Acceptance and commitment therapy with and without enhanced mindfulness training for chronic pain: A randomized controlled efficacy and mediator study

Section 1: Administrative Information

This SAP is based on the protocol registered in ClinicalTrials.gov with id NCT04057144. The structure and content of the SAP is adopted from the Guidelines for the Content of Statistical Analyses Plans in Clinical Trials(Gamble et al., 2017).

This SAP is developed as a collaborative effort between partners in the MUST (MESTRING – UTREDNING – SMERTE-TERAPI) research team.

Signatures

Senior Statistician	Project Researcher	Principal investigator

Section 2: Introduction

2.1 Background and rationale

Numerous population-based surveys have presented surprisingly high prevalence figures of chronic pain(Steingrimsdottir et al., 2017) and a pooled prevalence of 31% worldwide (Steingrimsdottir et al., 2017). As non-pharmacological alternatives, psychosocial treatments have been recommended for chronic pain management (Jensen, 2011). One such treatment is Acceptance and Commitment Therapy (ACT). (Ost, 2014). Among patients with chronic pain, several small clinical trials have shown that ACT is superior to controls in terms of increasing function and improving mental health, with small to medium effect sizes (Hughes et al., 2017). However, further methodologically robust trials are required (Veehof et al., 2011). The primary aim of this study is thus to examine in a large sample of patients from four multidisciplinary pain centers whether ACT for chronic pain is more effective than a patient education program, and whether adding daily mindfulness training will improve the outcome.

2.2 Objectives

The primary aim of the study is to investigate the effectiveness of ACT and whether adding a component of mindfulness training will improve outcomes on pain (primary outcome), attentional functioning, physical functioning and mental health (secondary outcomes), compared to a control group receiving an educational program A secondary aim is to assess the degree to which improvement in attentional functioning can act as a mechanism of change (mediator) in pain. A third aim is to identify patient characteristics (phenotypes) that predict treatment effects (moderators of change), or, equally important, that predict failure to achieve benefit.

Section 3: Study Methods

3.1 Trial design

The Study is designed as a multi-centre RCT where patients with chronic pain lasting longer than 6 months who are referred to a multidisciplinary pain clinic at either Oslo University Hospital, St Olavs University Hospital, Haukeland University Hospital or is the University Hospital of North Norway are included in three parallel groups; ACT; ACT with enhanced mindfulness or education group. This is a group treatment lasting over 8 weeks, where one session lasts four hours. Patients will be in groups of up to 10 patients.

3.2 Randomization

Randomisation is performed as a block randomisation where each treatment centre included up to 24 patients and randomised them into one of the three groups. Randomisation was performed by a web-based randomisation system (Web Case Report Form; WebCRF) developed and administered by Unit of Applied Clinical Research, Faculty of Medicine and Health Sciences, NTNU, Trondheim, Norway. This unit is not otherwise involved in the trial management or trial conduct.

3.3 Sample size

The sample size calculations are described in detail in the registered protocol. We calculated sample size based on an assumption of a mean baseline average pain intensity of 5.4 with a standard deviation of 2.1 (Thong et al., 2018) and a 10% reduction in pain intensity in the education group, 20% in the ACT group and 30% in the ACT with mindfulness training

group. These improvements may be regarded as minimally important vs moderate changes, respectively (R. H. Dworkin et al., 2008; Farrar et al., 2001). For a two-sided test with 5 % significance level and 80% power, we calculated that the number of patients needed to compare ACT with mindfulness to the education group was 58 in each group. Comparing ACT with and ACT without mindfulness training would require 141 in each group, and comparing ACT without mindfulness training to education would require 126 in each group. We increased group size to 162 participants per group to allow for dropout, to provide equality between groups and for secondary analyses.

3.4 Framework

The MUST study is a superiority RCT assessing the effectiveness of the ACT and ACT with mindfulness compared to an active control group for people with chronic pain referred to obe if four regional multidisciplinary pain clinics.

3.5 Interim analyses and stopping guidance

As serious adverse events are unexpected, no interim analysis or a priori defined stopping rules were defined or implemented for this trial.

3.6 Timing of outcome assessment

The primary and secondary outcome variables were assessed at baseline and at post-treatment, eight weeks, 16 weeks, 32 weeks and 52 weeks. This allows analyses of repeated measures on both primary and secondary outcomes, and thus increased statistical power compared to outcomes assessed at a single time-point. The main outcome of the study is pain intensity measured by BPI at 52 weeks follow-up.

Section 4: Statistical Principles

4.1 Confidence intervals and P-values

The precision of the estimated effects of the interventions will be assessed by a 95% confidence interval, and the effect will be described as a point estimate (mean difference or odds ratio) with accompanying confidence limits.

4.2 Adherence and protocol deviations

we will define adherence to the intervention as participating on at least 4 out of the eight group sessions. Both intention to treat and per protocol analyses will be conducted.

4.3 Analysis populations

The primary analysis will estimate mean difference and 95% confidence interval (CI) in BPI pain intensity score at post-treatment and 52-week follow-up between the two interventions and the active control group (ACT, ACT with enhanced mindfulness and education group). The analyses will be conducted according to the intention-to-treat principle using a linear mixed model for repeated measures. This model includes all available data for all participants at each time point (i.e. baseline, post-treatment, 16 weeks, 32 weeks and 52 weeks). The distribution of the BPI pain intensity score will be assessed, and the variable may be transformed (e.g. log transformation) to better fit with the assumptions for the regression analyses. In the regression model, individual participants will be specified as a random effect, accounting for the within subject covariance structure. The effect of group and time will be specified as fixed effects using a joint variable of intervention and time. Here, baseline levels are pooled over the three study groups assuming that any baseline differences are due to

chance; this also controls for any baseline differences in the outcome variable. The between group difference at 52-week follow-up will be adjusted for the variable used for stratification in the randomisation (i.e., center). Further adjustment for baseline levels of potentially important prognostic factors will also be conducted. We will also use GEE analyses to estimate an odds ratio (with 95% CI) for a two-point change in BPI between the groups taking into account the repeated observations. This analysis will be adjusted for the same factors as those included in the linear mixed model. In addition to the intention to treat analyses, we will conduct per protocol analyses using information on adherence to the trial.

All secondary outcomes will be analysed using a similar approach; for continuous we will use linear mixed models to estimate mean differences between groups, and for ordinal or binary variables we will use logistic GEE analyses to estimate odds ratios. For analyses of mean differences, the distribution of each outcome variable will be assessed to inform possible transformation or initiate alternative analytical procedures. The precision of all estimated effects will be assessed by a 95% CI.

Possible modifiers and mediators of the effect of intervention on the primary and secondary outcomes will be assessed in secondary analyses.

Missing data

Any missing values throughout the follow-up period are inherently accounted for in the mixed model approach, but multiple imputation methods and complete case analysis will be applied in sensitivity analyses (see chapter 6.2 and 6.3 below for further details).

Section 5: Trial Population

5.1 Eligibility

Inclusion criteria were all patient between 18 and 75 years old with pain lasting longer than 6 months and who had undergone an extensive multidisciplinary examination at the four pain centers. However, it was only possible for those who lived in a relatively short distance from the hospital. Moreover, inclusion in the study was not offered to those who were receiving other individual treatment courses which could interfere with the effects of the group treatment the next 52 weeks after inclusion.

Exclusion criteria were severe somatic disease or severe mental disorder (ongoing mania, psychosis, suicidal ideation or substance abuse/addiction), not being able to communicate in Norwegian or in need of 24-hour personal assistance.

5.2 Recruitment

The recruitment of participants was conducted in Trondheim, Oslo, Bergen and Tromsø. The recruitment started in March 2020, had to break because of COVID-19, and was completed in April 2023. Further details on recruitment are given in the registered protocol.

5.3 Withdrawal and follow-up

Each participant was informed that they can withdraw from the study at any time, and that they then have the right to have any personal, health and questionnaire data deleted.

Section 6: Analyses

6.1 Outcome definitions

All outcome variables described below are assessed at baseline, post-treatment, eight weeks, 16 weeks, 32 weeks and 52 weeks.

Primary outcome variable: Pain intensity measured by the Brief Pain Inventory(Cleeland & Ryan, 1994; Tan et al., 2004). The cut-off for clinically meaningful improvement is set to 2 points (Robert H Dworkin et al., 2008).

Secondary outcome variables: The primary outcome in the main RCT study is Pain interference measured by the Brief Pain Inventory (Cleeland & Ryan, 1994; Tan et al., 2004). Secondary outcomes include Physical Function and Social network by PROMIS(Garratt et al., 2021), anxiety and depression (Zigmond & Snaith, 1983).

6.2 Analyses methods

The primary analysis will estimate mean difference and 95% confidence interval (CI) in BPI pain intensity score at 52-week follow-up between the two intervention groups and control group (i.e., ACT vs. ACT with enhanced mindfulness or education). The analyses will be conducted according to the intention-to-treat principle using a linear mixed model for repeated measures. This model includes all available data for all participants at each time point (i.e. baseline, post-treatment, 8 weeks, 16 weeks, 32 weeks and 52 weeks). Further adjustment for baseline levels of potentially important prognostic factors, such as age, sex, socioeconomic status, pain duration, and pain intensity will also be conducted.

All secondary outcomes will be analysed using a similar approach; for continuous (or approximately continuous) we will use linear mixed models to estimate mean differences between groups, and for ordinal or binary variables we will use logistic GEE analyses to estimate odds ratios.

Possible modifiers of the effect of intervention on the primary outcome will be assessed in supplementary analyses stratified by sex, age groups, socioeconomic status, and accompanied by tests of statistical interaction to assess departure from additive effects (i.e., including a product term of group and modifier in the regression model).

6.3 Missing data

Any missing values are inherently accounted for in the mixed model approach, but multiple imputation methods will be applied in sensitivity analyses. Multiple imputation will include factors that predict missingness of a specific factor, as well as all factors that are included in the main model (outcome, intervention, or adjustment variables). The number of imputed datasets will be guided by the number of missing observations for each variable, but we aim at using a minimum of 10 imputed datasets for each variable.

6.3 Harms

As stated above, no harms are expected, and thus we do not plan any specific analyses for this. If any study related harms should occur, these will be described and reported.

6.4 Statistical software

All analyses related to the primary outcome will be conducted using Stata.

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