Statistical Analysis Plan (SAP)

for

Final Analysis

Full Study Title:	Long COVID: Psychological Risk Factors and Their Modification
Short Study Title:	SOMA.COV
ISRCTN Registry:	ISRCTN15068418
Authors:	Alexander Fierenz
Study Protocol Version:	24-08-2023
Sponsor's Protocol Code:	508447247
Sponsor:	Deutsche Forschungsgemeinschaft
Version / Date:	1.0 04.06.2025
Effective Date:	Date of last signature

Responsible Bio statistician:
Prof. Dr. Antonia Zapf
Institute of Medical Biometry and Epidemiology, University Medical Centre Hamburg-Eppendorf, Hamburg

4.6.25 Date

A. Zapf Signature

Responsible Employee / Representative of Responsible Employee :
Dr. Anna Suling
Institute of Medical Biometry and Epidemiology, University Medical Centre Hamburg-Eppendorf, Hamburg

04.06.25 Date

A. Suling Signature

Principal Investigator / Representative:
Prof. Dr. Bernd Löwe

Department of Psychosomatic Medicine and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Hamburg	12.06.2025 Date	 Signature
Principal Investigator / Representative: Dr. Petra Engelmann Department of Psychosomatic Medicine and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Hamburg	12.06.2025 Date	 Signature

Document History:

Version No.	Date	Chapter / Attachment	Reason for Review / Modification
First version	n.a.	n.a.	n.a.
00-02	06.11.24	All chapters	Adaptation to new SAP template and review by AS.
00-03	28.01.25	All chapters	Further adaptations after discussion of AF and AS
00-04	05.03.25	All chapters	Further adaptions based on comments of Dr. Engelmann
00-05	11.03.25	All chapters	Further adaptions based on meeting with Dr. Engelmann from 11.3.
00-06	02.04.25	All chapters	Further adaptions based on discussion of Dr. Engelmann and Prof. Löwe; Review of mediation analysis by Susanne Sehner
00-07	29.04.25	All chapters	Further adaptions based on comments of Dr. Engelmann (15.04.)
01	04.06.25	All chapters	Minor changes before finalisation

Abbreviations

Abbreviation	Definition
ACE-D	Adverse Childhood Experience Questionnaire German version
AE	Adverse event
B-IPQ	Brief Illness Perception Questionnaire
CFS	Chalder Fatigue Scale
CI	Confidence interval
CMA	Causual mediation analysis
CONSORT	Consolidated Standards of Reporting Trials
COV.EXPECT	Expectation management intervention
COV.SUPPORT	Supportive intervention
CSQ-CAT	Coping Strategies Questionnaire-Catastrophizing Subscale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSQ-PEM	DePaul Symptom Questionnaire Post-Exertional Malaise
EFS	Evaluated for Safety Set
ERQ	Emotion Regulation Questionnaire
EURONET SOMA	European Network to improve diagnostic, treatment and health care for patients with persistent somatic symptoms*)*
FAS	Full Analysis Set
FIML	Full information maximum likelihood
GAD-7	Generalized Anxiety Disorder-7
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intention-To-Treat
MAR	Missing at random
NRS	Numeric Rating Scale
PD	Protocol deviation
PDI	Pain Disability Index
PHQ-15	Patient Health Questionnaire 15
PHQ-15	PAIS Patient Health Questionnaire-15 Post-Acute Infection Syndromes
PHQ-9	*Patient Health Questionnaire-9*
PM	Percentage mediated
PP	Per Protocol
PSS-10	Perceived Stress Scale-10
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCID	Structured Clinical Interview for the DSM-5
SCQ-D	Self-Administered Comorbidity Questionnaire
SSAS S	omatosensory Amplification Scale
SSD-12	Somatic Symptom Disorder – B Criteria Scale
TAS-20	Toronto Alexithymia Scale-20
TAU	Treatment as usual
TEX-Q	Treatment Expectation Questionnaire
WI-7	Whiteley-Index-7

Content

1 Introduction

This Statistical Analysis Plan (SAP) is based on the published study protocol (Engelmann et al., 2023) and follows the guideline for statistical analysis plans (Gamble et al., 2017).
Some aspects of the statistical methods and the study design are already described in the study protocol. This SAP aims to further specify the procedures and statistical methods applied during the analysis of the study data.

1.1 Background and Rationale

After an infection with the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has abated, a substantial portion of affected patients do not fully recover, but suffer from persistent somatic symptoms - a phenomenon often described as “Long COVID”. There is growing evidence that the development of Long COVID is multifactorial and involves pathophysiological, psychological, and social mechanisms. Among psychological risk factors, particularly increased levels of illness-related anxiety and dysfunctional symptom expectations appear to contribute to processes of symptom persistence after COVID-19.

1.2 Study Objectives

With regard to the development of effective therapies, our primary aim is to investigate whether symptoms of Long COVID can be improved by a targeted modification of illness-related anxiety and dysfunctional symptom expectations. Second, we aim to prospectively identify further risk factors that contribute to the persistence of Long COVID, and compare them with risk factors for somatic symptom persistence in other medical conditions.

Hypothesis 1: The therapeutic modification of illness-related anxiety and dysfunctional symptom expectations improves Long COVID symptom severity.

Hypothesis 2 (exploratory): In addition to illness-related anxiety and dysfunctional symptom expectations, further risk factors contributing to the persistence of Long COVID symptoms can be identified.

Hypothesis 3 (exploratory, using results of SOMACROSS): Long COVID and other medical conditions share common risk factors for somatic symptom persistence.

1.3 Study Endpoint(s)

Primary endpoint:

- Change from baseline in overall somatic symptom severity at 3 months measured with the sum score of the Patient Health Questionnaire 15 (PHQ-15)

Secondary endpoints:

- Change from baseline in overall somatic symptom severity at 6 weeks and 6 months measured with the PHQ-15
- Subjective improvement of Long COVID symptoms (improved vs. stable / worsened) at 6 weeks, 3 months, and 6 months
- Change from baseline in fatigue measured with the Chalder Fatigue Scale (CFS) at 6 weeks, 3 months, and 6 months
- Change from baseline in pain measured with an adapted version of the Pain Disability Index (PDI) at 6 weeks, 3 months, and 6 months

- Post-exertional malaise measured with the DePaul Symptom Questionnaire Post-Exertional Malaise (DSQ-PEM) at 6 weeks, 3 months, and 6 months
- Change from baseline in long COVID symptoms measured with the Patient Health Questionnaire-15 Post-Acute Infection Syndromes (PHQ-15 PAIS) at 6 weeks, 3 months, and 6 months
- Somatic symptom disorder evaluated with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (SCID-5) at 3 months
- Change from baseline in symptom perception measured with the Brief Illness Perception Questionnaire (B-IPQ) at 3 months and 6 months

Mediator variables (all variables are measured at BL, 6 weeks, 3 and 6 months):

- Illness-related anxiety measured with the Somatic Symptom Disorder – B Criteria Scale (SSD-12)
- Treatment expectations measured with the Treatment Expectation Questionnaire (TEX-Q)
- Expectation of symptom severity, of symptom burden, and of coping with symptoms measured with the European Network to improve diagnostic, treatment and health care for patients with persistent somatic symptoms (EURONET SOMA) Numeric Rating Scales (NRS)

2 Study Methods

In this chapter, a summary of the basic study methods is provided.

2.1 Trial Design

The SOMA.COV trial is a monocentric, nationwide, prospective, observer-blinded, three-arm parallel randomised controlled trial in patients ≥ 18 years after SARS-CoV-2 infection with Long COVID and at least moderately severe ongoing symptoms (PHQ-15 ≥ 10). Eligible patients that gave informed consent are randomised in one of the two experimental arms or to the control arm with an allocation ratio of 1:1:1. In the control group patients receive treatment as usual (TAU) only. Patients randomised to one of the experimental groups receive either a supportive intervention (COV.SUPPORT) or an expectation management intervention (COV.EXPECT), both additional to TAU.
This study is associated with the SOMACROSS research unit (FOR 5211), funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) which investigates mechanisms of somatic symptom persistence across different medical conditions. (Löwe et al., 2022)

2.2 Randomisation

Patients are randomised to COV.EXPECT, COV.SUPPORT or TAU with an allocation ratio of 1:1:1. The randomisation is stratified by sex with a block randomisation procedure with varying block length. The randomisation list was generated using R software (R Project for Statistical Computing) by an independent member of the biostatistics unit and uploaded in REDCap (Research Electronic Data Capture), a software for building and managing online surveys and databases.
The randomisation is performed directly after verification that no inclusion criteria are violated and no exclusion criteria are met. Baseline data are collected afterwards.

2.3 Sample Size

The trial is powered for the comparison between the COV.EXPECT group and the TAU group. The type one error (alpha) is not adjusted for multiplicity due to the closed testing principle. A between-group effect size of d=0.5 is expected between COV.EXPECT and TAU for the change from baseline in the PHQ-15 score at 3 months. To detect this effect with a power of 80 % and using a two-sided alpha of 5 %, 64 patients in each group will be required, resulting in a total sample size of N=192. Assuming a loss to follow-up between baseline and 3 months (time point for primary outcome) of 25 %, this results in N=258 randomised patients. Assuming that 50 % of the screened patients meet the inclusion criteria, a total of N=516 patients will be assessed for eligibility.

2.4 Statistical Interim Analyses and Stopping Guidance

No interim analysis and stopping guidance is planned.

2.5 Timing of Analyses

Information on the outcomes are collected at baseline, 6 weeks (intermediate), 3 months (post-interventional), and 6 months (follow-up) after baseline.

The analysis will be conducted at two time points. First it will be conducted after all 3-month follow-up visits are conduced (3 months after randomisation of last patient) and after the database has been reviewed for completeness and accuracy. A soft database lock will be conducted.

The final statistical analysis of the study on all primary and secondary endpoints will be conducted after final database lock and data cleaning at the end of study, i.e. when all data from all subjects have been collected, checked for quality and released for analysis. This is scheduled at about 2 years after recruitment of the first patient.

3 Statistical Principles

In this chapter, the basic statistical principles for the analyses are summarised.

3.1 Confidence Intervals and *P* Values

For the primary analysis, the significance level is α=0.05 (two-sided). All further analyses are exploratory and will not be adjusted for multiplicity. All applicable statistical tests will be two-sided. All reported confidence intervals (CI) are at 95 % level and two-sided.

3.2 Adherence and Protocol Deviations

Both experimental arms (COV.EXPECT, COV.SUPPORT) receive three individual online video consultation sessions with an interval of 2 weeks with given homework after each session and a booster session after 3 months, each lasting 45 minutes. The adherence to the intervention is evaluated based on the number and duration of attended online sessions.

Major protocol deviations will lead to exclusion of a subject from the Per Protocol Population (see Section 3.3.2). Major protocol deviations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the independent ethics committee (IEC) / institutional review board (IRB) - approved protocol that may affect the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Protocol deviations (PD) are defined as follows:
Major PDs:

- Violation of in- and exclusion criteria
- PHQ-15 < 10 in the baseline assessment (in deviation from the inclusion screening)
- At 3-month follow-up:
    - More than 1 missing intervention session (COV.EXPECT, COV.SUPPORT)
    - More than 1 substantially shortened intervention session (< 30 minutes session time)

Additionally, there will be a blind review of a list of further detected protocol violations. The principal investigator will decide which reported protocol violations are considered major and potentially impact the study results.

3.3 Analysis Populations

Depending on the type of analysis, different analysis populations will be used which are defined in detail in this section.

3.3.1 Full Analysis Set (FAS)

The primary analysis is based on the full analysis set (FAS). The FAS is as complete as possible and as close as possible to the Intention-To-Treat (ITT) principle which includes all randomised patients, as belonging to their randomisation arm, regardless of whether they refused therapy, or whether other protocol violations are known.

3.3.2 Per Protocol Population (PP)

The Per Protocol population (PP) is a subset of the FAS and includes only patients who have no major protocol violation. Patients are analyzed as belonging to the randomised treatment group.

3.3.3 Evaluated for Safety Set (EFS)

The Evaluated for Safety (EFS) set consists of all randomised patients. Subjects are analysed as belonging to their randomised arm according to the ITT principle.

3.4 Missing Data

3.4.1 Description of missing data

Missing data on the primary and secondary endpoints (at baseline and follow-up time points) will be summarised by absolute and relative frequency (i.e. the number of patients with missing values divided by all patients and multiplied by 100) of missing values by treatment group and in total.

3.4.2 Handling of missing values

Missing values in the primary endpoint (missing total score of PHQ-15) will not be replaced for the primary analysis. Yet, for the analysis of the primary endpoint, the implicit “missing at random” (MAR) assumption of the mixed model will be utilised.

If more than 5% of values are missing for the primary outcome, we will use multiple imputation in a sensitivity analysis after final database lock with 100 imputations (White et al., 2011).

4 Description of Subject Flow (for CONSORT flow diagram)

In this chapter, details on how subjects flow from screening to the end of study is summarised are given.

4.1 Screening, Eligibility and Randomisation

The number of subjects screened, the number of screening failures (ineligible subjects), the number of eligible subjects who were not randomised and the number of eligible subjects who were randomised will be summarised by absolute and relative (%) frequencies and displayed in the CONSORT (Consolidated Standards of Reporting Trials) flow chart (see section 4.4).

4.2 Analysis Populations

The number of patients in the FAS, PP and EFS set will be given in total and by randomised treatment.

4.3 Withdrawal / Follow-up

The number and percentage of patients who withdraw their consent, who were lost to follow-up and who dropped out due to death will be summarised in total and by randomised treatment in the FAS, including information on time of drop-out and the reason for drop-out, if available.

4.4 CONSORT flow chart

A flow chart according to CONSORT statement will be given which will include the number of subjects

- Screened
- Not eligible (with reason)
- Eligible and not included (with reason)
- Randomised
- Allocated to treatment groups
- Withdrawals (with timing and reason by treatment group)
- Dropouts (with timing and reason by treatment group)
- Analysed after 6 weeks, 3 months and 6 months (by treatment group)

5 Analysis

In this chapter, the analysis of baseline data as well as efficacy and safety endpoints is described in detail.

5.1 Descriptive statistics

Continuous data will be summarised by arithmetic mean, standard deviation, minimum, 25 % quantile, median, 75 % quantile, maximum, and the number of available (non-missing) observations. If appropriate, continuous variables can also be presented in categories.

Categorical data will be summarised by the total number of patients in each category and the number of patients with non-missing values. Relative frequencies are displayed by the percent relative to non-missing values (100 times the number of patients per category divided by the number of patients with non-missing values).

5.1.1 Demographics and Baseline Characteristics

The following demographic and other baseline characteristics will be summarised in total and by randomised treatment as described in 5.1 in the FAS and PP set:

- Age in years
- Gender (male/female/divers)
- Duration of Long COVID
- Number of SARS-COV-2 infections
- Treatment setting of SARS-CoV-2 infections (At home, outpatient/At least one time in hospital on a normal ward)
- Number of SARS-COV-2 vaccinations
- Number of pre-existing physical conditions (Self-Administered Comorbidity Questionnaire [SCQ-D])
- Body mass index in kg/m^2
- Migration background (yes/no)
- Permanent partner (yes/no)
- Number of people living in household
- Years of formal education (Lower education/Higher education)
- Occupational status (Full-time employed/Part-time employed/Stay-at-home/Unemployed or job seeking/Retired (pension)/Retired (disability)/School, training, studying/Parental leave/Other)
- Current sick leave (No/Yes, shorter than 6 weeks/Yes, longer than 6 weeks)
- Number of appointments with the doctor in the last 6 months
- Current intake of medication (yes/no)
- Smoking (yes/no)
- Recruitment channel (UKE/Self-help group/Social media/Online search/Medical practitioner/Physiotherapy practice/Friends, acquaintances/Other)
- Overall somatic symptom severity (PHQ-15)
- Long COVID symptoms (PHQ-15 PAIS)
- Fatigue (CFS)
- Post-exertional malaise (DSQ-PEM)
- Pain (PDI)
- Illness-related anxiety (SSD-12)
- Treatment expectations (TEX-Q)
- Expectation of symptom severity (NRS)
- Expectation of symptom burden (NRS)
- Expectation of coping with symptoms (NRS)

- Depression severity (Patient Health Questionnaire-9 [PHQ-9])
- Anxiety severity (Generalized Anxiety Disorder-7 [GAD-7])

5.1.2 Endpoints

The descriptive analysis of primary and secondary endpoints will be conducted as described in 5.1.

5.3 Efficacy Evaluation

5.3.1 Analysis of Primary Endpoint(s)

The analysis of the primary endpoint is based on the FAS and thus is as close as possible to the ITT principle.
The primary outcome is analysed with a linear mixed effects model with the change from baseline of the PHQ-15 score at 6 weeks and 3 months as dependent variable, treatment group (COV.EXPECT, COV.SUPPORT, and TAU), time (categorical: 6 weeks and 3 months), the stratification variable gender as well as baseline PHQ-15 as fixed effects and patient as random effect. Further, the interaction between time and random group is included and will be excluded from the model if the test result of the interaction is $p \geq 0.05$. If the interaction remains in the model, the respective contrast at 3 months will be explored further. If it is removed from the model, the overall treatment effect remains stable over time and can also be interpreted as the effect at the interesting time point 3 months.
The estimation will be performed using Maximum-Likelihood estimation with an AR(1)-structure for residual errors.
For the primary hypothesis, the global treatment effect will be tested first using the F-Test (two-sided). If the p-value is < 0.05, the contrasts in change for COV.EXPECT vs. TAU and COV.SUPPORT vs. TAU at a 5% level (two-sided) will be tested using the Wald test. Because of the closed testing principle an adjustment of the contrast p-values for multiplicity is not necessary. Mean difference estimates together with 95% confidence intervals will be reported.

After final database closure this analysis is repeated with an analogous model that further includes the measurement of the 6 months follow-up. The 3-months estimates from this model will only be interpreted as sensitivity analyses of the primary endpoint analysis.

The assumptions regarding normality of residuals are examined graphically. Histograms and quantile-quantile plots are used to evaluate normality of residuals. In case of unmet assumptions data can be transformed accordingly.

5.3.2 Analysis of Secondary Endpoint(s)

The analysis of the secondary endpoints is based on the FAS and thus is as close as possible to the ITT principle. Missing values are not imputed, but the implicit MAR assumption of the analysis model will be used.

Continuous endpoints (PHQ-15, CFS, PDI, PHQ-15 PAIS) are analysed analogously to the primary endpoint. Mean changes for the respective time points together with 95% confidence intervals will be presented.

Dichotomous endpoints (Improvement of Long COVID symptoms, DSQ-PEM, DSM-5, B-IPQ) will be analysed with a mixed logistic model analogously to the linear mixed model used for primary analysis, except that the dependent variable is not the change from baseline, but the endpoint measurement at the respective time point. The improvement of Long COVID symptoms will further be displayed descriptively in the categories improvement, no change, and worsening over time by group.

5.3.3 Risk factor regression analyses

To identify risk factors for the persistence of somatic symptoms in Long COVID we will use longitudinal data from the control group (TAU) within the FAS. Patients from the intervention group (COV.EXPECT, COV.SUPPORT) are excluded because the treatment could bias the results. The risk factors are analysed with a multivariable mixed linear regression with symptom persistence (PHQ-15) as outcome and different risk factors as independent variables, while taking the number of predictors with respect to the sample size into account. The list of possible risk factors includes:

- Age
- Gender
- Chronic physical diseases (SCQ-D)
- BMI
- Smoking
- Education
- Migration background
- PHQ-15 Baseline score
- Depression severity (PHQ-9)
- Illness-related worries (Whiteley-Index-7 [WI-7])
- Expected symptom severity in 6 months (NRS)
- Expected coping with symptoms in 6 months (NRS)
- Catastrophizing (Coping Strategies Questionnaire-Catastrophizing Subscale [CSQ-CAT])
- Illness perception (B-IPQ)
- Life stressors (Perceived Stress Scale-10 [PSS-10])
- Somatosensory Amplification (Somatosensory Amplification Scale [SSAS])
- Alexithymia (Toronto Alexithymia Scale-20 [TAS-20])
- Emotion regulation (Emotion Regulation Questionnaire [ERQ] suppression scale)
- Adverse childhood experiences (Adverse Childhood Experience Questionnaire German version [ACE-D])
- Stigmatization (Stigma)

In case of no significant effects of the interventions on the outcome PHQ-15 in the primary analysis (within the testing of the global effect) an additional analysis will be conducted within observations from all three groups. In the specified risk factor regression model the intervention group (TAU, COV.EXPECT, COV.SUPPORT) will be included as an adjusting variable.
Common risk factors for somatic symptom persistence:
The disease-specific regression analysis from the model to identify risk factors for Long COVID symptoms will be compared to models from the research Unit SOMACROSS to identify shared risk factors across conditions. Also further exploratory analysis should be conducted.

5.3.4 Mediation analyses

In order to analyse whether effects on persistent Long COVID symptoms resulted through changes in dysfunctional symptom expectations or illness-related anxiety, we will conduct causal mediation analyses (CMA). CMA will examine whether in patients receiving COV.EXPECT, changes in the mediating variables at the 6 weeks' assessment predict a reduction in overall somatic symptom severity (PHQ-15) at 3 months (primary outcome) and 6 months. That is to say, the adjusted total treatment effect will be divided into the indirect effect, which describes the treatment effect on persistent long COVID symptoms via the mediators, and the direct effect, which describes the treatment effect not mediated through the mediators. Subsequently, the percentage mediated (PM) can be estimated. Only potential mediator-outcome confounders need to be controlled for due to randomisation and a possible treatment-mediator interaction must be considered. To account for mediator-outcome confounding, we adjust generally for gender and other relevant confounders.

In our main CMA we include expectations of symptom severity, symptom burden, coping with symptoms, as well as treatment expectations (TEX-Q), and illness-related anxiety (SSD-12) at 6 weeks follow-up as mediating variables. We estimate the effect of the mediating variables on the PHQ-15 at 3 months and will repeat this analysis when 6 month data is available.
The following sensitivity analyses are to be carried out to validate the results and investigate changes in the (in)direct effects and PM with regard to our main mediation model:

- Handling of missing values by using the full information maximum likelihood (FIML) approach in the adjusted model with all confounders.

5.3.5 Sensitivity Analyses

The primary analysis (mixed linear model based on implicit MAR assumptions) will be repeated in the PP set. Furthermore, for the primary analysis a multiple imputation procedure will be conducted in case more than 5% of values are missing for the primary outcome.
Also, a potential effect of recruitment setting will be investigated by including setting as a fixed effect in the primary analysis model.

5.3.6 Subgroup Analyses

The analysis of the subgroups is based on the FAS and thus is as close as possible to the ITT principle. Missing values are not imputed, but the implicit MAR assumption of the analysis model will be used.

Exploratory subgroup analyses will be performed for the primary endpoint by the appropriate interaction tests within the linear mixed regression model used within the primary analysis. The presented p-values are of descriptive nature only (two-sided tests). Relevant subgroups will be identified with a p-value for the interaction < 0.15 (EMA, 2019).

Predefined subgroups are:

- Age (young [≤first tercile] vs. middle aged vs. old [>third tercile])
- Gender (male vs. female)
- Education (≤ 10 years in school vs. > 10 years in school)
- Social support (number of people living in household ≤ 1 vs. > 1)
- Duration of Long COVID (< 1 year vs. ≤ 2 years vs. > 2 years)
- Severity of overall somatic symptoms at baseline (PHQ-15 score minimal/mild/moderate 0-14 vs. severe 15-30)
- Any chronic physical disease (SCQ-D)
- Any chronic mental illness (SCQ-D)
- Depression (PHQ-9 <10 vs. ≥10)
- Anxiety (GAD-7 <10 vs. ≥10)
- Biopsychosocial understanding of disease (yes vs. no; open question B-IPQ)
- Source of recruitment (University Medical Centre Hamburg-Eppendorf vs. Self-help group vs. Social media vs. Medical or physiotherapy practice vs. Other)
- Illness-related anxiety (SSD-12 < 24 vs. ≥ 24)
- Treatment expectations (TEX-Q <5 vs. ≥5)
- Alexithymia (TAS-20 <60 vs. ≥ 61)
- Emotion regulation (ERQ suppression split at median)

5.4 Safety Evaluation

Adverse events (AE) and serious adverse events (SAE) are analysed descriptively, i.e. event rates with percentages on patient level and event numbers on event level will be given in total and by randomised treatment in the EFS.

All AEs are reported, whether or not they are considered to be related to treatment. If not stated otherwise, AEs are counted over the complete trial duration, i.e. from randomisation up to 6 months.

5.6 Data Problems

None, at time point of finalisation of SAP.

5.7 Differences to Trial Protocol

- The secondary endpoint “SARS-CoV-2 infection and Long COVID” was changed to subjective improvement of long COVID symptoms as the progress of the disease is of more interest.
- The SOMACROSS core measures were excluded as secondary endpoints as they were not of interest regarding their efficacy. Only the B-IPQ of this core measures was included for the analysis of the secondary endpoints
- The risk factor regression analysis will be repeated in all treatment groups if the global intervention effect is not significant in primary analysis. Then the interventions is assumed not to bias the result and the model could gain more information through the raised number of observations.
- For the subgroups analyses the following variables were added: Biopsychosocial understanding of disease, Source of recruitment, Illness-related anxiety, Treatment expectations, Alexithymia, Emotion regulation

5.8 Statistical Software

- STATA© 18 or newer
- SAS© 9.4 or newer
- R 4.1.1 or newer

6 References

- CONSORT Statement (Consolidated Standards of Reporting Trials)
- Engelmann, P., C. Büchel, J. Frommhold, H. F. E. Klose, A. W. Lohse, K. Maehder, Y. Nestoriuc, M. Scherer, A. Suling, A. Toussaint, A. Weigel, A. Zapf, and B. Löwe. 2023. 'Psychological risk factors for Long COVID and their modification: study protocol of a three-arm, randomised controlled trial (SOMA.COV)', *BJPsych Open*, 9: e207.
- European Medicines Agency. Guideline on the investigation of subgroups in confirmatory clinical trials. 2019. (EMA/CHMP/539146/2013).
- Gamble, C., A. Krishan, D. Stocken, S. Lewis, E. Juszczak, C. Doré, P. R. Williamson, D. G. Altman, A. Montgomery, P. Lim, J. Berlin, S. Senn, S. Day, Y. Barbachano, and E. Loder. 2017. 'Guidelines for the Content of Statistical Analysis Plans in Clinical Trials', *Jama*, 318: 2337-43.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E3. Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E6. Guideline for good clinical practice (R2/R3)
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E 8. Note for guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95).
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E9. Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96).
- Löwe, B., V. Andresen, O. Van den Bergh, T. B. Huber, O. von dem Knesebeck, A. W. Lohse, Y. Nestoriuc, G. Schneider, S. W. Schneider, C. Schramm, S. Ständer, E. Vettorazzi, A. Zapf, M. Shedden-Mora, and A. Toussaint. 2022. 'Persistent SOMAtic symptoms ACROSS diseases - from risk factors to modification: scientific framework and overarching protocol of the interdisciplinary SOMACROSS research unit (RU 5211)', *BMJ Open*, 12: e057596.
- Medical Device Act (Medizinproduktegesetz – MPG).
- Medical Products Act (Arzneimittelgesetz – AMG).
- STROBE Statement (Strengthening the Reporting of Observational Studies in Epidemiology).
- TREND Statement (Transparent Reporting of Evaluations with Nonrandomized Designs).
- White, I. R., P. Royston, and A. M. Wood. 2011. 'Multiple imputation using chained equations: Issues and guidance for practice', *Statistics in Medicine*, 30: 377-99.