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## Feasibility of Cognitive Training in Combination With Transcranial Direct Current Stimulation in a Home-based Context (TrainStim-Home) – Study Protocol for a Randomized Controlled Trial

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Manuscripts

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3 **1 Feasibility of Cognitive Training in Combination With Transcranial Direct**  
4 **2 Current Stimulation in a Home-based Context (TrainStim-Home) – Study**  
5 **3 Protocol for a Randomized Controlled Trial**  
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## 39 Abstract

40 **Introduction:** With the worldwide increase of life expectancy leading to a higher proportion of older  
41 adults experiencing age-associated deterioration of cognitive abilities, the development of effective  
42 and widely accessible prevention and therapeutic measures has become a priority and challenge for  
43 modern medicine. Combined interventions of cognitive training and transcranial direct current  
44 stimulation (tDCS) have shown promising results for counteracting age-associated cognitive decline.  
45 However, access to clinical centers for repeated sessions is challenging, particularly in rural areas and  
46 for older adults with reduced mobility, and lack of clinical personnel and hospital space prevents  
47 extended interventions in larger cohorts. A home-based and remotely supervised application of tDCS  
48 would make the treatment more accessible for participants and relieve clinical resources. So far,  
49 studies assessing feasibility of combined interventions in a home-based setting are missing. With this  
50 study, we aim to provide evidence for the feasibility and the effects of a multi-session home-based  
51 cognitive training in combination with tDCS on cognitive functions of healthy older adults.

52 **Methods and analysis:** The TrainStim-Home trial is a monocentric, randomized, double-blind,  
53 placebo-controlled study. Thirty healthy participants, aged 60 to 80 years, will receive two weeks of  
54 combined cognitive training and anodal tDCS over left dorsolateral prefrontal cortex (dlPFC, target  
55 intervention), compared with cognitive training plus sham stimulation. The cognitive training will  
56 comprise a letter updating task, and the participants will be stimulated for 20 min with 1.5 mA. The  
57 intervention sessions will take place at the participants' home and primary outcome will be the  
58 feasibility, operationalized by 2/3 successfully completed sessions per participant. Additionally,  
59 performance in the training task and an untrained task will be analyzed.

60 **Ethics and dissemination:** Ethical approval was granted by the ethics committee of the  
61 University Medicine Greifswald. Results will be available through publications in peer-reviewed  
62 journals and presentations at national and international conferences.

63 **Trial registration:** The study was registered prospectively on 26 March 2021 at ClinicalTrials.gov with  
64 the Identifier: NCT04817124.

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**Keywords:** home use, neuromodulation, working memory, transfer, executive function, brain stimulation, behavioral intervention, multi-session

### **Strengths and limitations of this study**

- This is the first trial to investigate the feasibility of self-application of cognitive training combined with tDCS in older adults
- We implement thorough training of older adults in handling devices and materials, and collect structured feedback on satisfaction with procedures from participants, to obtain successful delivery of the intervention and high adherence rates
- A possible selection bias towards technical experienced participants may occur, as due to remote connection requirements we can only include participants with an internet access in their homes

## 78 **Background**

79 With the worldwide increase of life expectancy<sup>1</sup>, an increasing proportion of older adults will  
80 experience age-associated deterioration of cognitive abilities which will lead, in addition to individual  
81 suffering, to social and health economic strains<sup>2,3</sup>. Thus, investigation of non-invasive interventions to  
82 counteract cognitive decline and restore impaired functions, such as combined cognitive training and  
83 transcranial direct current stimulation (tDCS) protocols, is particularly relevant<sup>4-7</sup>. In general,  
84 combined approaches of training and tDCS have been shown to elicit immediate effects on cognitive  
85 abilities, transfer to untrained domains, and long-term effects, which persisted up to several  
86 months<sup>8-12</sup>. Mechanistically, tDCS is thought to additionally boost the effect of cognitive training by  
87 supporting already ongoing brain activity in task-related neural areas<sup>10,13</sup>. Possible underlying  
88 physiological mechanisms are tDCS-induced alterations of resting membrane potentials and long-  
89 term potentiation via glutamatergic neurotransmission<sup>14-16</sup>. However, multi-session interventions of  
90 combined cognitive training and tDCS involve frequent visits to the facility, which requires high  
91 compliance and motivation from the participants, especially from participants living in rural areas  
92 with no easy access to research facilities or from adults that are limited in their mobility due to  
93 advanced age or comorbidities. Additionally, the facilities need space and personnel to administer  
94 the intervention, which puts further limits on interventions applied over multiple sessions in large  
95 cohorts. As promising results of combined cognitive training and tDCS have been shown in on-site  
96 studies (i.e., in the clinic or lab environment)<sup>8-12</sup>, translation of the intervention to remotely-  
97 controlled self-administration in a home-based context would be the next necessary step for a widely  
98 accessible intervention.

99 Remotely-controlled tDCS enables the trained staff to monitor the intervention from a distance, for  
100 example from the hospital (e.g., by tracking the completed sessions, the quality, length, and any  
101 problems during the sessions remotely or via direct phone contact)<sup>17</sup>. The devices for the stimulation  
102 are programmed specifically for home-based use before being handed over to the participants. This  
103 programming only allows a pre-defined strength and length of the stimulation, thereby ensuring the

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3 104 safety of the participants<sup>17</sup>. A recent review of 22 studies of home-based tDCS interventions without  
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5 105 cognitive training has given a positive outlook on home-based tDCS<sup>17</sup>. So far, studies that  
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7 106 investigated home-use tDCS for the treatment of diseases such as trigeminal neuralgia, vascular-  
8  
9 107 related dementia, or multiple sclerosis, showed that a remote application of tDCS at home could lead  
10  
11 108 to an improvement in symptoms<sup>18-20</sup>. As the participants were, however, mostly young adults, and  
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13 109 most of the studies focused on effectiveness, research on the feasibility of home-based tDCS in older  
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15 110 adults is particularly relevant. Previous home-based tDCS studies with a wide age range reported a  
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17 111 large variance in the level of the participant's commitment. Dropout rates ranged from 4% only<sup>21</sup> to  
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19 112 high rates of 41%<sup>20</sup>. An easy, self-explanatory application, good communication, and unsolicited  
20  
21 113 support in keeping the participants engaged seem to be key factors for higher adherence rates<sup>17 21 22</sup>.  
22  
23 114 Thus, research assessing the feasibility of a combined home-based cognitive training and tDCS  
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25 115 approach is needed. Compared to home-use tDCS feasibility trials published so far, a combined  
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27 116 approach poses a bigger challenge for participants in terms of assembly of the study materials and  
28  
29 117 execution of the stimulation and behavioral task, especially in an older population, who is often less  
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31 118 experienced in handling of technical devices and software<sup>17</sup>. Nonetheless, when well instructed on  
32  
33 119 how to administer the intervention, the effectiveness of the combined approach and the possibility  
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35 120 of participating from home could serve as a motivator for long-term adherence. Moreover, a  
36  
37 121 combined approach of training and concurrent tDCS, will control for the participants' activity during  
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39 122 stimulation compared to previous home-based trials administering solely tDCS<sup>23</sup>.  
40  
41 123 In the TrainStim-Home study, we will therefore investigate the feasibility (primary) and the effects on  
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43 124 cognitive function of home-based cognitive training and tDCS in a monocentric, randomized, double-  
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45 125 blind, placebo-controlled design. Participants will accomplish a letter updating task over six training  
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47 126 sessions with concurrent tDCS over left dorsolateral prefrontal cortex (dlPFC) administered by the  
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49 127 participants themselves in their own home. Half of the study cohort will receive anodal tDCS while  
50  
51 128 performing the cognitive training, whereas the other half will undergo sham stimulation during  
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53 129 training. The intervention will span two weeks, with three training sessions per week. We will assess  
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3 130 feasibility and behavioral outcome measures, such as direct training effects, transfer to untrained  
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5 131 domains and performance sustainability for one month. We hypothesize that with appropriate  
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7 132 instruction and close supervision via remote cloud system and phone, the use of combined cognitive  
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9 133 training and tDCS (or sham) in an ecologically valid environment (i.e., at the participant's home) by  
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11 134 the participants themselves is feasible (i.e., the participants complete 2/3 of the home-based  
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13 135 sessions successfully (primary outcome) and achieve a high score in a feasibility questionnaire at  
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15 136 post-assessment). For assessment of feasibility, both groups will be included in the analysis. For the  
16  
17 137 assessment of efficacy, we hypothesize increased performance on the trained and untrained tasks at  
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19 138 post-assessment in the anodal compared to the sham stimulation group. Moreover, we expect  
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21 139 sustainability of the effects at four-week follow-up to be superior in the anodal group. This protocol,  
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23 140 describing the design and methods of the TrainStim-Home study, was prepared in accordance with  
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25 141 the SPIRIT guidelines <sup>24 25</sup>.

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## 143 **METHODS: Participants, intervention, and outcomes**

### 144 **Design and setting**

145 This is a monocentric, randomized, double-blind, placebo-controlled study to evaluate the feasibility  
146 and effectiveness of a two-week combined cognitive training and tDCS intervention administered by  
147 participants themselves. The intervention spans two weeks and comprises six sessions (3 per week)  
148 of cognitive training, accompanied by tDCS over the left dlPFC compared to sham tDCS. The  
149 intervention will take place at the participants' home. Additionally, pre- and post-assessments will be  
150 carried out at the University Medicine Greifswald. A follow-up assessment will follow one month  
151 after the intervention to assess possible long-term effects. In total, participants will complete 10  
152 sessions. A flowchart of the study is shown in Figure 1.

153

### 154 **Eligibility criteria**

155 Before randomization, participants eligible for the study must meet all the following criteria:



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3 156 • Age: 60-80 years  
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5 157 • Right-handedness  
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8 158 • Internet access at the home of the participants  
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10 159 • Performance in neuropsychological screening at baseline within normal range (defined as  
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12 160 performance of each subtest within -1.5 standard deviations (SD) from the normative  
13  
14 161 samples mean)<sup>26,27</sup>.

16 162 In case one or more of the following criteria are present at randomization, potential participants will  
17  
18 be excluded:  
19 163

- 20  
21 164 • Mild cognitive impairment (MCI), subjective cognitive decline (SCD), or dementia  
22  
23 165 (participants reporting decline in cognitive functions or performing below -1.5 SD in any  
24  
25 166 neuropsychological screening subtest will be excluded).  
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28 167 • Other neurodegenerative neurological illnesses, epilepsy or history of seizures, close  
29  
30 168 relatives with epilepsy or history of seizures; previous stroke.  
31  
32 169 • Severe untreated medical conditions that preclude participation in the training, as  
33  
34 170 determined by responsible physician  
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36  
37 171 • History of severe alcoholism or use of drugs  
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39 172 • Severe psychiatric disorders such as depression (if not in remission) or psychosis  
40  
41 173 • Contraindication to tDCS application<sup>28</sup>.  
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46 175 If all eligibility criteria are met and participants provide written informed consent, they will be  
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48 176 included in the study sample.  
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## 52 178 **Intervention**

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55 179 At each training session, participants will participate in a cognitive training with concurrent  
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57 180 administration of either anodal or sham stimulation. Participants will be presented with a letter  
58  
59 181 updating task (LU task, cf.<sup>5,29</sup>) on a tablet computer. This task targets working memory updating. The

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3 182 letters A to D will be presented one letter at a time in random order, and with differing list lengths (5,  
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5 183 7, 9, 11, 13 or 15 letters, six times each; total of 36 lists). After the presentation of each list  
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7 184 (presentation duration 2000ms, ISI 500ms), the participants will be asked to recall the last four  
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9 185 letters that were presented.  
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12 186 tDCS will be administered via a battery-operated stimulator (Starstim Home, Neuroelectronics,  
13  
14 187 Barcelona, Spain). Two sponge-based electrodes (Sponstim, NE026, Neuroelectronics, Barcelona, Spain)  
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16 188 will be mounted on the head in a neoprene cap using the 10-20 EEG grid. The anodal electrode will  
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18 189 be placed over the left dlPFC, in the position of F3, the cathodal electrode will be placed over the  
19  
20 190 right orbita in the Fp2 position. A current of 1.5 mA will be applied for 20 min, with 20 additional  
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22 191 seconds of ramping in the beginning and at the end of the stimulation. In the sham group, the  
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24 192 current will only be applied for 30 sec in total at the beginning of the 20 min, to elicit the typical  
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26 193 tingling sensation of stimulation on the scalp and to blind the participants regarding their stimulation  
27  
28 194 condition. Ramp times and montage will be equivalent to the anodal stimulation group. The cognitive  
29  
30 195 training task and the stimulation will be started simultaneously. Every three sessions, thus twice  
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32 196 over the intervention time, participants will be asked to complete an adverse events questionnaire <sup>28</sup>.  
33  
34 197 At each training session, the participants will be asked to fill in a questionnaire regarding self-  
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36 198 reported well-being, quality and duration of sleep as well as potential stressors in the last two hours  
37  
38 199 prior to the session. They will also be asked to complete the German version of the Positive and  
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40 200 Negative Affect Schedule (PANAS<sup>30</sup>), both before and after the session. Participants will be asked to  
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42 201 avoid excessive consumption of alcohol and nicotine on the day of the intervention, and one day  
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44 202 prior. Furthermore, they will be instructed to forgo caffeine 90 min before a session and adhere to  
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46 203 their regular sleep schedule.  
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#### 205 **Outcome measures**

206 Feasibility will be assessed directly after the intervention. Outcome measures of the training task will  
207 be acquired at each visit. Additionally, at pre-, post- and follow-up assessments outcomes for

208 possible transfer effects will be acquired. All outcome measures and assessment time points are  
209 displayed in Table 1. Each outcome measure will be analyzed regarding potential differences  
210 between intervention groups (anodal vs. sham tDCS).

### 211 **Primary outcomes**

212 Primary outcome measure will be the feasibility of home-based tDCS as operationalized by at least  
213 2/3 of successfully performed interventional sessions per participant for at least 60 % of all  
214 participants. A session is considered successful when its registered as fully completed in the cloud  
215 and the participant has not initiated contact concerning a problem or rescheduling.

### 216 **Secondary outcomes**

217 Feasibility will further be measured by questionnaire and analyzed as a secondary outcome. A single-  
218 item self-rate questionnaire on participant satisfaction, independence and self-confidence in the  
219 handling of the devices and program (adapted from Cha et al., 2016<sup>21</sup>) will be filled out by the  
220 participants. Feasibility will be assumed, if at least 60 % of all participants rated to “agree” or  
221 “strongly agree” (i.e., 4 or 5 on 5-point Likert scale) on the questionnaire item assessing overall  
222 satisfaction with the tDCS and training equipment. Additionally, working memory performance in the  
223 trained task will be assessed at each session, operationalized by number of correctly recalled lists in  
224 the letter updating task<sup>31</sup>. Performance in the untrained tasks will be assessed as secondary outcome  
225 at post- and follow-up assessments, operationalized by percentage of correct answers in the n-back  
226 task<sup>32</sup>.

227

### 228 **Participant timeline**

229 Participants will have to adhere to 10 sessions over the course of the study. Baseline and pre-  
230 assessment (V1, V2) will take place at the University Medicine Greifswald, the training sessions (V3-  
231 V8) will take place at the participants' own home during two consecutive weeks on 3 days a week.  
232 The first of the training sessions will be accompanied by a study investigator, the following five  
233 sessions will be performed independently and tracked via a cloud system. After the training, post-

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3 234 assessment (V9) will be conducted immediately and follow-up assessment will be administered four  
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5 235 weeks later, both at the University Medicine Greifswald.  
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10 237 **Baseline measures**

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12 238 At baseline assessment, the study and its execution will be explained to the participant by a member  
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14 239 of the study staff. Subsequently, the participants will be asked to provide written informed consent  
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16 240 and a demographic interview will be carried out. This interview will be followed by a comprehensive  
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18 241 battery of neuropsychological tests to quantify cognitive function on different domains, including the  
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20 242 CERAD-Plus test battery<sup>33</sup>. Additionally, handedness will be assessed with the Oldfield Handedness  
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22 243 Questionnaire<sup>34</sup> and possible depressive symptoms will be explored with the Geriatric Depression  
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24 244 Scale<sup>35</sup>.

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27 245 Following the tests and questionnaires, an instructional video explaining the assembly, disassembly,  
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29 246 handling and care of the devices and of the supplies for the stimulation will be shown to the  
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31 247 participants. Any questions and critical points will be discussed with a staff member. The participant  
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33 248 will then be asked to replicate the assembly and disassembly of an interventional session with the  
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35 249 help of a checklist and the study staff, and subsequently perform the training task as described  
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37 250 above. At baseline assessment, the training task will include 25 lists (36 lists at training sessions) and  
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39 251 a practice trial with four lists will be performed.  
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45 253 **Pre-, post- and follow-up-assessments**

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47 254 Self-reported well-being, quality and duration of sleep as well as potential stressors in the last two  
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49 255 hours prior to the visit will be assessed in the form of a semi-structured interview. Then, the  
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51 256 participants will complete the working memory training task (LU task<sup>29</sup>) and a working memory task  
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53 257 that will not be trained (n-back task<sup>32</sup>). At pre-assessment participants will additionally be instructed  
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55 258 once more in the handling of the stimulation set. The feasibility questionnaire will be completed at  
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57 259 post-assessment.  
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**261 Sample size**

262 As the primary goal of this study will be to assess feasibility, and as it is recommended to employ results  
263 of feasibility trials for sample size calculation of a planned subsequent trial<sup>36</sup>, we chose a sample size  
264 of  $N = 30$ <sup>37</sup>. To infer feasibility, the lower bound of the 95 % confidence interval of the proportion of  
265 participants who fulfilled the feasibility criterion needs to be at 60 %. Thus, 76 %, i.e.,  $n = 23$   
266 participants will have to meet the feasibility criterion.

267 With 15 participants per stimulation group (anodal vs. sham stimulation), we will be able to  
268 additionally explore the benefit of anodal tDCS over sham with regard to performance after the  
269 training on the trained working memory, and the untrained working memory tasks<sup>38 39</sup>. Using an  
270 independent t-test with a two-sided significance level of 0.05 and a power of 80 % we will be able to  
271 demonstrate an effect of Cohen's  $d = 1.06$  or higher on behavioral performance.

272

**273 Recruitment**

274 Participants will be recruited via adverts in the local newspaper and via the distribution of flyers at  
275 senior and adult education centers, local shops, restaurants and museums. All potential participants  
276 will be provided with information about the study over the phone, and a screening assessing  
277 exclusion and inclusion criteria will be carried out. All eligible participants will be invited for baseline  
278 assessment.

279

**280 METHODS: Assignment of interventions**

281 Allocation to anodal and sham tDCS group will be performed using stratified block randomization.  
282 Participants will be randomly allocated by a researcher not involved in assessments. Allocation to the  
283 experimental groups (anodal vs. sham) will be performed with a 1:1 ratio with age (two age strata;  
284 60-70, 71-80) and cognitive performance at baseline assessment ( $\leq 5$ ,  $> 5/25$  corrects lists in the LU  
285 task). Randomization blocks with varying block sizes will be generated for each of the four groups,

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3 286 using R software (<http://www.R-project.org>) and the blockrand package ([https://CRAN.R-](https://CRAN.R-project.org/package=blockrand)  
4  
5 287 [project.org/package=blockrand](https://CRAN.R-project.org/package=blockrand)). Participants will then be allocated to anodal or sham tDCS group,  
6  
7 288 based on the generated randomization sequences within each block and stratum.  
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## 11 290 **Blinding**

12 291 In this double-blind trial, both investigators and study participants and investigators will be blinded  
13  
14 291 In this double-blind trial, both investigators and study participants and investigators will be blinded  
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16 292 regarding the stimulation condition. The two stimulation protocols (anodal, sham) will be labeled  
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18 293 with unidentifiable labels such as A and B. A staff member not involved in data collection will  
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20 294 perform the randomization as described above and will subsequently assign the label of the  
21  
22 295 stimulation protocol accordingly to each participant. The investigator will schedule stimulation  
23  
24 296 sessions for each participant individually via a cloud-system. This investigator will select the labeled  
25  
26 297 protocol that corresponds to the participants ID number and will be able to plan the stimulation  
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28 298 without knowledge of the respective stimulation condition. As for participant blinding, study  
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30 299 participants will only be able to use the device if a stimulation session with given duration and  
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32 300 current intensity was scheduled beforehand in the online cloud-system. Participants will be unaware  
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34 301 whether the session entails active or sham stimulation. In the sham group the current will only be  
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36 302 applied at the beginning of the stimulation session for 20 sec ramp-up and -down respectively. This  
37  
38 303 method is used to elicit the typical tingling sensation under the electrodes during the stimulation and  
39  
40 304 to ensure blinding of the participants to the respective stimulation condition. Previous studies have  
41  
42 305 shown that sham tDCS is a safe and valid method of participant-blinding<sup>40-43</sup>. At post-assessment,  
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44 306 participants will be asked to state if they believe they received anodal or sham stimulation.  
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## 51 308 **METHODS: Data collection, management and analysis**

### 52 309 **Data collection methods**

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3 310 Neuropsychological and behavioral will be collected from each participant. Study investigators will be  
4  
5 311 thoroughly trained in administering the assessments. Time points of data collection are shown in  
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7 312 **Table 1.**

### 313 **Neuropsychological and behavioral assessment**

314 Neuropsychological testing at the baseline visit (V0) will comprise paper-pencil as well as computer-  
315 based assessment. The Geriatric Depression Scale<sup>35</sup> and the Edinburgh Handedness Inventory<sup>34</sup> will  
316 be administered. Cognitive function in different domains will be quantified using a comprehensive  
317 battery of neuropsychological tests including the CERAD (Consortium to Establish a Registry for  
318 Alzheimer's Disease, German version), extended to CERAD-Plus  
319 (<https://www.memoryclinic.ch/de/main-navigation/neuropsychologen/cerad-plus/>) with the Trail  
320 Making Test A + B and Phonematic Fluency (S-Words)<sup>33</sup>, and the digit span test<sup>44</sup>.

321 The training and transfer tasks are computer-based. Detailed description of the training task is  
322 provided in the intervention section. At pre-, post-, and follow-up-assessment (V2, V9-V10) an  
323 untrained task is administered: Participants will perform a numeric n-back task (1 and 2 back) to  
324 assess working memory function (18 trials total, 9 trials 1back and 9 trials 2back with 10 items each,  
325 presentation duration 1500ms, ISI 2500ms). A sequence of numerical stimuli is presented one after  
326 another, and the participants will have to state if the number that is currently presented is identical  
327 to the stimulus "n"-steps back.

328 Additionally, at post-assessments, participants will complete a 17-item feasibility questionnaire  
329 concerning independence and self-confidence in the handling of the devices and program as well as  
330 the participant satisfaction and comfort during the at-home part of the study participation (cf. Cha et  
331 al.<sup>21</sup>).

### 332 **Retention and adherence**

333 Participants will be provided with information on their appointments via telephone and if possible via  
334 e-mail to maximize retention over the course of the study. A few days prior to pre-assessment,  
335 participants will be contacted by a study investigator and will be reminded of the upcoming

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3 336 appointments. A copy of all study appointments will be handed out at pre-assessment. At every  
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5 337 appointment and during each phone call, the investigator will actively seek out any open questions  
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7 338 and remarks regarding the intervention and will provide assistance accordingly. Furthermore, the  
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9 339 online cloud-system, which interacts with the application on the tablet computer, allows the  
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11 340 investigators involved in this study to schedule and monitor stimulation sessions individually for each  
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13 341 participant. During stimulation and simultaneous performance of the training task, the participant  
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15 342 will be able to abort the stimulation at any time via button press, if necessary. After the completion  
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17 343 of the task, the stimulation will be turned off automatically, and information on whether the session  
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19 344 was completed or not will be transferred to the cloud-system, to be checked by the investigator.  
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21 345 Additionally, investigators will be notified automatically via e-mail alert about any reported adverse  
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23 346 events or problems. In such case, participants will be contacted immediately. The participants will be  
24  
25 347 reminded that their progress will be monitored closely through the cloud-system and that they  
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27 348 should not hesitate to contact the investigator in case problems or questions arise. If no contact is  
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29 349 initiated by the participant, they will be contacted by the day of their sixth training sessions. To assist  
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31 350 the participant in solving problems, the investigator has the possibility to remotely control the tablet  
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33 351 computer. Participants will be encouraged to use the 24/7 study answering machine if they cannot  
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35 352 attend a visit and want to reschedule. They will then be contacted by a member of the study team as  
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37 353 soon as possible. At the end of the study, i.e. at follow-up assessment, participants will receive a  
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39 354 financial reimbursement of 130 € and a report about their neuropsychological test performance. If  
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41 355 for whatever reason complete adherence is not possible, an effort will be made to collect as much  
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43 356 data as possible from the respective participant.  
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## 52 358 **Data management and monitoring**

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54 359 All collected data will be pseudonymized. Paper-based data such as questionnaires and the scoring  
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56 360 sheets of the neuropsychological test will be stored in lockable cabinets in rooms with restricted  
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58 361 access, sorted by participant ID for easy access at each stage of the study. Data acquired on paper  
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3 362 will be manually digitalized by one staff member, and double-checked by another. The progress of  
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5 363 data acquirement and digitalization will be documented. All digitally acquired data, such as task  
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7 364 output files, will be saved on a secure server and protected with password only known to the staff  
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9  
10 365 involved in this project. Protocols of the tDCS stimulation of each participant and session will also be  
11  
12 366 stored on this server. Spreadsheets concerning sensitive data, such as names, addresses and contact  
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14 367 information, will be further protected with another password if acquired digitally, and stored in a  
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16 368 separate lockable cabinet if in paper form. Following good scientific practice, data will be stored for  
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19 369 at least 10 years.

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### 22 23 371 **Patient and public involvement**

24  
25 372 In order to involve older adults, in December of 2020, we asked five former participants of our  
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27 373 TrainStim-Cog trial (study protocol, see <sup>45</sup>) which comprised a very similar procedure, to participate in  
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29 374 trial sessions. During these trial sessions, we simulated the home-based training sessions including  
30  
31 375 the assembly and disassembly of the stimulation set and the handling of the tablet computer. Any  
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33 376 difficulties, such as the complicated order of mounting the stimulation equipment, were identified in  
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35 377 these trial sessions and were solved by developing further aids, such as a check-list and a detailed  
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37 378 instruction manual. Using this check-list and manual, trial participants were then able to mount the  
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39 379 stimulation set confidently and correctly. Similarly, we were made aware of the importance of a  
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41 380 visual demonstration and consequently filmed an instruction video of 20 min duration, which will be  
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43 381 shown to every participant at baseline assessment and will be available over the treatment period as  
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45 382 on-demand video on the tablet computer. Continuing this feedback-based development of the  
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47 383 home-based approach during the feasibility trial, we will carry out a semi-structured interview at  
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49 384 post-assessment concerning ease of use, opinions and feelings of the participants about the system  
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51 385 and of our assistance, as well as concerning perceived challenges with this home-based approach.  
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53 386 Information obtained through these interviews will help optimize the trial design for a possible  
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55 387 subsequent clinical trial.  
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5 389 **Adverse events monitoring**

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7 390 The risk of health damage associated with anodal tDCS is expected to be minimal. Known adverse  
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9 391 effects (AEs) with the study parameters (20 min, 1.5 mA) are skin tingling, reddening and occasionally  
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11 392 a mild headache. These potential AEs will be monitored after each third stimulation session via an  
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13 393 adverse events questionnaire<sup>28</sup>. We will refrain from assessing AEs at every session, as we believe it  
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15 394 would only draw the participants' attention to minor sensations during the stimulation and  
16  
17 395 ultimately act as a distractor from the cognitive task. Investigators will be instructed to monitor for  
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19 396 and document all AEs and serious AEs throughout the trial. Participants will be informed about  
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21 397 possible risks and AEs at baseline assessment and can withdraw consent at any time without  
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23 398 providing reason. If a serious AE occurs, the study physician will be consulted and asked to make an  
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25 399 assessment whether or not a causal relationship with the intervention is considered possible. If more  
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27 400 than three of the enrolled participants suffer from serious AEs that are likely to be associated with  
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29 401 the intervention (as assessed by the study physician), the trial will be discontinued.

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36 403 **Statistical analysis**

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38 404 Feasibility data (primary outcome) will be analyzed using descriptive statistics. Feasibility will be  
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40 405 inferred when participants complete at least 2/3 of the home-based sessions successfully. Secondary  
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42 406 feasibility outcomes, as measured by questionnaire will be analyzed similarly. Data distributions of  
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44 407 the questionnaire items will be visually assessed for normality using q-q plots, and statistically using  
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46 408 the Shapiro-Wilk test<sup>37,46</sup>

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48 409 Secondary outcome data on behavioral tasks from all participants included at randomization will be  
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50 410 analyzed including data from all participants who finished post-assessment. Additionally, a "per  
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52 411 protocol" analysis will be conducted, including only those participants, who successfully completed  
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54 412 2/3 of the home-based sessions (thus fulfilling the criterion for feasibility). Focusing on the trained  
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56 413 task, we will conduct an ANCOVA model with the post-assessment working memory score (number  
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3 414 of correctly recalled lists in the letter updating task) as dependent variable, stimulation group  
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5 415 (anodal, sham) as factor, and working memory performance at pre-assessment as well as age as  
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7 416 covariates. We will furthermore analyze outcome measures from untrained WM tasks and their  
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9 417 interactions, using linear mixed models with time-point (e.g., pre- / post-assessment) as within-  
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11 418 subject factor and stimulation group (anodal, sham) as between-subject factor. In case of violation of  
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13 419 requirements for parametric methods, appropriate non-parametric tests will be conducted. Data  
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15 420 analysis will be conducted using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United  
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17 421 States), MatLab (The Mathworks Inc., 2016), and R software.  
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## 22 23 423 **Ethics and Dissemination**

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26 424 This study was approved by the ethics committee of the University Medicine Greifswald and will be  
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28 425 conducted in accordance with the Helsinki Declaration. All data collected will be pseudonymized. The  
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30 426 results of this study will be made accessible to scientific researchers and health care professionals via  
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32 427 publications in peer-reviewed journals and presentations at national and international conferences.  
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34 428 Furthermore, the scientific and lay public can access the study results on the ClinicalTrials.gov  
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36 429 website (Identifier: NCT04817124).  
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## 40 430 **Conclusion**

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42 431 With this trial, we will assess feasibility and efficacy a home-based combined cognitive training and  
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44 432 tDCS intervention in older adults. A successful implementation of the intervention in the home-based  
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46 433 setting will contribute to the development of home-based tDCS as a widely available therapy option  
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48 434 in clinical populations.  
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## 52 53 54 436 **Trial status**

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57 437 Recruitment of participants has started in April 2021.  
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## 59 438 **Declarations**

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3 439 **Consent or assent**  
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5 440 A member of the investigational team (study coordinator or study assessor) will collect written  
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7 441 informed consent during study enrollment after having reviewed the participant information sheet,  
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9 442 participant's questions, and study inclusion and exclusion criteria.  
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12 443 **Confidentiality**  
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14 444 The collected data will be treated as confidential. Direct access to personal information and source  
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16 445 data documentation will only be given to study monitors, study assessors, and the research team.  
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18  
19 446 **Funding**  
20

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22  
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24  
25 449 Research Foundation) Project number 327654276 – SFB 1315 to AF.  
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28 450 **Availability of data and materials**  
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30 451 Anonymized data will be made available to the scientific community upon request.  
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34 453 **Authors' contributions**  
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36 454 FT, DA and AF conceptualized and designed this trial. AF is supervising its implementation. FT is  
37  
38 455 implementing the trial and supervising its conduct. RN assisted in programming and software  
39  
40 456 development of the home-based stimulation application. RM programmed the training task and  
41  
42 457 implemented it to work with the stimulation application. MR is performing recruitment and  
43  
44 458 assessments. FT and MR drafted the study protocol. UG will be performing statistical analyses. All  
45  
46 459 authors will be contributing to interpretation of the data. All authors read and revised the original  
47  
48 460 draft and consecutive versions of the manuscript. All authors read and approved the final version of  
49  
50 461 the study protocol.  
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3 465 **Ethics approval and consent to participate**  
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5 466 The study was approved by the ethics committee of the University Medicine Greifswald, Germany

6  
7 467 (BB02 /21, date of first approval: 05 Feb 2021). All procedures conducted during the TrainStim-Home

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9  
10 468 trial will be carried out in compliance with the Declaration of Helsinki.

11  
12 469 **Competing interests**  
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14 470 RN is a part-time employee with NE. The other authors declare no actual or potential conflicts of

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16 471 interest.  
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For peer review only

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612 **Tables and Figures****Table 1.** *TrainStim-Home outcome measures.*

|                                 |   |                    | Baseline | Pre   | T1-T6<br>(2 weeks) | Post<br>(3 days) | FU<br>(1 month) |
|---------------------------------|---|--------------------|----------|-------|--------------------|------------------|-----------------|
|                                 |   |                    | ~3h      | ~1,5h | ~1h                | ~1,5h            | ~1,5h           |
| Time point                      | Measurement                                       | Mode               | V0       | V1    | V2-V7              | V8               | V9              |
| <b>Enrollment</b>               |   |                    |          |       |                    |                  |                 |
| Eligibility screening           |   | Paper              | x        |       |                    |                  |                 |
| Informed consent                |   | Paper              | x        |       |                    |                  |                 |
| Neuropsychological<br>Screening | Demographic data                                  | Paper              | x        |       |                    |                  |                 |
|                                 | Geriatric depression<br>scale <sup>35</sup>       | Paper              | x        |       |                    |                  |                 |
|                                 | Oldfield<br>handedness<br>inventory <sup>34</sup> | Paper              | x        |       |                    |                  |                 |
|                                 | CERAD Plus <sup>33</sup>                          | Paper              | x        |       |                    |                  |                 |
|                                 | Digit Span <sup>44</sup>                          | Paper              | x        |       |                    |                  |                 |
| <b>Intervention</b>             |   |                    |          |       |                    |                  |                 |
| Training task                   | Letter<br>updating <sup>5 29</sup>                | Tablet<br>computer | x        | x     | x                  | x                | x               |
| Brain stimulation               | tDCS (anodal vs.<br>sham)                         | Device             |          |       | x                  |                  |                 |
| Questionnaires                  | Self-reported<br>well-being<br>questionnaire      | Paper              |          | x     | x                  | x                | x               |
|                                 | PANAS <sup>30</sup>                               | Paper              |          |       | x                  |                  |                 |
|                                 | Adverse events<br>questionnaire <sup>28*</sup>    |                    |          |       | x                  |                  |                 |
| <b>Additional assessments</b>   |   |                    |          |       |                    |                  |                 |
| Untrained task                  | n-back <sup>32</sup>                              | Computer           |          | x     |                    | x                | x               |
| Feasibility                     | Sessions completed<br>(primary outcome)           | Cloud<br>system    |          |       | x                  | x                |                 |
|                                 | Feasibility<br>questionnaire                      | Paper              |          |       |                    | x                |                 |

Abbreviations: T1-T6, training 1-6; FU, follow-up-assessment; V0-V9, visits 0-9; CERAD Plus, The Consortium to Establish a Registry for Alzheimer's Disease, neuropsychological test battery, German version, extended to CERAD Plus with the Trail Making Test A + B and Phonematic Fluency (S-Words); tDCS, transcranial direct current stimulation; PANAS, positive and negative affect schedule. All measures were acquired on site or at the respective participants home, except for screening which was done via telephone. \*assessed only at the end of each training week (V4 and V7).

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3 615 **Figure Legend**  
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5 616 **Figure 1.** TrainStim-Home study flowchart. *tDCS*, transcranial direct current stimulation.  
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For peer review only

**Recruitment** via flyers  
distribution and newspaper articles

**Telephone screenings** for eligibility criteria  
If criteria are met, invitation for Baseline

**Baseline assessment**  
neuropsychological testing, training task,  
supervised mock training of the intervention

**Stratified Randomization**  
(n = 30)

Allocation of n = 15 to  
**Anodal tDCS group**

Allocation of n = 15 to  
**Sham tDCS group**

**Pre-assessment**  
training task, untrained task, questionnaires,  
supervised mock training of the intervention

**2-week intervention**  
tDCS, training task, questionnaires

**Post-assessment**  
training task, untrained task,  
questionnaires

**Follow-up (1 month)**  
training task, untrained task, questionnaires

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page no.             |
|-----------------------------------|---------|--|-----------------------------------|
| <b>Administrative information</b> |         |  |                                   |
| 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   | 1, 3                              |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | Yes (available under NCT04817124) |
| Protocol version                  | 3       | Date and version identifier  | 3                                 |
| Funding                           | 4       | Sources and types of financial, material, and other support  | 18                                |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | 1                                 |
|                                   | 5b      | Name and contact information for the trial sponsor   | 18                                |
|                                   | 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 | n/a                               |
|                                   | 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)                         | n/a                               |
| <b>Introduction</b>               |         |  |                                   |
| 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   | 4, 5, 6                           |
|                                   | 6b      | Explanation for choice of comparators  | 4, 5, 6                           |
| Objectives                        | 7       | Specific objectives or hypotheses  | 5, 6, 9                           |
| 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)  | 6, 11, 12                         |

**Methods: Participants, interventions, and outcomes**

|    |                      |     |  |                     |
|----|----------------------|-----|--|---------------------|
| 1  |                      |     |  |                     |
| 2  | 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   | 9, 10               |
| 3  |                      |     |  |                     |
| 4  |                      |     |  |                     |
| 5  | 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)   | 6, 7                |
| 6  |                      |     |  |                     |
| 7  |                      |     |  |                     |
| 8  |                      |     |  |                     |
| 9  | Interventions        | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered   | 7, 8, 13            |
| 10 |                      |     |  |                     |
| 11 |                      | 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)   | 16                  |
| 12 |                      |     |  |                     |
| 13 |                      | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)  | 13, 14              |
| 14 |                      |     |  |                     |
| 15 |                      | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial  | 8, 13, 14           |
| 16 |                      |     |  |                     |
| 17 |                      |     |  |                     |
| 18 |                      |     |  |                     |
| 19 | 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 | 9                   |
| 20 |                      |     |  |                     |
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| 28 |                      |     |  |                     |
| 29 | 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)   | 9, 10, 11, Figure 1 |
| 30 |                      |     |  |                     |
| 31 |                      |     |  |                     |
| 32 |                      |     |  |                     |
| 33 | 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  | 11                  |
| 34 |                      |     |  |                     |
| 35 |                      |     |  |                     |
| 36 |                      |     |  |                     |
| 37 | Recruitment          | 15  | Strategies for achieving adequate participant enrolment to reach target sample size  | 11                  |
| 38 |                      |     |  |                     |
| 39 |                      |     |  |                     |
| 40 |                      |     |  |                     |
| 41 |                      |     |  |                     |

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

#### Allocation:

|    |                                  |     |  |        |
|----|----------------------------------|-----|--|--------|
| 44 | 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 | 11, 12 |
| 45 |                                  |     |  |        |
| 46 |                                  |     |  |        |
| 47 |                                  |     |  |        |
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| 49 |                                  |     |  |        |
| 50 |                                  |     |  |        |
| 51 | 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  | 11,12  |
| 52 |                                  |     |  |        |
| 53 |                                  |     |  |        |
| 54 |                                  |     |  |        |
| 55 |                                  |     |  |        |
| 56 |                                  |     |  |        |
| 57 | Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | 12     |
| 58 |                                  |     |  |        |
| 59 |                                  |     |  |        |
| 60 |                                  |     |  |        |

|    |   |     |  |               |
|----|---|-----|--|---------------|
| 1  |   |     |  |               |
| 2  | Blinding  | 17a | Who will be blinded after assignment to interventions (eg, trial       | 12            |
| 3  | (masking)   |     | participants, care providers, outcome assessors, data analysts),       |               |
| 4  |   |     | and how  |               |
| 5  |   | 17b | If blinded, circumstances under which unblinding is permissible,       | n/a           |
| 6  |   |     | and procedure for revealing a participant's allocated intervention     |               |
| 7  |   |     | during the trial   |               |
| 8  |   |     |  |               |
| 9  | <b>Methods: Data collection, management, and analysis</b> |     |  |               |
| 10 | Data  | 18a | Plans for assessment and collection of outcome, baseline, and          | 12, 13, Table |
| 11 | collection  |     | other trial data, including any related processes to promote data      | 1             |
| 12 | methods   |     | quality (eg, duplicate measurements, training of assessors) and        |               |
| 13 |   |     | a description of study instruments (eg, questionnaires,                |               |
| 14 |   |     | laboratory tests) along with their reliability and validity, if known. |               |
| 15 |   |     | Reference to where data collection forms can be found, if not in       |               |
| 16 |   |     | the protocol   |               |
| 17 |   | 18b | Plans to promote participant retention and complete follow-up,         | 13, 14        |
| 18 |   |     | including list of any outcome data to be collected for participants    |               |
| 19 |   |     | who discontinue or deviate from intervention protocols                 |               |
| 20 | Data  | 19  | Plans for data entry, coding, security, and storage, including any     | 14, 15        |
| 21 | management  |     | related processes to promote data quality (eg, double data             |               |
| 22 |   |     | entry; range checks for data values). Reference to where details       |               |
| 23 |   |     | of data management procedures can be found, if not in the              |               |
| 24 |   |     | protocol   |               |
| 25 | Statistical   | 20a | Statistical methods for analysing primary and secondary                | 16, 17        |
| 26 | methods   |     | outcomes. Reference to where other details of the statistical          |               |
| 27 |   |     | analysis plan can be found, if not in the protocol                     |               |
| 28 |   | 20b | Methods for any additional analyses (eg, subgroup and adjusted         | 17            |
| 29 |   |     | analyses)  |               |
| 30 |   | 20c | Definition of analysis population relating to protocol non-            | 16, 17        |
| 31 |   |     | adherence (eg, as randomised analysis), and any statistical            |               |
| 32 |   |     | methods to handle missing data (eg, multiple imputation)               |               |
| 33 |   |     |  |               |
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| 35 |   |     |  |               |
| 36 |   |     |  |               |
| 37 |   |     |  |               |
| 38 |   |     |  |               |
| 39 | <b>Methods: Monitoring</b>                                |     |  |               |
| 40 | Data  | 21a | Composition of data monitoring committee (DMC); summary of             | n/a           |
| 41 | monitoring  |     | its role and reporting structure; statement of whether it is           |               |
| 42 |   |     | independent from the sponsor and competing interests; and              |               |
| 43 |   |     | reference to where further details about its charter can be found,     |               |
| 44 |   |     | if not in the protocol. Alternatively, an explanation of why a DMC     |               |
| 45 |   |     | is not needed  |               |
| 46 |   | 21b | Description of any interim analyses and stopping guidelines,           | n/a           |
| 47 |   |     | including who will have access to these interim results and            |               |
| 48 |   |     | make the final decision to terminate the trial                         |               |
| 49 | Harms   | 22  | Plans for collecting, assessing, reporting, and managing               | 16            |
| 50 |   |     | solicited and spontaneously reported adverse events and other          |               |
| 51 |   |     | unintended effects of trial interventions or trial conduct             |               |
| 52 | Auditing  | 23  | Frequency and procedures for auditing trial conduct, if any, and       | n/a           |
| 53 |   |     | whether the process will be independent from investigators and         |               |
| 54 |   |     | the sponsor  |               |
| 55 |   |     |  |               |
| 56 |   |     |  |               |
| 57 |   |     |  |               |
| 58 |   |     |  |               |
| 59 | <b>Ethics and dissemination</b>                           |     |  |               |
| 60 |   |     |  |               |

|    |                               |     |   |          |
|----|-------------------------------|-----|---|----------|
| 1  | Research ethics approval      | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 17, 18   |
| 2  |                               |     |   |          |
| 3  |                               |     |   |          |
| 4  |                               |     |   |          |
| 5  | 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)  | 18       |
| 6  |                               |     |   |          |
| 7  |                               |     |   |          |
| 8  |                               |     |   |          |
| 9  |                               |     |   |          |
| 10 | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | 10,18    |
| 11 |                               |     |   |          |
| 12 |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | n/a      |
| 13 |                               |     |   |          |
| 14 |                               |     |   |          |
| 15 |                               |     |   |          |
| 16 | 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  | 14,15,18 |
| 17 |                               |     |   |          |
| 18 |                               |     |   |          |
| 19 |                               |     |   |          |
| 20 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | 19       |
| 21 |                               |     |   |          |
| 22 |                               |     |   |          |
| 23 | 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   | 18       |
| 24 |                               |     |   |          |
| 25 |                               |     |   |          |
| 26 | 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   | n/a      |
| 27 |                               |     |   |          |
| 28 |                               |     |   |          |
| 29 | 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 | 18       |
| 30 |                               |     |   |          |
| 31 |                               |     |   |          |
| 32 |                               |     |   |          |
| 33 |                               |     |   |          |
| 34 |                               |     |   |          |
| 35 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | n/a      |
| 36 |                               |     |   |          |
| 37 |                               |     |   |          |
| 38 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | 18       |
| 39 |                               |     |   |          |
| 40 |                               |     |   |          |
| 41 | <b>Appendices</b>             |     |   |          |
| 42 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | n/a      |
| 43 |                               |     |   |          |
| 44 |                               |     |   |          |
| 45 | 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  | n/a      |
| 46 |                               |     |   |          |
| 47 |                               |     |   |          |
| 48 |                               |     |   |          |

\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Feasibility of Cognitive Training in Combination With Transcranial Direct Current Stimulation in a Home-based Context (TrainStim-Home) – Study Protocol for a Randomized Controlled Trial

|                                 |   |
|---------------------------------|---|
| Journal:                        | <i>BMJ Open</i>   |
| Manuscript ID                   | bmjopen-2021-059943.R1  |
| Article Type:                   | Protocol  |
| Date Submitted by the Author:   | 04-Apr-2022   |
| Complete List of Authors:       | Thams, Friederike; Universitätsmedizin Greifswald<br>Rocke, Merle; Universitätsmedizin Greifswald<br>Malinowski, Robert; Universitätsmedizin Greifswald<br>Nowak, Rafal; University of California San Francisco, Department of Neurology; Neuroelectrics Barcelona SL<br>Grittner, Ulrike; Berlin Institute of Health at Charite; Berlin Institute of Health Institute of Biometry and Clinical Epidemiology<br>Antonenko, Daria; Universitätsmedizin Greifswald, Neurology<br>Flöel, Agnes; Universitätsmedizin Greifswald; German Centre for Neurodegenerative Diseases |
| <b>Primary Subject Heading</b>: | Neurology   |
| Secondary Subject Heading:      | Neurology   |
| Keywords:                       | NEUROLOGY, PREVENTIVE MEDICINE, Clinical trials < THERAPEUTICS  |
|                                 |   |

SCHOLARONE™  
Manuscripts



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2  
3 **1 Feasibility of Cognitive Training in Combination With Transcranial Direct**  
4 **2 Current Stimulation in a Home-based Context (TrainStim-Home) – Study**  
5 **3 Protocol for a Randomized Controlled Trial**  
6  
7

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10 7

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45 36 \* Contributed equally  
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50 38 Word count: 5026  
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## 39 **Abstract**

40 **Introduction:** With the worldwide increase of life expectancy leading to a higher proportion of older  
41 adults experiencing age-associated deterioration of cognitive abilities, the development of effective  
42 and widely accessible prevention and therapeutic measures has become a priority and challenge for  
43 modern medicine. Combined interventions of cognitive training and transcranial direct current  
44 stimulation (tDCS) have shown promising results for counteracting age-associated cognitive decline.  
45 However, access to clinical centers for repeated sessions is challenging, particularly in rural areas and  
46 for older adults with reduced mobility, and lack of clinical personnel and hospital space prevents  
47 extended interventions in larger cohorts. A home-based and remotely supervised application of tDCS  
48 would make the treatment more accessible for participants and relieve clinical resources. So far,  
49 studies assessing feasibility of combined interventions with a focus on cognition in a home-based  
50 setting are rare. With this study, we aim to provide evidence for the feasibility and the effects of a  
51 multi-session home-based cognitive training in combination with tDCS on cognitive functions of  
52 healthy older adults.

53 **Methods and analysis:** The TrainStim-Home trial is a monocentric, randomized, double-blind,  
54 placebo-controlled study. Thirty healthy participants, aged 60 to 80 years, will receive two weeks of  
55 combined cognitive training and anodal tDCS over left dorsolateral prefrontal cortex (dlPFC, target  
56 intervention), compared with cognitive training plus sham stimulation. The cognitive training will  
57 comprise a letter updating task, and the participants will be stimulated for 20 min with 1.5 mA. The  
58 intervention sessions will take place at the participants' home and primary outcome will be the  
59 feasibility, operationalized by 2/3 successfully completed sessions per participant. Additionally,  
60 performance in the training task and an untrained task will be analyzed.

61 **Ethics and dissemination:** Ethical approval was granted by the ethics committee of the  
62 University Medicine Greifswald. Results will be available through publications in peer-reviewed  
63 journals and presentations at national and international conferences.

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3 64 **Trial registration:** The study was registered prospectively on 26 March 2021 at ClinicalTrials.gov with  
4  
5 65 the Identifier: NCT04817124.  
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8 66

9  
10 67 **Keywords:** home use, neuromodulation, working memory, transfer, executive function, brain  
11  
12 68 stimulation, behavioral intervention, multi-session  
13

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15  
16 70 **Strengths and limitations of this study**

- 17  
18 71 - This is the first trial to investigate the feasibility of self-application of cognitive training  
19  
20 72 combined with tDCS in older adults  
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22 73 - We implement thorough training of older adults in handling devices and materials, and  
23  
24 74 collect structured feedback on satisfaction with procedures from participants, to obtain  
25  
26 75 successful delivery of the intervention and high adherence rates  
27  
28 76 - A possible selection bias towards technical experienced participants may occur, as due to  
29  
30 77 remote connection requirements we can only include participants with an internet access in  
31  
32 78 their homes  
33  
34 79 - A more comprehensive training program including tasks from multiple cognitive domains (in  
35  
36 80 contrast to the one task trained in this study) could possibly show more general behavioral  
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38 81 effects. Nonetheless, for the primary purpose of assessing feasibility, our planned training  
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40 82 regimen is well justified.  
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## 83 **Background**

84 With the worldwide increase of life expectancy [1], an increasing proportion of older adults will  
85 experience age-associated deterioration of cognitive abilities which will lead, in addition to individual  
86 suffering, to social and health economic strains [2, 3]. Thus, investigation of non-invasive  
87 interventions to counteract cognitive decline and restore impaired functions, such as combined  
88 cognitive training and transcranial direct current stimulation (tDCS) protocols, is particularly relevant  
89 [4-7]. In general, combined approaches of training and tDCS have been shown to elicit immediate  
90 effects on cognitive abilities, transfer to untrained domains, and long-term effects, which persisted  
91 up to several months [8-12]. Executive functions, including working memory, are especially prone to  
92 age-related decline [13]. Brain regions implicated primarily in these functions, including the  
93 prefrontal cortex and associated functional networks, have shown to be sensitive to age-related  
94 changes such as cortical atrophy and functional reorganization [14-16]. Research combining training  
95 of executive functions with tDCS over the dorsolateral prefrontal cortex provided promising, but  
96 highly variable, results so far [8-12, 17]. Mechanistically, tDCS is thought to additionally boost the  
97 effect of cognitive training by supporting already ongoing brain activity in task-related neural  
98 areas[10, 18]. Possible underlying physiological mechanisms are tDCS-induced alterations of resting  
99 membrane potentials and long-term potentiation via glutamatergic neurotransmission[19-21].  
100 However, multi-session interventions of combined cognitive training and tDCS involve frequent visits  
101 to the facility, which requires high compliance and motivation from the participants, especially from  
102 participants living in rural areas with no easy access to research facilities or from adults that are  
103 limited in their mobility due to advanced age or comorbidities. Additionally, the facilities need space  
104 and personnel to administer the intervention, which puts further limits on interventions applied over  
105 multiple sessions in large cohorts. In light of promising results of combined cognitive training and  
106 tDCS interventions in an outpatient clinic, or laboratory environment [8-12], translation to remotely-  
107 controlled self-administration in a home-based context would be the next necessary step for a widely  
108 accessible intervention, requiring feasible and easy-to handle intervention protocols.

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3 109 Remotely-controlled tDCS enables the trained staff to monitor the intervention from a distance, for  
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5 110 example from the hospital (e.g., by tracking the completed sessions, the quality, length, and any  
6  
7 111 problems during the sessions remotely or via direct phone contact) [22]. The devices for the  
8  
9 112 stimulation are programmed specifically for home-based use before being handed over to the  
10  
11 113 participants. This programming only allows a pre-defined strength and length of the stimulation,  
12  
13 114 thereby ensuring the safety of the participants [22]. Two recent reviews, of 22 studies and 24 studies  
14  
15 115 respectively, of home-based tDCS interventions without cognitive training have given a positive  
16  
17 116 outlook on feasibility and possibly effectiveness of home-based tDCS in a number of cognitive  
18  
19 117 functions in various patient populations [22]. So far, studies that investigated home-use tDCS for the  
20  
21 118 treatment of diseases such as trigeminal neuralgia, vascular-related dementia, or multiple sclerosis,  
22  
23 119 showed that a remote application of tDCS at home could lead to an improvement in symptoms [23-  
24  
25 120 25]. As the participants were, however, mostly young adults, and most of the studies focused on  
26  
27 121 effectiveness, research on the feasibility of home-based tDCS in older adults is particularly relevant.  
28  
29 122 Previous home-based tDCS studies with a wide age range reported a large variance in the level of the  
30  
31 123 participant's commitment. Dropout rates ranged from 4% only [26] to high rates of 41% [25]. An  
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33 124 easy, self-explanatory application, good communication, and unsolicited support in keeping the  
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35 125 participants engaged seem to be key factors for higher adherence rates [22, 26, 27].  
36  
37 126 Thus, research assessing the feasibility of a combined home-based cognitive training and tDCS  
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39 127 approach is needed. Compared to home-use tDCS feasibility trials published so far, a combined  
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41 128 approach poses a bigger challenge for participants in terms of assembly of the study materials and  
42  
43 129 execution of the stimulation and behavioral task, especially in an older population, who is often less  
44  
45 130 experienced in handling of technical devices and software [22]. To our knowledge there is only one  
46  
47 131 previous feasibility study of a combined home-based tDCS and training intervention, i.e. an  
48  
49 132 intervention where participants performed the training as well as the stimulation on their own. What  
50  
51 133 turned out to be particularly important is a detailed training and guidance on the practical aspect of  
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53 134 this approach, as well as readily available support via telephone and regular contact with the study  
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3 135 team to keep participants engaged and to prevent drop-out out of frustration [28]. In contrast to the  
4  
5 136 present study, in their exploratory feasibility analysis, Maceira et al. included five participants of  
6  
7 137 younger age (51-68 years) than in the present trial and focused their home-based approach on  
8  
9 138 learning in the motor domain. Consequently, the requirements for setting up the equipment differ  
10  
11 139 from our trial and an older cohort may have difficulties in handling the technical equipment. Our  
12  
13 140 study will thus add to the already identified aspects by systematically assessing feasibility of a  
14  
15 141 cognitive training and tDCS approach in the form of a clinical feasibility trial in a larger cohort of older  
16  
17 142 adults [29]. Nonetheless, when well instructed on how to administer the intervention, the  
18  
19 143 effectiveness of the combined approach and the possibility of participating from home could serve as  
20  
21 144 a motivator for long-term adherence. Moreover, a combined approach of training and concurrent  
22  
23 145 tDCS, will control for the participants' activity during stimulation compared to previous home-based  
24  
25 146 trials administering solely tDCS[30].  
26  
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28  
29 147 In the TrainStim-Home study, we will therefore investigate the feasibility (primary) and the effects on  
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31 148 cognitive function of home-based cognitive training and tDCS in a monocentric, randomized, double-  
32  
33 149 blind, placebo-controlled design. We will assess feasibility and behavioral outcome measures, such as  
34  
35 150 direct training effects, transfer to untrained domains and performance sustainability for one month.  
36  
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38  
39 151 We hypothesize that with appropriate instruction and close supervision via remote cloud system and  
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41 152 phone, the use of combined cognitive training and tDCS (or sham) in an ecologically valid  
42  
43 153 environment (i.e., at the participant's home) by the participants themselves is feasible (i.e., the  
44  
45 154 participants complete 2/3 of the home-based sessions successfully (primary outcome) and achieve a  
46  
47 155 high score in a feasibility questionnaire at post-assessment). For assessment of feasibility, both  
48  
49 156 groups will be included in the analysis. With regard to behavioral outcomes, the purpose of the  
50  
51 157 present study is to collect data on direct training performance, transfer to untrained domains and  
52  
53 158 performance sustainability for one month, in order to inform planning (e. g., power analysis) of  
54  
55 159 future, definitive randomized controlled trials in older adults. This protocol, describing the design and  
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3 160 methods of the TrainStim-Home study, was prepared in accordance with the SPIRIT guidelines [31,  
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5 161 32] and in adherence with the CONSORT extension to randomized pilot and feasibility trials [29].  
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## 163 **METHODS: Participants, intervention, and outcomes**

### 164 **Design and setting**

165 This is a monocentric, randomized, double-blind, placebo-controlled study to evaluate the feasibility  
166 and effectiveness of a two-week combined cognitive training and tDCS intervention administered by  
167 participants themselves. Participants will accomplish a letter updating task over six training sessions  
168 (3 per week) with concurrent tDCS over the left dorsolateral prefrontal cortex (dlPFC) administered  
169 by the participants themselves in their own home. Half of the study cohort will receive anodal tDCS  
170 while performing the cognitive training, whereas the other half will undergo sham stimulation during  
171 training. The intervention will take place at the participants' home. Additionally, pre- and post-  
172 assessments will be carried out at the University Medicine Greifswald. A follow-up assessment will  
173 follow one month after the intervention to assess possible long-term effects. In total, participants  
174 will complete 10 sessions. A flowchart of the study is shown in Figure 1.  
175

### 176 **Eligibility criteria**

177 Before randomization, participants eligible for the study must meet all the following criteria:

- 178 • Age: 60-80 years
- 179 • Right-handedness
- 180 • Internet access at the home of the participants
- 181 • Performance in neuropsychological screening at baseline within normal range (defined as  
182 performance of each subtest within -1.5 standard deviations (SD) from the normative  
183 samples mean) [33, 34].

184 In case one or more of the following criteria are present at randomization, potential participants will  
185 be excluded:

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3 186 • Mild cognitive impairment (MCI), subjective cognitive decline (SCD), or dementia  
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5 187 (participants reporting decline in cognitive functions or performing below -1.5 SD in any  
6  
7 188 neuropsychological screening subtest will be excluded).  
8  
9  
10 189 • Other neurodegenerative neurological illnesses, epilepsy or history of seizures, close  
11  
12 190 relatives with epilepsy or history of seizures; previous stroke.  
13  
14 191 • Severe untreated medical conditions that preclude participation in the training, as  
15  
16 192 determined by responsible physician  
17  
18  
19 193 • History of severe alcoholism or use of drugs  
20  
21 194 • Severe psychiatric disorders such as depression (if not in remission) or psychosis  
22  
23  
24 195 • Contraindication to tDCS application [35].  
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27  
28 197 If all eligibility criteria are met and participants provide written informed consent, they will be  
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30 198 included in the study sample.  
31

32 199

## 34 200 **Intervention**

36 201 At each training session, participants will participate in a cognitive training with concurrent  
37  
38 202 administration of either anodal or sham stimulation. Participants will be presented with a letter  
39  
40 203 updating task ([LU task, cf. 5, 36]) on a tablet computer. This task targets working memory updating.  
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42 204 The letters A to D will be presented one letter at a time in random order, and with differing list  
43  
44 205 lengths (5, 7, 9, 11, 13 or 15 letters, six times each; total of 36 lists). After the presentation of each  
45  
46 206 list (presentation duration 2000ms, ISI 500ms), the participants will be asked to recall the last four  
47  
48 207 letters that were presented. With a list length of 36 lists, participants are expected to complete the  
49  
50 208 task in about 20-25 minutes, simultaneously to the stimulation. The letter updating task will be the  
51  
52 209 only task trained by the participants in this study. A more comprehensive training program including  
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54 210 tasks from multiple cognitive domains (in contrast to the one task trained in this study) could  
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3 211 possibly show more general behavioral effects [37, 38]. Nonetheless, for the primary purpose of  
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5 212 assessing feasibility, our planned training regimen is well justified.  
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10 214 tDCS will be administered via a battery-operated stimulator (Starstim Home, Neuroelectronics,  
11  
12 215 Barcelona, Spain). Two sponge-based electrodes (Sponstim, NE026, Neuroelectronics, Barcelona, Spain)  
13  
14 216 will be mounted on the head in a neoprene cap using the 10-20 EEG grid. The anodal electrode will  
15  
16 217 be placed over the left dlPFC, in the position of F3, the cathodal electrode will be placed over the  
17  
18 218 right orbita in the Fp2 position. In preparation for the independent electrode mounting done by the  
19  
20 219 participants over the intervention period (working memory training and tDCS), the participants will  
21  
22 220 be trained on the positioning and mounting of the cap with additional care. To ensure correct  
23  
24 221 assembly, the two electrode positions in the neoprene head-cap are color coded, matching the  
25  
26 222 respective colored cables to connect the electrodes with the device. During the training to assemble  
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28 223 the set-up, the electrode positions in the cap and on the head will be checked by study staff. For this  
29  
30 224 purpose, study staff will identify the 10-20 EEG system Cz position (vertex) by measuring half-way  
31  
32 225 distances between nasion and inion and pre-auricular points and check whether the cap is correctly  
33  
34 226 placed. Together with the participants, individual markers to find the correct positioning of the cap  
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36 227 on the head will be identified (e.g., the rim of the cap has to be aligned with the eyebrows). This  
37  
38 228 hands-on approach using caps with pre-defined electrode positions is suited for at home use by  
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40 229 participants and allows for precise electrode placement in a non-lab environment [28]. A current of  
41  
42 230 1.5 mA will be applied for 20 min, with 20 additional seconds of ramping in the beginning and at the  
43  
44 231 end of the stimulation. In the sham group, the current will only be applied for 30 sec in total at the  
45  
46 232 beginning of the 20 min, to elicit the typical tingling sensation of stimulation on the scalp and to blind  
47  
48 233 the participants regarding their stimulation condition. Ramp times and montage will be equivalent to  
49  
50 234 the anodal stimulation group. The cognitive training task and the stimulation will be started  
51  
52 235 simultaneously. Every three sessions, thus twice over the intervention time, participants will be  
53  
54 236 asked to complete an adverse events questionnaire [35]. At each training session, the participants  
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3 237 will be asked to fill in a questionnaire regarding self-reported well-being, quality and duration of  
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5 238 sleep as well as potential stressors in the last two hours prior to the session. They will also be asked  
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7 239 to complete the German version of the Positive and Negative Affect Schedule [PANAS, 39], both  
8  
9 240 before and after the session. Participants will be asked to avoid excessive consumption of alcohol  
10  
11 241 and nicotine on the day of the intervention, and one day prior. Furthermore, they will be instructed  
12  
13 242 to avoid excessive caffeine consumption, i.e. more than the usual amount for the participant, and if  
14  
15 243 possible forgo caffeine 90 min before a session and adhere to their regular sleep schedule.  
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### 21 245 **Outcome measures**

22  
23 246 Feasibility will be assessed directly after the intervention. Outcome measures of the training task will  
24  
25 247 be acquired at each visit. Additionally, at pre-, post- and follow-up assessments outcomes for  
26  
27 248 possible transfer effects will be acquired. All outcome measures and assessment time points are  
28  
29 249 displayed in Table 1. Each outcome measure will be analyzed regarding potential differences  
30  
31 250 between intervention groups (anodal vs. sham tDCS).  
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### 34 251 **Primary outcomes**

35  
36 252 Primary outcome measure will be the feasibility of home-based tDCS as operationalized by at least  
37  
38 253 2/3 of successfully performed interventional sessions per participant for at least 60 % of all  
39  
40 254 participants (corresponding to the lower bound of 95 % confidence interval, see section Sample size).  
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42 255 A session is considered successful when its registered as fully completed in the cloud and the  
43  
44 256 participant has not initiated contact concerning a problem or rescheduling. The thresholds were  
45  
46 257 chosen based on previous reports of dropout rates of up to 41 % in self-administered tDCS studies  
47  
48 258 [25, 40]. The criterion for the amount of successfully performed sessions per participant is based on  
49  
50 259 the idea that the induction of behaviorally relevant effects requires completion off a certain training  
51  
52 260 amount. Additionally, an overall high dropout rate of participants would indicate the need for  
53  
54 261 additional initial instructions and further training of setting-up and performing the intervention, or  
55  
56 262 changes in the usability of the set-up. Thus, our thresholds were set considering to not be too  
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3 263 conservative (taking into account the high dropout rates found by previous studies), but nonetheless  
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5 264 maintain a level that would allow to infer feasibility.

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10 266 **Secondary outcomes**

11  
12 267 Feasibility will further be measured by questionnaire and analyzed as a secondary outcome. A single-  
13  
14 268 item self-rate questionnaire on participant satisfaction, independence and self-confidence in the  
15  
16 269 handling of the devices and program [adapted from 26], see supplementary material for feasibility  
17  
18 270 questionnaire) will be filled out by the participants. Feasibility will be assumed, if at least 60 % of all  
19  
20 271 participants rated to “agree” or “strongly agree” (i.e., 4 or 5 on 5-point Likert scale) on the  
21  
22 272 questionnaire item assessing overall satisfaction with the tDCS and training equipment. Additionally,  
23  
24 273 working memory performance in the trained task will be assessed at each session, operationalized by  
25  
26 274 number of correctly recalled lists in the letter updating task[41]. Performance in the untrained task  
27  
28 275 (n-back) will be assessed as secondary outcome at post- and follow-up assessments, operationalized  
29  
30 276 by percentage of correct answers the sensitivity measure d-prime [42].  
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36 278 **Participant timeline**

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39 279 Participants will have to adhere to 10 sessions over the course of the study. Baseline and pre-  
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41 280 assessment (V1, V2) will take place at the University Medicine Greifswald, the training sessions (V3-  
42  
43 281 V8) will take place at the participants’ own home during two consecutive weeks on 3 days a week.  
44  
45 282 The first of the training sessions will be accompanied by a study investigator, the following five  
46  
47 283 sessions will be performed independently and tracked via a cloud system. After the training, post-  
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49 284 assessment (V9) will be conducted immediately and follow-up assessment will be administered four  
50  
51 285 weeks later, both at the University Medicine Greifswald.  
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56 287 **Baseline measures**  
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3 288 At baseline assessment, the study and its execution will be explained to the participant by a member  
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5 289 of the study staff. Subsequently, the participants will be asked to provide written informed consent  
6  
7 290 and a demographic interview will be carried out. This interview will be followed by a comprehensive  
8  
9 291 battery of neuropsychological tests to quantify cognitive function on different domains, including the  
10  
11 292 CERAD-Plus test battery [43]. Additionally, handedness will be assessed with the Oldfield Handedness  
12  
13 293 Questionnaire (to exclude variance due to functional hemispheric asymmetries and therefore ensure  
14  
15 294 consistent organization of the targeted brain areas)[44]. Possible depressive symptoms will be  
16  
17 295 explored with the Geriatric Depression Scale [45].  
18  
19 296 Following the tests and questionnaires, an instructional video explaining the assembly, disassembly,  
20  
21 297 handling and care of the devices and of the supplies for the stimulation will be shown to the  
22  
23 298 participants. Any questions and critical points will be discussed with a staff member. The participant  
24  
25 299 will then be asked to replicate the assembly and disassembly of an interventional session with the  
26  
27 300 help of a checklist and the study staff, and subsequently perform the training task as described  
28  
29 301 above. At baseline assessment, the training task will include 25 lists (36 lists at training sessions) and  
30  
31 302 a practice trial with four lists will be performed.  
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#### 39 304 **Pre-, post- and follow-up-assessments**

40  
41 305 Self-reported well-being, quality and duration of sleep as well as potential stressors in the last two  
42  
43 306 hours prior to the visit will be assessed in the form of a semi-structured interview. Then, the  
44  
45 307 participants will complete the working memory training task (LU task [36]) and a working memory  
46  
47 308 task that will not be trained (n-back task [42]). At pre-assessment participants will additionally be  
48  
49 309 instructed once more in the handling of the stimulation set. The feasibility questionnaire will be  
50  
51 310 completed at post-assessment.  
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#### 57 312 **Sample size**

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3 313 As the primary goal of this study will be to assess feasibility, and as it is recommended to employ results  
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5 314 of feasibility trials for sample size calculation of a planned subsequent trial [46], we chose a sample  
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7 315 size of  $N = 30$  [47]. To infer feasibility, the lower bound of the 95 % confidence interval of the  
8  
9  
10 316 proportion of participants who fulfilled the feasibility criterion needs to be at 60 %. Thus, 76 %, i.e.,  $n$   
11  
12 317 = 23 participants will have to meet the feasibility criterion.

13  
14 318 With 15 participants per stimulation group (anodal vs. sham stimulation), we will be able to able to  
15  
16 319 scope the general feasibility of this home-based intervention, and will be able to plan follow-up trails  
17  
18 320 accordingly. Additionally, we will be able to explore descriptively the benefit of anodal tDCS over sham  
19  
20 321 with regard to performance after the training on the trained and untrained working memory tasks to  
21  
22 322 obtain estimates of effect sizes for power calculations of future randomized controlled trials[48, 49].  
23  
24 323 Using an independent t-test with a two-sided significance level of 0.05 and a power of 80 % we will be  
25  
26 324 able to demonstrate an effect of Cohen's  $d = 1.06$  or higher on behavioral performance.  
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## 31 326 **Recruitment**

32  
33 327 Participants will be recruited via adverts in the local newspaper and via the distribution of flyers at  
34  
35 328 senior and adult education centers, local shops, restaurants and museums. All potential participants  
36  
37 329 will be provided with information about the study over the phone, and a screening assessing  
38  
39 330 exclusion and inclusion criteria will be carried out. All eligible participants will be invited for baseline  
40  
41 331 assessment.  
42  
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45 332

## 46 333 **METHODS: Assignment of interventions**

47  
48 334 Allocation to anodal and sham tDCS group will be performed using stratified block randomization.  
49  
50 335 Participants will be randomly allocated by a researcher not involved in assessments. Allocation to the  
51  
52 336 experimental groups (anodal vs. sham) will be performed with a 1:1 ratio with age (two age strata;  
53  
54 337 60-70, 71-80) and cognitive performance at baseline assessment ( $\leq 5$ ,  $> 5/25$  corrects lists in the LU  
55  
56 338 task). Randomization blocks with varying block sizes will be generated for each of the four groups,  
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2  
3 339 using R software (<http://www.R-project.org>) and the blockrand package ([https://CRAN.R-](https://CRAN.R-project.org/package=blockrand)  
4  
5 340 [project.org/package=blockrand](https://CRAN.R-project.org/package=blockrand)). Participants will then be allocated to anodal or sham tDCS group,  
6  
7 341 based on the generated randomization sequences within each block and stratum.  
8  
9

10 342

### 11 343 **Blinding**

12 344 In this double-blind trial, both investigators and study participants and investigators will be blinded  
13  
14 345 regarding the stimulation condition. The two stimulation protocols (anodal, sham) will be labeled  
15  
16 346 with unidentifiable labels such as A and B. A staff member not involved in data collection will  
17  
18 347 perform the randomization as described above and will subsequently assign the label of the  
19  
20 348 stimulation protocol accordingly to each participant. The investigator will schedule stimulation  
21  
22 349 sessions for each participant individually via a cloud-system. This investigator will select the labeled  
23  
24 350 protocol that corresponds to the participants ID number and will be able to plan the stimulation  
25  
26 351 without knowledge of the respective stimulation condition. Thus, study staff performing cognitive  
27  
28 352 assessments will be blinded to the stimulation condition. As for participant blinding, study  
29  
30 353 participants will only be able to use the device if a stimulation session with given duration and  
31  
32 354 current intensity was scheduled beforehand in the online cloud-system. Participants will be unaware  
33  
34 355 whether the session entails active or sham stimulation. In the sham group the current will only be  
35  
36 356 applied at the beginning of the stimulation session for 20 sec ramp-up and -down respectively. This  
37  
38 357 method is used to elicit the typical tingling sensation under the electrodes during the stimulation and  
39  
40 358 to ensure blinding of the participants to the respective stimulation condition. Previous studies have  
41  
42 359 shown that sham tDCS is a safe and valid method of participant-blinding [50-53]. At post-assessment,  
43  
44 360 participants will be asked to state if they believe they received anodal or sham stimulation.  
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## 365 **METHODS: Data collection, management and analysis**

### 366 **Data collection methods**

367 Neuropsychological and behavioral will be collected from each participant. Study investigators will be  
368 thoroughly trained in administering the assessments. Time points of data collection are shown in

#### 369 **Table 1.**

### 370 **Neuropsychological and behavioral assessment**

371 Neuropsychological testing at the baseline visit (V0) will comprise paper-pencil as well as computer-  
372 based assessment. The Geriatric Depression Scale [45] and the Edinburgh Handedness Inventory[44]  
373 will be administered. Cognitive function in different domains will be quantified using a  
374 comprehensive battery of neuropsychological tests including the CERAD (Consortium to Establish a  
375 Registry for Alzheimer's Disease, German version), extended to CERAD-Plus

376 (<https://www.memoryclinic.ch/de/main-navigation/neuropsychologen/cerad-plus/>) with the Trail

377 Making Test A + B and Phonematic Fluency (S-Words)[43], and the digit span test [54].

378 The training and transfer tasks are computer-based. Detailed description of the training task is

379 provided in the intervention section. At pre-, post-, and follow-up-assessment (V2, V9-V10) an

380 untrained task is administered: Participants will perform a numeric n-back task (1 and 2 back) to

381 assess working memory function (18 trials total, 9 trials 1back and 9 trials 2back with 10 items each,

382 presentation duration 1500ms, ISI 2500ms). A sequence of numerical stimuli is presented one after

383 another, and the participants will have to state if the number that is currently presented is identical

384 to the stimulus "n"-steps back.

385 Additionally, at post-assessments, participants will complete a 17-item feasibility questionnaire

386 concerning independence and self-confidence in the handling of the devices and program as well as

387 the participant satisfaction and comfort during the at-home part of the study participation (cf. [26]).

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389

### 390 **Retention and adherence**

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3 391 Participants will be provided with information on their appointments via telephone and if possible via  
4  
5 392 e-mail to maximize retention over the course of the study. A few days prior to pre-assessment,  
6  
7 393 participants will be contacted by a study investigator and will be reminded of the upcoming  
8  
9 394 appointments. A copy of all study appointments will be handed out at pre-assessment. At every  
10  
11 395 appointment and during each phone call, the investigator will actively seek out any open questions  
12  
13 396 and remarks regarding the intervention and will provide assistance accordingly. Furthermore, the  
14  
15 397 online cloud-system, which interacts with the application on the tablet computer, allows the  
16  
17 398 investigators involved in this study to schedule and monitor stimulation sessions individually for each  
18  
19 399 participant. During stimulation and simultaneous performance of the training task, the participant  
20  
21 400 will be able to abort the stimulation at any time via button press, if necessary. After the completion  
22  
23 401 of the task, the stimulation will be turned off automatically, and information on whether the session  
24  
25 402 was completed or not will be transferred to the cloud-system, to be checked by the investigator.  
26  
27 403 Additionally, three investigators will be notified automatically via e-mail alert about any reported  
28  
29 404 adverse events or problems. In such case, participants will be contacted immediately. At the end of  
30  
31 405 each day, study staff will check the cloud system and participants will then be contacted if anything is  
32  
33 406 out of the ordinary. The participants will be reminded that their progress will be monitored closely  
34  
35 407 through the cloud-system and that they should not hesitate to contact the investigator in case  
36  
37 408 problems or questions arise. For acute problems participants will be made aware of the study mobile  
38  
39 409 phone number and the office telephone number. If no contact is initiated by the participant, they will  
40  
41 410 be contacted by the day of their sixth training sessions. To assist the participant in solving problems,  
42  
43 411 the investigator has the possibility to remotely control the tablet computer. Participants will be  
44  
45 412 encouraged to use the 24/7 study answering machine or write an email to the study's email address  
46  
47 413 if they cannot attend a visit and want to reschedule. They will then be contacted by a member of the  
48  
49 414 study team as soon as possible. At the end of the study, i.e. at follow-up assessment, participants will  
50  
51 415 receive a financial reimbursement of 130 € and a report about their neuropsychological test  
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3 416 performance. If for whatever reason complete adherence is not possible, an effort will be made to  
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5 417 collect as much data as possible from the respective participant.  
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10 419 **Data management and monitoring**

11  
12 420 All collected data will be pseudonymized. Paper-based data such as questionnaires and the scoring  
13  
14 421 sheets of the neuropsychological test will be stored in lockable cabinets in rooms with restricted  
15  
16 422 access, sorted by participant ID for easy access at each stage of the study. Data acquired on paper  
17  
18 423 will be manually digitalized by one staff member, and double-checked by another. The progress of  
19  
20 424 data acquirement and digitalization will be documented. All digitally acquired data, such as task  
21  
22 425 output files, will be saved on a secure server and protected with password only known to the staff  
23  
24 426 involved in this project. Protocols of the tDCS stimulation of each participant and session will also be  
25  
26 427 stored on this server. Spreadsheets concerning sensitive data, such as names, addresses and contact  
27  
28 428 information, will be further protected with another password if acquired digitally, and stored in a  
29  
30 429 separate lockable cabinet if in paper form. Following good scientific practice, data will be stored for  
31  
32 430 at least 10 years.  
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39 432 **Patient and public involvement**

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41 433 In order to involve older adults, in December of 2020, we asked five former participants of our  
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43 434 TrainStim-Cog trial ([study protocol, 55]) which comprised a very similar procedure, to participate in  
44  
45 435 trial sessions. During these trial sessions, we simulated the home-based training sessions including  
46  
47 436 the assembly and disassembly of the stimulation set and the handling of the tablet computer. Any  
48  
49 437 difficulties, such as the complicated order of mounting the stimulation equipment, were identified in  
50  
51 438 these trial sessions and were solved by developing further aids, such as a check-list and a detailed  
52  
53 439 instruction manual. Using this check-list and manual, trial participants were then able to mount the  
54  
55 440 stimulation set confidently and correctly. Similarly, we were made aware of the importance of a  
56  
57 441 visual demonstration and consequently filmed an instruction video of 20 min duration, which will be  
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3 442 shown to every participant at baseline assessment and will be available over the treatment period as  
4  
5 443 on-demand video on the tablet computer. Continuing this feedback-based development of the  
6  
7 444 home-based approach during the feasibility trial, we will carry out a semi-structured interview at  
8  
9 445 post-assessment concerning ease of use, opinions and feelings of the participants about the system  
10  
11 446 and of our assistance, as well as concerning perceived challenges with this home-based approach.  
12  
13 447 Information obtained through these interviews will help optimize the trial design for a possible  
14  
15 448 subsequent clinical trial.  
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19 449

#### 20 21 450 **Adverse events monitoring**

22  
23 451 The risk of health damage associated with anodal tDCS is expected to be minimal. Known adverse  
24  
25 452 effects (AEs) with the study parameters (20 min, 1.5 mA) are skin tingling, reddening and occasionally  
26  
27 453 a mild headache. These potential AEs will be monitored after each third stimulation session via an  
28  
29 454 adverse events questionnaire [35]. We will refrain from assessing AEs at every session, as we believe  
30  
31 455 it would only draw the participants' attention to minor sensations during the stimulation and  
32  
33 456 ultimately act as a distractor from the cognitive task. Investigators will be instructed to monitor for  
34  
35 457 and document all AEs and serious AEs throughout the trial. Participants will be informed about  
36  
37 458 possible risks and AEs at baseline assessment and can withdraw consent at any time without  
38  
39 459 providing reason. If a serious AE occurs, the study physician will be consulted and asked to make an  
40  
41 460 assessment whether or not a causal relationship with the intervention is considered possible. If more  
42  
43 461 than three of the enrolled participants suffer from serious AEs that are likely to be associated with  
44  
45 462 the intervention (as assessed by the study physician), the trial will be discontinued.  
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50 463

#### 51 52 464 **Statistical analysis**

53  
54 465 Feasibility data (primary outcome) will be analyzed using descriptive statistics. Feasibility will be  
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56 466 inferred when participants complete at least 2/3 of the home-based sessions successfully. Secondary  
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58 467 feasibility outcomes, as measured by questionnaire will be analyzed similarly. Data distributions of  
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3 468 the questionnaire items will be visually assessed for normality using q-q plots, and statistically using  
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5 469 the Shapiro-Wilk test [47, 56].  
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### 9 471 **Secondary analysis of measures for future RCT**

11 472 Data on behavioral tasks from all participants included at randomization and completed post-  
12  
13 473 assessment will be analyzed within an exploratory framework. Additionally, a subgroup analysis will  
14  
15 474 include only those participants, who successfully completed 2/3 of the home-based sessions (thus  
16  
17 475 fulfilling the criterion for feasibility). In detail, descriptive statistics (i.e., mean and SD) will be  
18  
19 476 reported for the post- and follow-up-assessment working memory score (number of correctly  
20  
21 477 recalled lists in the letter updating task) and outcome measures from the untrained working memory  
22  
23 478 task (% correct and d-prime from the n-back task). As this is a feasibility trial, i.e., not powered for  
24  
25 479 testing hypotheses about effectiveness, group differences between anodal and sham stimulation  
26  
27 480 groups will be calculated reporting means and 95 % confidence intervals [29]. Data analysis will be  
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29 481 conducted using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States), MatLab  
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31 482 (The Mathworks Inc., 2016), and R software.  
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### 39 484 **Ethics and Dissemination**

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41 485 This study was approved by the ethics committee of the University Medicine Greifswald and will be  
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43 486 conducted in accordance with the Helsinki Declaration. All data collected will be pseudonymized. The  
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45 487 results of this study will be made accessible to scientific researchers and health care professionals via  
46  
47 488 publications in peer-reviewed journals and presentations at national and international conferences.  
48  
49  
50 489 Furthermore, the scientific and lay public can access the study results on the ClinicalTrials.gov  
51  
52 490 website (Identifier: NCT04817124).  
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### 55 491 **Trial status**

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58 492 Recruitment of participants has started in April 2021.  
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60 493

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3 494 **Declarations**  
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6 495 **Consent or assent**  
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8 496 A member of the investigational team (study coordinator or study assessor) will collect written  
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10 497 informed consent during study enrollment after having reviewed the participant information sheet,  
11  
12 498 participant's questions, and study inclusion and exclusion criteria.  
13

14  
15 499 **Confidentiality**  
16

17 500 The collected data will be treated as confidential. Direct access to personal information and source  
18  
19 501 data documentation will only be given to study monitors, study assessors, and the research team.  
20

21  
22 502 **Funding**  
23

24 503 Funding for this study was provided by "Bundesministerium für Bildung und Forschung" (FKZ  
25  
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27  
28 505 Research Foundation) Project number 327654276 – SFB 1315 to AF.  
29

30  
31 506 **Availability of data and materials**  
32

33 507 Anonymized data will be made available to the scientific community upon request.  
34

35 508

36  
37 509 **Authors' contributions**  
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39 510 FT, DA and AF conceptualized and designed this trial. AF is supervising its implementation. FT is  
40  
41 511 implementing the trial and supervising its conduct. RN assisted in programming and software  
42  
43 512 development of the home-based stimulation application. RM programmed the training task and  
44  
45 513 implemented it to work with the stimulation application. MR is performing recruitment and  
46  
47 514 assessments. FT and MR drafted the study protocol. UG will be performing statistical analyses. All  
48  
49 515 authors will be contributing to interpretation of the data. All authors read and revised the original  
50  
51 516 draft and consecutive versions of the manuscript. All authors read and approved the final version of  
52  
53 517 the study protocol.  
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3 520 **Ethics approval and consent to participate**  
4

5 521 The study was approved by the ethics committee of the University Medicine Greifswald, Germany

6  
7 522 (BB02 /21, date of first approval: 05 Feb 2021). All procedures conducted during the TrainStim-Home

8  
9  
10 523 trial will be carried out in compliance with the Declaration of Helsinki.

11  
12 524 **Competing interests**  
13

14 525 RN is a part-time employee with NE. The other authors declare no actual or potential conflicts of

15  
16 526 interest.  
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681 **Tables and Figures****Table 1.** *TrainStim-Home outcome measures.*

|                                 |  |                    | Baseline | Pre   | T1-T6<br>(2 weeks) | Post<br>(3 days) | FU<br>(1 month) |
|---------------------------------|--|--------------------|----------|-------|--------------------|------------------|-----------------|
|                                 |  |                    | ~3h      | ~1,5h | ~1h                | ~1,5h            | ~1,5h           |
| Time point                      | Measurement                                  | Mode               | V0       | V1    | V2-V7              | V8               | V9              |
| <b>Enrollment</b>               |  |                    |          |       |                    |                  |                 |
| Eligibility screening           |  | Paper              | x        |       |                    |                  |                 |
| Informed consent                |  | Paper              | x        |       |                    |                  |                 |
| Neuropsychological<br>Screening | Demographic data                             | Paper              | x        |       |                    |                  |                 |
|                                 | Geriatric depression<br>scale[45]            | Paper              | x        |       |                    |                  |                 |
|                                 | Oldfield<br>handedness<br>inventory[44]      | Paper              | x        |       |                    |                  |                 |
|                                 | CERAD Plus[43]                               | Paper              | x        |       |                    |                  |                 |
|                                 | Digit Span[54]                               | Paper              | x        |       |                    |                  |                 |
| <b>Intervention</b>             |  |                    |          |       |                    |                  |                 |
| Training task                   | Letter<br>updating[5, 36]                    | Tablet<br>computer | x        | x     | x                  | x                | x               |
| Brain stimulation               | tDCS (anodal vs.<br>sham)                    | Device             |          |       | x                  |                  |                 |
| Questionnaires                  | Self-reported<br>well-being<br>questionnaire | Paper              |          | x     | x                  | x                | x               |
|                                 | PANAS[39]                                    | Paper              |          |       | x                  |                  |                 |
|                                 | Adverse events<br>questionnaire[35]*         |                    |          |       | x                  |                  |                 |
| <b>Additional assessments</b>   |  |                    |          |       |                    |                  |                 |
| Untrained task                  | n-back[42]                                   | Computer           |          | x     |                    | x                | x               |
| Feasibility                     | Sessions completed<br>(primary outcome)      | Cloud<br>system    |          |       | x                  | x                |                 |
|                                 | Feasibility<br>questionnaire                 | Paper              |          |       |                    | x                |                 |

Abbreviations: T1-T6, training 1-6; FU, follow-up-assessment; V0-V9, visits 0-9; CERAD Plus, The Consortium to Establish a Registry for Alzheimer's Disease, neuropsychological test battery, German version, extended to CERAD Plus with the Trail Making Test A + B and Phonematic Fluency (S-Words); tDCS, transcranial direct current stimulation; PANAS, positive and negative affect schedule. All measures were acquired on site or at the respective participants home, except for screening which was done via telephone. \*assessed only at the end of each training week (V4 and V7).

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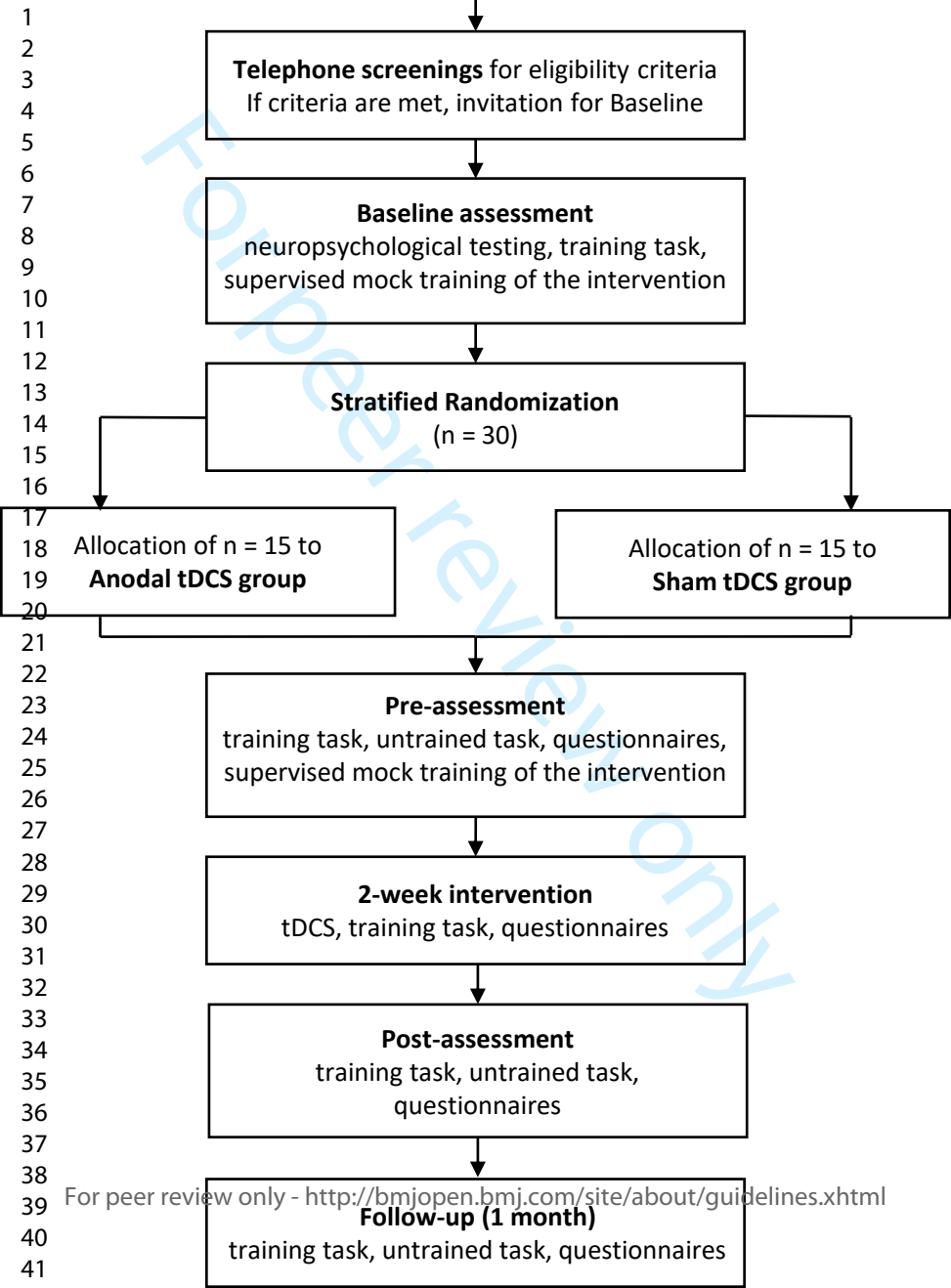
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684 **Figure 1.** TrainStim-Home study flowchart. *tDCS*, transcranial direct current stimulation.

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TS4-OG-\_\_\_\_\_

Feasibility

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### Machbarkeits-Fragebogen

Bitte lesen Sie sich die nachfolgenden Aussagen sorgfältig durch und kreuzen Sie an wie sehr diese Aussagen auf Sie und Ihre Erfahrungen bei den Trainingssitzungen zutreffen!

|  | Trifft zu                | Trifft eher zu           | Neutral                  | Trifft eher nicht zu     | Trifft nicht zu          |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Es war insgesamt einfach dieses Stimulationsset zu verwenden.                    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Es war einfach den Stimulator zu verwenden.                                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Es war einfach das Tablet zu verwenden.  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Es war einfach das Stimulator-Zubehör (Kappe, Elektroden, etc.) zu verwenden.    | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Ich habe mich bei der Vorbereitung der Trainingssitzungen sicher gefühlt.        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Es ist mir schwergefallen, die Trainingssitzungen vorzubereiten.                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Ich konnte die Trainingssitzungen gut in meinen Alltag integrieren.              | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Die Trainingssitzungen haben meinen Alltagsablauf gestört.                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Ich wurde ausreichend persönlich betreut und geschult.                           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Mehr persönliche Betreuung und Schulung hätte mir geholfen.                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Wenn ein Problem aufgetreten ist, konnte ich dieses insgesamt gut lösen.         | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Das Problem war mithilfe des Tablets gut zu lösen.                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Das Problem war mithilfe des Manuals gut zu lösen.                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Das Problem war mithilfe der telefonischen Betreuung gut zu lösen.               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Insgesamt glaube ich, dass ich von der elektrischen Stimulation profitiert habe. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

TS4-OG-\_\_\_\_\_

Feasibility

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|  | Sehr selbstsicher                     | Selbstsicher                               | Neutral                             | Unsicher   | Sehr Unsicher                               |
|--|---------------------------------------|--|-------------------------------------|--|---|
| Wie selbstsicher schätzen Sie sich bei der Durchführung der Trainingssitzungen ohne Kontrolle und Hilfestellung durch ein*e Studienmitarbeiter*in ein? | <input type="checkbox"/>              | <input type="checkbox"/>                   | <input type="checkbox"/>            | <input type="checkbox"/>                         | <input type="checkbox"/>                    |
| Zusammengefasst bin ich zufrieden mit diesem Stimulationsset.  | Trifft zu<br><input type="checkbox"/> | Trifft eher zu<br><input type="checkbox"/> | Neutral<br><input type="checkbox"/> | Trifft eher nicht zu<br><input type="checkbox"/> | Trifft nicht zu<br><input type="checkbox"/> |
| Haben Sie noch Kommentare oder Wünsche?  |                                       |  |                                     |  |   |

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## CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial\*

| Section/Topic                    | Item No | Checklist item  | Reported on page No |
|----------------------------------|---------|---|---------------------|
| <b>Title and abstract</b>        |         |   |                     |
|                                  | 1a      | Identification as a pilot or feasibility randomised trial in the title  | 1                   |
|                                  | 1b      | Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)   | 2                   |
| <b>Introduction</b>              |         |   |                     |
| Background and objectives        | 2a      | Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial  | 1-7                 |
|                                  | 2b      | Specific objectives or research questions for pilot trial   | 6                   |
| <b>Methods</b>                   |         |   |                     |
| Trial design                     | 3a      | Description of pilot trial design (such as parallel, factorial) including allocation ratio  | 7                   |
|                                  | 3b      | Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons  | n/a                 |
| Participants                     | 4a      | Eligibility criteria for participants   | 7-8                 |
|                                  | 4b      | Settings and locations where the data were collected  | 7                   |
|                                  | 4c      | How participants were identified and consented  | 13                  |
| Interventions                    | 5       | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered   | 8-10                |
| Outcomes                         | 6a      | Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed                                | 10-11               |
|                                  | 6b      | Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons  | n/a                 |
|                                  | 6c      | If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial   | 10                  |
| Sample size                      | 7a      | Rationale for numbers in the pilot trial  | 13                  |
|                                  | 7b      | When applicable, explanation of any interim analyses and stopping guidelines  | n/a                 |
| Randomisation:                   |         |   |                     |
| Sequence generation              | 8a      | Method used to generate the random allocation sequence  | 13-14               |
|                                  | 8b      | Type of randomisation(s); details of any restriction (such as blocking and block size)  | 13-14               |
| Allocation concealment mechanism | 9       | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 13-14               |

|   |     |   |        |
|---|-----|---|--------|
| Implementation  | 10  | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions   | 13-14  |
| Blinding  | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how  | 13-14  |
|   | 11b | If relevant, description of the similarity of interventions   | 14     |
| Statistical methods   | 12  | Methods used to address each pilot trial objective whether qualitative or quantitative  | 15     |
| <b>Results</b> <i>(not applicable as the present work is a study protocol)</i>    |     |   |        |
| Participant flow (a diagram is strongly recommended)                              | 13a | For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective | n/a    |
|   | 13b | For each group, losses and exclusions after randomisation, together with reasons  | n/a    |
| Recruitment   | 14a | Dates defining the periods of recruitment and follow-up   | n/a    |
|   | 14b | Why the pilot trial ended or was stopped  | n/a    |
| Baseline data   | 15  | A table showing baseline demographic and clinical characteristics for each group  | n/a    |
| Numbers analysed  | 16  | For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group  | n/a    |
| Outcomes and estimation   | 17  | For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group        | n/a    |
| Ancillary analyses  | 18  | Results of any other analyses performed that could be used to inform the future definitive trial  | n/a    |
| Harms   | 19  | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)   | n/a    |
|   | 19a | If relevant, other important unintended consequences  | n/a    |
| <b>Discussion</b> <i>(not applicable as the present work is a study protocol)</i> |     |   |        |
| Limitations   | 20  | Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility   | n/a    |
| Generalisability  | 21  | Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies   | n/a    |
| Interpretation  | 22  | Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence                                   | n/a    |
|   | 22a | Implications for progression from pilot to future definitive trial, including any proposed amendments   | n/a    |
| <b>Other information</b>  |     |   |        |
| Registration  | 23  | Registration number for pilot trial and name of trial registry  | 3 / 19 |
| Protocol  | 24  | Where the pilot trial protocol can be accessed, if available  | n/a    |
| Funding   | 25  | Sources of funding and other support (such as supply of drugs), role of funders   | 20     |
|   | 26  | Ethical approval or approval by research review committee, confirmed with reference number  | 19     |



1 Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.  
 2 \*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important  
 3 clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological  
 4 treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).  
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page no.             |
|-----------------------------------|---------|--|-----------------------------------|
| <b>Administrative information</b> |         |  |                                   |
| 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   | 1, 3                              |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | Yes (available under NCT04817124) |
| Protocol version                  | 3       | Date and version identifier  | 3                                 |
| Funding                           | 4       | Sources and types of financial, material, and other support  | 20                                |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | 1                                 |
|                                   | 5b      | Name and contact information for the trial sponsor   | 20                                |
|                                   | 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 | n/a                               |
|                                   | 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)                         | n/a                               |
| <b>Introduction</b>               |         |  |                                   |
| 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   | 4, 5, 6, 7                        |
|                                   | 6b      | Explanation for choice of comparators  | 4, 5, 6, 7                        |
| Objectives                        | 7       | Specific objectives or hypotheses  | 6, 10                             |
| 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)  | 7, 12, 13                         |

**Methods: Participants, interventions, and outcomes**

|    |                      |     |  |                  |
|----|----------------------|-----|--|------------------|
| 1  |                      |     |  |                  |
| 2  | 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   | 7                |
| 3  |                      |     |  |                  |
| 4  |                      |     |  |                  |
| 5  | 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)   | 7, 8             |
| 6  |                      |     |  |                  |
| 7  |                      |     |  |                  |
| 8  |                      |     |  |                  |
| 9  | Interventions        | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered   | 8, 9, 10, 12     |
| 10 |                      |     |  |                  |
| 11 |                      | 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)   | 18               |
| 12 |                      |     |  |                  |
| 13 |                      | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)  | 15, 16           |
| 14 |                      |     |  |                  |
| 15 |                      | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial  | 15, 16           |
| 16 |                      |     |  |                  |
| 17 |                      |     |  |                  |
| 18 |                      |     |  |                  |
| 19 | 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 | 10, 11           |
| 20 |                      |     |  |                  |
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| 29 | 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)   | 11, 12, Figure 1 |
| 30 |                      |     |  |                  |
| 31 |                      |     |  |                  |
| 32 |                      |     |  |                  |
| 33 | 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  | 12               |
| 34 |                      |     |  |                  |
| 35 |                      |     |  |                  |
| 36 |                      |     |  |                  |
| 37 | Recruitment          | 15  | Strategies for achieving adequate participant enrolment to reach target sample size  | 13               |
| 38 |                      |     |  |                  |
| 39 |                      |     |  |                  |
| 40 |                      |     |  |                  |

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

#### Allocation:

|    |                                  |     |  |        |
|----|----------------------------------|-----|--|--------|
| 44 | 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 | 13, 14 |
| 45 |                                  |     |  |        |
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| 51 | 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  | 13,14  |
| 52 |                                  |     |  |        |
| 53 |                                  |     |  |        |
| 54 |                                  |     |  |        |
| 55 |                                  |     |  |        |
| 56 |                                  |     |  |        |
| 57 | Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | 13, 14 |
| 58 |                                  |     |  |        |
| 59 |                                  |     |  |        |
| 60 |                                  |     |  |        |

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|----|---|-----|--|-------------|
| 1  |   |     |  |             |
| 2  | Blinding  | 17a | Who will be blinded after assignment to interventions (eg, trial       | 14          |
| 3  | (masking)   |     | participants, care providers, outcome assessors, data analysts),       |             |
| 4  |   |     | and how  |             |
| 5  |   | 17b | If blinded, circumstances under which unblinding is permissible,       | n/a         |
| 6  |   |     | and procedure for revealing a participant's allocated intervention     |             |
| 7  |   |     | during the trial   |             |
| 8  |   |     |  |             |
| 9  | <b>Methods: Data collection, management, and analysis</b> |     |  |             |
| 10 | Data  | 18a | Plans for assessment and collection of outcome, baseline, and          | 12, 13, 14, |
| 11 | collection  |     | other trial data, including any related processes to promote data      | Table 1     |
| 12 | methods   |     | quality (eg, duplicate measurements, training of assessors) and        |             |
| 13 |   |     | a description of study instruments (eg, questionnaires,                |             |
| 14 |   |     | laboratory tests) along with their reliability and validity, if known. |             |
| 15 |   |     | Reference to where data collection forms can be found, if not in       |             |
| 16 |   |     | the protocol   |             |
| 17 |   | 18b | Plans to promote participant retention and complete follow-up,         | 15, 16      |
| 18 |   |     | including list of any outcome data to be collected for participants    |             |
| 19 |   |     | who discontinue or deviate from intervention protocols                 |             |
| 20 | Data  | 19  | Plans for data entry, coding, security, and storage, including any     | 17          |
| 21 | management  |     | related processes to promote data quality (eg, double data             |             |
| 22 |   |     | entry; range checks for data values). Reference to where details       |             |
| 23 |   |     | of data management procedures can be found, if not in the              |             |
| 24 |   |     | protocol   |             |
| 25 |   | 20a | Statistical methods for analysing primary and secondary                | 18, 19      |
| 26 | Statistical   |     | outcomes. Reference to where other details of the statistical          |             |
| 27 | methods   |     | analysis plan can be found, if not in the protocol                     |             |
| 28 |   | 20b | Methods for any additional analyses (eg, subgroup and adjusted         | 19          |
| 29 |   |     | analyses)  |             |
| 30 |   | 20c | Definition of analysis population relating to protocol non-            | 18, 19      |
| 31 |   |     | adherence (eg, as randomised analysis), and any statistical            |             |
| 32 |   |     | methods to handle missing data (eg, multiple imputation)               |             |
| 33 |   |     |  |             |
| 34 |   |     |  |             |
| 35 |   |     |  |             |
| 36 |   |     |  |             |
| 37 |   |     |  |             |
| 38 |   |     |  |             |
| 39 | <b>Methods: Monitoring</b>                                |     |  |             |
| 40 | Data  | 21a | Composition of data monitoring committee (DMC); summary of             | n/a         |
| 41 | monitoring  |     | its role and reporting structure; statement of whether it is           |             |
| 42 |   |     | independent from the sponsor and competing interests; and              |             |
| 43 |   |     | reference to where further details about its charter can be found,     |             |
| 44 |   |     | if not in the protocol. Alternatively, an explanation of why a DMC     |             |
| 45 |   |     | is not needed  |             |
| 46 |   | 21b | Description of any interim analyses and stopping guidelines,           | n/a         |
| 47 |   |     | including who will have access to these interim results and            |             |
| 48 |   |     | make the final decision to terminate the trial                         |             |
| 49 | Harms   | 22  | Plans for collecting, assessing, reporting, and managing               | 18          |
| 50 |   |     | solicited and spontaneously reported adverse events and other          |             |
| 51 |   |     | unintended effects of trial interventions or trial conduct             |             |
| 52 | Auditing  | 23  | Frequency and procedures for auditing trial conduct, if any, and       | n/a         |
| 53 |   |     | whether the process will be independent from investigators and         |             |
| 54 |   |     | the sponsor  |             |
| 55 |   |     |  |             |
| 56 |   |     |  |             |
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| 59 | <b>Ethics and dissemination</b>                           |     |  |             |
| 60 |   |     |  |             |

|    |                               |     |   |        |
|----|-------------------------------|-----|---|--------|
| 1  | Research ethics approval      | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 19     |
| 2  |                               |     |   |        |
| 3  |                               |     |   |        |
| 4  |                               |     |   |        |
| 5  | 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)  | 19     |
| 6  |                               |     |   |        |
| 7  |                               |     |   |        |
| 8  |                               |     |   |        |
| 9  |                               |     |   |        |
| 10 | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | 12, 19 |
| 11 |                               |     |   |        |
| 12 |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | n/a    |
| 13 |                               |     |   |        |
| 14 |                               |     |   |        |
| 15 |                               |     |   |        |
| 16 | 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  | 14,17  |
| 17 |                               |     |   |        |
| 18 |                               |     |   |        |
| 19 |                               |     |   |        |
| 20 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | 21     |
| 21 |                               |     |   |        |
| 22 |                               |     |   |        |
| 23 | 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   | 20     |
| 24 |                               |     |   |        |
| 25 |                               |     |   |        |
| 26 | 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   | n/a    |
| 27 |                               |     |   |        |
| 28 |                               |     |   |        |
| 29 | 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 | 19     |
| 30 |                               |     |   |        |
| 31 |                               |     |   |        |
| 32 |                               |     |   |        |
| 33 |                               |     |   |        |
| 34 |                               |     |   |        |
| 35 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | n/a    |
| 36 |                               |     |   |        |
| 37 |                               |     |   |        |
| 38 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | 19     |
| 39 |                               |     |   |        |
| 40 |                               |     |   |        |
| 41 | <b>Appendices</b>             |     |   |        |
| 42 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | n/a    |
| 43 |                               |     |   |        |
| 44 |                               |     |   |        |
| 45 | 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  | n/a    |
| 46 |                               |     |   |        |
| 47 |                               |     |   |        |
| 48 |                               |     |   |        |

\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.