Statistical Analysis Plan

Full Title of Study	Anti-Stress Intervention Among Physicians Study (ASIP)
Short-Title	ASIP study
Principal Investigator	Valentin Vetter, MD Institute of Public Health, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
Protocol Identification Number	-
ClinicalTrials.gov identifier	NCT06368791
Author	Responsible statistician: Stefan Konigorski, PhD Digital Health – Machine Learning Group, Hasso Plattner, Institute for Digital Engineering, Potsdam, Germany & Hasso Plattner Institute for Digital Health at Mount Sinai, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA & Department of Statistics, Harvard University, 150 Western, Ave, Boston, MA 02134, USA Responsible PI: Valentin Vetter, MD Institute of Public Health, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
Version	01
Document Date	August 24, 2024
Sponsor	Charité University, Berlin, Germany

Inhaltsverzeichnis

Introduction

Please see the study protocol paper for more information:
https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2024.1420097/full

Study Methods

Please see the study protocol paper for information on the study methods:
https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2024.1420097/full

Statistical Analysis

Trial Profile

A CENT CONSORT extension (1) flow chart will be used to show the flow of participants through the study.

Baseline Characteristics of Participants

The initial participant characteristics will cover both demographic and work-related aspects. Categorical data will be represented by their counts and relative percentages. For continuous data, the summary will include the mean, standard deviation, range (minimum and maximum), or median along with percentiles.

Analysis Principles for Final Analyses

The primary analyses will provide individual-level and population-level estimates of the average efficacy of anti-stress interventions in reducing same-day stress levels and reducing the level of expected stress on the following day (the two primary outcomes) based on the series of N-of-1 trials. Both individual-level and population-level analyses will be based on the intention-to-treat population. That is, the individual-level analyses will include all observed data points and the pre-specified intervention schedule, independently of whether the intervention was performed. The population-level analyses will include all participants of the study population that started a trial and their pre-specified study design and intervention schedule, and all their recorded data, independently of whether the intervention was performed as pre-specified and independently if or when the study participants dropped out of the study. As a result of this, all analyses will evaluate the effect of the availability of the anti-stress interventions which mirrors the effect of the intervention if there is high adherence to the pre-defined intervention schedule.

Analyses of Individual N-of-1 Trials

At the end of the individual N-of-1 trials, statistical analyses will be conducted to compare the outcomes of anti-stress interventions vs. no treatment. In a first step, the data will be presented descriptively by producing line plots of the N-of-1 trials. In a second step, Bayesian linear regression models with normally distributed errors will be used to compare the average ratings of same-day stress levels and the level of stress expected for the following day (the two primary outcomes) during periods of anti-stress interventions to those with no treatment using R's "brms" package. Non-informative priors will be used for all parameters since no prior information was available before the study to provide a reasonable effect estimate of anti-stress interventions in reducing daily stress levels. Given the longitudinal nature of our data, we will employ a first-order autoregressive (AR1) error structure to recognize that measurements taken at adjacent times have a higher dependence compared to those taken at more distant intervals. Algorithm convergence will be assessed by the parameters R^2, Bulk_ESS and Tail_ESS and assumptions of the models with be checked. Separate analyses will be performed for each individual to compare the average response to treatment. Based on this model, estimates of the posterior distribution of the average anti-stress intervention effect on the primary outcomes (daily stress and expected level of stress for the following day) at the individual level will be obtained. We will report the mean posterior distribution and the 95% credible interval. Additionally, we will report the probability to achieve a clinically relevant intervention effect which is defined as a reduction of 0.5 points of the stress scale (range 1 to 10).

Analyses of the Aggregated N-of-1 Trials

In order to estimate population-level intervention effects, a Bayesian multi-level linear regression model will be utilized to evaluate the efficacy of anti-stress interventions compared to no treatment on the primary outcomes, the same-day stress levels and the level of stress expected for the following day, at the population level. This will be done separately for those participants that chose the mindfulness intervention and the box breathing exercise. Bayesian multi-level mixed models will be employed to estimate the posterior distribution of the population-level average treatment effect. For the aggregated analysis, non-informative priors will be used for all parameters since no prior information was available to reasonably estimate the effect of anti-stress interventions on reducing daily stress levels. In line with the analyses of the individual N-of-1 trials described above, we will include a first-order autoregressive (AR1) error structure to account for the higher dependence of measurements taken at adjacent times compared to those taken further apart. Similar to the individual-level model previously described, estimates of the posterior distribution of the average anti-stress intervention effect on the population level in reducing daily stress levels will be obtained. The posterior distribution of the mean difference between the outcomes of anti-stress interventions and no treatment will be derived from the aggregated Bayesian model. Similarly to the individual-level analyses, we will report the mean of the posterior probability distribution, the 95% credible interval, and the probability to achieve a clinically relevant reduction in stress levels of 0.5 points.

As a secondary analysis, we will perform a joint analysis of both interventions to estimate the effect of the availability of an anti-stress intervention among the participants who

chose the respective intervention on the daily stress level and the level of stress expected for the following day. Secondary outcomes will be modeled and reported similarly.

Effect Measure Modifiers

The impact of baseline effect measure modifiers, which were recorded before randomization to the treatment schedule, namely sex, the baseline stress level (Cohen's PSS) and the place of work (hospital vs. outpatient clinic), will be assessed exploratively in stratified subgroup analyses and by incorporating these variables as interaction terms in the Bayesian models.

Additional Analyses

As additional analyses, frequentist linear mixed regression models are calculated using the same model-specifications as described for the Bayesian models above. Additionally, a per-protocol analysis will be performed (see below).

Protocol deviations

Protocol adherence will be assessed by comparing the response to the daily question about the performance of the intervention/exercise matches with the current period (intervention vs. control). Additionally, if less than n=16 PROs are documented, the participant will be excluded from the per-protocol analysis which will be performed as part of the sensitivity analyses.

Missing Data

Regarding the data obtained from the StudyU App, we will conduct complete-case analyses, assuming that the missing values are completely random. If participants did not complete the N-of-1 trial, we will analyze all the available data. In the psychological questionnaires, the final scores are calculated as the mean of all answered items. If more than 50% of the items remain unanswered, a score is not calculated.

Analysis Populations

Intention-To-Treat (ITT)

The main analyses utilize the ITT population, which includes all randomized participants, irrespective of whether they completed the entire study period and received the assigned intervention. Data from participants who did not complete the N-of-1 trial will be included in the analyses up to that point.

Per-Protocol (PP)

As an additional analysis, a per-protocol analysis will be performed including only participants with at least n=16 documented PROs and a protocol adherence of 85% or higher.

Safety and Adverse Events

Adverse events were not recorded during the study period but are assessed as part of the follow-up questionnaire and will be reported descriptively.

Statistical Software

Analyses will be conducted using R version 4.4.1.

Difference to trial protocol

--

References

1. Shamseer L, Sampson M, Bukutu C, Schmid CH, Nikles J, Tate R, et al. CONSORT extension for reporting N-of-1 trials (CENT) 2015: Explanation and elaboration. Bmj. 2015;350.