# Statistical Analysis Plan (SAP)

Cognitive Rehabilitation in Post-COVID-19 Condition: A Randomized Controlled Trial

| | |
|---|---|
| ClinicalTrials.gov identifier | NCT05494424 |
| SAP version | No 1.0 |
| Date: 22.09.22 | |


| | |
|---|---|
| Principal Investigator | Jan Stubberud, PhD<br>Associate professor,<br>Department of Psychology,<br>University of Oslo,<br>Oslo, Norway |
| Author | Bjørn Ingulfsvann Hagen, PhD<br>Lecturer,<br>Department of Social Education,<br>UiT – The Artic University of Norway,<br>Harstad, Norway |

**SIGNATURE PAGE**

Principal Investigator

Jan Stubberud (22.09.22)

Author

Bjørn Ingulfsvann Hagen (22.09.22)

## Abbreviations

| | |
|---|---|
| BRIEF-A | Behavior Rating Inventory of Executive Function – Adult Version |
| CR | Cognitive rehabilitation |
| EF | Executive function |
| GMT | Goal Management Training |
| ITT | Intention-to-treat |
| MI | Metacognitive Index |
| RCT | Randomized controlled trial |
| WL | Wait list |

## Table of Contents

**Section 1: Introduction** ..... 5
*Background* ..... 5
*Objectives and study hypotheses* ..... 5
**Section 2: Study methods** ..... 5
*Trial design* ..... 5
*Randomization and blinding* ..... 5
**Section 3: Outcomes** ..... 6
*Primary outcome* ..... 6
*Secondary outcomes* ..... 6
*Tertiary outcomes* ..... 6
**Section 4: Sample size calculation** ..... 6
**Section 5: Trial population and eligibility** ..... 6
*Trial population* ..... 6
*Eligibility* ..... 6
*Recruitment and lost to follow-up* ..... 7
**Section 6: Analyses** ..... 7
*Samples to be analysed* ..... 7
*Statistical analyses* ..... 7
*Statistical interim analyses and stopping guidance* ..... 8
*Timing of final analysis* ..... 8
*Missing data* ..... 8
*Adverse events* ..... 8
*Statistical software* ..... 8
**References** ..... 8

# Section 1: Introduction

*Background*

Post-COVID-19 condition is frequently comprised of persistent perceived cognitive sequela, including deficits in attention and executive functions (EFs), which can act as a barrier for regaining pre-illness functional levels [1]. Consistent with self-reported cognitive symptoms, a heterogenous pattern of mild deficits has been identified using performance-based neurocognitive measures, with the most pronounced impairment in processing speed, attention, and EFs [2]. Concerning neurocognitive outcomes specifically, prior research suggests that persistent cognitive difficulties following COVID-19 are associated with elevated levels of psychological distress and concurrently that cognitive deficits are more prevalent in those with pre-existing mental disorders [3].

*Objectives and study hypotheses*

The primary aim of the present study is to determine the efficacy of Goal Management Training (GMT) [4], a cognitive rehabilitation (CR) intervention, compared to a wait list control condition, for improving everyday attention and EFs in adults who experience persistent cognitive deficits after COVID-19.

Study hypotheses:

- Primary hypothesis: GMT will result in greater improvement in self-reported daily-life EF, compared to wait list (WL).
- Secondary hypothesis: GMT will result in greater improvement on performance-based neurocognitive measures of EF and attention, compared to WL.
- Tertiary hypothesis: GMT will result in greater improvement on rating scales of emotional health, quality of life, and fatigue, compared to WL.

# Section 2: Study methods

*Trial design*

The proposed study is a single-center parallel RCT, comparing GMT to WL, using a repeated-measures design across three time-points, including the baseline (T1), post-intervention (T2), and a six-month follow-up (T3).

*Randomization and blinding*

Following completion of the baseline assessment, participants will be randomized to either GMT or WL in a 1:1 ratio using unstratified block randomization with a block-size of six. The allocation sequence will be computer generated by a person not otherwise involved in the study and will be stored inaccessible to the study staff. Study staff involved in the assessment of outcomes will be blind to treatment allocation.

## Section 3: Outcomes

*Primary outcome*

The primary outcome will be the Metacognition Index of the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A MI) [5], a self-report measure assessing everyday EF difficulties, specifically metacognition. The MI comprises 40 items (item range: 1-3; total range: 40-120) and includes the subscales Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials.

*Secondary outcomes*

Secondary outcomes include a selection of tests from the Cambridge Neuropsychological Test Automated Battery (The Stop Signal Task, Spatial Working Memory, Intra-Extra Dimensional Set Shift and Rapid Visual Information Processing), a performance-based neurocognitive test battery, used to assess attention and EFs [6].

*Tertiary outcomes*

Tertiary outcomes include rating scales of cognition, emotional health, quality of life, and fatigue, namely the Hospital Anxiety and Depression Scale [7], the Generalized Self-Efficacy Scale [8], the Fatigue Severity Scale [9], the Perceived Deficits Questionnaire [10], the Everyday Memory Questionnaire [11], BRIEF-A Behavior Regulation Index, the RAND 36-Item Health Survey [12], and EQ-5D [13].

## Section 4: Sample size calculation

Based on our previous research on GMT in a depression sample [14], we anticipated a change of seven points in BRIEF-A MI raw score in the intervention group and a change of at most two points in the control group. We further assumed a common standard deviation of nine points. To adjust for multiple testing, we lowered the predefined significant level to 1%, and used a power of 90% ($\beta = 0.1$). Based on the above, we would need 99 individuals in each group, but to allow for a dropout rate of about 20%, we aim to include 120 participants in each group, totaling 240.

## Section 5: Trial population and eligibility

*Trial population*

The trial will primarily be recruiting from the Norwegian Corona Cohort (clinical.trials.gov identifier: NTC04320732).

*Eligibility*

Inclusion criteria are a history of laboratory- or home-test confirmed, SARS-CoV-2 infection (> 3 months since infection), age between 18–65 years, and perceived cognitive difficulties (attention, memory, EF) affecting everyday functioning that have lasted for at least two months and that cannot be explained by an alternative diagnosis.

Exclusion criteria are ongoing alcohol- or substance abuse, premorbid insult and/or comorbid neurological disease (e.g., acquired brain injury, epilepsy, dementias, and multiple sclerosis),

severe neurocognitive problems interfering with the capacity to participate (defined as scoring < 10 points on the shortened version of the Montreal Cognitive Assessment), sensory disorders biasing cognitive assessment, schizophrenia spectrum disorders or bipolar disorder with mood congruent psychotic features, lack of proficiency in Norwegian, and being previously enrolled in a GMT trial. All eligibility evaluations are intended completed by the same rater, a clinical psychologist, in conference with a senior researcher.

*Recruitment and lost to follow-up*

A CONSORT flow diagram will be presented together with study outcomes, and comprise the number of:

- Invited patients assessed for 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 in the primary analysis *

* Reasons will be provided

## Section 6: Analyses

*Samples to be analysed*

Intention-to-treat (ITT): All randomized study subjects will be analysed according to ITT principles, including all individuals, belonging to the group they were randomized to.

The individual follow-up assessments (T2 and T3) must be completed within a timeframe of four weeks following treatment completion, or the six-month post-intervention mark, to be included in the final analyses.

*Statistical analyses*

Results from all primary-, secondary-, and tertiary outcomes will be presented separately by treatment allocation using an intention-to-treat (ITT) approach. Firstly, to assess if randomization resulted in balanced groups, baseline differences between groups will be investigated using chi-square tests or t-tests (or its non-parametrical equivalent), depending on the nature of the variables. Secondly, mixed model analyses will be carried out to assess both within- and between differences regarding the primary outcome measure, with BRIEF-A MI as dependent variable, and *Group* (treatment allocation) and *Time* (T1, T2, T3) as factors. *Group*, *Time*, and *Group-Time* interactions will be included as fixed group differences, and the restricted maximum likelihood method (REML) selected for estimation. Analysis of the primary outcome will be done with raw scores. The same model will be applied for analysing secondary- and tertiary outcomes. For a selection of secondary and tertiary outcomes assessed at two time-points only, *Time* will include T1 and T3.

Distributional assumptions will be checked by visual inspection of residual plots, and if the normality assumption is violated, a log-transformations or other appropriate transformations will be applied on the dependent variables.

*Statistical interim analyses and stopping guidance*

No interim analyses are planned for in this trial, and no stop rules are prespecified.

*Timing of final analysis*

Final analysis of the RCT is planned to take place when the six months (T3) follow-up has been reached for all intervention groups.

*Missing data*

No imputation of missing scores on each time point is planned, as the primary analyses involves a linear mixed model using all available information as complete data is not required.

*Adverse events*

Adverse events will be recorded and reported in any publication reporting trial outcomes.

*Statistical software*

Data analysis will be performed using IBM-SPSS version 27, and Stata17.

## References

[1] Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun 2022;101:93–135. https://doi.org/10.1016/j.bbi.2021.12.020.

[2] Hampshire A, Trender W, Chamberlain SR, Jolly AE, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19. EClinicalMedicine 2021;39:101044. https://doi.org/10.1016/j.eclinm.2021.101044.

[3] Krishnan K, Miller AK, Reiter K, Bonner-Jackson A. Neurocognitive profiles in patients with persisting cognitive symptoms associated with COVID-19. Arch Clin Neuropsychol 2022. https://doi.org/10.1093/arclin/acac004.

[4] Stamenova V, Levine B. Effectiveness of goal management training® in improving executive functions: A meta-analysis. Neuropsychol Rehabil 2019:1–31. https://doi.org/10.1080/09602011.2018.1438294.

[5] Roth RM, Isquith PK, Gioia G. Behavioral Rating Inventory of Executive Function-Adult Version (Psychological Assessment Resources, Lutz, FL) 2005.

[6] CANTAB CC. Cognitive assessment software. Cambridge Cogn Cambridge, UK 2016.

[7] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.

[8] Schwarzer R, Jerusalem M. Generalized self-efficacy scale. Meas Heal Psychol A

User's Portfolio Causal Control Beliefs 1995;1:35–7.

[9] Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–3. https://doi.org/10.1001/archneur.1989.00520460115022.

[10] Sullivan MJ, Edgley K, Dehoux E. A survey of multiple sclerosis: I. Perceived cognitive problems and compensatory strategy use. Can J Rehabil 1990.

[11] Royle J, Lincoln NB. The Everyday Memory Questionnaire–revised: Development of a 13-item scale. Disabil Rehabil 2008;30:114–21. https://doi.org/10.1080/09638280701223876.

[12] Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992:473–83.

[13] The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy (New York) 1990;16:199–208.

[14] Hagen BI, Lau B, Joormann J, Småstuen MC, Landrø NI, Stubberud J. Goal management training as a cognitive remediation intervention in depression: A randomized controlled trial. J Affect Disord 2020;275:268–77. https://doi.org/10.1016/j.jad.2020.07.015.