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Augmenting neurocognitive remediation therapy to Preventive Cognitive Therapy for partial remitted depressed patients: protocol of a pragmatic multi-centre randomised controlled trial.

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Keywords: Major Depressive Disorder; Partial Remission; Randomised Controlled Trial;
Preventive Cognitive Therapy; Neurocognitive Remediation Therapy

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Abstract

Introduction: Major Depressive Disorder (MDD) affects 163 million people globally every year. Individuals who experience subsyndromal depressive symptoms during remission (i.e. partial remission of MDD) are especially at risk for a return to a depressive episode within on average 4 months. Simultaneously, partial remission of MDD is associated with work and (psycho)social impairment and a lower quality of life. Brief psychological interventions such as Preventive Cognitive Therapy (PCT) can reduce depressive symptoms or relapse for patients in partial remission, although achieving full remission with treatment is still a clinical challenge. Treatment might be more effective if cognitive functioning of patients is targeted as well since cognitive problems are the most persisting symptom in partial remission and predict poor treatment response and worse functioning. Studies show that cognitive functioning of (remitted) MDD patients can be improved by online Neurocognitive Remediation Therapy (oNCRT). Augmenting oNCRT to PCT might improve treatment effects for these patients by strengthening their cognitive functioning alongside a psychological intervention.

Methods and analysis: This study will examine the effectiveness of augmenting oNCRT to PCT in a pragmatic national multicentre superiority randomised controlled trial. We will include 115 adults partially remitted from MDD with subsyndromal depressive symptoms defined as a Hamilton Depression Rating Scale score between 8 and 15. Participants will be randomly allocated to PCT with oNCRT, or PCT only. Primary outcome measure is the effect on depressive symptomatology over one year. Secondary outcomes include time to relapse, cognitive functioning, quality of life, and health care costs.

Ethics and dissemination: This study is the first to investigate augmenting oNCRT to PCT compared to PCT alone in partial remitted depressed patients. This dual approach might facilitate full remission in partial remitted individuals as well as prevent relapse over time. Ethical approval was obtained, outcomes will be made publicly available.

Trial registration: Netherlands Trial Register (NTR), ID: https://www.trialregister.nl/trial/9582 (URL). Registered on 2021-07-09.
Strengths and limitations of this study

- Strengths are the national, pragmatic, multicentre, superiority randomised controlled trial design, with measurements focusing on various levels of patient functioning, where the outcome assessors are blinded to treatment allocation of the participants.

- In our multimodal approach, we provide the patients who are partially remitted from a major depressive episode with Preventive Cognitive Therapy with online Neurocognitive Remediation Therapy, or only Preventative Cognitive Therapy.

- A limitation is that the study is single blinded and focuses on a specific group of patients.
Introduction

Major Depressive Disorder (MDD) affects 163 million people globally every year[1]. Approximately 28% - 47% of patients treated with pharmacotherapy and 18% - 45% of patients treated with psychotherapy and/or pharmacotherapy achieve no more than partial remission of MDD[2–11]. Approximately 16 - 24% of these patients spend a substantial amount of time in partial remission, ranging from 5 to 10 years following the index depressive episode[12,13]. Partial remission has been defined as a period of improvement during which a patient no longer meets criteria for MDD yet continues to experience symptoms[14–18]. In line with this consensus statement, we define partial remission as the presence of subsyndromal depressive symptoms during the remission phase of MDD with a Hamilton Depression Rating Scale (HAM-D) score in the range of 8 up to 15.

Partial remission is associated with a high risk of relapse (76% experience a relapse within 15 months) as well as a fast return of the full episode, as the depressive episode returns on average within 3.7 months in the year following partial remission[19]. Aside from the symptoms and risks, partial remission is associated with impairment in work as well as (psycho)social impairment[20–22], and lower quality of life[22,23]. The most persisting symptoms reported by patients in partial remission are cognitive problems[24,25]. Cognitive problems are present in 46% of patients in partial remission and 44% of the time[26,27] and might therefore be a target for novel treatments. Taken together, partial remission of MDD has a considerable impact on a person’s life, which underscores the need for innovative strategies that tackle partial remission in MDD.

To treat partial remission, current guidelines recommend continuing, switch or add antidepressants, to switch to (another) psychotherapy, or to combine antidepressants with psychotherapy[28,29]. Previous randomised controlled trials (RCTs), including a variety of definitions of partially remission, demonstrated that cognitive behavioural therapy (CBT)[30], mindfulness-based cognitive therapy (MBCT; N = 460)[31], and potentially rumination focussed cognitive behavioural therapy (rf-CBT; N = 60; N = 42)[32,33], can further reduce depressive symptoms for patients in partial remission from MDD. CBT for this patient group improved psychological functioning as well as social functioning[34]. Alongside the effect on depressive symptoms, these treatments decreased relapse risk[30,35,36] and internet-based CBT increased time to relapse (N = 84)[37]. Furthermore, preventive cognitive therapy (PCT) has been shown to reduce depressive symptomatology[38–42], and relapse risk for up to 5.5 to 10 years in studies that included partially and fully remitted MDD patients (HAM-D score below 10 or 14)[39,43–48].
Interestingly, most psychological treatments do not focus on improving cognitive functioning, whereas cognitive problems are the most persistent symptoms in partial remission\[26,27\]. Deficits in cognitive functioning are present during the acute phase of MDD and often remain during remission\[49–52\], and predict poor treatment response and worse functioning\[53–55\]. These deficits in emotion-independent information processing are also referred to as ‘cold cognition’- deficits\[56\]. Rather than focussing on deficits in cold cognition, psychological treatments for partial remission address so-called ‘hot cognitions’, defined as emotion-dependent thinking (e.g. self-schemata)\[57,58\]. Targeting cold cognition (i.e. improving cognitive functioning) alongside hot cognition in a combined treatment might facilitate full remission in individuals with partial remission.

Available evidence-based treatments for cold cognition include neurocognitive remediation therapy (NCRT), which involves exercises to train cognitive functions. Recent meta-analyses demonstrated that NCRT enhances attention, processing speed, executive functioning, working memory, and verbal memory in (remitted) depressed patients\[59–63\].

For patients in partial remission specifically, NCRT improved attention\[64\]. NCRT also decreased depressive symptomatology in patients with (remitted) MDD\[65–68\], although the robustness of the effect on depressive symptomatology is questionable as the beneficial effect disappeared when only high-quality studies were included\[68\]. Despite these inconsistent effects on depressive symptomatology, beneficial effects of NCRT on cognitive functioning (i.e. cold cognition) throughout several stages of MDD have been demonstrated.

Previous studies show that NCRT may enhance the effect of psychotherapy that targets hot cognitions\[69\]. Targeting cold cognition with NCRT augmented to targeting hot cognitions using PCT, might promote full remission for patients in partial remission.

Therefore, in a nationwide pragmatic multi-centre superiority RCT, we will compare PCT with online NCRT (oNCRT) to PCT alone (1:1 allocation) to assess if augmenting oNCRT to PCT further reduces depressive symptoms in partial remitted depressed patients over one year. We hypothesize that over a period of one year, augmentation of oNCRT to PCT further reduces depressive symptoms, reduces the risk of relapse and time to relapse, strengthens cognitive functioning, increases overall quality of life, and decreases health care costs.

**Methods and analysis**

The HERSTEL-study is funded by the Dutch Brain Foundation (Hersenstichting). The study has been approved by the medical research ethics committee of the Academic Medical Center, Amsterdam.
**Study design**

This study is a national pragmatic multi-centre superiority RCT with a 1:1 parallel group design. In total, 115 partial remitted depressed adults will be randomised to adding oNCRT to PCT (PCT+ group) or PCT alone (PCT- group). Both groups will be assessed monthly up to one-year post-baseline assessment. Total duration of participation in the study is 12 months. Allocation of participants is concealed for study assessors to ascertain independent assessments. An overview of the study design is provided in Figure 1.

**Participants**

**Recruitment.** Participants will be recruited in participating mental health care centres and hospitals across the Netherlands, and through advertisements, (social) media, and websites. A full list of participating centres is available upon request.

**Inclusion and exclusion criteria.** Eligible patients must fulfil the following criteria at randomization: 1) is currently in remission from MDD according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5)[70] for at least 8 weeks and no longer than 2 years, as assessed with the Structured Clinical Interview for DSM-5 disorders (SCID-5-S)[71]; 2) has a Hamilton Depression Rating Scale (HAM-D)[72] score of ≥8 and ≤15; 3) is aged 18 years or older; and 4) speaks Dutch or English. Exclusion criteria are current (hypo)mania or a history of bipolar illness, any psychotic disorder, substance misuse, primary anxiety disorder diagnosis, electroconvulsive therapy in the previous 12 months, neurological disorder, or a disabling sensory and/or motor deficit. Patients must provide written informed consent before the study procedures occur.

**Informed consent and assessment of eligibility**

Patients who either declare interest in the study or are referred by a health care provider will first be informed about the study by one of the researchers. Patients who are interested in the study will receive an information letter and an informed consent form. After informed consent is obtained, patients will be screened for in- and exclusion criteria using the SCID-5-S, HAM-D, and additional questions regarding age, language, current and previous treatments of DSM-5 disorders, and neurological disorders. The screening results will be discussed with an experienced mental health professional to decide if a participant is eligible. Eligible participants will continue with a baseline assessment, consisting of various...
questionnaires and neuropsychological tests. See Table 1 and ‘outcomes’ for an overview of all assessments. Upon completion of the baseline assessment, participants will be randomised.

**Table 1. Overview of schedule of enrolment, interventions, and assessments**

**Randomisation**

In total, 115 participants will be randomised with a 1:1 allocation ratio to PCT with oNCRT (PCT+) or PCT alone (PCT). To that end, an independent researcher will use a computer-generated block randomisation scheme with randomly varying block size (e.g. 2, 3 or 4), stratified for number of previous depressive episodes (1 versus ≥ 2). After randomisation, the participants will be informed by one of the coordinating researchers on their treatment allocation. Allocation of participants is concealed for the outcome assessors. Participants are requested not to share treatment allocation with the outcome assessor. If the blinding is violated, this will be registered.

**Interventions**

*Preventive Cognitive Therapy.* All participants will receive PCT, which consists of 8 weekly individual PCT-sessions. PCT is an adapted form of cognitive therapy (CT) that was developed to prevent relapse in remitted MDD patients with recurrent MDD[73]. During PCT, patients identify and evaluate presumed vulnerability factors of MDD recurrence, i.e. dysfunctional beliefs[74]. Furthermore, patient’s autobiographical memory and retrieval of positive experiences is trained in PCT. In addition, patients create a tailored relapse prevention plan. A recent RCT (N = 195) showed that PCT is effective in patients with partial remission[40]. PCT was also evaluated in several RCTs which demonstrated that PCT reduces the risk of relapse over 12 months up to 10 years[38–40,42,48,75–79].

PCT will be delivered via a videoconferencing program by trained and licensed health care and clinical psychologists at one of the participating centres. Treatment delivered via videoconferencing yields similar results as face-to-face treatment[80], and a previous study demonstrated that using a videoconferencing program for PCT is feasible[41]. Therapists who deliver PCT will follow a one-day training in PCT and subsequent monthly group supervision. To assess adherence to the PCT protocol, therapists will be asked to complete a checklist after every PCT session, and the number of sessions attended by the participants will be noted.

*Neurocognitive Remediation Therapy.* Participants assigned to the PCT+ group will receive oNCRT alongside PCT during the same 8-week period as the PCT. oNCRT is
provided by CogniFit and targets cognitive abilities that are often diminished in patients with MDD (i.e. (working) memory, executive functioning (task shifting), and attention (divided attention, inhibition and updating))[81]. Engaging game-like cognitive exercises are played to strengthen these cognitive abilities. The difficulty level of the exercises adjusts to the participant’s performance level. Participants will play three sessions of these exercises per week, with a duration of 45 minutes per session, over a period of 8 weeks. oNCRT is delivered as an online programme that can be accessed at home at the participant’s own computer. We will register the number of sessions completed to assess adherence.

Concomitant care. Psychiatric medication or any other medication is allowed during the entire study if necessary, which is in line with the pragmatic nature of the trial. However, patients and health care providers will be asked not to change or switch medication during the trial. Medication use and potential changes will be recorded.

Withdrawal

Participants can withdraw from the treatment or from the study at any time without consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Participants who withdraw from treatment are asked if they are willing to complete the remaining assessments.

Outcome measures and timeline

Data will be collected at baseline, post-treatment, and at several time points over one year (see Figure 1 and Table 1 for an overview). To proceed with the study and comply with (potential) COVID-19 restrictions, all assessments are completed without any face-to-face contact (e.g. assessments via secured online videoconferencing, telephone calls, online questionnaires). The outcome assessors will be blinded to treatment allocation.

Primary outcome. The primary outcome measure is change in depressive symptomatology as assessed monthly with the Inventory of Depression Symptomatology-Self Report (IDS-SR) over a one-year follow-up period[82]. See Table 1 for an overview of all assessments.

Secondary outcomes. Time related proportion of relapse/recurrence within a year will be examined with the SCID-5-S[83]. The SCID-5-S will be administered at baseline (T-1) and one-year follow-up (T12). The HAM-D will be administered at baseline (T-1), post-treatment (T2), and one year follow-up (T12) to assess clinician rated depressive symptoms[84]. At baseline (T0) and post-treatment (T2), cognitive functioning will be assessed with tests from the Amsterdam Cognition Scan (ACS)[85] and PowerPoint presentations via a secured online videoconferencing assessment. The following neuropsychological tests from
the ACS are included: Wordlist learning, Delayed recall & Recognition to assess verbal learning; Connect the Dots II to measure mental flexibility (inhibition and set-shifting ability); Digit Sequences I & II for verbal working memory; Place the Beads and Connect the Dots I to assess planning and processing speed. Using a videoconferencing meeting, the Stroop Colour-Word Interference Test will be used to test mental flexibility, and the Test of Memory Malingering (TOMM)[86] to assess malingering. Online cognitive functioning assessment can be an alternative to traditional pen-and-paper tests that yields similar results[85,87,88].

Participants will be asked to complete online questionnaires every three months during the one-year study period (T0, T3, T6, T9, T12) to assess among others quality of life and health care costs. The following questionnaires are included: Health-related quality of life as measured with the 5 level EQ-5D (EQ-5D-5L)[89], positive and negative affect measured with the Positive and Negative Affect Scale (PANAS)[90], dysfunctional attitudes assessed with the Dysfunctional Attitude Scale (DAS)[91], daily hassles using the Everyday Problem Checklist (EPCL)[92], Disability with the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)[93], and Health care and associated costs and costs from productivity loss measured using the TiC-P[94].

Additional outcomes. At baseline, we will furthermore assess socio-demographic and participant characteristics, including age, gender, socio-economic status, and psychiatric history. At baseline, Childhood trauma will be measured as well using the Childhood Trauma Questionnaire (CTQ), a self-report 28-item questionnaire that measures 5 types of maltreatment: emotional, physical, and sexual abuse, and emotional and physical neglect[95].

Sample size

A power analysis based on a linear mixed (fixed and random) effects model analysis (intraindividual rho: 0.5)[96] indicated that a sample size of 92 is needed to detect a moderate (Cohen’s $d$: 0.5) effect size on the primary outcome with 90% power and using a two-sided 5% significance level. To account for an expected 20% drop-out, 115 participants will be included.

Statistical analysis

Our primary hypothesis is that PCT with oNCRT will lead to a larger decrease in depressive symptoms (measured with the IDS-SR) over the course of one year, as compared to PCT alone.

The secondary hypotheses are that, compared to PCT alone, PCT plus oNCRT will lead to: Longer time to depressive relapse; Improved neuropsychological functioning; Higher self-reported health-related quality of life; Less self-reported disability; Lower health care and
284 associated costs and costs from productivity loss; Changes in positive and negative affect, dysfunctional attitudes, and stress.
285
286 The primary analyses will be intention-to-treat, i.e., participants will be analysed according to their randomized allocation, regardless of the actual treatment and time in the study after baseline. Secondary analyses will be per protocol, defined as at least 6 PCT sessions and 6 weeks of oNCRT (in case of PCT+oNCRT allocation).
289
290 The effect of PCT+ relative to PCT- will be estimated using linear mixed models for fixed (treatment) and random effects (for patient, and possibly for centre) for all continuously distributed outcome variables. Continuous measures that are measured once, for instance results of neuropsychological tests, will be compared using unpaired t-tests. Categorical outcomes will be tested with Chi-Square Tests. Time to depressive relapse (as measured by the SCID-5-S) will be graphically analysed using the Kaplan-Meier method and the curves will be statistically compared between the randomised groups using the log rank test. To obtain a hazard ratio as measure of effect size for the time to relapse outcome we will construct a Cox proportions hazards model to enable adjustment in the analyses of time to relapse. Prior to performing Cox regression, we will check the proportional hazards assumption graphically by creating log minus log plots.
290
296 In each analysis, adjustment will be performed for the stratification variable. If despite randomisation other prognostically important factors differ between the groups, they will be adjusted for in supplemental analyses. This will be done by adding them as covariates to the linear mixed models and the Cox regression model. Results are considered statistically significant at a two-sided significance level of alpha < .05.
290
301 To deal with missing data, we will perform multiple imputation (MI) to avoid potential bias and decreased statistical power associated with complete case analysis. MI will be done by chained equations under the assumption that missing values were missing at random or missing completely at random. The missing data mechanism will be studied to as much as possible substantiate these assumptions. The amount of missing data and reasons for non-participation or non-response will be reported and a complete case analysis will be added as a sensitivity analysis.
301
301 Discussion
315 Partial remission of MDD is prevalent[19,22,97–101], and is associated with a fast return to the full depressive episode[102], a high risk of relapse[103,104], work and (psycho)social impairment[22,105,106], and lower quality of life[22,107]. This considerable
burden highlights the importance of effective treatment for partial remission. Brief psychological interventions, including PCT, seem to reduce depressive symptoms and relapse[35,36,38–42,48,78,79,108–110]. However, achieving full remission is still a clinical challenge. Treatment might be more effective if cognitive functioning of patients is targeted as well since cognitive deficits are present in (remitted and partially remitted) MDD[111–114] and predict poor treatment response and worse functioning[115–117]. Cognitive functioning of (remitted) MDD patients can be improved by NCRT[65–68,118]. Therefore, this study will examine the effectiveness of a multimodal approach, i.e. adding oNCRT to PCT in a pragmatic RCT. To our knowledge, the current study is the first to assess if augmenting oNCRT to PCT further reduces depressive symptoms in partial remitted depressed patients. Our approach could provide an effective multimodal treatment for partial remitted individuals, for which currently few evidence-based treatments are available.

Abbreviations

(o)NCRT = (online) neurocognitive remediation therapy
ACS = Amsterdam Cognition Scan
CBT = cognitive behavioural therapy
CT = Cognitive Therapy
CTQ = Childhood Trauma Questionnaire
DAS = Dysfunctional Attitude Scale
DSM-5 = Diagnostic and Statistical Manual of Mental Disorders 5
EPCL = Everyday Problem Checklist
HAM-D = Hamilton Depression Rating Scale
IDS-SR = Inventory of Depression Symptomatology-Self Report
MBCT = mindfulness-based cognitive therapy
MDD = Major Depressive Disorder
PANAS = Positive and Negative Affect Scale
PCT = Preventive Cognitive Therapy
RCT = Randomized Controlled Trial
rf-CBT = rumination focussed cognitive behavioural therapy
SCID-5-S = Structured Clinical Interview for DSM-5 disorders
TOMM = Test of Memory Malingering
WHODAS = World Health Organization Disability Assessment Schedule

Ethics approval and consent to participate
The study was approved by the medical research ethics committee of the Academic Medical Center, Amsterdam before study onset (protocol ID: NL74547.018.20, trial register: https://www.trialregister.nl/trial/9582 (URL). Registered on 2021-07-09). The procedures listed above are in accordance with the Declaration of Helsinki. All participants will be informed about the study and will consent with participation before assessments.

### Consent for publication

### Availability of data and materials

### Competing interests

All authors declare that they have no competing interests.

### Funding

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### Authors' contributions

CB, HB, GG, MB, AL, MS and were responsible for the funding. CB is the principal investigator and wrote the draft of the manuscript with JS and MB, MB and CB are responsible for the coordination of the project. CB designed the PCT intervention. MB, JS and AL are responsible for data collection, inclusion of participants, monitoring of the study, and continued ethical approval. All authors were involved in the design and ethical approval of the study. NL is involved for the patient perspective of the study. All authors read and approved the final manuscript.

### Patient and Public Involvement

NL was involved as a representative of the Depressie Vereniging, an association for people with depression and their relatives. NL contributed perspectives from members of the association during the design phase and will continue to do so over the course of this trial.

### Acknowledgements

There are none.

### Protocol version

V.1

### Sponsor contact information
Trial sponsor: Amsterdam UMC, location AMC

Sponsor’s reference: NL74547.018.20

Address: Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands

Access to data

Only staff members (e.g. clinical interns, clerical personnel) authorized by the principal investigators, monitoring agency of the AMC, and the Health and Youth Care Inspectorate will be allowed access to the data.

Dissemination policy

The (anonymised) results of the study will be shared with the participating centres. The results will be presented on seminars and published in peer-reviewed journals.
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| TIMEPOINT | Description | Entry | Baseline | Post-allocation | Last assessment |
|-----------|-------------|-------|----------|----------------|----------------|
| ENROLMENT: |             |       | T-1      | T0  | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 |
| Eligibility screen | | X | | | | | | | | | | | | | |
| Informed consent | Before T-1 assessments | X | | | | | | | | | | | | | |
| Allocation | Randomisation after baseline assessments | X | | | | | | | | | | | | | |
| INTERVENTIONS: | | | | | | | | | | | | | | | |
| PCT + oNCRT | | | | | | | | | | | | | | | |
| PCT alone | | | | | | | | | | | | | | | |
| ASSESSMENTS: | | | | | | | | | | | | | | | |
| Clinical interviews | | X | | | | | | | | | | | | | |
| SCID-5-S | DSM-5 disorders | X | | | | | | | | | | | | | |
| HAM-D | Depressive symptoms | X | X | | | | | | | | | | | | | |
| Patient characteristics and psychiatric history | | X | | | | | | | | | | | | | |
| Self-reports: | | | | | | | | | | | | | | | |
| IDS-SR | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| EPCL | | X | X | | | | | | | | | X | X | X | X |
| DAS | | X | | X | X | | | | | | | | | | | |
| CTQ | | X | | | | | | | | | | | | | |
| TIC-P | | X | | X | | X | | | | | | | | X | X | X |
| EQ-5D-5L | | X | | X | | X | | X | | | | | | | | |
| WHODAS 2.0 | | X | | | | | X | | X | | | | | | | |
| PANAS | | X | | | | | | X | | | | | | | | | |
| Neuropsychological tests: |       |       |
|--------------------------|-------|-------|
| TOMM                     | X     | X     |
| Wordlist learning        | X     | X     |
| Place the beads          | X     |       |
| Connect the dots I & II  | X     | X     |
| Digit sequences I & II   | X     | X     |
| Stroop                   | X     | X     |
| Computer skills          |       | X     |
| Adherence:               |       |       |
| PCT                      | X     | X     |
| oNCRT                    | X     | X     |

Note: All assessments will be conducted online. T0 = baseline, T1 = 1 month, T2 = directly post-treatment (8 weeks), T3-T11 = 3-11 months, T12 = one year follow-up. Abbreviations: oNCRT = online neurocognitive remediation therapy; CTQ = Childhood Trauma Questionnaire DAS = Dysfunctional Attitude Scale; EPCL = Everyday Problem Checklist; EQ-5D-5L = EuroQol Group 5 dimensions questionnaire for Health-related quality of life; HAM-D = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depression Symptomatology-Self Report; PANAS = Positive and Negative Affect Scale; PCT = Preventive Cognitive Therapy; SCID-5-S = Structured Clinical Interview for DSM-5 disorders; TiC-P = Questionnaire on healthcare utilization and productivity losses; TOMM = Test of Memory Malingering; WHODAS = World Health Organization Disability Assessment Schedule;
Figures

Figure 1. Study flow-chart

Notes: (o)NCRT = (online) neurocognitive remediation therapy; HAM-D = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depression Symptomatology-Self Report; PCT = Preventive Cognitive Therapy; SCID-5-S = Structured Clinical Interview for DSM-5 disorder
Notes: (o)NCRT = (online) neurocognitive remediation therapy; HAM-D = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depression Symptomatology-Self Report; PCT = Preventive Cognitive Therapy; SCID-5-S = Structured Clinical Interview for DSM-5 disorders.
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item          | Item No | Description                                                                                     | Addressed on page number |
|-----------------------|---------|-------------------------------------------------------------------------------------------------|--------------------------|
| **Administrative information** |         |                                                                                                 |                          |
| Title                 | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1                        |
| Trial registration    | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry              | 12 - 13                  |
|                       | 2b      | All items from the World Health Organization Trial Registration Data Set                         |                          |
| Protocol version      | 3       | Date and version identifier                                                                      | 13                       |
| Funding               | 4       | Sources and types of financial, material, and other support                                      |                          |
| Roles and responsibilities | 5a      | Names, affiliations, and roles of protocol contributors                                           | 1, 13                    |
|                       | 5b      | Name and contact information for the trial sponsor                                               | 13                       |
|                       | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 13                       |
|                       | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |                          |
Introduction

Background and rationale

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

6b Explanation for choice of comparators

Objectives

7 Specific objectives or hypotheses

Trial design

8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting

9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria

10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Interventions

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes

12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
|------------|----|----------------------------------------------------------------------------------|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size |

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |
|---------------------|-----|----------------------------------------------------------------------------------|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |

**Blinding (masking):**

| 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
| 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial |

**Methods: Data collection, management, and analysis**

| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol |
|-------------------------|----|----------------------------------------------------------------------------------|
|                        | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols |
Data management  

19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Statistical methods  

20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring  

Data monitoring  

21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms  

22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing  

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination  

Research ethics approval  

24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments  

25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
| Consent or assent 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 7 |
|----------------------|-----------------------------------------------------------------------------------------------------------------|---|
| 26b                  | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | - |
| Confidentiality 27   | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 7-10, 14 |
| Declaration of interests 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 13 |
| Access to data 29    | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 14, trial registration |
| Ancillary and post-trial care 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | - |
| Dissemination policy 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 14 |
| 31b                  | Authorship eligibility guidelines and any intended use of professional writers | - |
| 31c                  | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 14 |

**Appendices**

| Informed consent materials 32 | Model consent form and other related documentation given to participants and authorised surrogates | - |
| Biological specimens 33     | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | - |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.*
Augmenting neurocognitive remediation therapy to Preventive Cognitive Therapy for partial remitted depressed patients: protocol of a pragmatic multi-centre randomised controlled trial.

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Augmenting neurocognitive remediation therapy to Preventive Cognitive Therapy for partial remitted depressed patients: protocol of a pragmatic multi-centre randomised controlled trial.

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Keywords: Major Depressive Disorder; Partial Remission; Randomised Controlled Trial; Preventive Cognitive Therapy; Neurocognitive Remediation Therapy
Abstract

Introduction: Major Depressive Disorder (MDD) affects 163 million people globally every year. Individuals who experience subsyndromal depressive symptoms during remission (i.e. partial remission of MDD) are especially at risk for a return to a depressive episode within an average 4 months. Simultaneously, partial remission of MDD is associated with work and (psycho)social impairment and a lower quality of life. Brief psychological interventions such as Preventive Cognitive Therapy (PCT) can reduce depressive symptoms or relapse for patients in partial remission, although achieving full remission with treatment is still a clinical challenge. Treatment might be more effective if cognitive functioning of patients is targeted as well since cognitive problems are the most persisting symptom in partial remission and predict poor treatment response and worse functioning. Studies show that cognitive functioning of (remitted) MDD patients can be improved by online Neurocognitive Remediation Therapy (oNCRT). Augmenting oNCRT to PCT might improve treatment effects for these patients by strengthening their cognitive functioning alongside a psychological intervention.

Methods and analysis: This study will examine the effectiveness of augmenting oNCRT to PCT in a pragmatic national multicentre superiority randomised controlled trial. We will include 115 adults partially remitted from MDD with subsyndromal depressive symptoms defined as a Hamilton Depression Rating Scale score between 8 and 15. Participants will be randomly allocated to PCT with oNCRT, or PCT only. Primary outcome measure is the effect on depressive symptomatology over one year. Secondary outcomes include time to relapse, cognitive functioning, quality of life, and health care costs. This first dual approach study of augmenting oNCRT to PCT might facilitate full remission in partial remitted individuals as well as prevent relapse over time.

Ethics and dissemination: Ethical approval was obtained by Academic Medical Center, Amsterdam. Outcomes will be made publicly available.

Trial registration: Netherlands Trial Register (NTR), ID: https://www.trialregister.nl/trial/9582 (URL). Registered on 2021-07-09.
Strengths and limitations of this study

- Strengths are the national, pragmatic, multicentre, superiority randomised controlled trial design, with measurements focusing on various levels of patient functioning, where the outcome assessors are blinded to treatment allocation of the participants.

- In our multimodal approach, we provide the patients who are partially remitted from a major depressive episode with Preventive Cognitive Therapy with online Neurocognitive Remediation Therapy, or only Preventative Cognitive Therapy.

- A limitation is that the study is single blinded and focuses on a specific group of patients.
Introduction

Major Depressive Disorder (MDD) affects 163 million people globally every year[1]. Approximately 28% - 47% of patients treated with pharmacotherapy and 18% - 45% of patients treated with psychotherapy and/or pharmacotherapy achieve no more than partial remission of MDD[2–11]. Approximately 16 - 24% of these patients spend a substantial amount of time in partial remission, ranging from 5 to 10 years following the index depressive episode[12,13]. Partial remission has been defined as a period of improvement during which a patient no longer meets criteria for MDD yet continues to experience symptoms[14–18]. In line with this consensus statement, we define partial remission as the presence of subsyndromal depressive symptoms during the remission phase of MDD with a Hamilton Depression Rating Scale (HAM-D) score in the range of 8 up to 15.

Partial remission is associated with a high risk of relapse (76% experience a relapse within 15 months) as well as a fast return of the full episode, as the depressive episode returns on average within 3.7 months in the year following partial remission[19]. Aside from the symptoms and risks, partial remission is associated with impairment in work as well as (psycho)social impairment[20–22], and lower quality of life[22,23]. The most persisting symptoms reported by patients in partial remission are cognitive problems[24,25]. Cognitive problems are present in 46% of patients in partial remission and 44% of the time[26,27] and might therefore be a target for novel treatments. Taken together, partial remission of MDD has a considerable impact on a person’s life, which underscores the need for innovative strategies that tackle partial remission in MDD.

To treat partial remission, current guidelines recommend continuing, switch or add antidepressants, to switch to (another) psychotherapy, or to combine antidepressants with psychotherapy[28,29]. Previous randomised controlled trials (RCTs), including a variety of definitions of partially remission, demonstrated that cognitive behavioural therapy (CBT)[30], mindfulness-based cognitive therapy (MBCT; N = 460)[31], and potentially rumination focussed cognitive behavioural therapy (rf-CBT; N = 60; N = 42)[32,33], can further reduce depressive symptoms for patients in partial remission from MDD. CBT for this patient group improved psychological functioning as well as social functioning[34]. Alongside the effect on depressive symptoms, these treatments decreased relapse risk[30,35,36] and internet-based CBT increased time to relapse (N = 84)[37]. Furthermore, preventive cognitive therapy (PCT) has been shown to reduce depressive symptomatology[38–42], and relapse risk for up to 5.5 to 10 years in studies that included partially and fully remitted MDD patients (HAM-D score below 10 or 14)[39,43–48].

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Interestingly, most psychological treatments do not focus on improving cognitive functioning, whereas cognitive problems are the most persistent symptoms in partial remission[26,27]. Deficits in cognitive functioning are present during the acute phase of MDD and often remain during remission[49–52], and predict poor treatment response and worse functioning[53–55]. These deficits in emotion-independent information processing are also referred to as ‘cold cognition’- deficits[56]. Rather than focussing on deficits in cold cognition, psychological treatments for partial remission address so-called ‘hot cognitions’, defined as emotion-dependent thinking (e.g. self-schemata)[57,58]. Targeting cold cognition (i.e. improving cognitive functioning) alongside hot cognition in a combined treatment might facilitate full remission in individuals with partial remission.

Available evidence-based treatments for cold cognition include neurocognitive remediation therapy (NCRT), which involves exercises to train cognitive functions. Recent meta-analyses demonstrated that NCRT enhances attention, processing speed, executive functioning, working memory, and verbal memory in (remitted) depressed patients[59–63]. For patients in partial remission specifically, NCRT improved attention[64]. NCRT also decreased depressive symptomatology in patients with (remitted) MDD[65–68], although the robustness of the effect on depressive symptomatology is questionable as the beneficial effect disappeared when only high-quality studies were included[68]. Despite these inconsistent effects on depressive symptomatology, beneficial effects of NCRT on cognitive functioning (i.e. cold cognition) throughout several stages of MDD have been demonstrated.

Previous studies show that NCRT may enhance the effect of psychotherapy that targets hot cognitions[69]. Targeting cold cognition with NCRT augmented to targeting hot cognitions using PCT, might promote full remission for patients in partial remission.

Therefore, in a nationwide pragmatic multi-centre superiority RCT, we will compare PCT with online NCRT (oNCRT) to PCT alone (1:1 allocation) to assess if augmenting oNCRT to PCT further reduces depressive symptoms in partial remitted depressed patients over one year. We hypothesize that over a period of one year, augmentation of oNCRT to PCT further reduces depressive symptoms, reduces the risk of relapse and time to relapse, strengthens cognitive functioning, increases overall quality of life, and decreases health care costs.

Methods and analysis

The HERSTEL-study is funded by the Dutch Brain Foundation (Hersenstichting). The study has been approved by the medical research ethics committee of the Academic Medical Center, Amsterdam.
Study design

This study is a national pragmatic multi-centre superiority RCT with a 1:1 parallel
group design. In total, 115 partial remitted depressed adults will be randomised to adding
oNCRT to PCT (PCT+ group) or PCT alone (PCT- group). Both groups will be assessed
monthly up to one-year post-baseline assessment. Total duration of participation in the study
is 12 months. Allocation of participants is concealed for study assessors to ascertain
independent assessments. An overview of the study design is provided in Figure 1.

Figure 1. Study flow-chart

Participants

Recruitment. Participants will be recruited in participating mental health care centres
and hospitals across the Netherlands, and through advertisements, (social) media, and
websites. A full list of participating centres is available upon request.

Inclusion and exclusion criteria. Eligible patients must fulfil the following criteria at
randomization: 1) is currently in remission from MDD according to the Diagnostic and
Statistical Manual of Mental Disorders 5 (DSM-5)[70] for at least 8 weeks and no longer than
2 years, as assessed with the Structured Clinical Interview for DSM-5 disorders (SCID-5-
S)[71]; 2) has a Hamilton Depression Rating Scale (HAM-D)[72] score of ≥8 and ≤15; 3) is
aged 18 years or older; and 4) speaks Dutch or English. Exclusion criteria are current
(hypo)mania or a history of bipolar illness, any psychotic disorder, substance misuse, primary
anxiety disorder diagnosis, electroconvulsive therapy in the previous 12 months, neurological
disorder, or a disabling sensory and/or motor deficit. Patients must provide written informed
consent before the study procedures occur.

Informed consent and assessment of eligibility

Patients who either declare interest in the study or are referred by a health care
provider will first be informed about the study by one of the researchers. Patients who are
interested in the study will receive an information letter and an informed consent form. After
informed consent is obtained, patients will be screened for in- and exclusion criteria using the
SCID-5-S, HAM-D, and additional questions regarding age, language, current and previous
treatments of DSM-5 disorders, and neurological disorders. The screening results will be
discussed with an experienced mental health professional to decide if a participant is eligible.

Eligible participants will continue with a baseline assessment, consisting of various
questionnaires and neuropsychological tests. See Table 1 and ‘outcomes’ for an overview of all assessments. Upon completion of the baseline assessment, participants will be randomised.
Table 1. Overview of schedule of enrolment, interventions, and assessments

| TIMEPOINT | Description | T-1 | T0 | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 |
|-----------|-------------|-----|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|
| ENROLMENT:|             |     |    |    |    |    |    |    |    |    |    |    |     |     |     |
| Eligibility screen | Before T-1 assessments | X | | | | | | | | | | | | |
| Informed consent | Randomisation after baseline assessments | X | | | | | | | | | | | | |
| Allocation | | | | | | | | | | | | | | |
| INTERVENTIONS: | | | | | | | | | | | | | | |
| PCT + oNCRT | | | | | | | | | | | | | | |
| PCT alone | | | | | | | | | | | | | | |
| ASSESSMENTS: | | | | | | | | | | | | | | |
| Clinical interviews: | | | | | | | | | | | | | | |
| SCID-5-S | DSM-5 disorders | X | | | | | | | | | | | | X |
| HAM-D | Depressive symptoms | X | X | | | | | | | | | | | |
| Patient characteristics and psychiatric history | X | | | | | | | | | | | | | |
| Self-reports: | | | | | | | | | | | | | | |
| IDS-SR | | X | X | X | X | X | X | X | X | X | X | | | |
| EPCL | | X | X | X | X | X | X | X | X | X | X | | | |
| DAS | | X | X | X | X | X | X | X | X | X | X | | | |
| CTQ | | X | | | | | | | | | | | | |
| TIC-P | | X | X | X | X | X | X | X | X | X | X | | | |
| EQ-5D-5L | | X | X | X | X | X | X | X | X | X | X | | | |
| WHODAS 2.0 | | X | X | X | X | X | X | X | X | X | X | | | |
| PANAS | | X | X | X | X | X | X | X | X | X | X | | | |
| Neuropsychological tests: |   |   |
|--------------------------|---|---|
| TOMM                     | X | X |
| Wordlist learning        | X | X |
| Place the beads          | X | X |
| Connect the dots I & II  | X | X |
| Digit sequences I & II   | X | X |
| Stroop                   | X | X |
| Computer skills          | X | X |
| Adherence:               | X | X |
| PCT                      | X | X |
| oNCRT                    | X | X |

Note: All assessments will be conducted online. T0 = baseline, T1 = 1 month, T2 = directly post-treatment (8 weeks), T3-T11 = 3-11 months, T12 = one year follow-up. Abbreviations: oNCRT = online neurocognitive remediation therapy; CTQ = Childhood Trauma Questionnaire DAS = Dysfunctional Attitude Scale; EPCL = Everyday Problem Checklist; EQ-5D-5L = EuroQol Group 5 dimensions questionnaire for Health-related quality of life; HAM-D = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depression Symptomatology-Self Report; PANAS = Positive and Negative Affect Scale; PCT = Preventive Cognitive Therapy; SCID-5-S = Structured Clinical Interview for DSM-5 disorders; TiC-P = Questionnaire on healthcare utilization and productivity losses; TOMM = Test of Memory Malingering; WHODAS = World Health Organization Disability Assessment Schedule.
Randomisation

In total, 115 participants will be randomised with a 1:1 allocation ratio to PCT with oNCRT (PCT+) or PCT alone (PCT). To that end, an independent researcher will use a computer-generated block randomisation scheme with randomly varying block size (e.g. 2, 3 or 4), stratified for number of previous depressive episodes (1 versus ≥ 2). After randomization, the participants will be informed by one of the coordinating researchers on their treatment allocation. Allocation of participants is concealed for the outcome assessors. Participants are requested not to share treatment allocation with the outcome assessor. If the blinding is violated, this will be registered.

Interventions

Preventive Cognitive Therapy. All participants will receive PCT, which consists of 8 weekly individual PCT-sessions. PCT is an adapted form of cognitive therapy (CT) that was developed to prevent relapse in remitted MDD patients with recurrent MDD[73]. During PCT, patients identify and evaluate presumed vulnerability factors of MDD recurrence, i.e. dysfunctional beliefs[74]. Furthermore, patient’s autobiographical memory and retrieval of positive experiences is trained in PCT. In addition, patients create a tailored relapse prevention plan. A recent RCT (N = 195) showed that PCT is effective in patients with partial remission[40]. PCT was also evaluated in several RCTs which demonstrated that PCT reduces the risk of relapse over 12 months up to 10 years[38–40,42,48,75–79].

PCT will be delivered via a videoconferencing program by trained and licensed health care and clinical psychologists at one of the participating centres. Treatment delivered via videoconferencing yields similar results as face-to-face treatment[80], and a previous study demonstrated that using a videoconferencing program for PCT is feasible[41]. Therapists who deliver PCT will follow a one-day training in PCT and subsequent monthly group supervision. To assess adherence to the PCT protocol, therapists will be asked to complete a checklist after every PCT session, and the number of sessions attended by the participants will be noted.

Neurocognitive Remediation Therapy. Participants assigned to the PCT+ group will receive oNCRT alongside PCT during the same 8-week period as the PCT. oNCRT is provided by CogniFit and targets cognitive abilities that are often diminished in patients with MDD (i.e. (working) memory, executive functioning (task shifting), and attention (divided attention, inhibition and updating))[81]. Engaging game-like cognitive exercises are played to strengthen these cognitive abilities. The difficulty level of the exercises adjusts to the participant’s performance level. Participants will play three sessions of these exercises per...
week, with a duration of 45 minutes per session, over a period of 8 weeks. oNCRT is delivered as an online programme that can be accessed at home at the participant’s own computer. We will register the number of sessions completed to assess adherence.

**Concomitant care.** Psychiatric medication or any other medication is allowed during the entire study if necessary, which is in line with the pragmatic nature of the trial. However, patients and health care providers will be asked not to change or switch medication during the trial. Medication use and potential changes will be recorded.

**Withdrawal**

Participants can withdraw from the treatment or from the study at any time without consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Participants who withdraw from treatment are asked if they are willing to complete the remaining assessments.

**Outcome measures and timeline**

Data will be collected at baseline, post-treatment, and at several time points over one year (see Figure 1 and Table 1 for an overview). To proceed with the study and comply with (potential) COVID-19 restrictions, all assessments are completed without any face-to-face contact (e.g. assessments via secured online videoconferencing, telephone calls, online questionnaires). The outcome assessors will be blinded to treatment allocation.

**Primary outcome.** The primary outcome measure is change in depressive symptomatology as assessed monthly with the Inventory of Depression Symptomatology-Self Report (IDS-SR) over a one-year follow-up period[82]. See Table 1 for an overview of all assessments.

**Secondary outcomes.** Time related proportion of relapse/recurrence within a year will be examined with the SCID-5-S[83]. The SCID-5-S will be administered at baseline (T-1) and one-year follow-up (T12). The HAM-D will be administered at baseline (T-1), post-treatment (T2), and one year follow-up (T12) to assess clinician rated depressive symptoms[84].

At baseline (T0) and post-treatment (T2), cognitive functioning will be assessed with tests from the Amsterdam Cognition Scan (ACS)[85] and PowerPoint presentations via a secured online videoconferencing assessment. The following neuropsychological tests from the ACS are included: Wordlist learning, Delayed recall & Recognition to assess verbal learning; Connect the Dots II to measure mental flexibility (inhibition and set-shifting ability); Digit Sequences I & II for verbal working memory; Place the Beads and Connect the Dots I to assess planning and processing speed. Using a videoconferencing meeting, the Stroop Colour-Word Interference Test will be used to test mental flexibility, and the Test of Memory
Malingering (TOMM)\[86\] to assess malingering. Online cognitive functioning assessment can be an alternative to traditional pen-and-paper tests that yields similar results\[85,87,88\]. Participants will be asked to complete online questionnaires every three months during the one-year study period (T0, T3, T6, T9, T12) to assess among others quality of life and health care costs. The following questionnaires are included: Health-related quality of life as measured with the 5 level EQ-5D (EQ-5D-5L)\[89\], positive and negative affect measured with the Positive and Negative Affect Scale (PANAS)\[90\], dysfunctional attitudes assessed with the Dysfunctional Attitude Scale (DAS)\[91\], daily hassles using the Everyday Problem Checklist (EPCL)\[92\], Disability with the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)\[93\], and Health care and associated costs and costs from productivity loss measured using the TiC-P\[94\].

**Additional outcomes.** At baseline, we will furthermore assess socio-demographic and participant characteristics, including age, gender, socio-economic status, and psychiatric history. At baseline, Childhood trauma will be measured as well using the Childhood Trauma Questionnaire (CTQ), a self-report 28-item questionnaire that measures 5 types of maltreatment: emotional, physical, and sexual abuse, and emotional and physical neglect\[95\].

**Sample size**

A power analysis based on a linear mixed (fixed and random) effects model analysis (intraindividual rho: 0.5)\[96\] indicated that a sample size of 92 is needed to detect a moderate (Cohen’s \(d\): 0.5) effect size on the primary outcome with 90% power and using a two-sided 5% significance level. To account for an expected 20% drop-out, 115 participants will be included.

**Statistical analysis**

Our primary hypothesis is that PCT with oNCRT will lead to a larger decrease in depressive symptoms (measured with the IDS-SR) over the course of one year, as compared to PCT alone. The secondary hypotheses are that, compared to PCT alone, PCT plus oNCRT will lead to: Longer time to depressive relapse; Improved neuropsychological functioning; Higher self-reported health-related quality of life; Less self-reported disability; Lower health care and associated costs and costs from productivity loss; Changes in positive and negative affect, dysfunctional attitudes, and stress.

The primary analyses will be intention-to-treat, i.e., participants will be analysed according to their randomized allocation, regardless of the actual treatment and time in the
study after baseline. Secondary analyses will be per protocol, defined as at least 6 PCT sessions and 6 weeks of oNCRT (in case of PCT+oNCRT allocation).

The effect of PCT+ relative to PCT- will be estimated using linear mixed models for fixed (treatment) and random effects (for patient, and possibly for centre) for all continuously distributed outcome variables. Continuous measures that are measured once, for instance results of neuropsychological tests, will be compared using unpaired t-tests. Categorical outcomes will be tested with Chi-Square Tests. Time to depressive relapse (as measured by the SCID-5-S) will be graphically analysed using the Kaplan-Meier method and the curves will be statistically compared between the randomised groups using the log rank test. To obtain a hazard ratio as measure of effect size for the time to relapse outcome we will construct a Cox proportions hazards model to enable adjustment in the analyses of time to relapse. Prior to performing Cox regression, we will check the proportional hazards assumption graphically by creating log minus log plots.

In each analysis, adjustment will be performed for the stratification variable. If despite randomisation other prognostically important factors differ between the groups, they will be adjusted for in supplemental analyses. This will be done by adding them as covariates to the linear mixed models and the Cox regression model. Results are considered statistically significant at a two-sided significance level of alpha < .05.

To deal with missing data, we will perform multiple imputation (MI) to avoid potential bias and decreased statistical power associated with complete case analysis. MI will be done by chained equations under the assumption that missing values were missing at random or missing completely at random. The missing data mechanism will be studied to as much as possible substantiate these assumptions. The amount of missing data and reasons for non-participation or non-response will be reported and a complete case analysis will be added as a sensitivity analysis.

**Ethics and dissemination**

The study was approved by the medical research ethics committee of the Academic Medical Center, Amsterdam, before study onset (protocol ID: NL74547.018.20, trial register: https://www.trialregister.nl/trial/9582 (URL). Registered on 2021-07-09). The procedures listed above are in accordance with the Declaration of Helsinki. All participants will be informed about the study and will consent with participation before assessments. Only staff members (e.g. clinical interns, clerical personnel) authorized by the principal investigators, monitoring agency of the AMC, and the Health and Youth Care Inspectorate will be allowed
access to the data. Data will be shared anonymised with other researchers upon reasonable request and after a data sharing agreement has been signed. The (anonymised) results of the study will be shared with the participating centres. The results will be presented on seminars and published in peer-reviewed journals.

**Discussion**

Partial remission of MDD is prevalent[19,22,97–101], and is associated with a fast return to the full depressive episode[102], a high risk of relapse[103,104], work and (psycho)social impairment[22,105,106], and lower quality of life[22,107]. This considerable burden highlights the importance of effective treatment for partial remission. Brief psychological interventions, including PCT, seem to reduce depressive symptoms and relapse[35,36,38–42,48,78,79,108–110]. However, achieving full remission is still a clinical challenge. Treatment might be more effective if cognitive functioning of patients is targeted as well since cognitive deficits are present in (remitted and partially remitted) MDD[111–114] and predict poor treatment response and worse functioning[115–117]. Cognitive functioning of (remitted) MDD patients can be improved by NCRT[65–68,118]. Therefore, this study will examine the effectiveness of a multimodal approach, i.e. adding oNCRT to PCT in a pragmatic RCT. To our knowledge, the current study is the first to assess if augmenting oNCRT to PCT further reduces depressive symptoms in partial remitted depressed patients. Our approach could provide an effective multimodal treatment for partial remitted individuals, for which currently few evidence-based treatments are available.

**Abbreviations**

(o)NCRT = (online) neurocognitive remediation therapy

ACS = Amsterdam Cognition Scan

CBT = cognitive behavioural therapy

CT = Cognitive Therapy

CTQ = Childhood Trauma Questionnaire

DAS = Dysfunctional Attitude Scale

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders 5

EPCL = Everyday Problem Checklist

HAM-D = Hamilton Depression Rating Scale

IDS-SR = Inventory of Depression Symptomatology-Self Report

MBCT = mindfulness-based cognitive therapy
MDD = Major Depressive Disorder
PANAS = Positive and Negative Affect Scale
PCT = Preventive Cognitive Therapy
RCT = Randomized Controlled Trial
rf-CBT = rumination focussed cognitive behavioural therapy
SCID-5-S = Structured Clinical Interview for DSM-5 disorders
TOMM = Test of Memory Malingering
WHODAS = World Health Organization Disability Assessment Schedule

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Competing interests statement
All authors declare that they have no competing interests.

Authors’ contributions
CB, HB, GG, MB, AL, MS and were responsible for the funding. CB is the principal investigator and wrote the draft of the manuscript with JS and MB, MB and CB are responsible for the coordination of the project. CB designed the PCT intervention. MB, JS and AL are responsible for data collection, inclusion of participants, monitoring of the study, and continued ethical approval. CB, AL, JS, GG, MS, HB, IB, NL, DD, MB were involved in the design and ethical approval of the study. NL is involved for the patient perspective of the study. CB, AL, JS, GG, MS, HB, IB, NL, DD, MB read, commented and approved the final manuscript.

Patient and Public Involvement
NL was involved as a representative of the Depressie Vereniging, an association for people with depression and their relatives. NL contributed perspectives from members of the association during the design phase and will continue to do so over the course of this trial.

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Figures

Figure 1. Study flow-chart

Notes: (o)NCRT = (online) neurocognitive remediation therapy; HAM-D = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depression Symptomatology-Self Report; PCT = Preventive Cognitive Therapy; SCID-5-S = Structured Clinical Interview for DSM-5 disorder
Notes: (o)NCRT = (online) neurocognitive remediation therapy; HAM-D = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depression Symptomatology-Self Report; PCT = Preventive Cognitive Therapy; SCID-5-S = Structured Clinical Interview for DSM-5 disorders.
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item                  | Item No | Description                                                                                                                                                                                                 | Addressed on page number |
|--------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| **Administrative information**|         |                                                                                                                                                                                                             |                          |
| Title                          | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym                                                                                                 | 1                        |
| Trial registration             | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry                                                                                                                            | 12 - 13                  |
|                                | 2b      | All items from the World Health Organization Trial Registration Data Set                                                                                                                                      | -                        |
| Protocol version               | 3       | Date and version identifier                                                                                                                                                                                  | -                        |
| Funding                        | 4       | Sources and types of financial, material, and other support                                                                                                                                                  | 13                       |
| Roles and responsibilities     | 5a      | Names, affiliations, and roles of protocol contributors                                                                                                                                                      | 1, 13                    |
|                                | 5b      | Name and contact information for the trial sponsor                                                                                                                                                           | 13                       |
|                                | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 13                       |
|                                | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | -                        |
# Introduction

## Background and rationale
Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

## Objectives
Specific objectives or hypotheses

## Trial design
Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

# Methods: Participants, interventions, and outcomes

## Study setting
Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

## Eligibility criteria
Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

## Interventions
Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Relevant concomitant care and interventions that are permitted or prohibited during the trial

## Outcomes
Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

## Participant timeline
Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
|-------------|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size                                                                                                                                 |

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |
|---------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |

#### Blinding (masking):

| Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 17a | 8 |
| If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial | 17b | 8 |

### Methods: Data collection, management, and analysis

| Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 18a | 9-10 |
| Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 18b | 9-10 |
| Section               | Subsection | Details                                                                                                                                                                                                 | Reference |
|-----------------------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Data management       | 19         | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol |
| Statistical methods   | 20a        | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol                                         | 10-11     |
| Statistical methods   | 20b        | Methods for any additional analyses (e.g., subgroup and adjusted analyses)                                                                                                                                               | 10-11     |
| Statistical methods   | 20c        | Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)                           | 11        |
| Methods: Monitoring   |            |                                                                                              | Amsterdam UMC standard policies for clinical research apply (see p.12). |
| Data monitoring       | 21a        | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | -         |
| Data monitoring       | 21b        | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial                                                                                   | -         |
| Harms                 | 22         | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct                                                                       | -         |
| Auditing              | 23         | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor                                                                                                 | -         |
| Ethics and dissemination |        | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval                                                                                                                            | 12-13     |
| Protocol amendments   | 24         | Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | -         |
Consent or assent 26a  Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  

26b  Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable  

Confidentiality 27  How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  

Declaration of interests 28  Financial and other competing interests for principal investigators for the overall trial and each study site  

Access to data 29  Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators  

Ancillary and post-trial care 30  Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  

Dissemination policy 31a  Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions  

31b  Authorship eligibility guidelines and any intended use of professional writers  

31c  Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code  

Appendices  

Informed consent materials 32  Model consent form and other related documentation given to participants and authorised surrogates  

Biological specimens 33  Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.*