Moderation analysis of the MI-NAV trial: statistical analysis plan

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This document is a statistical analysis plan for a moderation analysis of the MI-NAV trial. Detailed information on the MI-NAV trial, including primary analyses can be found in the trial article:

Aanesen F, Grotle M, Rysstad TL*, et al*. Effectiveness of adding motivational interviewing or a stratified vocational advice intervention to usual case management on return to work for people with musculoskeletal disorders: the MI-NAV randomised controlled trial. *Occupational and Environmental Medicine* 2023;**80**:42-50.

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The MI-NAV trial (1) was a three-arm parallel pragmatic randomised controlled trial evaluating the effectiveness of two vocational treatment packages (MI, motivational interviewing plus usual case management; SVAI, stratified vocational advice intervention plus usual case management) compared to usual case management alone, on sickness absence days among 514 people on sick leave due to musculoskeletal disorders. The MI-NAV trial showed that adding MI or a SVAI to usual case management resulted in a non-statistically significant reduction in seven sickness absence days over 6 months for workers on sick leave due to musculoskeletal disorders in Norway. The trial findings were uncertain due to wide confidence intervals. To determine if potential relationship between the intervention and the outcome depends on the value of a third factor, moderation analysis can be conducted. This information can be used to tailor treatments to specific patient populations, leading to better clinical outcomes. Therefore, this statistical analysis plan describes the planned moderation analysis of the MI-NAV trial.

Primary objective

The primary objective in this study is to assess any moderation of the two vocational treatment effects by considering a set of plausible baseline patient characteristics. We aim to identify the characteristics of sick listed workers due to musculoskeletal disorders who are more likely to benefit from either MI or SVAI.

Primary outcome

The primary outcome for the MI-NAV trial and for this study is sickness absence days, measured as the number of sickness absence days from baseline assessment date until the six-month follow-up. Sickness absence days will be calculated from information provided by different national registries including information on sick leave payments, sick leave certificates, work assessment allowance, disability pensions and employment percentage. To convert time on sick leave to actual time away from work we will account for the participants' contracted work hours and the amount of sick leave. This will be summed up and converted to sickness absence days, according to a 5-day working week when working full-time.

Moderators

Potential treatment effect modifiers for this study are presented in Table 1. The selection of potential treatment effect modifiers for this study was based on published literature investigating treatment moderators in musculoskeletal disorders, prognostic cohort studies, and theoretical support.

Table 1. Potential treatment effect modifiers

Variable	Description/ categories	Evidence to support	Hypothesis direction
Age (18-67 years)	Continuous, years	Gurung et al.,2015 (2) Garcia et al., 2016 (3) Broderick et al., 2016 (4)	Younger > Older
Gender	Male Female	Gurung et al.,2015 (2) Hee et al,. 2021 (5)	Female > Male
Education	Lower Education Higher Education	Gurung et al.,2015 (2) Broderick et al., 2016 (4) Roseen et al., 2021 (6) Beneciuk et al., 2017 (7)	Higher level of education > Lower level of education
Smoking Status	Non-smoker Smoker	Roseen et al., 2021 (6) Beneciuk et al., 2023 (8) De Zoete et al,. 2021 (9)	Non-smoker > Smoker
Body Mass Index (BMI)	Continuous, number	Hayden et al., 2020 (10)	Normal BMI > Abnormal BMI
Type of Work	White collar Blue Collar	Gurung et al.,2015 (2) Hayden et al., 2020 (10)	White collar > Blue collar
Distress "How much have you been bothered by feeling depressed in the past week?"	Continuous, 0-10 scale (higher scores indicate more distress)	Gurung et al.,2015 (2) Hee et al,. 2021 (5)	Low distress > Increased distress

Pain intensity "How would you rate the pain that you have had during the past week"	Continuous, 0-10 scale (higher scores indicate worse pain)	Gurung et al.,2015 (2) Hahne et al., 2017 (11) Kuijer et al., 2006 (12) Jensen et al., 2013 (13)	Lower Pain intensity > Pain intensity
Return to work expectation?	Continuous, 0-10 scale (higher scores indicate better return to work expectancy)	Hagen, Svensen & Eriksen., 2006 (14) Kuijer et al., 2006 (12) Jensen et al., 2013 (13)	
Analgesic medication use	Yes No	Gurung et al.,2015 (2) Roseen et al., 2021 (6) Beneciuk et al., 2017 (7) Beneciuk et al., 2023 (8) Hayden et al., 2020 (10)	No medication > Medication use
First language	Norwegian Other	Campbell & Edwards., 2012 (15) Fillingim, 2016 (16)	Norwegian > Other
Previous sickness absence in the last year	Continuous, days	Dekkers- Sánchez et al., 2008 (17)	Less previous sickness absence > Increased previous sickness absence
Self-perceived Health Status "How good or bad is your health today?"	Continuous, 0-100 scale (higher scores indicate better perceived health)	Laaksonen et al., 2011(18)	Greater self-perceived health > Reduced self-perceived health.

Statistical analysis

Baseline demographic and clinical characteristics will be summarized using counts and percentages for categorical variables and means and standard deviations or median and interquartile range for continuous variables.

We will investigate any potential modification of the effect of MI vs UC and SVAI vs UC separately considering the set of plausible patient characteristics. To identify potential effect modifiers, we will conduct a formal moderation analysis using a test for statistical interaction (19, 20). We will create separate linear regression models for each potential moderator variable for each intervention comparison investigating *treatment modification* by incorporating a group x potential moderator interaction term. Specifically, we will build each model including a term for the outcome sickness absence days, group allocation, potential modifier, and a group allocation x potential modifier interaction term. We will estimate the treatment effect, 95% confidence interval and p-value for each potential modifier interaction. Interaction coefficients for dichotomous variables will be interpreted as the effect of the vocational intervention, relative to usual case management comparison, in those with the baseline characteristic compared with those who do not have the characteristic. Interaction coefficients for continuous variables will be interpreted as the additional benefit of the vocational intervention, relative to the usual case management comparison, for every one-unit increase in the continuous variable. All statistical analyses will be conducted using R.

Missing data

We will assess the proportion and patterns of missing moderator and outcome data. We will conduct all analyses on complete cases if the proportion of missing data is less than 5% for any of the moderators or outcome. If missing data exceeds 5%, we will use multiple imputations by chain equations to impute datasets using the 'mice' package.

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