assignment, at the 3-month follow-up.

STATISTICAL ANALYSIS

The statistical analysis plan will be performed blinded according to group allocation and results will be interpreted in an author consensus statement prior to disclosing/revealing group allocation on the basis of a blinded review of the data from the primary endpoint (changes from treatment A compared to changes from treatment B), assuming that treatment A is the active treatment (SINEX), and the other assuming that treatment B is the active treatment (SINEX). Not until a signed consent from all of the authors of this trial (identical to the authors of this SAP) has been obtained, agreeing on one interpretation of the results only, the randomization code will be broken. This is done to reduce bias in the interpretation of the current findings.
All analyses will follow the intention-to-treat principle; i.e. all randomized participants in the trial will be included in the analysis according to the group to which they were originally allocated, regardless of dropout/departures from allocated treatment. For the primary analysis, missing values, due to patient's absence from follow-up or withdrawal from the study will be replaced using a non-responder imputation, in which the baseline value is carried forward [26]. The rationale behind this type of analysis builds on the assumption that patients absent from follow up returns to scores obtained at baseline [27].

An analysis of covariance (ANCOVA) model will be used to analyze mean changes in continuous endpoints. The model will include test for interaction between treatment (SINEX/Standard Care) and Time (baseline/follow up), as well as treatment (SINEX/Standard Care), study center (Aalborg, Esbjerg Odense), injury status (primary or recurrent shoulder dislocation) and gender as fixed effects, with the baseline value of the relevant variable as covariates. Categorical outcomes for dichotomous endpoints will be analyzed with the use of logistic regression with the same covariates as the respective ANCOVA.

For the longitudinal part of the trial a linear mixed effect ANCOVA model with repeated measures of the WOSI (4, 8 and 12 weeks) will be performed to test the difference over time between the SINEX and Standard Care group with interaction: treatment (SINEX/Standard Care) and Time (4, 8, 12 weeks), with the same fixed effects and covariates as the respective ANCOVA. For these analyses the 'data as observed' will be applied (i.e. no imputation for missing data).

Overall, results will be expressed as the difference between groups with 95% confidence intervals and the associated p-values. Based on the principles related to superiority designs (in potential favor of SINEX), we prespecify that a 95% CI excluding differences between groups of greater than 200 WOSI-total units would be interpreted as indicating the absence of a clinically meaningful difference [28]. Sensitivity analysis for difference between missing and completed data will be performed. Per protocol analyses will be performed between those who were exercise compliant in both groups.

Statistical analyses will be performed with the Statistical Package form Social Sciences (SPSS), version 24.0.

DISCONTINUED THE INTERVENTION

Withdrawals and the reason for their withdrawal (if identified) were registered by the database manager and primary investigator (HE). Dropouts are defined as those who were not assessed at 3 month follow up. All dropout patients are included in the ITT analysis with the baseline observations carried forward procedure.

IMPLEMENTATION OF ANALYSIS PLAN

A statistical analyst will perform the analysis of the primary outcome with no involvement from any of the study investigators.
The implementation of the SAP for the SINEX study will follow the procedure below:

1. A database model will be lined up in collaboration between the statistical advisor (RC) and principal investigator (HE).
2. The database manager (AMR) will code each treatment arm into ‘group treatment A’ and ‘group treatment B’, thus leaving all others blinded to treatment allocation during analysis.
3. Blinded data will be delivered to the statistician (EB) according to the data base model.
4. Primary analyses will be conducted blinded from allocation to any of the two treatment arms.
5. Results will be presented to the primary investigator (HE) and co-authors of the manuscript.

The authors will then agree upon two possible interpretations based on the analysis of the primary outcome data: one assuming that group A will be the active group, and the other assuming that B will be the active group. Therefore, a blinded interpretation of the primary endpoint results will be conducted before breaking the allocation. Thereafter, a consensus between all investigators will be reached regarding clinical interpretation of the results. Furthermore, all members of the author group will approve and sign the interpretations before any publication procedures are initiated [29].

TABLE AND FIGURE LEGENDS

Figure 1: Flow of participants throughout the study

Table 1: Baseline demographic and historical information for patients with trauma initiated primary and subsequent recurrent anterior shoulder dislocation allocated to the SINEX vs. Standard care groups. Estimates are reported for each group and the total with Mean ± SD, n (%).

Figure 2: Western Ontario Shoulder Instability (WOSI) total score at baseline, week 4, 8 and 12 for the SINEX vs. Standard Care Groups among patients with trauma initiated primary and recurrent anterior shoulder dislocation. Data are derived from repeated-measures Linear Mixed model and adjusted for baseline WOSI-total scores. The graph illustrates the results from the Intention-To-Treat population. Data points represent least squares means and error bars indicate 95% CIs.

Table 2: Primary and secondary outcomes from baseline to 12-week follow-up for SINEX vs. Standard care groups among patients with trauma initiated primary and subsequent recurrent anterior shoulder dislocation, Intention-to-treat population.

Table 3. Adverse Events from baseline to 12-week follow-up for SINEX vs. Standard care groups among patients with trauma initiated primary and subsequent recurrent anterior shoulder dislocation.

Table 4. 12-week follow-up self-reported historical information for SINEX vs. Standard Care groups among patients with trauma initiated primary and subsequent recurrent anterior shoulder dislocation.

Figure 1
Flowchart of the SINEX study

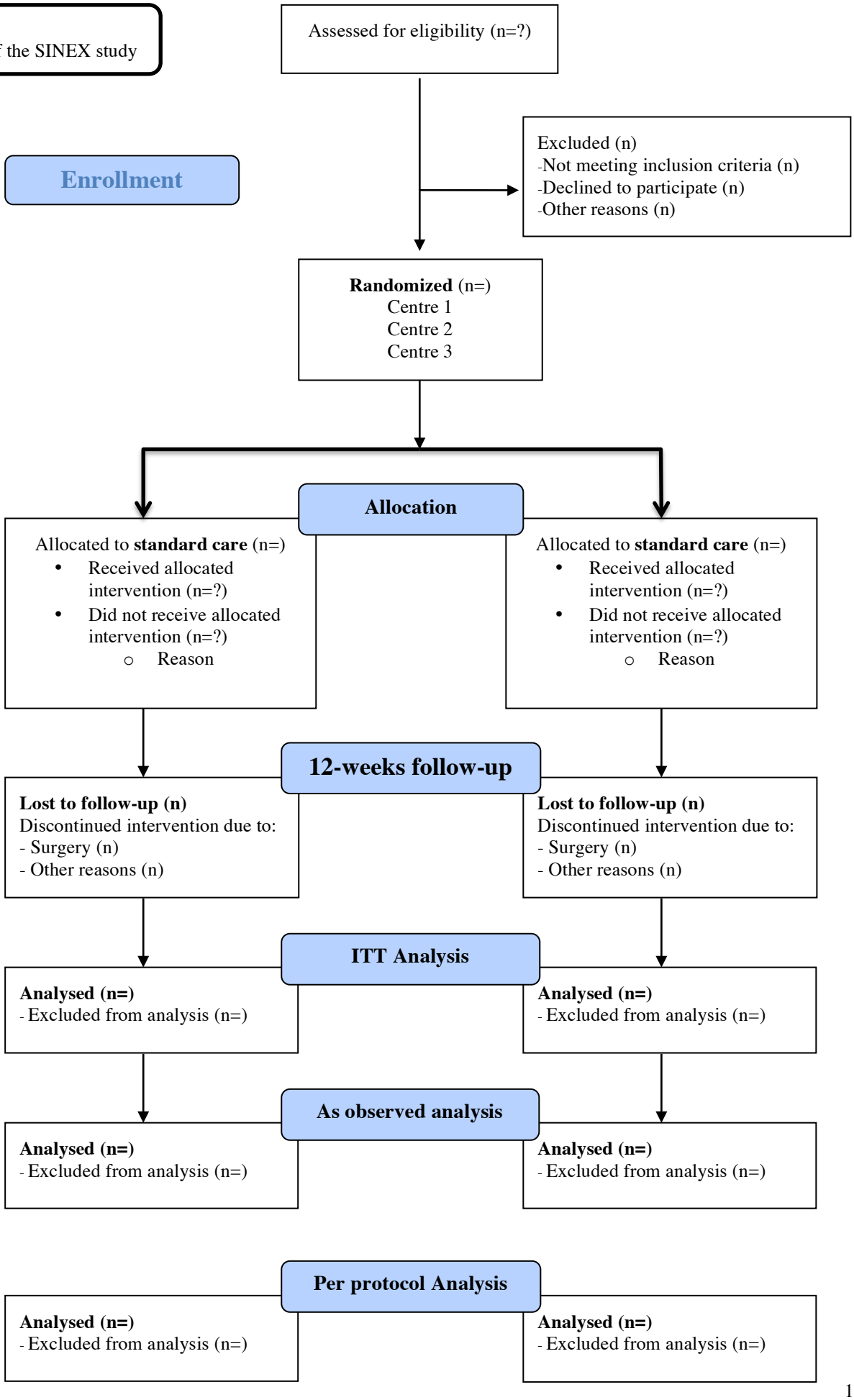

Table 1. Baseline demographic and historical information for patients with trauma initiated primary and recurrent anterior shoulder dislocation allocated to the SINEX vs. Standard care groups. Estimates are reported for each group and the total with Mean ± Standard Deviation (SD), n (%).

Variables	**SINEX Group (n=..)**	**Standard Care Group (n=..)**
Gender (male (%))		
Age (yrs) Mean (SD)		
Weight (kg) Mean (SD)		
Height (cm) Mean (SD)		
Educational level (n (%))		
Academic		
White collar		
Blue collar		
Uneducated		
Employment status (n (%))		
Full-time		
Part-time		
Student		
Un-employed/retired		
Sick-leave		
Dominant arm (right (%))		
Injured shoulder (right (%))		
Injury mechanism (n (%))		
Fall on the arm		
Pull in the arm		
External force to the shoulder		
Other		
Number of orthopedic treated shoulder reductions (n (%))		
Unknown		
1		
2		
3		
4		
5		
Have you previously received any shoulder treatment? (n (%))		
No		
Yes		
Active PT exercise treatment		
Passive treatment		
Chiropractic		
Analgesic medication (medically prescribed)		
Physically active? (n (%))		
No		
Yes		
≥4 hours/week		
Primary outcome		
WOSI-total (0-2100)		
Secondary outcomes		
WOSI domains		
-Physical symptoms (0-1000)		
-Sport function (0-400)		
-Lifestyle (0-400)		
-Emotions (0-300)		
TSK (17-68)		
≥37 (high re-injury fear), yes (%)		

NPRS (latest 24 hours) (0-10)
NPRS (latest 7 days) (0-10)
EQ VAS (0-100)
EQ-5D (-0.59 – +1)
PSFS (0-10)
GJH (0-9, positive ≥4, yes (%))
Clinical tests (positive, yes, (%)):
-Apprehension
-Relocation
-Surprise
Total CMS (combined score, 0-100)
CMS-ROM (combined score, 0-40)
CMS-strength (kg)
-Injured shoulder
-Non-injured shoulder
Shoulder JPS[a] (cm, AE)
-Flexion (60 +/-10)
-Abduction (60 +/-10)

Abbreviations: WOSI Western Ontario Shoulder Instability Index; **TSK** Tampa Scale of Kinesiophobia; **NPRS** Numeric Pain Rating Scale; **EQ VAS** Euroqol Visual Analogue Scale; **EQ-5D** Cost-effectiveness, total score of EuroQol-5D-5L; GJH Generalized Joint Hypermobility; **PSFS** Patients Specific Function Scale; **CMS** Constant Murley shoulder Score; **CMS-ROM** Range of Motion; **JPS** Joint Position Sense; **cm** centimeter; **AE** absolute error. Missing data =

Figure 2: Western Ontario Shoulder Instability (WOSI) total score at baseline, week 4, 8 and 12 for the SINEX vs. Standard Care Groups among patients with trauma initiated primary and recurrent anterior shoulder dislocation. Data are derived from repeated-measures Linear Mixed model and adjusted for baseline WOSI-total scores. The graph illustrates the results from the Intention-To-Treat population. Data points represent least squares means and error bars indicate 95% CIs.

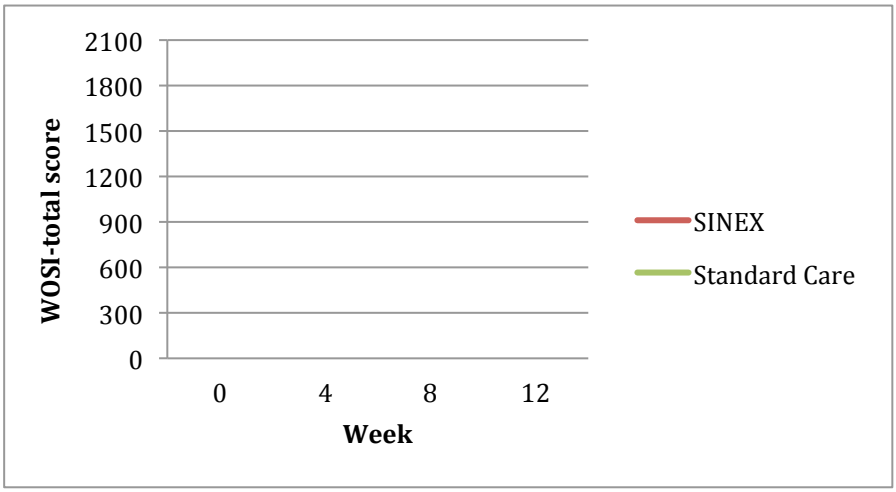

Table 2: Primary and secondary outcomes from baseline to 12 weeks follow-up for SINEX vs. Standard care groups among patients with trauma initiated primary and recurrent anterior shoulder dislocation, Intention-to-treat population

	SINEX group (n=) Change (95% CI)	**Standard Care group (n=)** Change (95% CI)	Between-Group difference (95% CI)	P Value
Primary outcome				
WOSI-total (0-2100)				
Secondary outcomes				
WOSI domains				
-Physical symptoms (0-1000)				
-Sport function (0-400)				
-Lifestyle (0-400)				
-Emotions (0-300)				
TSK (17-68)				
≥37 (high re-injury fear), yes (%)				
NPRS (latest 24 hours) (0-10)				
NPRS (latest 7 days) (0-10)				
EQ VAS (0-100)				
EQ-5D (-0.59 – +1)				
PSFS (0-10)				
Clinical tests (positive, yes, (%))				
-Apprehension				
-Relocation				
-Surprise				
Total CMS (combined score, 0-100)				
CMS-ROM (combined score, 0-40)				
CMS-strength (kg)				
-Injured shoulder				
-Non-injured shoulder				
Shoulder JPS[a] (cm, AE)				
-Flexion (60 +/- 10)				
-Abduction				

Abbreviations: WOSI Western Ontario Shoulder Instability Index; **TSK** Tampa Scale of Kinesiophobia; **NPRS** Numeric Pain Rating Scale; **EQ VAS** Euroqol Visual Analogue Scale; **EQ-5D** Cost-effectiveness, total score of EuroQol-5D-5L; **PSFS** Patients Specific Function Scale; **CMS** Constant Murley shoulder Score; **CMS-ROM** Range of Motion; **JPS** Joint Position Sense; **cm** centimeter; **AE** absolute error.
Missing data =.

Table 3. Adverse Events (specific, serious, withdrawals due to adverse events, and deaths), as well as Between-Group Risk Difference with 95% CI, from baseline to 12-week follow-up for SINEX vs. Standard Care groups among patients with trauma initiated primary and recurrent anterior shoulder dislocation.

Adverse events	**SINEX group (n=)**	**Standard Care group (n=)**	**Between-Group Risk Difference with 95%CI**
-No. of shoulder related adverse events due the exercise program (n, (%))			
-Pain			
-Soreness			
-Muscle fatigue			
-Other			
-No. of contacts to general practitioner due to shoulder related adverse events (n, (%))			
-No. of contacts to orthopedic surgeon due to shoulder related adverse events (n, (%))			
-Adverse events to other body parts due to the current exercise program (n, (%))			
-No			
-Yes			
-Adverse events related to other body parts that lead to:			
-Orthopedic consultation (n, (%))			
-General practitioner consultation (n, (%))			

Table 4. 12-week follow-up self-reported historical information for SINEX vs. Standard Care groups among patients with trauma initiated primary and subsequent recurrent anterior shoulder dislocation.

	SINEX group (n=)	**Standard Care group (n=)**	**P value**
Currently employed/under education (n (%))			
-Yes			
-Yes, however, on sick-leave due to the current shoulder injury			
-No, due to the current shoulder injury			
-No, for other reasons than the current shoulder injury			
No. of days away from work/education due to the actual shoulder injury (n, (%))			
-None			
-1-9 days			
-10-24 days			
-25-99 days			
No. of patients referred to or having completed shoulder stabilizing surgery (n, (%))			
Experience of recurrent anterior shoulder dislocation (n, (%))			
-no			
-yes			
-Experience of recurrent anterior shoulder instability (shoulder subluxation) (1-4)[a]			
No. of patients that went to/received other treatment than provided in the current study (n, (%))			
-None			
-Physiotherapy			
-Corticosteroid injection			
-Massage			
-Acupuncture			
-Zone therapy			
-Other			
Use of painkillers (>3 days/week) due to the actual shoulder injury (n, (%))			
-No			
-1-4/day			
-5-8/day			
-9-12/day			
->12/day			
No. of days sick listed from sport attributed to the actual shoulder injury (n, (%))			
-None			
-1-9 days			
-10-24 days			
-25-99 days			
No. of days sick listed from work/education attributed to the actual shoulder injury (n, (%))			
-None			
-1-9 days			
-10-24 days			
-25-99 days			
To what extent has your shoulder affected the quality of your duties at work/education within the last four weeks? (1-4)[a], Mean (SD)			
To what extent has your shoulder affected the amount of duties solved at work/education within			

the last four weeks? (1-4)[a], Mean (SD)
Returned to pre-injury level of sport (RTS) (1-4)[a], Mean (SD)
Thinking of your overall shoulder function, do you then consider your actual shoulder condition as satisfying (1-4)[a], Mean (SD)
Thinking of your overall shoulder function, do you then consider the current 12-week treatment to have failed (1-4)[a], Mean (SD)
GPE (-3 to +3) Mean (SD)
-Compared to when this treatment first started, how would you describe your:
-Actual shoulder function
-Capability to perform activities of daily living
-Capability to perform sport/leisure activities
-Shoulder-related Quality of life
Thinking of your current shoulder function, do you then consider having shoulder surgery performed? n, (%))
-No
-Yes
No. of patients that complied with exercise protocol? (n, (%))

[a]1 being "largely", 4 being "not at all"); **GPE** Global Perceived Effect

REFERENCES

1. Longo, U.G., et al., *Management of primary acute anterior shoulder dislocation: systematic review and quantitative synthesis of the literature.* Arthroscopy, 2014. **30**(4): p. 506-22.
2. Sofu, H., et al., *Recurrent anterior shoulder instability: Review of the literature and current concepts.* World J Clin Cases, 2014. **2**(11): p. 676-82.
3. Monk, A.P., et al., *Evidence in managing traumatic anterior shoulder instability: a scoping review.* Br J Sports Med, 2015. **49**(5): p. 307-11.
4. Dawson, J., R. Fitzpatrick, and A. Carr, *Questionnaire on the perceptions of patients about shoulder surgery.* J Bone Joint Surg Br, 1996. **78**(4): p. 593-600.
5. Matsen, F.A., 3rd and J.D. Zuckerman, *Anterior glenohumeral instability.* Clin Sports Med, 1983. **2**(2): p. 319-38.
6. Gartsman, G.M., et al., *Self-assessment of general health status in patients with five common shoulder conditions.* J Shoulder Elbow Surg, 1998. **7**(3): p. 228-37.
7. Tjong, V.K., et al., *A Qualitative Investigation of Return to Sport After Arthroscopic Bankart Repair: Beyond Stability.* Am J Sports Med, 2015. **43**(8): p. 2005-11.
8. O'Brien, S.J., R.F. Warren, and E. Schwartz, *Anterior shoulder instability.* Orthop Clin North Am, 1987. **18**(3): p. 395-408.
9. Gibson, K., et al., *The effectiveness of rehabilitation for nonoperative management of shoulder instability: a systematic review.* J Hand Ther, 2004. **17**(2): p. 229-42.
10. Kirkley, A., et al., *The development and evaluation of a disease-specific quality of life measurement tool for shoulder instability. The Western Ontario Shoulder Instability Index (WOSI).* Am J Sports Med, 1998. **26**(6): p. 764-72.
11. Eshoj, H., et al., *A neuromuscular exercise programme versus standard care for patients with traumatic anterior shoulder instability: study protocol for a randomised controlled trial (the SINEX study).* Trials, 2017. **18**(1): p. 90.
12. Plancher, K.D. and S.L. Lipnick, *Analysis of evidence-based medicine for shoulder instability.* Arthroscopy, 2009. **25**(8): p. 897-908.
13. Eshoj, H., et al., *Translation, adaptation and measurement properties of an electronic version of the Danish Western Ontario Shoulder Instability Index (WOSI).* BMJ Open, 2017. **7**(7): p. e014053.
14. Vlaeyen, J.W., et al., *Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance.* Pain, 1995. **62**(3): p. 363-72.
15. Mintken, P.E., et al., *Psychometric Properties of the Fear-Avoidance Beliefs Questionnaire and Tampa Scale of Kinesiophobia in Patients With Shoulder Pain.* Archives of Physical Medicine and Rehabilitation, 2010. **91**(7): p. 1128-1136.
16. Downie, W.W., et al., *Studies with pain rating scales.* Ann Rheum Dis, 1978. **37**(4): p. 378-81.
17. Donnelly, C. and A. Carswell, *Individualized outcome measures: a review of the literature.* Can J Occup Ther, 2002. **69**(2): p. 84-94.
18. Rabin, R. and F. de Charro, *EQ-5D: a measure of health status from the EuroQol Group.* Ann Med, 2001. **33**(5): p. 337-43.
19. Lo, I.K., et al., *An evaluation of the apprehension, relocation, and surprise tests for anterior shoulder instability.* Am J Sports Med, 2004. **32**(2): p. 301-7.
20. Vind, M., et al., *Inter-examiner reproducibility of clinical tests and criteria used to identify subacromial impingement syndrome.* BMJ Open, 2011. **1**(1): p. e000042.

21. Tzannes, A., et al., *An assessment of the interexaminer reliability of tests for shoulder instability.* J Shoulder Elbow Surg, 2004. **13**(1): p. 18-23.
22. Ban, I., et al., *Standardised test protocol (Constant Score) for evaluation of functionality in patients with shoulder disorders.* Dan Med J, 2013. **60**(4): p. A4608.
23. Vafadar, A.K., J.N. Cote, and P.S. Archambault, *Interrater and Intrarater Reliability and Validity of 3 Measurement Methods for Shoulder-Position Sense.* J Sport Rehabil, 2016. **Technical Report 19**: p. 2014-0309.
24. Cacchio, A., et al., *Cross-cultural adaptation and measurement properties of an Italian version of the Western Ontario Shoulder Instability Index (WOSI).* J Orthop Sports Phys Ther, 2012. **42**(6): p. 559-67.
25. Eshoj, H., et al., *Reproducibility and validity of the Nintendo Wii Balance Board for measuring shoulder sensorimotor control in prone lying.* Gait Posture, 2017. **52**: p. 211-216.
26. Little, R.J., et al., *The prevention and treatment of missing data in clinical trials.* N Engl J Med, 2012. **367**(14): p. 1355-60.
27. White, I.R., et al., *Strategy for intention to treat analysis in randomised trials with missing outcome data.* BMJ, 2011. **342**: p. d40.
28. Bland, J.M., *The tyranny of power: is there a better way to calculate sample size?* BMJ, 2009. **339**: p. b3985.
29. Jarvinen, T.L., et al., *Blinded interpretation of study results can feasibly and effectively diminish interpretation bias.* J Clin Epidemiol, 2014. **67**(7): p. 769-72.