Allowing pain versus avoiding pain during shoulder exercises: does pain matter in the effectiveness of an exercise program in patients with rotator cuff tendinopathy?

The #PASEtrial: PAin during Shoulder Exercise

Statistical Analysis Plan (SAP) for The PASE trial

SAP version 01, 19. December 2024

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Table of content

1. Purpose and Protocol Version

This statistical analysis plan (SAP) describes detailed aspects of data preparation and analysis according to the guidelines for the content of statistical analysis plans in clinical trial (1) and was written before starting the final analysis. The SAP is based on the final trial protocol version 1.5_10-07-2024 and the study protocol article: Kjær BH, Cools AM, Johannsen FE, Trøstrup J, Bieler T, Siersma V, Magnusson PS. To allow or avoid pain during shoulder rehabilitation exercises for patients with chronic rotator cuff tendinopathy-Study protocol for a randomized controlled trial (the PASE trial). Trials. 2024 Feb 21;25(1):135. doi: 10.1186/s13063-024-07973-6. PMID: 38383459; PMCID: PMC10880378 (2).

2. Study synopsis

Introduction

Shoulder disorders are the third most common musculoskeletal disorder with a lifetime prevalence of up to 70% in the general population (3, 4). Rotator cuff (RC) tendinopathy is the most reported shoulder disorder in the general population with highest prevalence in overhead athletes and adult working-age population (5, 6). A growing body of evidence support exercise therapy as an effective intervention, but to date there are no prospective randomized controlled trials addressing pain as an intervention variable (7, 8). For more details about the background and rationale see the protocol article (2).

Objectives

The primary purpose of this project is to examine the effect of allowing pain versus avoiding pain during shoulder exercises for patients with symptomatic chronic RC tendinopathy measured on patient-reported pain and disability and objective outcomes.

Hypothesis

We hypothesize that allowing pain during exercises will result in a better outcome measured on Shoulder Pain And Disability Index (SPADI) (the primary outcome) compared to avoiding pain in patients with RC tendinopathy.

3. Study methods

Trial design

This is a single-site, prospective, outcome assessorblinded, pragmatic, randomized, controlled, superiority trial with a two-group parallel design, comparing a pain allowance program (PAllow) with a pain avoidance program (PAvoid). Patients are randomized equally (1:1) to receive either PAllow or PAvoid. The study has two phases; a main trial phase lasting 26 weeks, which corresponds to the planned duration of the individualized rehabilitation program, and a follow-up phase lasting an additional 26 weeks.

Randomization

Participants are randomly assigned to either PAllow or PAvoid with a 1:1 allocation ratio..To counter potential imbalance in the randomization both stratification and blocking are employed. Stratification by including department (department of sports medicine/ department of occupational medicine) is necessary because of possible differences in clinical practices furthermore stratification by sex and age (± 35 years) are employed. The allocation sequence is computer-generated with permuted random blocks, set up by a data manager outside the project.

Sample size

The sample size is calculated to test the superiority of PAllow over PAvoid based on the change in the SPADI (primary outcome) from baseline to week 26 (primary endpoint). We aim at having a power of 80% to verify an effect equal to or higher than the Minimal Clinical Important Difference (MCID) of 10 points on SPADI at a 5% significance level. A total of 35 patients are required per group to establish this mean difference of 10 points with a common standard deviation of 15 (0–100 scale). To account for dropouts (max 20%), we are planning to include a total of 42 per group (2).

Intervention and datacollection

For both groups the intervention period lasts 26 weeks. During that period, participants in both groups are offered 8 individual on-site sessions with an assigned sports physiotherapist. Additionally, participants have a home exercise program. Two exercise programs were developed with the principal difference being allowing or avoiding pain during the exercises.
Data are collected on three occasions at the hospital; at baseline before randomization and to times after; at 26 weeks (post intervention/primary endpoint), and at 1-year (follow-up/secondary endpoint).

4. Statistical analysis plan

Study Population definitions

Intention-to-treat (ITT)

The primary efficacy analysis performed is assessment of the between-group difference in change in the SPADI score after 26 weeks in the ITT population. ITT population is defined as all randomized participants irrespective of compliance or withdrawals. A patient will be considered randomized as soon as intervention/training group is assigned by according to the allocation sequence.

As-observed population (AO)

The AO population is defined as participants who have the outcome of interest assessed at a given time point of interest (i.e. no imputation of missing data), primarily used for demographics presentation.

Per-protocol population (PP)

The per-protocol (PP) population is defined as participants who adhere to this protocol, defined by the following criteria in both groups:

- Are included in the AO population, and
- have attended at least 75 % of the scheduled on-site physiotherapist appointments, and
- have 75% compliance to pain perception during exercises (documented by pain diary), and
- have a minimum of 6 home-based training sessions weekly for the first 16 weeks of the 26 weeks intervention (documented by the exercise logbook), and
- do not engage in concomitant supervised exercise-based treatment for the shoulder and do not receive new, important interventions (e.g., no surgery, no shock-wave therapy or cortico-steroid injection) in the main trial phase

Primary analysis

The mean SPADI at each of the study time points, which includes the primary outcome SPADI at week 26, will be analyzed for each of the randomization groups in linear regression models; the models will be parameterized such that they directly produce inference on the difference between

the randomization groups at each of the follow-up time points, beyond the difference that may be present at baseline. The analyses will account for repeated measurement by means of Generalized Estimating Equations (GEE).

Secondary outcome analysis

Secondary outcomes will be analysed similar to the primary outcome, in linear regression models with GEE.

Missing data

The presence of missing data at the various study time points is modelled by logistic regression models using age, sex, clinic, group allocation (masked) and baseline value as explanatory variables. Estimated probabilities for the data being not missing from these models will be used in inverse probability weights (IPW) to account for possible differential attrition; GEE adjusts inference to account for these weights (2, 9).

General statistical approach

Summary tables for quantitative variables included in publication are expected to include at least mean and standard deviation (SD) by treatment group. All summary tables for qualitative variables will display counts and percentages by treatment group. Baseline data are defined as the all measurements performed at the baseline visit.

An alpha level of 0.05 (two-sided) will be considered statistically significant. All data analysis will be carried out according to the pre-established analysis plan by a statistician who is blinded to the allocated interventions for the analysis. Data analysis is performed in SAS version 9.4 and R version 4.3.1.

5. Timing and implementation of analysis

The analysis of both primary and secondary outcome will be performed at the same time.

The implementation procedure of the SAP for the PASE trial:

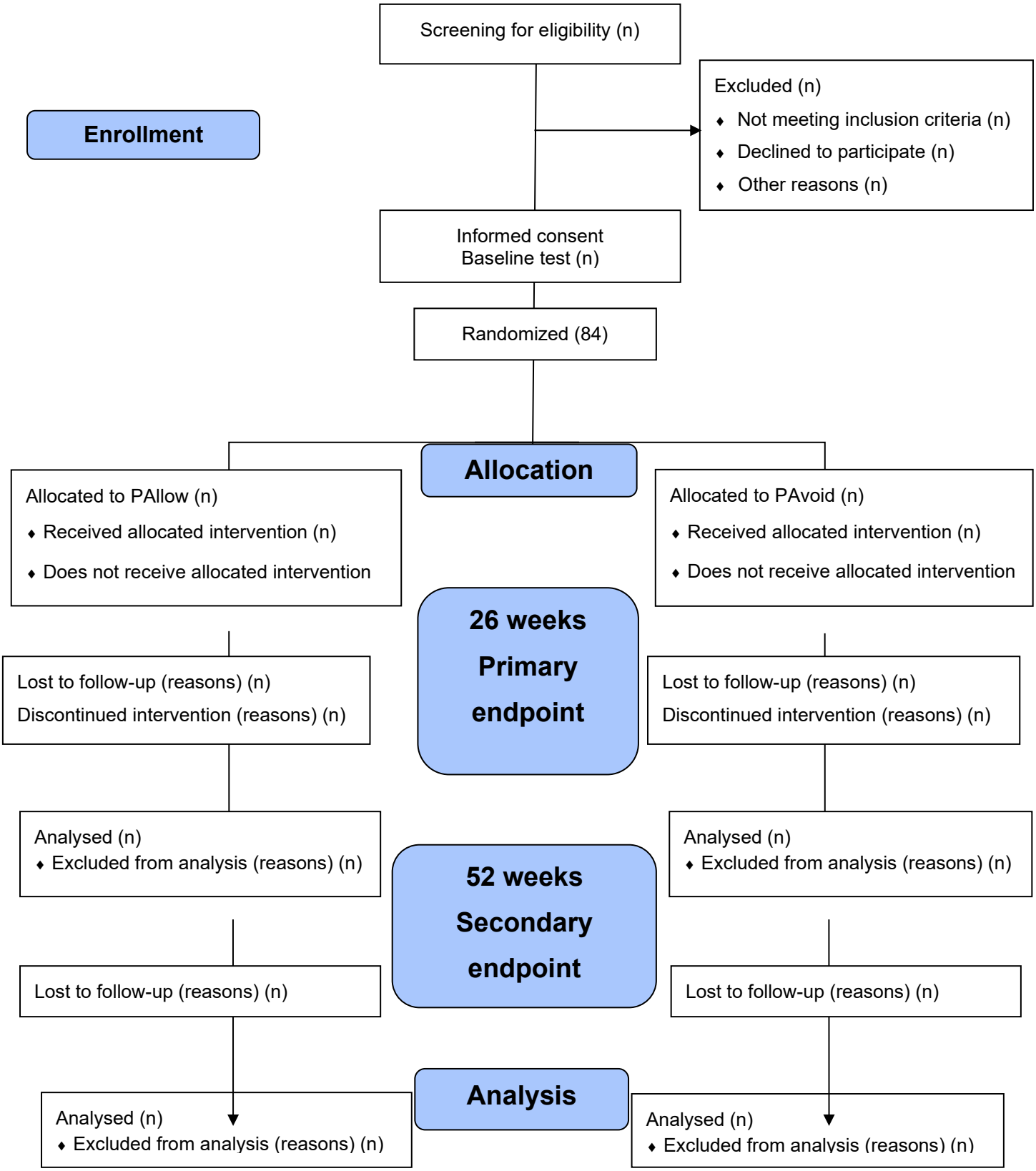
- An otherwised not involved research secretary will export the blinded data from the REDCAP Research Database
- The treatment arms will be coded into “A” and “B” thus leaving all others blinded to treatment allocation during analysis

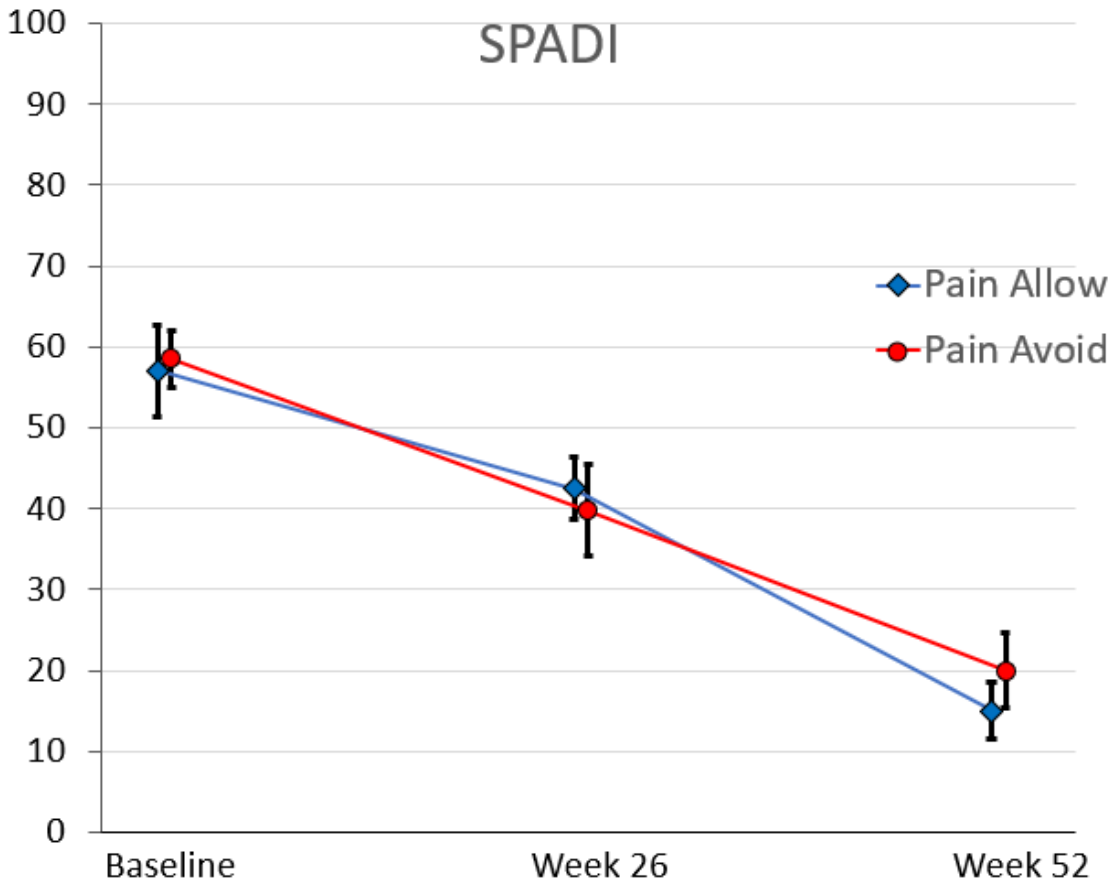
- Blinded data will be delivered to VS according to the statistical model requirements
- All analyses will be conducted blinded from allocation to any of the two treatment arms by an external statistician (VS). Before unblinding a consensus document will be described and signed by all authors of the study.

6. Figure legends

Figure 1: Flow of participants throughout the study

Figure 2: SPADI at baseline, week 26 and week 52. The graphs illustrate the results from the Intention-To-Treat population with datapoints representing means and error bars indicate 95% CI´s. PAllow, allowing pain group; PAvoid, avoiding pain group; SPADI, Shoulder Pain and Disability Index


Screening for eligibility (n)
Enrollment
Excluded (n)
♦ Not meeting inclusion criteria (n)
♦ Declined to participate (n)
♦ Other reasons (n)
Informed consent
Baseline test (n)
Randomized (84)
Allocation
Allocated to PAllow (n)
♦ Received allocated intervention (n)
♦ Does not receive allocated intervention
Allocated to PAvoid (n)
♦ Received allocated intervention (n)
♦ Does not receive allocated intervention
26 weeks
Primary
endpoint
Lost to follow-up (reasons) (n)
Discontinued intervention (reasons) (n)
Lost to follow-up (reasons) (n)
Discontinued intervention (reasons) (n)
Analysed (n)
♦ Excluded from analysis (reasons) (n)
Analysed (n)
♦ Excluded from analysis (reasons) (n)
52 weeks
Secondary
endpoint
Lost to follow-up (reasons) (n)
Lost to follow-up (reasons) (n)
Analysis
Analysed (n)
♦ Excluded from analysis (reasons) (n)
Analysed (n)
♦ Excluded from analysis (reasons) (n)



(This particular figure is made as an example and based on fantasy data)

Table 1 Demographics and Baseline Data for PAllow and PAvoid group[a]

Characteristics	PAllow Group (n=xx)	PAvoid Group (n=xx)
Age in years Male Height in cm Weight in kg BMI in kg/m^2 Dominant side affected Symptom duration in months Smoking - Never - Not anymore - Yes		
Pain medication past 4 weeks - 1-4 times a day - 2-6 times a week - 1-4 times a month Less than once a month or never		
Work Shoulder demanding job (y/n) Working status - working full-time/part-time - Partially on sick leave - Not working		
Sport participation - Elite - Recreational - No		
Primary outcome measure SPADI (0-100; 100 = most disabled)		
Secondary self-reported outcomes Quick DASH (0-100; 100 = most disabled) Quick DASH Work[c] Quick DASH Sport[d]		
Pain in NPRS (0-10); 10 = most pain - Pain at rest[b] - Pain during daily activity[b] - Worst pain past 24 hours[b] - Pain at night[b] - Pain acceptance during training[b]		
Work Ability Index		

[a] Data are reported as mean ± SD or n (%) unless otherwise indicated.
PAllow, allowing pain; PAvoid, avoiding pain; BMI, Body Mass Index; SPADI, Shoulder Pain and Disability Index; Quick DASH, Disability Arm Shoulder Hand short form; SD, Standard Deviation
[b] All pain is measured using Numeric Pain Rating Scale (NPRS)
[c] Optional module (answered if working)
[d] Optional module (answered if sport participation)

Table 2	Changes From Baseline to 26 and 52 weeks follow-up for primary and secondary outcome (Intention-to-Treat population)							
	From baseline to 26 weeks				**From baseline to 52 weeks**			
	Within group change [a)]		**Adjusted [a)]**		**Within group change [a)]**		**Adjusted [a)]**	
	PAllow (n=x) Change (SE)	**PAvoid (n=x) Change (SE)**	**Between-Group difference on change (95% CI)**	**p-value**	**PAllow (n=x) Change (SE)**	**PAvoid (n=x) Change (SE)**	**Between-Group difference on change (95% CI)**	**p-value**
Primary Outcome SPADI								
Secondary Outcomes Quick DASH Quick DASH Work[c] Quick DASH Sport[d]								
Pain in NPRS - Pain at rest - Pain during daily activity - Worst pain past 24 hours - Pain at night - Pain acceptance during training								
Work Ability Index								
GRS								
ROM (°) Scaption passive Scaption active External rotation passive External rotation active								
Strength (MVC) (Nm) Scaption External rotation								
Pressure Pain Threshold (kPa)								

[a] Adjusted for age, sex and clinic.
PAllow, allowing pain; PAvoid, avoiding pain; SPADI, Shoulder Pain and Disability Index; Quick DASH, Disability Arm Shoulder Hand short form; SE, Standard Error; 95%CI, 95% Confidence Intervals; NPRS, Numeric Pain Rating Scale; GRS, Global Rating Scale; °, degrees; MVC, Maximum isometric voluntary contraction; kPa, kilo Pascal
[c] Optional module (answered if working)
[d] Optional module (answered if sport participation)

Corresponding table is made for the Per Protocol population for supplementary file

Table 3 Changes From Baseline to 26 and 52 weeks follow-up for primary and secondary outcome (Intention-to-Treat population)								
	From baseline to 26 weeks				**From baseline to 52 weeks**			
	Within group change [a)]		**Adjusted [a)]**		**Within group change [a)]**		**Adjusted [a)]**	
	PAllow (n=x) Change (SE)	**PAvoid (n=x) Change (SE)**	**Between-Group difference on change (95% CI)**	**p-value**	**PAllow (n=x) Change (SE)**	**PAvoid (n=x) Change (SE)**	**Between-Group difference on change (95% CI)**	**p-value**
Primary Outcome SPADI								
Secondary Outcomes Quick DASH Quick DASH Work[c] Quick DASH Sport[d]								
Pain in NPRS - Pain at rest - Pain during daily activity - Worst pain past 24 hours - Pain at night - Pain acceptance during training								
Work Ability Index								
GRS								
ROM (°) Scaption passive Scaption active External rotation passive External rotation active								
Strength (MVC) (Nm) Scaption External rotation								
Pressure Pain Threshold (kPa)								

[a] Adjusted for age, sex and clinic.
PAllow, allowing pain; PAvoid, avoiding pain; SPADI, Shoulder Pain and Disability Index; Quick DASH, Disability Arm Shoulder Hand short form; SE, Standard Error; 95%CI, 95% Confidence Intervals; NPRS, Numeric Pain Rating Scale; GRS, Global Rating Scale; °, degrees; MVC, Maximum isometric voluntary contraction; kPa, kilo Pascal
[c] Optional module (answered if working)
[d] Optional module (answered if sport participation)

7. References

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