Statistical analysis Plan

Section 1: Administrative information

Title

Statistical analysis plan for the COVID-19 MindPreP study: Mindful Prevention of Psychopathology in healthcare workers during the COVID-19 crisis.

Trial registration

NCT04720404

SAP Version

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Protocol Version

This document has been written based on information contained in the study protocol version 5, dated 8 December 2020.

SAP revisions

Roles and responsibility

Non-signatory names and contribution

Dirk Geurts – supervision

Eric Ruhe – supervision

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Section 2: Introduction

Background and rationale

Healthcare personnel in COVID-19 care has experienced substantial amounts of stress which has been shown to result in the development or increase of stress-related disorders like psychological distress and psychopathology in 50-70%.[1] Adaptive reconsolidation of stressful events is required for resilience against prolonged stress and prevent development and/or recurrence of psychopathology. Mindfulness-based interventions (MBIs) are promising interventions with positive outcomes in many people with and without stress-related disorders. MBIs invite people to allow bodily sensations, thoughts and feelings in reaction to and in the aftermath of stressors and pay attention to them in a particular way: on purpose, in the present moment, and without judgment.[2] The effectiveness of these interventions on stress reduction has recently been demonstrated in meta-analyses of both clinical[3] (n= 12.005 patients) and non-clinical[4] (n= 2668) populations.

Mindfulness-based Stress Reduction (MBSR) is specifically focused on the reduction of stress, and has been shown to reduce burnout symptoms, ruminative thoughts, and anxiety and increase empathy, self-compassion, wellbeing, flexibility and emotional stability.[5, 6] In healthcare professionals, MBSR training increased well-being, mindfulness skills, empathy and emotional stability and decreased burnout, anxiety, and depression.[6, 7] Moreover, MBSR can be delivered effectively via interactive video-conferencing, which makes it extremely suited to quickly support relatively large groups of healthcare workers.

Consequently, MBSR is a potentially useful intervention to prevent psychopathological sequela of the high-stress situations that healthcare workers went through in the current COVID-19 pandemic. The aim of this study is to examine the effectiveness of an adapted MBSR intervention delivered via videoconferencing to reduce psychological distress in COVID-19 healthcare professionals.

Objectives

Primary research question:

I. Is an adapted videoconferencing MBSR intervention + support as usual (SAU) superior to a standalone online mindfulness intervention (SOM) + SAU in terms of reducing psychological distress (measured by a compound measure of depressive, anxiety, and somatic symptoms) at 6 months after completing the intervention (= 7 months follow-up)?

Secondary research questions:

Additional outcome measures

II.1 Is there less psychiatric psychopathology diagnosed by clinical interviews after adapted MBSR + SAU compared to SOM + SAU at 7 months follow-up?

II.2. Is an adapted MBSR + SAU more effective than SOM + SAU in reducing psychological distress (depressive, anxiety, and somatic symptoms) and post-traumatic stress symptoms, insomnia and alcohol use over the course of 7 months after baseline?

II.3. Is an adapted MBSR + SAU more effective than SOM + SAU in improving post-traumatic growth and positive mental health over the course of 7 months after baseline?

Moderation of the effect

II.4 Is the effect of an adapted MBSR to reduce psychological distress moderated by gender, age, work setting, profession, prior mindfulness training, adherence, baseline depressive, anxiety and somatic symptoms, and baseline perseverative thinking, mindfulness and self-compassion?

Mediation of the effect

II.5 Is the effect of and adapted MBSR and SOM + SAU to reduce psychological distress mediated by a decrease of perseverative thinking, and an increase in mindfulness skills and self-compassion?

Section 3: Study Methods

Trial design

A nationwide, parallel-group randomized controlled superiority trial is conducted comparing an adapted MBSR + SAU (intervention) with SOM + SAU (control). The intervention is an interactive adapted videoconferencing MBSR group-training. The training consists of eight 1,5 hour sessions twice a week during 4 weeks. The sessions will be held via interactive videoconferencing. Participants in the control condition will have the possibility to use a self-help daily mindfulness exercise (30 minutes) on a YouTube channel. In total the participants will receive 24 mindfulness and compassion exercises in 4 weeks. Treatment allocation is a 1:1 ratio. Assessments will be conducted at baseline (T0), mid-treatment (T1), and at 1 (T2), 4 (T3) and 7 (T4) months follow-up. Participants randomized to the SOM + SAU condition will be able to participate in an adapted MBSR intervention after they completed the study (7 months).

Randomization

Random assignment to adapted MBSR + SAU or SOM + SAU is electronically conducted by CastorEDC. Randomization is stratified by setting (3 levels: hospital, nursing home, other), prior mindfulness training (yes/no), and profession (3 levels: physician, nurse, other). Block randomization with predefined blocks are used (2 or 4) in order to ensure balanced groups. Diagnostic research assessors conducting clinical interviews were blinded to the treatment allocation.

Sample size

Based on Lai et al.[1], high post-exposure levels of depression, anxiety, insomnia and distress are expected (in 50-70% of healthcare workers). So far, no data exist on changes of these levels of distress in healthcare workers in the COVID-19 pandemic due to interventions.

Therefore, we aim to detect an effect-size of 0.4 (α=0.05; β=0.20; two-tailed). When using t-tests, a sample size of 200 (100 in each arm) is needed. This will suffice to reveal a clinically relevant difference of 5 points on the PHQ-SADS[8] (scale of sum-score 0-78). To overcome attrition, we will increase the size of our groups with 10%. Thus, a total of 220 participants (110 in each group) will be included in this randomized controlled study.

Framework

Both primary and secondary outcomes will be assessed for superiority of an adapted MBSR + SAU above SOM + SAU.

Statistical interim analyses and stopping guidance

Not applicable

Timing of final analysis

All outcomes will be analyzed collectively after the T4 measurement and the SCID5 interviews have taken place in the last participants (anticipated being June 2022).

Timing of outcome assessments

At baseline participants complete the questionnaires used for our primary/secondary outcomes. The same questionnaire are send after 1 month (post-intervention), and after 4 and 7 months. To measure possible mediators three questionnaires are used at mid-treatment (2 weeks after start of

the intervention). At 7 months the occurrence of psychopathology is measured by the Structured Clinical Interview for DSM-5 (SCID5).

Section 4: Statistical Principles

Confidence intervals and *P* values

Level of statistical significance

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

Description and rationale for any adjustment for multiplicity

Not applicable

Confidence intervals to be reported

All confidence intervals presented will be 95% and two-sided.

Adherence and protocol deviations

Definition of adherence to the intervention and how this is assessed

Adherence implies that participants attended ≥ 4 sessions in the adapted MBSR + SAU group. The MBSR trainer will keep an attendance register.

Participants in the SOM + SAU group will be asked at timepoint T1 and T2 how often they did a mindfulness exercise in the last two weeks.

Analysis populations

All analyses will be conducted in SPSS version 25 and will be performed as intention-to-treat (ITT). The intention-to-treat population will include all randomized patients, according to the treatment they were randomized to receive. Secondary, per protocol analyses will be conducted.

Section 5: Trial Population

Screening data

Potential participants fill out an online registration form expressing their interest for the study. Next, a screening interview by telephone is planned. Study information will be given and in- and exclusion criteria will be checked during this interview. All screened potential participants and their eligibility will be registered.

Eligibility

Participants are eligible if they are healthcare workers who either currently or recently have been working in the acute care for COVID-19 patients on COVID-19 wards/intensive care units or in primary care or nursing homes. The exclusion criteria are insufficient comprehension of the Dutch language, and inability to access the interactive videoconferencing. The number of ineligible participants will be reported with reasons for ineligibility. Eligible participants who refrain from participating before randomization will reported with reasons for withdrawal.

Recruitment

A CONSORT flow diagram will be used to summarize the number of participants who were:

- Assessed for eligibility at screening
    - Eligible at screening
    - Ineligible at screening*
- Eligible and randomized
- Eligible but not randomized*
- Received the randomized allocation
- Did not receive the randomized allocation*
- Discontinued the intervention*
- Lost to follow-up*
- Randomized and included in the primary analysis
- Randomized and excluded from the primary analysis*

*reasons will be provided.

Withdrawal/follow-up

The level of consent of withdrawal will be classified as “consent to continue data collection” or “no further data collection”. The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial will be summarized by intervention arm and presented in the CONSORT diagram.

Baseline patient characteristics

Participants will be described by intervention arm with respect to age, gender, marital status, having children, level of education, previous and current psychological treatment, prior mindfulness training, work setting, profession, working years in healthcare.

Categorical data will be summarized by numbers and percentages. Continuous data will be summarized by mean, SD and range if data are normal distributed and median, IQR and range if data are skewed.

Section 6: Analysis

Outcome definitions

Primary outcome

The primary outcome will be the change in psychological distress between baseline and 7 months follow-up, as assessed by the total score on the *Patient Health Questionnaire – Somatic, Anxiety and Depressive Symptoms (PHQ-SADS)*[8] scale. This is a 31-item self-report measurement combining PHQ-9, GAD-7, and PHQ-15. The 9-item *Patient Health Questionnaire (PHQ-9)*[9] evaluates the presence of the nine DSM-5 criteria of a depressive episode in the past 2 weeks: depressed mood, anhedonia, trouble sleeping, feeling tired, change in appetite or weight, guilt or worthlessness, trouble concentrating, feeling slowed down or restless and suicidal thoughts. There are four answer categories: 0 (not at all), 1 (few days), 2 (more than half the days) and 3 (almost every day). The *7-item Generalized Anxiety Disorder (GAD-7)*[10, 11] scale measures severity of anxiety. Frequency of anxiety symptoms are rated within the last 2 weeks on a 4-point scale ranging from 'not at all' to 'almost every day'. The *15-item Patient Health Questionnaire (PHQ-15)*[12] is a self-administered questionnaire includes 15 symptoms that account for more than 90% of all symptoms seen in primary care. Subjects were asked for the last 4 weeks to rate the severity of 15 symptoms as 0 (not bothered at all), 1 (bothered a little), and 2 (bothered a lot).
Cut-off scores of ≥5, ≥10, and ≥15 representing mild, moderate, and severe symptoms, respectively, on all three scales. The total score of the PHQ-SADS will be calculated by the sum of PHQ-9, GAD-7 and PHQ-15, and ranges from 0 to 78.

Confirmatory factor analysis will be performed, in line with the research on the PHQ-ADS[13], to investigate sufficient unidimensionality of the PHQ-SADS to support the use of the total score as a composite measure for depression, anxiety and somatic symptoms.

Secondary outcome

The *Structured Clinical Interview for DSM-5 Axis I Disorders Research Version (SCID5)* will be used to retrospectively assess the occurrence of psychopathology (depression, anxiety disorder, posttraumatic stress disorder (PTSD), insomnia, substance abuse, somatoform disorder, obsessive compulsive disorder, eating disorder, illness anxiety disorder, adjustment disorder) at 7 months follow-up. The psychometric properties of the Dutch translation of the SCID have been shown to be excellent.[14] The SCID-5 will provide dichotomous score (presence or absent of psychopathology).

The *Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5)[15]* is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. The PCL-5 demonstrated excellent reliability and validity.[16]

The *Insomnia Severity Index (ISI)* is a 7-item scale assessing global insomnia. Total scores range from 0 to 28 with higher scores indicating greater severity.[17, 18]

The *AUDIT-C (Alcohol Use Disorders Identification Test)[19]* is a 10-item, effective method of screening for unhealthy alcohol use, defined as risky or hazardous consumption or any alcohol use disorder.

The *Mental Health Continuum – Short Form (MHC-SF)[20]* will be used to assess emotional, psychological, and social well-being. The MHC-SF is a 14-item measure with a total score range of 0 to 70. The psychometric properties of the MHC-SF have been shown to be adequate.[20]

The degree of posttraumatic growth will be measured with the *Posttraumatic Growth Inventory – Short Form (PTGI-SF)*.[21] The PTGI-SF measures the general tendency to experience difficult events in such a way that benefits are perceived. The measure consists of 10 items. The psychometric properties of the PTGI-SF have shown to be adequate.

The *Five Facet Mindfulness Questionnaire – Short Form (FFMQ-SF)[22]*, a 24-item questionnaire, will be used to assess different aspects of mindfulness, including observing, describing, acting with awareness, non-judging of inner experiences, and non-reactivity to inner experiences. The psychometric properties of the FFMQ-SF have been shown to be adequate.

The *Self Compassion Scale – Short Form (SCS-SF)[23]* will be used to assess levels of self-compassion. The SCS-SF is a 12-item measure that consists of three concepts that are related to self-compassion, including self-kindness versus self-judgment, common humanity versus isolation, mindfulness versus over-identification. The psychometric properties of the SCS-SF have been shown to be adequate.[23]

The *Perseverative Thinking Questionnaire (PTQ)[24]* consists of 15 items and will be used to assess repetitive negative thinking (RNT). The PTQ comprises of three core characteristics of repetitive negative thinking (repetitiveness, intrusiveness, and difficulties to disengage) and two associated features (unproductiveness of RNT and RNT capturing mental capacity). The psychometric properties of the PTQ have shown to be adequate.[24]

The Trimbos/iMTA questionnaire for Costs associated with Psychiatric illness (TiC-P)[25] will be used to collect information on direct healthcare use and paid and informal work-related productivity losses at 7 months. The EuroQol-5D-3L (EQ-5D) will be used to measure health-related quality of life.

COVID-19 related questions and mindfulness practice questions will be asked.

Analysis methods

Treatment effects at T4

Primary analyses will be performed on the intention-to-treat (ITT) sample. ANCOVA will be used to examine the main effect (PHQ-SADS) of the intervention at T4. Roughly, every month during approximately one year a group will start with the intervention (cohort). Due to the expected differences in these groups, cohort effects will be added. Therefore, a Linear Mixed Effect Model will be used for the analyses. Group (adapted MBSR + SAU / SOM + SAU) will be added as fixed effects, while controlling for baseline levels. A random effect for cohort will be added, and if applicable as a fixed effect. Cohen's *d* effect size will be calculated by dividing the adjusted group difference at T4 by the pooled standard deviation at T0.[26]

Difference in occurrence of psychopathology (present/absent) between adapted MBSR + SAU and SOM + SAU assessed by SCID-5 interview at T4 will tested with Chi-square test.

Course to treatment effect at T4

The course of treatment effects from baseline to T4 for both primary and secondary outcomes (post-traumatic stress symptoms, insomnia, alcohol use, post-traumatic growth, positive mental health) at

T2, T3, and T4 will be evaluated with Linear Mixed Effects Models. Time, group (adapted MBSR + SAU / SOM + SAU) and their interaction will be added as fixed effects, while controlling for baseline levels. A random effect for participant and cohort (random slope and intercept) will be added. Heterogeneous first-order autoregressive (ARH(1)) covariance structure will be used, which assumes that measurements closer in time are more strongly related to each other. Restricted maximum likelihood will be used as estimation method to handle missing data. Cohen's *d* effects size will be calculated by dividing the adjusted group difference between the pooled means (T2, T3, T4) by the pooled standard deviations at T0.[26]

Moderation of the effect

Moderation will be examined by adding the potential moderator and its interaction with group to the model. Separate models will be run for each possible moderator. The following possible moderators will be used: gender, age, work setting, profession, prior mindfulness training, adherence, baseline depressive, anxiety and somatic symptoms, and baseline perseverative thinking, mindfulness and self-compassion.

Mediation of the effect

Mediation analysis will be performed on per-protocol sample, using the multiple mediation model by Preacher & Hayes.[27] We will examine whether T0 to T1 change in potential mediators (mindfulness skills, self-compassion, and perseverative negative thinking) mediated T0 to T2 change in depressive, anxiety and somatic symptoms, post-traumatic stress symptoms, insomnia, post-traumatic growth and positive mental health.

Any adjustment for covariates

See above

Methods used for assumptions to be checked for statistical methods

Assumptions of normality will be checked and, in case of lack of normality, bootstrapping will be used to account for this problem.

Any planned sensitivity analyses for each outcome

Sensitivity analyses will be conducted by performing the primary and secondary analyses in the per-protocol (PP) sample. The per-protocol analysis set consists of subjects who have a minimum exposure of 4 MBSR sessions (intervention group (adapted MBSR + SAU)). Further sensitivity analysis will be performed depending on possible patterns in missing values and when relevant disbalance in covariates will be observed.

Any planned subgroup analyses for each outcome

Moderation will be examined by adding the potential moderator and its interaction with group to the model. Separate models will be run for each possible moderator. The following possible moderators

will be used: gender, age, profession, work setting, prior mindfulness training, baseline levels of depressive, anxiety and somatic symptoms.

Missing data

No imputation will be needed for baseline measures, because participants were only randomized if T0 was completed. The questionnaires will be filled in an online platform (CastorEDC), in which it is required to fill in an item before continuing to the next item. Therefore, we expect a low number of missing data.

Additional analysis

None

Harms

The number (and percentage) of participants experiencing AE/SAE will be presented for each treatment arm categorized by severity. The number (and percentage) of occurrences of each type of AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Statistical software

The analysis will be carried out using SPSS Statistic 25.

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