STATISTICAL ANALYSIS PLAN (SAP). 12 and 24 months Follow-up of the Randomized Controlled SINEX (supervised shoulder instability neuromuscular exercise program) Trial

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

Publication date:
2021

Document version:
Final published version

Citation for pulished version (APA):
Eshoj, H., Rasmussen, S., Frich, L. H., Christensen, R., Jensen, S. L., Søndergaard, J., Boyle, E., Søgaard, K., & Juul-Kristensen, B. (2021, Jan 22). STATISTICAL ANALYSIS PLAN (SAP). 12 and 24 months Follow-up of the Randomized Controlled SINEX (supervised shoulder instability neuromuscular exercise program) Trial.

STATISTICAL ANALYSIS PLAN (SAP)

12 and 24 months Follow-up of the Randomized Controlled SINEX (supervised shoulder instability neuromuscular exercise program) Trial

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

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, Denmark
[5] Department of Clinical Research, University of Southern Denmark
[6] Musculoskeletal Statistics Unit, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark.
[7] Research Unit of General Practice, Department of Public Health, University of Southern Denmark, Odense, Denmark
[8] 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, & Department of Clinical Research, University of Southern Denmark, Odense University Hospital, 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: 22/01/2021.
Citation for published version:
Henrik Eshoj, Sten Rasmussen, Lars Henrik Frich, Robin Christensen, Steen Lund Jensen, Jens Søndergaard, Eleanor Boyle, Karen Søgaard and Birgit Juul-Kristensen

Statistical Analysis plan (SAP): Neuromuscular Shoulder Exercise Program for Patients with Traumatic Anterior Shoulder Dislocations: One and two-years follow-up of a Randomized Controlled Trial (The SINEX study).

THE SINEX TRIAL

In March 2015 we started to recruit participants with traumatic anterior shoulder dislocation (TASD) to our two-arm parallel randomized controlled trial entitled "the Randomized Control SINEX trial". We required a sample size of 72 participants to determine a mean change group difference from baseline to 3-month follow-up of 250 points on the WOSI (Western Ontario Shoulder Instability Index) questionnaire with a standard deviation of 320, an alpha of 0.05 and a power of 90%. To account for possible barriers, non-compliant patients and patients lost-to-follow-up, a total sample size of 80 participants (40:40) was required.

The SINEX (Shoulder Instability Neuromuscular Exercise program) arm consisted of 12-week individually physiotherapist-supervised exercise program for the rotator cuff and scapular muscles, with a total of seven exercises that can be individually progressed from basic to elite level (A to G). Participants were 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. The other arm, HOMEX (self-managed, home-based, standardized shoulder exercise program), included one introductory physiotherapist-supervised session and one physiotherapist phone call on how to perform and progress the 12-week self-managed, home-based shoulder exercise program targeting the same muscles as in the SINEX arm, but with fewer exercises and limited possibilities for progression. Participants were provided with a leaflet containing photos and descriptions of each exercise.

Some changes were made to the trial: exclusion of clinical tests as inclusion criteria, and keeping only selfreported poor shoulder function, and exclusion of shoulder stability test on Nintendo Wii balance board as outcome due to poor validity. The recruitment into the SINEX trial was, a priori, decided to run for two years and closed on March 2019 [1]. At this time 56 participants had been included.

Following baseline assessment, participants were randomly assigned to either SINEX or HOMEX. The outcome measures up to three months were collected electronically for the self-reported outcomes by a secretary who was not involved in the treatment and outcome assessments collected previously and by the project leader (HE) and one research assistant for the objective outcomes. Since the primary endpoint was three months, we analyzed the data up to three months (see below for a summary of the findings). The outcome measures collected at 12 and at 24 months follow-up, selfreported data only, were collected electronically by the same secretary as for the three months follow-up.

The twelve weeks of a physiotherapist supervised SINEX program with a three months follow up [2], showed statistically and close to clinically important improvement of self-reported shoulder related QoL without adverse events compared with the HOMEX.
The SINEX trial received ethical approval and was registered at Clinical Trials.gov.
Ethical Trial registration: S-20140093.
Clinicaltrial.gov registration: NCT02371928.

EXAMINING THE LONG-TERM EFFECTS OF THE SINEX TRIAL.

It has been shown between 12 and 24 months after the primary shoulder dislocation, that patients tend to experience re-dislocation of their shoulder [3]. This results in substantial setbacks in terms of their shoulder-related function and QoL. Since long-term effects of non-surgical shoulder rehabilitation following TASDs (primary and recurrent) are unknown, the current study will shed light on the long-term effects of our two treatment arms on our trial participants.

STUDY HYPOTHESES

This study test the hypotheses that patients with TASD treated with the intervention (SINEX program) will in total, have fewer shoulder re-dislocations and a slower rate/fewer events of shoulder stabilization surgery than those in HOMEX. Further to this, we hypothesize that the participants in SINEX will experience and report greater long-term effect in the form of improvements in shoulder related QoL, pain, and function than those treated with the control (HOMEX program).

OBJECTIVES

The objectives for the long-term follow-up of the SINEX trial are as follows:

1) To determine if the register-based number and rate of shoulder re-dislocations differ between the two arms of the trial over the 24-month follow-up (numbers, rate of time),
2) To determine if the register based number and rate of shoulder surgery differ between the two arms of the trial over the 24-month follow-up (numbers, rate of time),
3) To determine if there is a difference in WOSI-total score between the two arms of the trial over the 24-month follow-up (21 items, each rated 0-100),
4) To determine if there is a difference in each of the WOSI subdomains scores between the two arms of the trial over the 24-month follow-up (especially Sport function (4 items, each rated 0-100), Lifestyle (4 items, each rated 0-100), and Physical symptoms (10 items rated 0-1000),
5) To determine if there is a difference in each of the Global Perceived Effect (GPE) measures compared to before training, between the two arms of the trial over the 21-month follow-up (especially GPE actual shoulder function, GPE ability to perform sport/leisure activities, and GPE ability to perform activities of daily living), each rated on 7-levels (from markedly worsened to markedly improved),
6) To determine if there is a difference in the Tampa Scale of Kinesiophobia (TSK) between the two arms of the trial over the 24-month follow-up (17 items, rated on 4-levels; and on 2-levels with high fear of movement TSK>/=37),
7) To determine if there is a difference in the self-reported data on re-dislocations between the two arms of the trial over the 24-month follow-up (numbers),
8) To determine if there is a difference in the self-reported data on surgery and visits to the health care system between the two arms of the trial over the 24-month follow-up (numbers),

9) To determine if there is a difference in the EuroQoL between the two arms of the trial over the 24-month follow-up (VAS scale 0-100),
10) To determine if the selfreported number of sick-list days from work/education due to the shoulder injury differs between the two arms of the trial over the 24-month follow-up (4-levels)
11) To determine if there is a difference in mean pain intensity in the past 24 hours and in the past week between the two arms of the trial over the 24-month follow-up (each rated 0-100).

SUMMARY OF OUTCOMES (1) AT BASELINE, 3, 12 AND 24 MONTHS

Self-reported WOSI-total score (21 items, each rated 0-100), WOSI subdomains (Sport function (4 items, each rated 0-100), Lifestyle (4 items, each rated 0-100), Physical symptoms (10 items, rated 0-100), Emotions 3 items, rated 0-100), Tampa Scale of Kinesiophobia (TSK) (17 items, rated on 4-levels; and on 2-levels with high fear of movement TSK>/=37), and mean pain intensity in the past 24 hours and in the past week (each rated 0-100), EuroQoL - 5D (VAS scale 0-100).

SUMMARY OF OUTCOMES (2) AT 3, 12 AND 24 MONTHS

Selfreported Global Perceived Effect (GPE) measures compared to before training (actual shoulder function, ability to perform activities of daily living, ability to perform sport/leisure activities, shoulder-related Quality of Life) all rated on 7-levels, re-dislocations (numbers), currently employment/under education (4-levels), received other treatment (7 choices), impact on quality of duties (work/education) (4-levels), impact on number of duties (work/education) (4-levels), actual shoulder experience after training period (7-levels), extent of return to pre-injury level sport (4-levels), experience of treatment effect (4-levels), desire to undergo shoulder surgery (3 choices).

SUMMARY OF OUTCOMES (3) AT 12 AND 24 MONTHS

Self-reported re-dislocations (injury mechanism and type), surgery (numbers, rate of time), visit to the general practitioner, orthopedic surgeon (2-levels), new acute trauma reason for shoulder surgery (2-levels), number of physiotherapy treatments after surgery (numbers), use of pain medication (5-levels), shoulder function after surgery (7-levels), number of sick-list days from work/education due to the shoulder injury (4-levels).
Register-based number of shoulder re-dislocations (numbers, rate of time), register based events of shoulder surgery (number and rate of shoulder surgery).

ADHERENCE

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

- Satisfactory (as defined per protocol, pp) adherence for the patients is 50% participation (at least seven supervised sessions out of 14 possible sessions).

- Completion of at least two thirds (66%) of the scheduled home-based exercises registered by use of training diary.

Adherence to the HOMEX program included completion of at least two thirds (66%) of the scheduled home-based exercises, registered by use of training diary.

STATISTICAL ANALYSIS

We will conduct the register-based analyses first. Analyses of each outcome will be performed across the time periods by trial arm. For the continuous variables, we will report either means and 95% confidence intervals (for the normally distributed data) or medians and 95% confidence intervals (for the non-normal data). For the categorical variables, we will report proportions with their 95% confidence intervals.

For the register-based outcomes we will construct a count model with the number of shoulder dislocations and events of surgery as reported in the Danish National Patient Register (Landspatient register) from the Danish Health Data Protection Agency (Sundhedsdatastyrelsen, SDS) as the outcome/dependent variable, and the trial arm with age, sex, study centre as the independent variables. For the analysis of surgery we will use selfreported baseline and three months follow-up of WOSI-total, and for the analysis of redislocations we will use selfreported baseline and three months information on number of redislocations from the register. The model will be adjusted for clustering around study centre. Comparing the AICs and BICs of the different count models (Poisson regression, negative binomial regression, zero-inflated Poisson regression and zero-inflated negative bionomial regression), we will choose the most appropriate model using the countfit.ado program (free) in STATA. To ease interpretation of the results, the expected number of shoulder dislocations and events of shoulder surgery with its 95% confidence intervals will be reported by group.

We will visually explore the rate (time to re-dislocation, surgery) of re-dislocations and surgeries by constructing Kaplan-Meier curves by trial arm. We will conduct Cox proportional hazards regression to determine if the rate of redislocations and surgeries differ across the two trial arms. We will adjust the model by the potential clustering around the study centre.

To determine if there are differences in the outcomes of shoulder dislocations and surgeries over time by trial arm, we will conduct multilevel modeling. We will first fit the model with the interaction between time period and trial arm, the main effects of the interaction term (any covariates) and adjust for dependence of the outcome variable, by fitting the subject identification as a random effect (level 2). Since participants who attended the same study centre may have similar outcomes, we will fit study centre as a random effect (level 3). We will first see if study centre explains a significant amount of the variation of the data by comparing the intraclass correlation of the 3-level model against the 2-level model. If study centre does not add anything to the model, we will drop this variable from the analysis. We will then test the interaction between time period and trial arm. If this interaction is significant at the 5% level of significance, there is a difference in the mean value of the outcome across time by trial arm.

For the self-reported outcomes all p-values and 95% confidence intervals (95%CI) will be two sided. We will not apply explicit adjustments for multiplicity, rather we will analyze the outcomes in a prioritized order as listed in the order of hypotheses.
All analyses will follow the intention-to-treat principle (ITT); 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. Our primary analysis will be based on the ITT population, including all randomized participants with available data at baseline. Missing data will be handled indirectly and statistically modeled using repeated-measures linear mixed models (see below). These models will be valid if data are 'Missing at Random' (MAR): "Any systematic difference between the missing values and the observed values can be explained by differences in observed data" [4]. Contrasts between groups will be estimated based on the (difference between) the least squares means derived from the repeated-measures, mixed linear models (i.e., at 12 and 24 months from baseline).

Using mixed linear models, we will analyze mean changes in continuous endpoints. The primary statistical model will consist of fixed effects and random effects. Fixed effects define the expected values of the observations, and random effects define the variance and covariances of the observations. In this study, participants were randomly assigned to two treatment groups (SINEX vs HOMEX), and selfreported outcomes (group 1) were made at 3 time points after baseline for (i.e., at 3, 12 and 24 months from baseline), while for the selfreported outcomes (group 2) and (group 3) there were 2 or 1 point(s) measured after baseline, and these different timepoints will be included in the respective statistical analyses. Basically for the outcomes (group 1), there are two fixed-effect factors: training groups (2 levels; SINEX/HOMEX) and testing times (4 levels; T=0, 3, 12, 24 months). Random effects result from variation between and within participants. We anticipate that measures on the same patient at different times are correlated, and with measures taken closely together in time being more highly correlated than measures taken more apart in time; observations on different participants will be assumed as being independent. To reduce the random variation measures we will adjust for the level at baseline for all continuous and categorical outcomes. Further due to the original design of this study [1] we will also adjust for stratifying factors used in the randomization: study center (3 levels; Aalborg, Esbjerg Odense), injury status (2 levels; primary or recurrent shoulder dislocation) and sex (2 levels) as fixed effects, with baseline value of the relevant variable and age as covariates.
Categorical outcomes for dichotomous endpoints will be analyzed with the use of logistic regression with the same covariates as in the respective continuous outcome models.

Overall, results will be expressed as the difference between groups with 95% confidence intervals (CI) 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 [5].

MISSING DATA, SENSITIVITY ANALYSES AND ROBUSTNESS

Sensitivity analyses for difference between missing and complete data will be performed to assess the "robustness of the trial findings". Robustness is a concept that refers to the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis [6]. Robustness implies that the treatment effect and primary conclusions of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches.

Loss to follow-up and missing data for various reasons are difficult to avoid in randomized trials and in particular in pragmatic trials like the present with long-term follow-up. We will apply the analysis framework suggested by White et al (2011) in which missing data related to the ITT approach depends on making plausible assumptions about the missingness of the data, and including all participants in subsequent sensitivity analyses [7]:

1) Attempt to follow up all randomized participants, even if they withdraw from allocated treatment (i.e., contact all individuals unless they explicitly stated that they had withdrawn their consent)
2) Perform a main analysis of all observed data that are valid under a plausible assumption about the missingness of the data (i.e., Model-based: data as observed; using linear mixed models, assuming that data are '*Missing at Random'* [MAR])
3) Perform sensitivity analyses to explore the effect of departures from the assumption made in the main (#2) analysis (i.e., a non-responder-imputation: using the value at baseline to replace missing data will correspond to a non-responder imputation; these models will potentially be informative even if data are '*Missing Not At Random'* [MNAR])
4) Account for all randomized participants, at least in the sensitivity analyses (covered by #2 and #3 above, plus the corresponding analyses based on the Per Protocol, pp, population).

The interpretation of the corresponding statistical measures of uncertainty of the treatment effect and treatment comparisons will involve consideration of the potential contribution of bias to the P-value, 95% confidence interval, and of the inference in general.

When the different sensitivity analyses are in agreement, and the analyses on the sensitivity analyses and the main analysis lead to essentially the same conclusions, confidence in the trial results is increased.

Statistical analyses of the register-based outcomes will be performed with the STATA program, while for the self-reported outcomes they will be performed by the Statistical Package form Social Sciences (SPSS), version 24.0.

DEFINING THE PER PROTOCOL (PP) POPULATION

To be included in the pp (per-protocol) analyses patients must have available data at baseline and at 12 and 24 months follow up. Patients having surgery after randomization will not be included in the pp analyses. For the intervention group patients will be included in the pp analyses if they have satisfactory adherence at three months follow up. That means that for the SINEX group patients should have 50% participation (at least seven supervised sessions out of 14 possible sessions), besides having completed at least 66% (two thirds) of the scheduled home-based exercises, as registered by use of the training diary. For the HOMEX group patients will be

included if they have completed at least 66% (two thirds) of the scheduled home-based exercises, as registered by use of the training diary.

DISCONTINUED THE INTERVENTION

Withdrawals during the 12 weeks intervention period 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 months 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 (EB) will perform the analysis of the register based outcomes with no involvement from any of the study investigators.
The implementation of the current SAP for 12 and 24 months follow up for the SINEX study will follow the procedure below:

1) A database model will be lined up in collaboration between the statistical advisor (RC/EB) and principal investigators (HE/BJK).
2) The database manager/principal author (AMR/BJK) will code each treatment arm into 'group treatment A' and 'group treatment B', thus leaving all others blinded to treatment allocation during analysis of register based data.
3) Blinded register data will be delivered to the statistician (EB) according to the database model.
4) Analyses of the register based data will be conducted blinded from allocation to any of the two treatment arms.
5) Results will be presented to the authors of the manuscript.

The authors will then agree upon two possible interpretations of the register data based on the analysis: 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 register based results will be conducted before breaking the allocation code. 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 [8].

TABLE AND FIGURE LEGENDS

Figure 1: Flowchart of the SINEX study.

Figure 2: Graphs for each of the following measures: WOSI-total, subscales, surgery, dislocations, with means (95% CI) for baseline, 3 months, 12 months and 24 months by trial arm, as reported from the multilevel model analyses.

Table 1. Baseline outcome demographics and clinical characteristics of the SINEX (intervention) and the HOMEX (control) group.

Table 2. Changes in Self-reported Outcome measure from Baseline to 12 months, and from Baseline to 24 months, in Intention-to-Treat Population of the SINEX (intervention) and HOMEX (control) group.

Table 3. Register and self-reported data at 12 and 24 months follow-up, in Intention-to-Treat Population of the SINEX (intervention) and HOMEX (control) group.

Table 4. Self-reported data at 12 months and 24 months follow-up in Intention-to-Treat Population of the SINEX (intervention) and HOMEX (control) group.

Apendices 1-3.
Per protocol analyses of the same characteristics as in table 2-4..

Figure 1

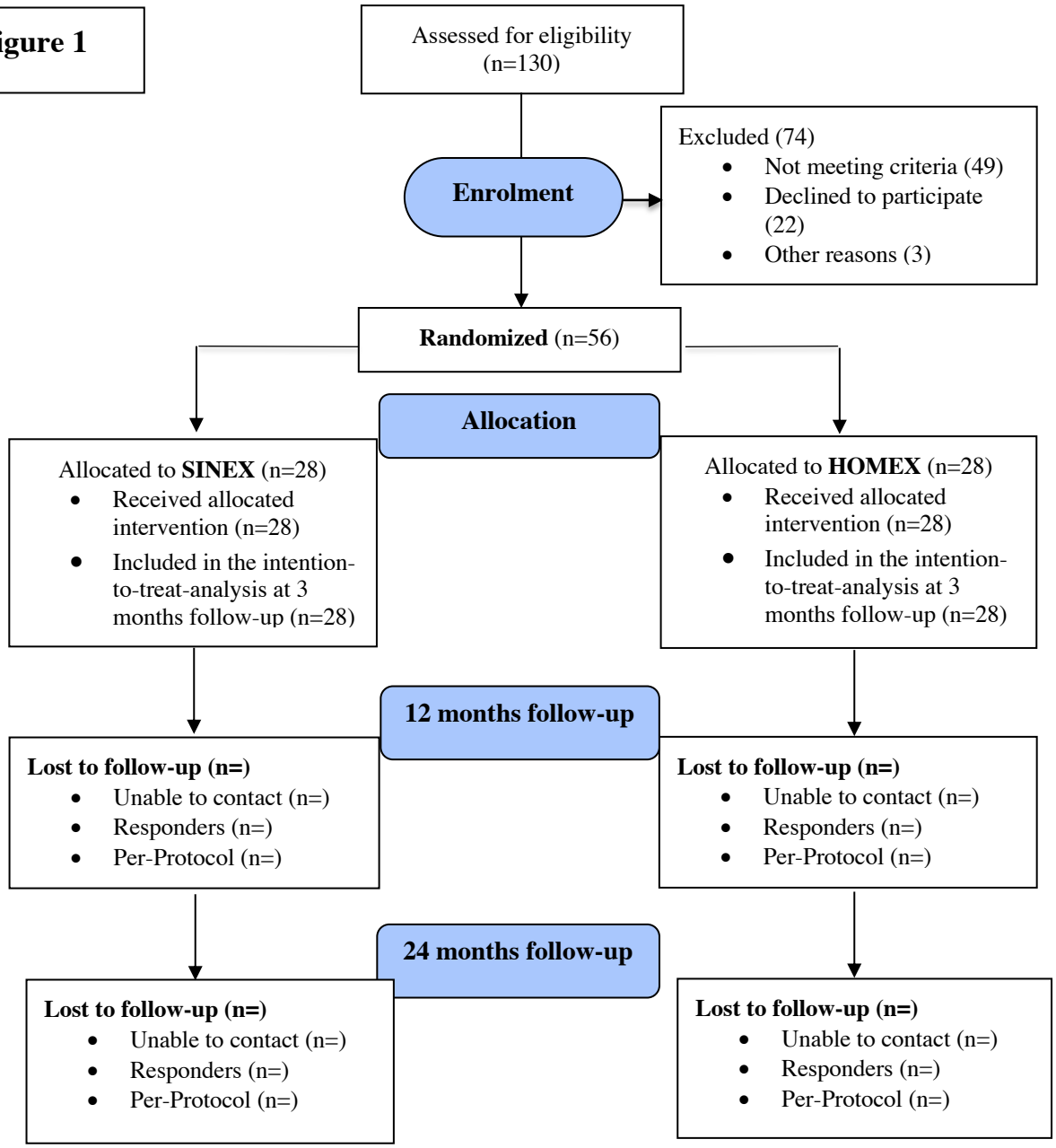
Assessed for eligibility (n=130)
Enrolment
Excluded (74)
Not meeting criteria (49)
Declined to participate (22)
Other reasons (3)
Randomized (n=56)
Allocation
Allocated to SINEX (n=28)
Received allocated intervention (n=28)
Included in the intention-to-treat-analysis at 3 months follow-up (n=28)
Allocated to HOMEX (n=28)
Received allocated intervention (n=28)
Included in the intention-to-treat-analysis at 3 months follow-up (n=28)
12 months follow-up
Lost to follow-up (n=)
Unable to contact (n=)
Responders (n=)
Per-Protocol (n=)
Lost to follow-up (n=)
Unable to contact (n=)
Responders (n=)
Per-Protocol (n=)
24 months follow-up
Lost to follow-up (n=)
Unable to contact (n=)
Responders (n=)
Per-Protocol (n=)
Lost to follow-up (n=)
Unable to contact (n=)
Responders (n=)
Per-Protocol (n=)

Figure 2

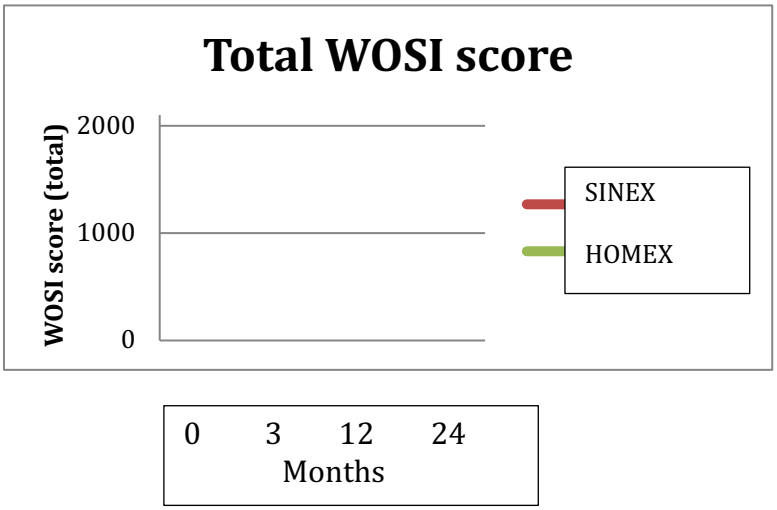
Total WOSI score
WOSI score (total)
2000
1000
0
SINEX
HOMEX
0
3
12
24
Months

Table 1. Baseline demographics and self-reported clinical characteristics of the SINEX (intervention) and the HOMEX (control) group for the Intention-to-Treat Population of the those included in the 12 and 24 months follow-up. Data are reported as mean (95%CI), and frequency (%, 95% CI).

Variables	12months-group		24 months-group	
	SINEX group (n=)	HOMEX group (n=)	SINEX group (n=)	HOMEX group (n=)
Sex (males)				
Age (yrs)				
Weight (kg)				
Height (cm)				
Educational level				
University				
College/technical school				
Below high school				
No formal education				
Occupational status				
Full-time employed				
Part-time employed				
Student				
On sick-leave				
Primary outcome				
WOSI-total (range, 0-2100)				
Secondary outcomes				
WOSI domains[a]				
Physical symptoms (range, 0-1000)				
Sport function (range, 0-400)				
Lifestyle (range, 0-400)				
Emotions (range, 0-300)				
TSK (range 17-68)[a]				
High fear of movement and reinjury (TSK≥37)				
Pain intensity for current shoulder injury (NPRS, range, 0-100)[a]				
Currently				
Mean during past 24 h				
Mean during past 7 d				
EQ - 5D VAS (range, 0-100)[b]				

CI, Confidence Interval; EQ-5D-5L, EuroQol 5-Dimensions questionnaire; EQ-5D VAS, EuroQol 5-Dimensions questionnaire visual analog scale; HOMEX, self-managed, home-based, standard care shoulder exercise program; NPRS, Numerical Pain Rating Scale; SINEX, nonsurgical, supervised, progressive shoulder instability neuromuscular exercise; TSK, Tampa Scale of Kinesiophobia; WOSI, Western Ontario Shoulder Instability Index.

[a]Higher scores reflect worse status.

[b]Lower scores reflect worse status

Table 2: Changes in Self-reported Outcome measure from Baseline to 12 and from baseline to 24 months, for the Intention-to-Treat Population of the SINEX (intervention) and HOMEX (control) group. Data are reported as mean (95% CI), unless stated otherwise. Bolded P-values indicate significance.

	Mean change 12 months		**Difference**		**Mean change 24 months**		**Difference**	
	SINEX group (n=22)	**HOMEX group (n=21)**	**HOMEX vs SINEX (95% CI)**	***p*-value**	**SINEX group (n=15)**	**HOMEX group (n=19)**	**HOMEX vs SINEX (95% CI)**	***p*-value**
Primary outcome								
WOSI, total (0-2100)[a]								
Seconday outcomes								
WOSI domains[a]								
-Physical symptoms (0-1000)								
-Sport function (0-400)								
-Lifestyle (0-400)								
-Emotions (0-300)								
TSK[a]								
High fear of movement and reinjury at baseline (TSK>/=37) and low fear of movement and reinjury at follow-up (TSK<37 n (%)								
Pain intensity of current shoulder injury (NPRS 0-100)[a]								
Currently								
Mean in past 24 hours								
Mean in previous 7 days								
EQ-5D VAS (0-100)[b]								

CI, Confidence Interval; EQ-5D VAS, EuroQol 5-Dimensions questionnaire visual analog scale; HOMEX, self-managed, home-based, standard care shoulder exercise program; NPRS, Numerical Pain Rating Scale; PSFS, Patient-Specific Functional Scale; SINEX, nonsurgical, supervised, progressive shoulder instability neuromuscular exercise; TSK, Tampa Scale of Kinesiophobia; WOSI, Western Ontario Shoulder Instability Index.

[b]Higher scores reflect worse status.

[c]Lower scores indicate worse status.

Table 3. Register and self-reported data at 12 and 24 months follow-up for the Intention-to-Treat Population of the SINEX (intervention) and HOMEX (control) group. Data are reported as mean (95% CI), unless stated otherwise. Bolded P-values indicate significance.

Adverse events	**12 months**				**24 months**			
	SINEX group (n=22)	**HOMEX group (n=21)**	**Between-Group Risk Difference (95%CI)**	***p*-value**	**SINEX group (n=15)**	**HOMEX group (n=19)**	**Between-Group Risk Difference (95%CI)**	***p*-value**
SELF-REPORTED DATA								
No. of patients with re-dislocations (n (%))								
Injury mechanism (n (%))								
Fell on the arm								
Arm was pulled								
External force to shoulder								
Unprovoked								
Other								
Relocation by physician (yes) (n (%))								
Sought health care due to shoulder related issues from								
general practitioner (yes) (n (%))								
orthopedic surgeon (yes) (n (%))								
Shoulder surgery during/since completed training (yes) (n (%))								
Reason for shoulder surgery								
new acute trauma with dislocation (yes) (n (%))								
Time since surgery (mths) (mean (SD))								
No. of physiotherapy treatments after surgery(n (%))								
Rated shoulder function after surgery (1-7, markedly worsened, to markedly improved) (mean(SD))								
REGISTER DATA								
No. of patients with re-dislocation (n (%))								
No. of re-dislocations, in total (n (%))								
No. of patients with stabilisation surgery (n (%))								

CI, Confidence Interval; HOMEX, self-managed, home-based, standard care shoulder exercise program; SINEX, nonsurgical, supervised, progressive shoulder instability neuromuscular exercise

Table 4. Self-reported data at 12 months and 24 months follow-up for the Intention-to-Treat Population of the of the SINEX (intervention) and HOMEX (control) group. Data are reported as mean (95% CI), unless stated otherwise. Bolded P-values indicate significance.

	12 months			24 months		
	SINEX group (n=22)	**HOMEX group (n=21)**	***p*-value**	**SINEX group (n=15)**	**HOMEX group (n=19)**	***p*-value**
Rated extent of impact from actual shoulder injury since completed training (1-4, from largely to not at all) (n, (%)) at work/education on						
quality of duties						
number of duties						
Rated actual shoulder experience after training period (range 1-7, from spontaneous re-dislocation, to stable shoulder) (mean (SD))						
Rated returned pre-injury level of sport (1-4, from largely to not at all) (n, (%))						
Rated current shoulder exercise treatment to have failed (1-4, from largely to not at all) (n, (%))						
Desire to undergo shoulder (n, (%)) surgery due to actual shoulder function						
No, not enough shoulder problems						
No, due to fear of surgery						
Yes						
Rated GPE level compared to before training (range 1-7, markedly worsened, to markedly improved) (mean(SD))						
Actual shoulder function						
Ability to perform activities of daily living						
Ability to perform sport/leisure activities						
Shoulder-related Quality of life						

CI, Confidence Interval; GPE, General Perceived Effect; HOMEX, self-managed, home-based, standard care shoulder exercise program; SINEX, nonsurgical, supervised, progressive shoulder instability neuromuscular exercise.

Appendix 1: Changes in Self-reported Outcome measure from Baseline to 12 months, and from Baseline to 24 months, in the Per Protocol Population of the SINEX (intervention) and HOMEX (control) group. Data are reported as mean (95% CI), unless stated otherwise. Bolded P-values indicate significance.

	Mean change 12 months		**Difference**		**Mean change 24 months**		**Difference**	
	SINEX group (n=22)	**HOMEX group (n=21)**	**HOMEX vs SINEX (95% CI)**	***p*-value**	**SINEX group (n=15)**	**HOMEX group (n=19)**	**HOMEX vs SINEX (95% CI)**	***p*-value**
Primary outcome								
WOSI, total (0-2100)[a]								
Seconday outcomes								
WOSI domains[a]								
-Physical symptoms (0-1000)								
-Sport function (0-400)								
-Lifestyle (0-400)								
-Emotions (0-300)								
TSK[a]								
High fear of movement and reinjury at baseline (TSK>/=37) and low fear of movement and reinjury at follow-up (TSK<37 n (%)								
Pain intensity of current shoulder injury (NPRS 0-100)[a]								
Currently								
Mean in past 24 hours								
Mean in previous 7 days								
EQ-5D VAS (0-100)[b]								

CI, Confidence Interval; EQ-5D VAS, EuroQol 5-Dimensions questionnaire visual analog scale; HOMEX, self-managed, home-based, standard care shoulder exercise program; NPRS, Numerical Pain Rating Scale; PSFS, Patient-Specific Functional Scale; SINEX, nonsurgical, supervised, progressive shoulder instability neuromuscular exercise; TSK, Tampa Scale of Kinesiophobia; WOSI, Western Ontario Shoulder Instability Index.

[b]Higher scores reflect worse status.

[c]Lower scores indicate worse status.

Appendix 2: Changes in Self-reported Outcome measure and register-based data from Baseline to 12 months, and from Baseline to 24 months, in the Per Protocol Population of the SINEX (intervention) and HOMEX (control) group. Data are reported as mean (95% CI), unless stated otherwise. Bolded P-values indicate significance.

Adverse events	**12 months**				**24 months**			
	SINEX group (n=22)	**HOMEX group (n=21)**	**Between-Group Risk Difference (95%CI)**	***p*-value**	**SINEX group (n=15)**	**HOMEX group (n=19)**	**Between-Group Risk Difference (95%CI)**	***p*-value**
SELF-REPORTED DATA								
No. of patients with re-dislocations (n (%))								
Injury mechanism (n (%))								
Fell on the arm								
Arm was pulled								
External force to shoulder								
Unprovoked								
Other								
Relocation by physician (yes) (n (%))								
Sought health care due to shoulder related issues from								
general practitioner (yes) (n (%))								
orthopedic surgeon (yes) (n (%))								
Shoulder surgery during/since completed training (yes) (n (%))								
Reason for shoulder surgery								
new acute trauma with dislocation (yes) (n (%))								
Time since surgery (mths) (mean (SD))								
No. of physiotherapy treatments after surgery(n (%))								
Rated shoulder function after surgery (1-7, markedly worsened, to markedly improved) (mean(SD))								
REGISTER DATA								
No. of patients with re-dislocation (n (%))								
No. of re-dislocations, in total (n (%))								
No. of patients with stabilisation surgery (n(%))								

CI, Confidence Interval; HOMEX, self-managed, home-based, standard care shoulder exercise program; SINEX, nonsurgical, supervised, progressive shoulder instability neuromuscular exercise

Appendix 3: Changes in Self-reported Outcome measure from Baseline to 12 months, and from Baseline to 24 months, in the Per Protocol Population of the SINEX (intervention) and HOMEX (control) group. Data are reported as mean (95% CI), unless stated otherwise. Bolded P-values indicate significance.

	12 months			24 months		
	SINEX group (n=22)	**HOMEX group (n=21)**	***p*-value**	**SINEX group (n=15)**	**HOMEX group (n=19)**	***p*-value**
Rated extent of impact from actual shoulder injury since completed training (1-4, from largely to not at all) (n, (%)) at work/education on						
quality of duties						
number of duties						
Rated actual shoulder experience after training period (range 1-7, from spontaneous re-dislocation, to stable shoulder) (mean (SD))						
Rated returned pre-injury level of sport (1-4, from largely to not at all) (n, (%))						
Rated current shoulder exercise treatment to have failed (1-4, from largely to not at all) (n, (%))						
Desire to undergo shoulder (n, (%)) surgery due to actual shoulder function						
No, not enough shoulder problems						
No, due to fear of surgery						
Yes						
Rated GPE level compared to before training (range 1-7, markedly worsened, to markedly improved) (mean(SD))						
Actual shoulder function						
Ability to perform activities of daily living						
Ability to perform sport/leisure activities						
Shoulder-related Quality of life						

CI, Confidence Interval; GPE, General Perceived Effect; HOMEX, self-managed, home-based, standard care shoulder exercise program; SINEX, nonsurgical, supervised, progressive shoulder instability neuromuscular exercise.

REFERENCES

1. 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.
2. Eshoj, H.R., et al., *Neuromuscular Exercises Improve Shoulder Function More Than Standard Care Exercises in Patients With a Traumatic Anterior Shoulder Dislocation: A Randomized Controlled Trial.* Orthop J Sports Med, 2020. **8**(1): p. 2325967119896102.
3. Robinson, C.M., et al., *Functional outcome and risk of recurrent instability after primary traumatic anterior shoulder dislocation in young patients.* Journal of Bone and Joint Surgery, 2006. **88**(11): p. 2326-36.
4. Detry, M.A. and Y. Ma, *Analyzing Repeated Measurements Using Mixed Models.* Jama, 2016. **315**(4): p. 407-8.
5. Bland, J.M., *The tyranny of power: is there a better way to calculate sample size?* BMJ, 2009. **339**: p. b3985.
6. 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.
7. White, I.R., et al., *Strategy for intention to treat analysis in randomised trials with missing outcome data.* Bmj, 2011. **342**: p. d40.
8. 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.