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Group Cognitive Behavioural Therapy with Virtual Reality Exposure vs Group Cognitive Behavioural Therapy with In Vivo Exposure for Social Anxiety Disorder and Agoraphobia: A Randomized Clinical Trial

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8 2 **Group Cognitive Behavioural Therapy with Virtual Reality**

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11 3 **Exposure vs Group Cognitive Behavioural Therapy with In**

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15 4 **Vivo Exposure for Social Anxiety Disorder and Agoraphobia:**

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19 5 **A Randomized Clinical Trial**
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20 Abstract

21 **Introduction** Anxiety disorders have a high lifetime prevalence, early-onset, and long duration or
22 chronicity. Exposure therapy is considered one of the most effective elements in cognitive
23 behavioral therapy (CBT) for anxiety, but *in vivo* exposure can be challenging to access and control,
24 and is sometimes rejected by patients because they consider it too aversive. Virtual reality allows
25 flexible and controlled exposure to challenging situations in an immersive and protected
26 environment. **Aim** The SoREAL-trial aims to investigate the effect of group cognitive-behavioral
27 therapy (*CBT-in vivo*) versus group cognitive behavioral therapy with virtual reality exposure (*CBT-*
28 *in virtuo*) for patients diagnosed with social anxiety disorder and/or agoraphobia, in mixed groups.

29 **Methods & Analysis** The design is an investigator-initiated randomized, assessor-blinded, parallel-
30 group and superiority-designed clinical trial. Three hundred two patients diagnosed with social
31 anxiety disorder and/or agoraphobia will be included from the regional mental health centers of
32 Copenhagen and North Sealand and the Northern Region of Denmark. All patients will be offered a
33 manual-based 14-week cognitive behavioral group treatment program, including eight sessions with
34 exposure therapy. Therapy groups will be centrally randomized with concealed allocation sequence
35 to either *CBT-in virtuo* or *CBT-in vivo*. Patients will be assessed at baseline, post-treatment and
36 one-year follow-up by treatment blinded researchers and research assistants. The primary outcome
37 will be diagnosis-specific symptoms measured with the Liebowitz Social Anxiety Scale for patients
38 with social anxiety disorder and the Mobility Inventory for Agoraphobia for patients with
39 agoraphobia. Secondary outcome measures will include depression symptoms, social functioning,
40 and patient satisfaction. Exploratory outcomes will be substance and alcohol use, working alliance
41 and quality of life. **Ethics and dissemination:** The trial has been approved by the research ethics
42 committee in the Capital Region of Denmark. All results, positive, negative as well as inconclusive,
43 will be published as quickly as possible and still in concordance with Danish law on the protection

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4 44 of confidentially and personal information. Results will be presented at national and international
5
6 45 scientific conferences. **Trial registration:** The project was registered at clinicaltrials.gov on
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9 46 02/19/2019 as NCT03845101. Can be found online at
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11 47 <https://clinicaltrials.gov/ct2/show/NCT03845101>
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16 49 Article Summary

20 50 Strengths and limitations of this study

- 22 51 • The present study will be the first large randomized clinical trial to investigate virtual reality
23
24 52 exposure therapy for social anxiety disorder and agoraphobia in group therapy.
- 26 53 • The present study is very closely integrated with clinical practice, making results highly
27
28
29 54 transferable to similar real-life settings.
- 31 55 • Mixing patients with social anxiety disorder and agoraphobia in the same therapy groups
32
33 56 have never been investigated systematically, which may confound the interpretation of
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36 57 results.
- 38 58 • Because the study is embedded in an outpatient hospital setting, the intervention was
39
40 59 designed to be flexible. This increases the ecological validity but also the risk of systematic
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43 60 bias in treatment administration.

46 61 Keywords

49 62 Virtual Reality Exposure Therapy, Social Anxiety Disorder, Agoraphobia, Cognitive Behavioral
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51 63 Therapy, Randomized Clinical Trial.

54 64 Word Count

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65 Background

66 Social anxiety disorder is characterized by paying attention to oneself in an exaggerated manner and
67 having marked fear of being negatively evaluated by other people [1,2]. Agoraphobia is
68 characterized by avoidance or enduring with dread, situations in which escape is perceived difficult
69 or where help might not be available in the event of a panic attack, panic-like symptoms or
70 incapacitating symptoms such as loss of bladder and/or bowel control [1,3]. Both social anxiety
71 disorder and agoraphobia are associated with marked functional consequences [1]. In Denmark,
72 anxiety disorders represent the costliest disease burden in terms of lost production, due to their early
73 onset, long duration and high prevalence [4].

74 The first-line treatment for social anxiety disorder and agoraphobia is cognitive-behavioral therapy
75 (CBT) with exposure therapy [5,6]. Several meta-analyses have found that patients with social
76 anxiety disorder and agoraphobia respond well to CBT with exposure therapy, provided in
77 individual as well as group format [7–10]. Exposure therapy aims to change expectations and
78 emotional responses associated with feared stimuli, by exposing the patient to the stimuli and
79 challenging the patients' expectancies of the likelihood and consequences of a feared outcome [11].
80 However, in clinical practice, in-vivo exposure stimuli can be difficult to access and control and
81 patients or therapists sometimes reject the treatment, because they consider it too aversive or too
82 logistically demanding [12–14].

83 **Virtual Reality Exposure Therapy for Social Anxiety Disorder and Agoraphobia**

84 Virtual Reality (VR) technology allows the user to experience virtually mediated environments that
85 are perceived as real or almost real, due to multisensory stimulation and blocking of real-world
86 sensory input. Numerous possibilities for psychological intervention using VR are currently being
87 researched owing to its immersive quality [15,16]. As a therapy tool, VR is most widely used to

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4 88 perform Virtual Reality Exposure Therapy (VRET) [16,17], either as a standalone treatment, e.g.
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6 89 [18], or integrated into a CBT treatment e.g. [19].
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10 90 The use of VR allows flexible and controlled exposure to challenging situations in an immersive
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12 91 and safe environment. Therefore, using VRET can mitigate the challenges of in-vivo exposure
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14 92 therapy by producing greater user acceptance and access to situations that would otherwise be too
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16 93 difficult to control, too resource-intensive to find and/or have unacceptable confidentiality risks
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18 94 [15,19,20]. Based on this, VRET may improve the efficacy and cost-effectiveness of
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20 95 psychotherapeutic interventions for anxiety disorders.
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24 96 Recent reviews and meta-analysis of VRET either as a standalone treatment or combined with
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26 97 cognitive interventions, conclude that VRET is more effective than waitlist and placebo control and
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28 98 equally as effective as first-line treatment controls for anxiety disorders [21–23]. However, in one
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30 99 meta-analysis, the authors find significantly worse treatment effects of VRET for social anxiety
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32 100 disorder, when compared with control groups that received equal amounts of in-vivo exposure [24].
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36 101 It has been suggested that it is more difficult to produce VRET environments for social anxiety
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38 102 disorder, as compared to other phobic disorders because human interaction is complex and therefore
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40 103 difficult to realistically recreate [25] which may explain these results. Accordingly, the same meta-
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42 104 analysis found no significant difference in treatment efficacy for CBT with VRET vs CBT with in-
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44 105 vivo exposure for agoraphobia and specific phobia [24].
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48 106 In general, there is a scarcity of high-quality randomized clinical trials (RCT) evaluating the use of
49
50 107 VRET for social anxiety disorder and agoraphobia [16,26,27]. For social anxiety disorder, there are
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52 108 five trials published, the largest having 97 participants [28,19,18,29,30]. For agoraphobia, there are
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54 109 six trials published, the largest having 80 participants [31–36]. All in all, the evidence-base for
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110 using VRET compared to in-vivo exposure for social anxiety disorder and agoraphobia remain
111 small. Therefore, larger studies that capitalize on the unique qualities of VRET are needed.

112 **Virtual Reality Exposure in Group Therapy**

113 VRET has never been investigated in a group format. Group therapy for social anxiety disorder and
114 agoraphobia is popular in outpatient settings because it has similar treatment efficacy [37–39] and is
115 proposed to have better cost-efficiency, compared to individual therapy [37,39]. However, the claim
116 of cost-efficiency for social anxiety disorder is disputed, at least in a UK mental healthcare setting
117 [40]. Beyond that, therapeutic interpersonal processes such as peer learning and modeling as been
118 suggested to be a distinct benefit of group therapy [41,42], though this has never been
119 systematically evaluated for mixed anxiety groups. A suggested drawback of group CBT compared
120 with individual CBT is that in-vivo exposure in group therapy is restrained by the logistics of
121 managing several patients simultaneously, leading to comparatively less individualized exposure
122 exercises [43,44].

123 The use of VRET in group therapy may therefore be especially beneficial, since it should allow for
124 individualized exposure, as well as a greater amount of exposure therapy because less time will be
125 spent on logistical issues (transport, planning, waiting, etc.), whilst at the same time retaining the
126 proposed benefits of the therapeutic interpersonal processes and cost-efficiency.

127 **Treatment of social anxiety disorder and agoraphobia in the Danish mental health system**

128 In the Danish mental health services, patients with social anxiety disorder or agoraphobia as their
129 primary diagnosis, are generally offered group CBT. To reduce wait time, patients with these
130 diagnoses are treated in the same therapy groups, generally referred to as “mixed anxiety groups” or
131 “phobia groups”. These mixed anxiety groups are considered to be as effective as diagnosis-specific
132 groups, due to the overlap in symptoms and diagnostic criteria [45], high degree of comorbidity

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4 133 [46], as well as recent evidence of the acceptable treatment efficacy of CBT-based transdiagnostic
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6 134 therapies [47].
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10 135 However, it is worth noting, that the pragmatic mixed anxiety group format has never been
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12 136 systematically evaluated and that the official treatment recommendation remain diagnoses specific
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14 137 CBT delivered in group or individually [48]. To maximize the study's clinical representitativenes, as
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16 138 defined by Shadish et al. [49], the treatment structure in the present study, including the comperator,
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19 139 will mimic the treatment offered by the Danish mental health services.
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22 140 **Aim and objectives:**

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25 141 In summary in-vivo exposure is considered effective, but can be challenging to perform. Virtual
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27 142 Reality Exposure therapy may alleviate these challenges. However, the usefulness of VRET for
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30 143 social anxiety disorder and agoraphobia remains unclear. Larger studies that capitalize on the
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32 144 benefits of VRET are needed. Group therapy may be one way to capitalize on the benefits of VRET
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34 145 because it could allow for more individualized exposure exercises. Mixed anxiety groups are
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37 146 commonly used in Danish mental healthcare to reduce wait time, but have not been systematically
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39 147 evaluated. The treatment, inclusion and exclusion criteria described in the present study match the
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41 148 eligibility criteria for treatment and treatment format of the Danish mental healthcare system to
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44 149 maximize transferability of results to clinical practice.
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47 150 Therefore, the SoREAL trial aims to evaluate the treatment efficacy of VRET in mixed anxiety
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49 151 CBT groups (CBT-in virtuo) compared to mixed anxiety CBT groups where exposure therapy is
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51 152 performed in-vivo (CBT-*in vivo*).
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54 153 Thus, in the SoREAL trial, the following hypotheses' will be tested:
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58 154 Primary hypothesis:
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4 155 1. Post-treatment, patients treated with CBT-*in virtuo* will have a lower level of anxiety
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6 156 symptoms compared to patients treated with CBT-*in vivo*, measured as total scores on the
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9 157 Liebowitz Social Anxiety Scale (LSAS) for patients with social anxiety disorder and the
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11 158 Mobility Inventory for Agoraphobia (MIA) for patients with agoraphobia converted to the
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13 159 percent of maximum possible scores (POMP) and averaged within treatment arms.

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16 160 Secondary hypotheses:

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18 161 1. One year after treatment, patients treated with CBT-*in virtuo* will have lower levels of anxiety
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20 162 symptoms compared to patients treated with CBT-*in vivo*.
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23 163 2. Post-treatment and one year after treatment, patients treated with CBT-*in virtuo* will have lower
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25 164 levels of fear of negative evaluation compared to patients treated with CBT-*in vivo*.

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30 166 Overall, we believe that the SoREAL trial will contribute with knowledge about the efficacy and
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32 167 feasibility of VRE for treating social anxiety disorder and agoraphobia in a clinical outpatient
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34 168 setting. The results of this trial may guide future applications of VR in clinical settings across a
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36 169 wide breadth of use-cases.
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39 170 40 41 42 171 **Methods and design**

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45 172 This article was written in accordance with the SPIRIT (Standard Protocol Items:
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47 173 Recommendations for Interventional Trials) 2013 explanation and elaboration: guidance for
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49 174 protocols of clinical trials [50]. The SPIRIT Checklist was followed and the SPIRIT flowchart was
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52 175 used [See Additional file 1 and Figure 1].
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54 176 **Recruitment**

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56 177 The SoREAL trial is embedded directly into five outpatient clinics offering group CBT for social
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59 178 anxiety disorder and agoraphobia. These clinics are part of the Danish mental health care system.
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4 179 To be eligible for treatment in these clinics, patients must be referred by their primary care
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7 180 physicians to a Center for Visitation and Diagnosis in their area, where their symptomatology will
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9 181 be assessed. At the Center for Visitation and Diagnosis, they must be referred to one of the five
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11 182 outpatient clinics involved in the study. At the outpatient clinic, the patient will again be clinically
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13 183 assessed, and a diagnosis and treatment plan will be formulated. If social anxiety disorder and/or
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15 184 agoraphobia is considered the primary diagnosis for the patient, they will be asked if they are
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18 185 interested in getting more information about the trial. If they consent to it, their contact details will
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20 186 be given to a researcher, who will invite them to an interview concerning the study.
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25 188 Mini International Neuropsychiatric Interview (MINI), v. 7.0 for DSM-5 will be used to screen for
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27 189 diagnosis. Psychometric analyses of the MINI have demonstrated acceptable test-retest and inter-
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30 190 rater reliability [51,52]. Diagnostic screening is sufficient due to the thorough assessment from both
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32 191 Center for Visitation and Diagnostics and the outpatient clinics which must have confirmed social
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34 192 anxiety disorder or agoraphobia as the primary diagnosis of the patient, for the patient to be eligible
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36 193 for the study. If eligibility is confirmed, informed consent is acquired. Patients that cannot or will
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39 194 not participate in the study will be offered treatment as usual, which is identical to the control group
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41 195 treatment. Inclusion and exclusion criteria were based on the eligibility criteria for receiving the
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43 196 treatment package in Danish outpatient clinics.
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45 197 **Inclusion criteria**

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48 198 1) Fulfilling diagnostic criteria for social anxiety disorder (ICD-code: F40.1) and/or Agoraphobia
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50 199 (ICD-code: 40.0)
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52 200 2) Age 18-75 years
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55 201 3) Sufficient knowledge of the Danish language
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57 202 4) Informed consent
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203 **Exclusion criteria**

204 1) Alcohol or drug dependence (ICD-code: F10-19.20-26).

205 **Feasibility**

206 Five psychotherapeutic outpatient clinics are involved in the study. All patients referred to these
207 clinics with the relevant diagnosis, who also agree to be contacted, will be invited to an interview
208 about their potential participation. Each of the clinics provides treatment for approximately 30
209 patients with social anxiety disorder and/or agoraphobia every year. Thus we anticipate that 450
210 patients will be eligible for the trial during a three-year recruitment period. We expect a high
211 eligibility rate, due to the previously mentioned assessment procedures the patients will have
212 completed. We also expect a high acceptance rate, due to the novel use of VR technology and the
213 use of a control group that is identical to the treatment they would be offered if they refused
214 participation. See Figure 2 for a flow diagram of the SoREAL trial.

215 **Treatment format**

216 The treatment for social anxiety disorder and Agoraphobia offered at the outpatient clinics must
217 follow the national guidelines for the treatment of these disorders. The guidelines are encapsulated
218 in specified “treatment packages”. For social anxiety disorder and agoraphobia, this package
219 contains:

- 220 • 1 hour of assessment
- 221 • 1 hour of individual therapy in preparation for group therapy
- 222 • 1 hour of psychometric testing
- 223 • 14 sessions of 2 hours of group therapy
- 224 • 1.5 hours of next of kin involvement
- 225 • 1 hour of pharmacological treatment planning with a psychiatrist
- 226 • 2.5 hours coordination with social services, relapse prevention and follow-up meetings

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4 227 Not all of this is necessary for every patient, but every patient can receive every part of the package,
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6 228 should they want to. The treatment in the present study must live up to the standards of the national
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9 229 guidelines. Patients are not allowed to be in any other form of psychotherapeutic treatment.
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13 231 The therapeutic intervention is manual-based cognitive-behavioral CBT group therapy adapted from
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16 232 the approach of Turk, Heimberg & Magee [53] and Graskie & Barlow [54] with worksheets from
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18 233 Arendt & Rosenberg [55] and inspiration from Bouchard et al. [56]. The treatment will consist of 14
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20 234 weekly two-hour group sessions following the manual to ensure equal and uniform treatment for
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22
23 235 every patient throughout the study. The manual allows flexibility to ensure clinically representative
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25 236 conditions [49]. E.g. it is allowed to change the order of the sessions if it is considered beneficial for
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27 237 the group and multiple exercises are optional. However, the time dedicated to exposure is fixed in
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30 238 both groups. Concurrent psychopharmacological treatment is allowed in both intervention arms.
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34 240 Groups will consist of 8-9 patients with social anxiety disorder and/or agoraphobia as their primary
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36 241 diagnosis, and every session will be led by two trained clinicians (i.e. psychologists, psychiatrists or
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39 242 psychotherapists) with practical experience in CBT and *in vivo* exposure. Throughout the course of
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41 243 the study, the clinicians involved will treat both *CBT-in vivo* and *CBT-in virtuo* groups. Medical
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43 244 consultation, acute individual sessions, supplementary social counseling and physical therapy, are
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46 245 possible in both intervention arms. In both intervention arms, the sessions dedicated to exposure are
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48 246 scheduled from the fifth to the eleventh session with approximately 45 min of exposure in each
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50 247 session. From the fifth session and onwards, all patients in both interventions will have in-vivo
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53 248 exposure as homework. The cognitive therapy strategies used in the non-exposure sessions (first
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55 249 four and last two therapy sessions) are as follows; (a) introduction to CBT; (b) psychoeducation
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57 250 about anxiety and cognitive restructuring of dysfunctional assumptions and beliefs; (c) shifting self-
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4 251 focused attention and modifying cognitive distortions; (d) developing an understanding of safety
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6 252 behavior and the rationale of exposure; (f) evaluation, discussion and feedback on the use of
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9 253 patient-acquired techniques; and (d) relapse prevention. In both conditions, the exposure exercises
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11 254 aim to develop adaptive responses to anxiety-provoking situations, reinforce cognitive restructuring
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13 255 by framing exercises as behavioral experiments (though these were limited by the non-interactive
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15 256 medium), train attention exercises, train general cognitive strategies (e.g. identifying negative
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17 257 automatic thoughts) and train social skills. See Table 1 and Table 2 for an overview of the content
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20 258 of the CBT sessions for both conditions.
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274 *Table 1. Group Cognitive Behavioural Therapy Manual session overview for Social Anxiety Disorder and*
 275 *Agoraphobia*

Session	Content
Individual session	Case conceptualization. Psychoeducation on CBT. Treatment goal. Introduction to treatment setting.
1	Psychoeducation about anxiety. CBT anxiety model.
2	Psychoeducation about anxiety. Registration of thoughts, feelings, behavior and introduction to cognitive restructuring.
3	Psychoeducation and exercise: Cognitive bias, attention and self-focus. Repetition about Cognitive Restructuring. Attention exercises.
4	Psychoeducation about exposure therapy. Optionally, an introductory exposure exercise.
5	Exposure therapy.
6	Behavioral experiments in exposure exercises.
7	Repetition of the methods presented so far. Additional attention/mindfulness exercise linked to exposure.
8	Conversational skills and small-talk exposure exercises.
9	Introduction to Core beliefs. Additional exposure exercises.
10	Repetition of Core beliefs, resources and skills. Additional exposure exercises.
11	Exposure therapy, out of the clinic.
12	Repetition and evaluation of methods learned/used so far. Revising problem-goal list.
13	Evaluation, discussion and feedback on the different methods used by each patient.
14	Maintenance and relapse prevention; review of skills; review of progress and future goals; plan for continued exposures; relapse prevention strategies.

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4 277 *Table 2. Group Cognitive Behavioural Therapy Manual session overview for Social Anxiety Disorder and*
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6 278 *Agoraphobia with Virtual Reality Exposure Therapy.*
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Session	Content
Individual session	Case conceptualization. Psychoeducation on CBT. Treatment goal. Introduction to treatment setting.
1	Psychoeducation about anxiety. CBT anxiety model.
2	Psychoeducation about anxiety. Registration of thoughts, feelings, behavior and introduction to cognitive restructuring.
3	Psychoeducation and exercise: Cognitive bias, attention and self-focus. Repetition about Cognitive Restructuring. Attention exercises.
4	Psychoeducation about exposure therapy. Introduction to VRET.
5	VRET
6	Behavioral experiments in VRET
7	Repetition of the methods presented so far. Additional attention/mindfulness exercise linked to VRET.
8	Conversational skills and VRET.
9	Introduction to Core beliefs. Additional VRET exercises.
10	Repetition of Core beliefs, resources and skills. Additional VRET exercises.
11	VRET combined with in-vivo out-of-the-clinic exposure exercises.
12	Repetition and evaluation of methods learned/used so far. Revising problem-goal list.
13	Evaluation, discussion and feedback on the different methods used by each patient.
14	Maintenance and relapse prevention; review of skills; review of progress and future goals; plan for continued exposures; relapse prevention strategies.

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4 283 In the *in virtuo* condition, exposure will take place during 8 out of the 14 group sessions, as in the
5
6 284 CBT-*in vivo* condition. Patients will be exposed to VR situations, which are relevant to them, and
7
8
9 285 which they are motivated to engage in. Patients in CBT-*in virtuo* condition will be assigned *in vivo*
10
11 286 exposure homework between sessions in the same way as the CBT-*in vivo* group.

13 287 **Fidelity to the treatment manual**

15
16 288 The intervention is manual-based, which improves the standardization of the treatment. Fidelity to
17
18 289 the treatment manual will be assessed through a self-report questionnaire answered by the clinicians
19
20 290 at five different time points throughout each group treatment. The questionnaire (and the timepoints
21
22 291 whence it is delivered) are designed to correspond to the treatment manual. This type of fidelity
23
24 292 measurement has proved useful and adequate in trials where the effect of treatment is tested [57].

25
26
27 293 The VR headsets will also record statistics of the use of the 360° films. This data shows which
28
29 294 specific scenes were watched and how much and can be matched to the individual patient. This data
30
31 295 will be used to keep track of the VR usage throughout the study to see how well it matches the
32
33 296 treatment manual.

34 297 **Treatment completion and discontinuation**

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36
37 298 Criteria for *treatment completion*, *partial treatment* and *no treatment* were based on clinical
38
39 299 guidelines for writing epicrisis as well as discussions within the research group.

- 40
41 300 • The attendance of ten or more group therapy sessions will be coded as 'treatment
42
43 301 completion'.
- 44
45 302 • The attendance of between four to nine group therapy sessions will be coded as 'partial
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47 303 treatment'.
- 48
49 304 • The attendance of less than four group therapy sessions will be coded as 'no treatment'.
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305 Treatment will be discontinued if participants do not show up to treatment three weeks in a row and
306 cannot be contacted after multiple attempts by the therapists. Participants that have their treatment
307 discontinued will still be included in the statistical analysis.

308 **Virtual reality equipment**

309 The patients receiving the *in virtuo* exposure will be immersed using an Oculus Go head-mounted
310 display, enabling viewing of 360° spherically camera recorded VR environments. The VR scenarios
311 will thus be high-resolution 360° stereoscopic films, that are played around the viewer. For audio,
312 the patients will use high-quality sound-blocking headphones. For ease of use, the individual videos
313 will be administered from an app that has been designed to be as intuitive to operate as possible.

314 The patient will only have to put on the headset, adjust the focus and choose the desired
315 environment by looking at it in the app. 360° video was chosen because it gives the most
316 photorealistic visuals, while also being the cheapest to produce. The downside is that it does not
317 allow direct user-interaction (e.g. the viewer cannot affect the environment in any way). To
318 circumvent this, there are multiple junctions throughout the films where the actors will talk directly
319 and unsolicited to the viewer (e.g. greetings, common questions) while also allowing time for the
320 viewer to respond. The actors respond in a generic way to the actions of the viewer. Unsolicited and
321 direct referral from a virtual environment seems to be an essential factor in triggering realistic
322 responses to it [58]. Though the non-interactability of the environment limits the flexibility of
323 behavioral experiments, it does not make them impossible. E.g., it is still possible to hypothesize
324 about internal states (e.g. “I will clam up if I have to present in front of people”) and identify and
325 challenge negative automatic thoughts.

326 **Virtual Reality scenarios**

327 13 VR exposure scenarios relevant for social anxiety disorder and Agoraphobia were chosen for the
328 *CBT-in virtuo* condition. The 13 scenarios are as follows:

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- 4 329 1) Standing in line in a supermarket
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- 6 330 2) Being in a crowded shopping center
- 7
- 8
- 9 331 3) Attending a party
- 10
- 11 332 4) Attending a formal meeting and giving a presentation
- 12
- 13 333 5) A job interview
- 14
- 15
- 16 334 6) Small talking/discussing in a university canteen with young adults
- 17
- 18 335 7) Small talking/discussing in a canteen in a work setting
- 19
- 20 336 8) Entering an auditorium
- 21
- 22
- 23 337 9) Leaving your apartment
- 24
- 25 338 10) Waiting for- and taking the bus
- 26
- 27 339 11) Crossing a bridge
- 28
- 29
- 30 340 12) Taking an elevator
- 31
- 32 341 13) Taking a commercial airplane
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36 343 Each scenario has four to six scenes of increasing difficulty as well as a neutral scene to familiarize

37

38 patients with the VR setting. All scenes skip to a looping version of a scene in the same

39 344

40 environment after being played, to allow patients to achieve within-session habituation if needed.

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43 346 See additional file 2 for screenshots and descriptions of the individual scenes. All identifiable

44

45 persons depicted in the virtual environments are paid actors.

46 347

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48 348 **Patient and Public Involvement: Development of virtual reality scenarios and manual**

49

50 349 The pilot phase was a continuous iterative process between the developers of the VR media, CBT-

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52 trained clinicians and a panel of patients with social anxiety disorder and/or agoraphobia. The

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54 process lasted approximately 16 months (12 for social anxiety disorder environments and 4 for

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56 agoraphobia) and consisted of regular meetings following each scenario's initial filming wherein the

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353 patients saw the VR scenario in question. Their experience (e.g. anxiety level provoked from the
354 films, the validity of the scenarios) was then used as a starting point for a discussion of further
355 development and alterations to the scenarios. Towards the end of the development of the scenarios
356 and application to launch them, two clinicians tested the usability of VRE in a group format. The
357 clinicians and patients then gave further feedback on the films and the delivery of the exposure in
358 the group. This guided the initial draft for a group CBT manual with VRE for social anxiety
359 disorder and agoraphobia.

360 **Assessment**

361 *Diagnostics*

362 MINI version 7.0 for DSM-5 will be used to screen for diagnosis. At the inclusion interview, all
363 modules but P will be used to assess diagnostic eligibility. At the baseline interview, all modules
364 but P will be used to assess diagnosis and detect comorbidity. At the post-treatment interview, all
365 modules but P will be used to assess diagnosis and detect comorbidity. At the follow-up interview,
366 all modules but P will be used to assess diagnosis and detect comorbidity.

367 *Outcomes and sample size calculation*

368 We originally designed the trial around inclusion of only patients with social anxiety disorder,
369 basing the sample size calculation on the following parameters on the LSAS: With $\alpha=0.05$, 80%
370 power, and an expected standard deviation of 21, 302 patients would be required to detect the
371 minimal relevant difference of 6.8 on the LSAS total score between the groups.

372 Upon deciding to expand the diagnostic criteria for inclusion to also include patients with
373 agoraphobia, it was necessary to change our primary outcome measure. For patients with
374 agoraphobia, we primarily rate symptoms using MIA. To include both patients with social anxiety
375 disorder and patients with agoraphobia, we thus decided to recalculate scores on these two scales to
376 POMP as described below. Since the sample size calculation for LSAS was based on a Cohen's

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4 377 $d=0.33$, we also set the minimum clinically relevant difference on MIA, and by extension on the
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6 378 POMP, to $d=0.33$. Consequently, the required sample size remained unaffected by this change of
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9 379 primary outcome measures and is thus still 302 patients. See Figure 3 for power calculations on
10
11 380 secondary outcomes.

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14 381 Primary outcome:

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16 382 Total scores on the LSAS for patients with social anxiety disorder and the MIA for patients with
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19 383 Agoraphobia measured pre-treatment, post-treatment and at one-year follow-up converted to the
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21 384 POMP and averaged within treatment arms. POMP calculations can bring differently measured
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23 385 items to the same metric and do not change the multivariate distribution and covariance matrix of
24
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26 386 the transformed variables. Therefore, scales transformed with the POMP method can be used to
27
28 387 examine mean-level differences between groups [59–61]. Using POMP transformed scores on two
29
30 388 different measures of phobic anxiety makes it possible to include patients with different primary
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33 389 diagnoses in the same analysis, thus, avoiding the need for approximately double the number of
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35 390 participants to reach a sufficient sample size. The downside of this method is that differences in the
36
37 391 sensitivity of the outcome measures and potential differences in treatment effect between patients
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40 392 with social anxiety disorder and agoraphobia, which has been observed in diagnosis-specific
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42 393 treatment [62], are also averaged out, thus possibly skewing results.

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46 395 Social anxiety disorder symptom severity will be measured using a danish version of the LSAS.

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49 396 LSAS assesses 24 situations typically feared by individuals with social anxiety disorder, rated on
50
51 397 anxiety and avoidance, divided into subscales of performance anxiety and social situations. It has
52
53 398 acceptable psychometric properties [63]. Agoraphobia symptom severity will be measured using a
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55
56 399 danish version of the MIA. The MIA assesses avoidance of 26 situations typically feared by
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4 400 agoraphobic patients [64]. The MIA has demonstrated excellent psychometric properties and has
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6
7 401 been validated in multiple languages, including Swedish [65,66].
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11 403 Secondary outcomes:

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14 404 • Depressive symptoms measured pre-treatment, post-treatment and at follow-up as total scores
15
16 405 on the Hamilton Depression Rating Scale, 6 item version (HAM-6) [67]

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18 406 • Fear of negative evaluation measured pre-treatment, post-treatment and at follow-up with the
19
20
21 407 Brief Version of the Fear of Negative Evaluation Scale (FNES) [68].

22

23 408 • Work and Social Adjustment measured pre-treatment, post-treatment and at follow-up with the
24
25 409 Work and Social Adjustment Scale (WSAS) [69].

26

27 410 • User acceptability and satisfaction of treatment measured post-treatment with the Client

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30 411 Satisfaction Questionnaire (CSQ). The CSQ is an 8-item scale loading to one factor of

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32 412 satisfaction with mental health care service [70].

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34 413 • Quality of Life measured pre-treatment, post-treatment and at follow-up with the WHO Well-
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36
37 414 Being Index, five items (WHO-5). It is considered a very sensitive outcome measure as it does
38
39 415 not incorporate negative quality of life, i.e. distress, and has no ceiling effect [71].
40

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42 416 • Treatment response on social anxiety disorder symptoms measured as LSAS below 50 or a 15
43
44 417 points drop.

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47 418 • Treatment response on agoraphobia symptoms measured as MIA below 2 or a 0.5 points drop.

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50 419 • Remission of social anxiety disorder symptoms measured post-treatment and at follow-up as
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52 420 LSAS below 25 and not qualifying for social anxiety disorder as measured using the MINI.

53

54 421 • Remission of agoraphobia symptoms measured post-treatment and at follow-up as MIA below
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57 422 1.5 and not qualifying for agoraphobia as measured using the MINI.
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4 423 Explorative outcomes:

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7 424 • Social functioning measured with Personal and Social Performance Scale [72] (PSP) pre-
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9 425 treatment, post-treatment and at one-year follow-up.
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11 426 • Substance and alcohol use measured with timeline followback [73] (TLFB) pre-treatment, post-
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13 427 treatment and at one-year follow-up.
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15
16 428 • Self-belief of coping measured with General Self Efficacy [74] (GSE) pre-treatment, post-
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18 429 treatment and at one-year follow-up.
19
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21 430 • Working alliance measured with the Working Alliance Inventory [75] (WAI) post-treatment.
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23 431 • Social anxiety symptoms in patients with social anxiety disorder, measured with the LSAS pre-
24
25 432 treatment, post-treatment and at one-year follow-up.
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28 433 • Agoraphobia symptoms in patients with agoraphobia, measured with the MIA pre-treatment,
29
30 434 post-treatment and at one-year follow-up.
31

32 435 Other measures:

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35 436 • Unwanted negative side-effects induced by immersions in VR (commonly referred to as
36
37 437 cybersickness) will be measured with the Simulator Sickness Questionnaire [76] (SSQ) at the
38
39 438 end of VRE sessions.
40
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42 439 • Deterioration and adverse effects of psychotherapy on social anxiety disorder symptoms
43
44 440 measured post-treatment and at follow-up as a 6.8+ point increase in total LSAS score. Patients
45
46 441 who have deteriorated will be interviewed about their experiences in therapy.
47
48
49 442 • Deterioration and adverse effects of psychotherapy on Agoraphobia symptoms measured post-
50
51 443 treatment and at follow-up as a 0.3 point increase in total MIA score. Patients who have
52
53 444 deteriorated will be interviewed about their experiences in therapy.
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56 445 • The experience of Social Presence, as described by Lee [77], will be measured after each VR
57
58 446 exposure session with a scale consisting of 9 questions rated on a 1-7 Likert scale. This scale
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4 447 was developed specifically for this trial because existing scales are too specific for the VR
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6 448 equipment and content they were developed for. Social Presence is measured instead of the
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9 449 more general construct of Presence, because it has been theorized to be a critical element in the
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11 450 effective use of VRE for socially related fears [78,79].
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16 452 **Data from medical report**

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18 453 The following data will be retrieved from the participants' medical report with consent, only if the
19
20 454 participant cannot remember it:

- 23 455 1. Number of previous hospitalizations for mental health conditions or medical conditions.
- 24
25 456 2. Use of mental health services during the follow-up period
- 26
27 457 3. Current and previous psychopharmacological medication
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30 458 4. Attendance rate of the CBT treatment.
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34 460 **Setting of assessment**

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37 461 Assessment will take place at the outpatient clinics where the patients also receive treatment. Self-
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39 462 report questionnaires (MIA, FNE, CSQ, WAI, WSAS, WHO-5) will be answered by following a
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42 463 link sent to the patient's email address, which the patients can access either on a personal device or
43
44 464 on one of the clinic's computers. If preferred by the patient, the self-report questionnaires can be
45
46 465 filled out on printed copies of the scales while at the assessment interview. MINI, LSAS, PSP,
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49 466 HAM-D6 and TLFB will be administered by trained researchers and research assistants. After each
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51 467 session with VRE, specific questionnaires (Social Presence & Simulator Sickness Questionnaire)
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53 468 will be administered by the clinicians delivering the intervention. If necessary, due to the global
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56 469 COVID-19 pandemic, assessment interviews will be performed via telephone.
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59 470 **Randomization**

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4 471 Randomization is performed by randomizing each therapy group, one week before the first
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6 472 treatment session. This means that no patient is included while their treatment allocation is known.
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9 473 The Randomization is done with a hidden allocation sequence generated from
10
11 474 www.sealedenvelope.com and is centralized and handled with the randomization module in
12
13 475 REDCap by a project manager uninvolved in the data collection. Block sizes will be unknown to
14
15
16 476 the outcome assessors and clinicians. The factor for stratification is the treatment site. Allocation
17
18 477 tables will be handled by external researchers with no affiliation with the project. An email of the
19
20 478 group's assigned randomization will be sent to the team leaders organizing the logistics of the
21
22
23 479 interventions in the Psychotherapeutic clinics. Assigned randomization of the groups will be stored
24
25 480 by the research team data manager. The randomization code will be stored at redcap.
26

27 481 **Blinding**

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30 482 The assessors are blinded when interviewing at pre-treatment, post-treatment and at follow-up.
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32 483 Should unblinding occur, another researcher will perform the assessment. Blinded researchers will
33
34 484 perform analysis and draft conclusions.
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37 485 **Data collection methods and management**

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40 486 See Figure 1 for an overview of data collection. Self-reported data will be collected through surveys
41
42 487 send via REDCap (Research Electronic Data Capture) or filled out on paper. Assessors are trained
43
44 488 in the interview instruments and will do regular co-ratings of recorded interviews. Interrater
45
46 489 reliability of clinician-rated outcome measures will be calculated throughout the trial. The
47
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49 490 interviewers will import data from the assessments directly into the electronic CRF (Case Report
50
51 491 Form) using the data entry system REDCap [80]. REDCap is an electronic data capture tool hosted
52
53 492 at CIMT (Center for IT, Medico and Telephony) in the Capital Region of Denmark. For non-self-
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56 493 report measures, data will first be captured on paper and then entered electronically. REDCap
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58 494 complies with Danish legislation (the Act on Processing Personal Data) due to it having both
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495 comprehensive user rights and access control management and a complete audit trail on all data
496 transactions. The data from individual patients are tied to a unique serial number. Assigned
497 researchers and GCP (Good Clinical Practice) monitors will be the only people who can access the
498 database. Non-electronic data will be stored locally in secure archives. Data will be exported from
499 REDCap without personal identifiers. Data will be exported to all well-known software packages:
500 (SPSS, SAS, Stata, R.) and stored on a secure network drive under the control of CIMT. A data
501 manager will ensure that all variables are correctly defined with variable and value labels. All
502 derived variables will be correctly defined, and algorithms will be kept in individual files. All data
503 will be scrutinized to identify errors in data entry. The sponsor and the principal investigators
504 ensure that data is stored at least ten years after the trial is ended.

505 **Statistical methods**

506 The analysis will all be from intention-to-treat. All included patients will also be included in the
507 analyses. All statistical tests of significance will be two-tailed. The primary outcome analysis will
508 be an intention-to-treat analysis. Missing data will be handled by multiple imputations (m=100). As
509 predictors in the imputation model, we will select variables if they are independent predictors of the
510 outcome or predictors of missing data ($P < 0.05$ in a univariate model). Each group will have
511 imputations done separately. Analysis of covariance will be used to calculate any significant results
512 between the two groups, using the baseline value and the stratification variables.
513 The continuous variables will be imputed with linear regression. Binary variables will be imputed
514 with binary logistic regression. Multinomial variables will be imputed with multinomial logistic
515 regression. Ordinal variables will be imputed with ordinal logistic regression. For every type of
516 variable, we will perform 100 imputations.

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4 517 All distributions will be assessed for normality using visual inspection of histograms and Q-Q plots.

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6 518 If not normally distributed, variables will be log-transformed, and if unsuccessful, a non-parametric
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9 519 test will be used.

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11 520 For dichotomous outcomes, we will perform multiple logistic regressions with treatment as usual as
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13 521 reference and stratification variables as covariates after having imputed missing values using a
14
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16 522 logistic regression model.

17
18 523 *Dissemination*

19
20 524 A trial protocol, including a plan for statistical procedures, has been published at
21
22
23 525 www.clinicaltrials.gov/ct2/show/NCT03845101. This will ensure that the SoREAL trial is
24
25 526 conducted and analyzed as planned. Possible deviations and reasons for those will be described in
26
27 527 publications. All data published will be verified for authenticity by controlling for internal
28
29
30 528 inconsistency. All results, positive, negative as well as inconclusive, will be published as quickly as
31
32 529 possible and still in concordance with Danish law on the protection of confidentially and personal
33
34 530 information. Results will be presented at national and international scientific conferences. Lastly,
35
36
37 531 results will be presented at relevant mental health centers in Denmark.

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41 533 *Data monitoring and auditing:*

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43 534 Like in GCP monitoring, an independent committee will check the following data for included
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45 535 patients: Informed consent, inclusion and exclusion from intervention, serious adverse events and
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47
48 536 severe adverse reactions. It will be checked whether there is a link between trial allocation and the
49
50 537 serious adverse events and severe adverse reactions.

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55 539 *Safety:*

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4 540 In the clinical setting, the clinicians will register Adverse Events and Adverse Reactions and report
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6 541 all Serious Adverse Events and Severe Adverse Reactions to the sponsor. Other events or side
7
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9 542 effects will be collected from patient files and registers. International Conference on Harmonization
10
11 543 of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical
12
13 544 Practice guidelines define serious adverse events and serious adverse reactions. The patients in the
14
15
16 545 SoREAL trial are ensured by Danish law and the patient care regulation. Every patient in the
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18 546 SoREAL trial will have access to their results of the trial if they wish to. The clinicians will not
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20
21 547 have access to data collected from assessments done by the researchers.
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23 548

25 549 Trial status

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30 550 Inclusion began on February 4th, 2019. Inclusion is expected to stop on June 4th, 2023. Inclusion
31
32 551 was delayed by approximately three months due to the COVID-19 pandemic.
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35 552 List of abbreviations

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40 553 VRET: Virtual Reality Exposure Therapy; CBT: Cognitive behavioral therapy; RCT: Randomised
41
42 554 Controlled Trial. MINI: Mini international neuropsychiatric interview. VR: Virtual reality. LSAS:
43
44 555 Liebowitz social anxiety scale. MIA: Mobility Inventory for Agoraphobia. POMP: Percentage of
45
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47 556 Maximum Possible Score. PSP: Personal and social performance scale. TLFB: Timeline
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49 557 followback. FNE: Fear of negative evaluation scale. CSQ: Client satisfaction questionnaire. WAI:
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51 558 Working alliance inventory. WSAS: Work and social adjustment scale. HAMD-6: Hamilton
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54 559 depression scale, 6 item version.
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57 560 Declarations

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4 561 **Sponsor details**
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7 562 Name: Merete Nordentoft.
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10 563 Contact: merete.nordentoft@regionh.dk
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19 567 **Ethics approval and consent to participate**
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22 568 The trial has obtained approval by the Regional Ethics Committee of Zealand (H-6-2013-015) and
23
24 569 the Danish Data Protection Agency (RHP-2014-009-02670). The trial is registered at
25
26
27 570 ClinicalTrials.gov as NCT03845101. The patients will receive information on the trial both verbally
28
29 571 and in written form. Written informed consent will be obtained from each patient before inclusion
30
31 572 in the trial. The consent form will be scanned and stored in the database system and the physical
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34 573 copy will be destroyed. It is emphasized that participation in the trial is voluntary and that the
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36 574 patient can withdraw his or her consent at any time without consequences for further and continued
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38 575 treatment.
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41 576 **Protocol amendments**
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44 577 Changes in protocol will be reported to the trial registry by a researcher via the designated website,
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46
47 578 to participants if it affects them in any way via email, to the ethical committee and Danish Data
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49 579 Protection Agency via their online forms.
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52 580 **Availability of data and materials**
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581 After completed analyses and publication, data will be transferred to The Danish National Archives
582 and made available for other researchers upon reasonable request and with permission of The
583 Danish National Archives.

584 **Additional file data**

585 Additional file 1. Format: docx. Title: SPIRIT 2013 Checklist. Description of data: Checklist of
586 recommended items to address in a clinical trial protocol and related documents.

587 Additional file 2. Format: docx. Title: Screenshots and descriptions of Virtual Reality Exposure
588 environments.

589 **Author contributions**

590 All authors have read, revised and approved the manuscript. MN and NR had the original idea for
591 the trial. MN wrote the application for the NovoNordic Foundation and is the PI of the trial. CH
592 generated the allocation sequence, carried out the power calculations and will be responsible for
593 supervising the statistical analyses. NR was responsible for the non-experimental content of the
594 CBT. CW, KM, CS, PB and BTA directed the development of the VR films. CW, KM, UKG, DS,
595 PW, BTA and PB developed the manual and guidelines for using VRET in group therapy. MHP
596 was responsible for outcome measures. BTA and PB developed the Social Presence Scale and
597 fidelity measures. BTA set up randomization, built and manage the database, and is responsible for
598 all participant assessment, including training and managing research assistants.

599 **Competing interests**

600 The authors declare that they have no competing interests.

601 **Consent for publication**

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4 602 Not applicable.
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7 603 **Acknowledgments**
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11 604 N/A.
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14 605 **Funding**
15

16 606 MN and NR initiated the project. MN applied to Novo Nordisk Foundation, and the SoREAL trial
17
18 607 was granted 5.000.000 DKK [NNF17OC0027780]. MN and NR have no affiliation to the Novo
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20 608 Nordisk Foundation. MN, PB and BTA applied to TrygFonden and the trial was granted an
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23 609 additional 3.517.500 DKK [ID: 146169]. MN, PB and BTA have no affiliation to TrygFonden.
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26 610 The project is entirely independent of the Novo Nordisk Foundation and TrygFonden and therefore,
27
28 611 the funding body plays no role in the design of the study, the collection, analysis and interpretation
29
30 612 of data and in writing the manuscript. Nor will the Novo Nordisk Foundation or TrygFonden play
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33 613 any role in future publications that may derive from the project.
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36 614 **Protocol version and date**
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39 615 Protocol Version 4 – Revised 02.03.21
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617 **Figure legends**

618 Figure 1. Overview of data collection

619 Figure 2. Flow diagram of the SoREAL trial

620 Figure 3. Power calculation for secondary outcomes in the SoREAL trial

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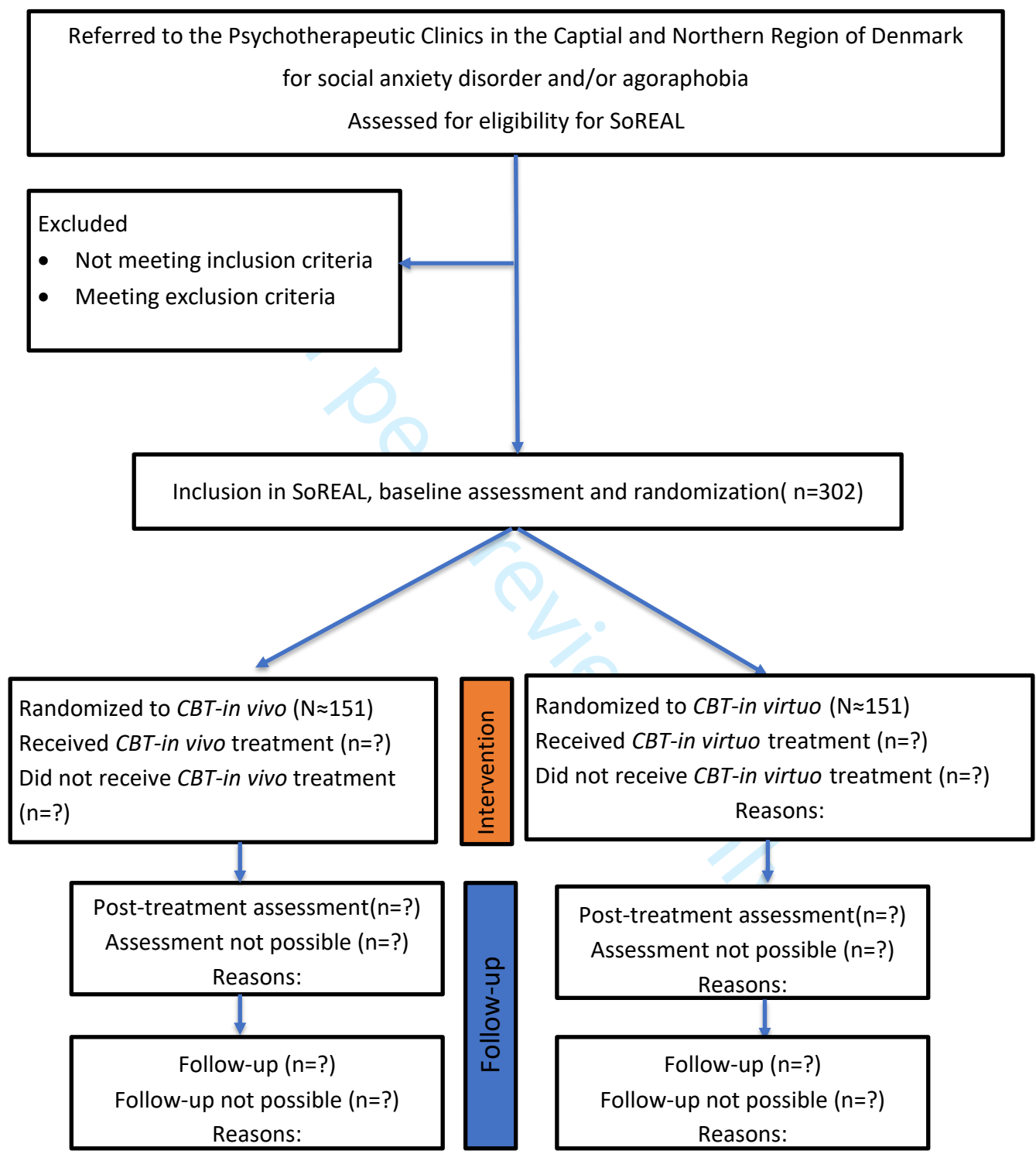
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Schedule of enrolment, interventions, and assessments.		STUDY PERIOD		
		Enrolment and allocation	Follow-up	
TIMEPOINT**		Baseline	Post-treatment	One-year
ENROLMENT:				
	ENROLMENT:	X		
	Eligibility screen	X		
	Informed consent and inclusion	X		
	Allocation	X		
INTERVENTIONS:				
	CBT-In vivo			
	CBT-In virtuo			
ASSESSMENTS:				
	Sociodemographic data (Interview + registries)	X		
	Diagnosis, using Mini International Neuropsychiatric Interview	X	X	X
	Liebowitz Social Anxiety Scale	X	X	X
	Agoraphobia Mobility Inventory	X	X	X
	Hamilton Depression Rating Scale 6	X	X	X
	Timeline Follow Back, Alcohol & Substance	X	X	X
	Fear of Negative Evaluation Scale	X	X	X
	Work and Social Adjustment Scale	X	X	X
	World Health Organization 5	X	X	X
	Personal and Social Performance Scale	X	X	X
	General Self Efficacy Scale	X	X	X
	Client Satisfaction Questionnaire		X	
	Social Presence Scale	(During treatment for CBT-In virtuo) X		
	Simulator Sickness Questionnaire	(During treatment for CBT-In virtuo) X		
	Working Alliance Inventory		X	

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Outcome	Lowest clinically relevant difference	Expected standard deviation	Calculated power	Reference
Fear of Negative Evaluation	4.5	10	97 %	[68]
Hamilton Depression Rating Scale, 6 items	1.6	4	93 %	[67]
Client Satisfaction Questionnaire	2	5	93 %	[70]
WHO Well-Being Index, 5 items	10	25	93 %	[71]
Work and Social Adjustment Scale	8	10	~100 %	[69,81]
Remission (LSAS<30)	20 % in control group vs. 35 % in the VR group		84%	[63,82]
Response (LSAS<50 or a 15 point drop)	65 % in control group vs. 80 % in VR group		84%	[63]
Remission (MIA<1.5)				
Response (MIA <2 or a 0.5 point drop)				



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, Line 2-5
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3, Line 45-47
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Page 29, Line 614
Funding	4	Sources and types of financial, material, and other support	Page 29, Line 604-612
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 28, Line 589-597 & Page 1, Line 9-16
	5b	Name and contact information for the trial sponsor	Page 27, Line 561-562
	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	Page 29, Line 609-612

1	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
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9	Introduction		
10			
11	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
12			Page 4-7, Line 66-149
13		6b	Explanation for choice of comparators
14			Page 6-7, Line 128-139
15	Objectives	7	Specific objectives or hypotheses
16			Page 8, Line 155-164
17			
18	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)
19			Page 2, Line 29-30
20			
21	Methods: Participants, interventions, and outcomes		
22			
23	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
24			Page 8, Line 177-178
25	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)
26			Page 9-10, Line 188-204
27	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
28			Page 10-18, Line 216-358
29		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)
30			Page 16, Line 305-307 & page 26 line 539-546
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1		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 15, Line 287-296
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4		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 10-11, Line 216-238
5				
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7	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	Page 19 – 22, Line 381-468
8				
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13	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)	See attached SPIRIT figure
14				
15				
16	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	Page 18-19, Line 367-379
17				
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19	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 8-9, Line 177-186 & page 10, line 206-214
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Methods: Assignment of interventions (for controlled trials)

Allocation:

28	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	Page 23, Line 472-474
29				
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34	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	Page 23, Line 472-476
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38	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 23, Line 474-476; Page 22, Line 464-468.
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1	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 23, line 481-483
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4		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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Methods: Data collection, management, and analysis

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10	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 23-24, line 485-503; Page 19 – 22, Line 381-468 ; Figure 3
11				
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15		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 21, line 438-443
16				
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19	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 23-24, line 485-503
20				
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23	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 24-25, line 505-521
24				
25				
26		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
27				
28		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 24-25, line 505-506; 507
29				
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Methods: Monitoring

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35	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 25, line 533-536
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1		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
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4	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 26, line 539-546
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7	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
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11	Ethics and dissemination			
12				
13	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 27, line 567
14				
15				
16	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)	Page 27, line 576-578
17				
18				
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20	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 27, line 569-574
21				
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23				
24		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
25				
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27	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	Page 23-24, line 485-503
28				
29				
30	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 28, line 599.
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33	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	Page 28, line 580-582
34				
35				
36	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
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1	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 25, line 523-530
2				
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5		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
6				
7		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 28, line 580-582
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11	Appendices			
12				
13	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A. Can be send on inquiry.
14				
15				
16	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
17				
18				

*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/4.0/)" license.

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Additional file 2 – Descriptions and screenshots of virtual environments used in the SoREAL trial.

Environment 1 – Supermarket


Scene 0. Loop – Standing by the register. The supermarket is empty.

Scene 1. 1:00 – Loop of scene 0. Standing in line. A man asks if you would use a ware separator.

Scene 2. 1:39 – Loop of scene 0. Intimidating man cuts in line. Person in line is upset. You have forgotten to weigh your vegetables.

Scene 3. 1:57 – Loop of scene 0. Your credit card is declined. Person in line is increasingly impatient and upset.



<p>1 2 3 4 5 6</p> <p>Scene 4. 0:50 – Loop of scene 0. You win a prize for being customer number 1.000.000.</p>	
<p>7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46</p> <p>Environment 2 – Presentation</p> <p>Scene 0. Loop – Standing in meeting room alone.</p> <p>Scene 1. 2:20 – Loop of scene 0. Meeting preparations with colleague.</p> <p>Scene 2. 3:29 – Loop of scene 0. Contact person arrives. Short conversation.</p> <p>Scene 3. 2:35 – Loop of scene 0. Two important meeting participants arrive.</p> <p>Scene 4. 2:01 – Loop of scene 0. The rest of the meeting participants arrive. Introductions to the group.</p>	

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4 Scene 5. 4:02 – Loop of scene 0.
5 Presentation has technical
6 difficulties. Partner leaves mid-
7 presentation.
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12 Scene 6. 2:07 – Loop of scene 0.
13 Scolding from the boss.
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15 **Environment 3 – Cafeteria**
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17 Scene 0. Loop – Sitting by table.
18 One person sits down nearby.
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22 Scene 1. 3:04 – Loop of scene 0.
23 Someone small talks near you.
24 You are asked about parking.
25 Few people in the room.
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30 Scene 2. 4:30 – Loop of scene 0.
31 More small talk. You are asked if
32 there is room by the table.
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Scene 3. 5:15 – Loop of scene 0.
You are in the middle of a discussion about art.

Scene 4. 5:11 – Loop of scene 0.
You are in the middle of a heated discussion about transgender issues.

Environment 4 – Party

Scene 0. Loop – Arrived at door.
Party audible inside.

Scene 1. 1:19 – Loop of scene 0.
Guest arrives. Host opens door and greets guest.

Scene 2. Loop – In kitchen with many partygoers. You are offered a shot of an alcoholic beverage.



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Scene 3. 3:35 – Loop of scene 2.

Participate in drinking game in the kitchen

Scene 4. 3:37 – Loop of scene 2.

In corner of room. Two guests have an intimate conversation close by.

Scene 5. 2:54 – Loop of scene 2.

On the dancefloor. A circle of dancing revelers forms around you.

ew only

Environment 5 – Auditorium

Scene 0A. Loop. Sitting at a lecture.

Scene 0B. Loop. Waiting for lecture to start. Few other people.

Scene 1. 1:14 – Loop of scene 0A. Arrived before class start to empty auditorium.

Scene 2. 0:49 – Loop of scene 0A. Arrived exactly at the right time. Few people in the auditorium.

Scene 3. 1:02 – Loop of scene 0A. Arrived too late. Professor notes it as you enter.

Scene 4. 1:18 – Loop of scene 0A. Arrived much too late.



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Scolded in front of full
auditorium by professor.

Environment 6 – Job interview

A variety of relevant questions
to be posed can be chosen by
the patient such as “What are
your weaknesses” etc., after the
question a “listening loop” is
played that allows the patient to
talk while the two interviewers
appear to listen.



Environment 7 – Crossing a bridge

Scene 0A. Loop. Waiting in a highway rest area.

Scene 0B. Loop. Waiting to get picked up in sub-urban area.

Scene 1. 1:38 – Loop of scene 2.
Driving in sub-urban area.
Picking up other passengers.

Scene 2. Loop. Driving, no conversation.

Scene 3. Loop. Crossing a bridge, no conversation.

Scene 4. 4:25 -- Loop of scene 2.
Passenger gets carsick.

Scene 5. 5:27. Car breaks down while crossing bridge.



**Environment 8 - Small
talking/discussing in a canteen
in a work setting**

Scene 0. Loop. At the buffet.

Scene 1. 1:00 – Loop of Scene 0.

Standing in line.

Scene 2. 3:00 – Loop of Scene 0.

In the middle of the canteen.

Scene 3. Loop. Eating with
colleagues. Small talk.

Scene 4. 2:00 – Loop of Scene 3.

Standing by table. Positive
mood.

Scene 5. 5:40 – Loop of Scene 3

Eating with colleagues. Negative
mood.



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Scene 6. 2:00 – Loop of Scene 0.
Drops tray with food next to table.

Environment 9 - Taking a commercial airplane

Scene 0. 7:26. Taking a plane, from boarding to landing.

It is possible to only play specific segments, e.g. "Turbulence" or "Boarding".



Environment 10 - Being in a crowded shopping center

Scene 0. Loop. At entrance to mall.

Scene 1. Loop. Inside mall, not crowded.

Scene 2. Loop. Inside mall, crowded.

Scene 4. Loop. Standing in line to toilet. One is out of order.



For peer review only

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Environment 11 - Taking an
elevator

Scene 0. Loop. Waiting for
elevator.

Scene 1. Loop. Taking the
elevator alone.

Scene 2. 1:45 – Loop of Scene 1.
Taking the elevator with other
people.

Scene 3. 6:30 – Loop of Scene 1.
Elevator malfunctions with other
people.

Scene 4. 6:20 – Loop of Scene 1
Elevator malfunctions with other
people. You have a panic attack.



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Environment 12 - Waiting for-
and taking the bus

Scene 0. Loop. Waiting for bus.

Scene 1. 0:50 – Loop of Scene
2A. Bus arrives. Entering bus.

Scene 2A. Loop. In driving bus,
sitting.

Scene 2B. Loop. In driving bus,
standing.

Scene 3. 0:50 – Loop of Scene
2A. Baby driving in bus.

Scene 4. 2:00 – Loop of Scene
2A. Man speaks loudly on the
phone next to you.



<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46</p> <p>Scene 5. 3:30 – Loop of Scene 2A. Drunk man enters bus and addresses you.</p> <p>Scene 6. 1:20 – Loop of Scene 2A. Elderly lady asks for your seat. You refuse.</p> <p>Scene 7. 2:00 – Loop of Scene 2A. Baby cries, man speaks loudly on phone and drunk man addresses you.</p>	
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Environment 13 - Leaving your apartment

Scene 0. Loop. In entrance of apartment.

Scene 1. Loop. On apartment staircase outside apartment.

Scene 2. Loop. Standing in the entrance to the apartment building.

Scene 3. Loop. Standing in the street outside apartment.



“—Loop of 0/1/2” indicates that the scene automatically jumps to that loop after finishing. All identifiable persons depicted are paid actors.

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BMJ Open

Group Cognitive Behavioural Therapy with Virtual Reality Exposure vs Group Cognitive Behavioural Therapy with In Vivo Exposure for Social Anxiety Disorder and Agoraphobia: A Protocol for a Randomized Clinical Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-051147.R1
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice
Keywords:	Anxiety disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, PSYCHIATRY

SCHOLARONE™
Manuscripts

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4 1 **Title page**

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6 2 **Group Cognitive Behavioural Therapy with Virtual Reality Exposure vs Group Cognitive Behavioural**
7 3 **Therapy with In Vivo Exposure for Social Anxiety Disorder and Agoraphobia: A Protocol for a**
8 4 **Randomized Clinical Trial**

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52 25 Randomized Clinical Trial.

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30 Abstract

31 **Introduction** Anxiety disorders have a high lifetime prevalence, early-onset, and long duration or
32 chronicity. Exposure therapy is considered one of the most effective elements in cognitive
33 behavioral therapy (CBT) for anxiety, but *in vivo* exposure can be challenging to access and control,
34 and is sometimes rejected by patients because they consider it too aversive. Virtual reality allows
35 flexible and controlled exposure to challenging situations in an immersive and protected
36 environment. **Aim** The SoREAL-trial aims to investigate the effect of group cognitive-behavioral
37 therapy (*CBT-in vivo*) versus group cognitive behavioral therapy with virtual reality exposure (*CBT-*
38 *in virtuo*) for patients diagnosed with social anxiety disorder and/or agoraphobia, in mixed groups.

39 **Methods & Analysis** The design is an investigator-initiated randomized, assessor-blinded, parallel-
40 group and superiority-designed clinical trial. Three hundred two patients diagnosed with social
41 anxiety disorder and/or agoraphobia will be included from the regional mental health centers of
42 Copenhagen and North Sealand and the Northern Region of Denmark. All patients will be offered a
43 manual-based 14-week cognitive behavioral group treatment program, including eight sessions with
44 exposure therapy. Therapy groups will be centrally randomized with concealed allocation sequence
45 to either *CBT-in virtuo* or *CBT-in vivo*. Patients will be assessed at baseline, post-treatment and
46 one-year follow-up by treatment blinded researchers and research assistants. The primary outcome
47 will be diagnosis-specific symptoms measured with the Liebowitz Social Anxiety Scale for patients
48 with social anxiety disorder and the Mobility Inventory for Agoraphobia for patients with
49 agoraphobia. Secondary outcome measures will include depression symptoms, social functioning,
50 and patient satisfaction. Exploratory outcomes will be substance and alcohol use, working alliance
51 and quality of life. **Ethics and dissemination:** The trial has been approved by the research ethics
52 committee in the Capital Region of Denmark. All results, positive, negative as well as inconclusive,
53 will be published as quickly as possible and still in concordance with Danish law on the protection

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4 54 of confidentially and personal information. Results will be presented at national and international
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6 55 scientific conferences. **Trial registration:** The project was registered at clinicaltrials.gov on
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9 56 02/19/2019 as NCT03845101. Can be found online at
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11 57 <https://clinicaltrials.gov/ct2/show/NCT03845101>
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16 59 Article Summary

20 60 **Strengths and limitations of this study**

- 22 61 • The present study will be the first large randomized clinical trial to investigate virtual reality
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24 62 exposure therapy for social anxiety disorder and agoraphobia in group therapy.
- 26 63 • The present study is very closely integrated with clinical practice, making results highly
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29 64 transferable to similar real-life settings.
- 31 65 • Mixing patients with social anxiety disorder and agoraphobia in the same therapy groups
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34 66 have never been investigated systematically, which may confound the interpretation of
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36 67 results.
- 38 68 • Because the study is embedded in an outpatient hospital setting, the intervention was
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41 69 designed to be flexible. This increases the ecological validity but also the risk of systematic
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43 70 bias in treatment administration.

72 Background

73 Social anxiety disorder is characterized by paying attention to oneself in an exaggerated manner and
74 having marked fear of being negatively evaluated by other people [1,2]. Agoraphobia is
75 characterized by avoidance or enduring with dread, situations in which escape is perceived difficult
76 or where help might not be available in the event of a panic attack, panic-like symptoms or
77 incapacitating symptoms such as loss of bladder and/or bowel control [1,3]. Both social anxiety
78 disorder and agoraphobia are associated with marked functional consequences [1]. In Denmark,
79 anxiety disorders represent the costliest disease burden in terms of lost production, due to their early
80 onset, long duration and high prevalence [4].

81 The first-line treatment for social anxiety disorder and agoraphobia is cognitive-behavioral therapy
82 (CBT) with exposure therapy [5,6]. Several meta-analyses have found that patients with social
83 anxiety disorder and agoraphobia respond well to CBT with exposure therapy, provided in
84 individual as well as group format [7–10]. Exposure therapy aims to change expectations and
85 emotional responses associated with feared stimuli, by exposing the patient to the stimuli and
86 challenging the patients' expectancies of the likelihood and consequences of a feared outcome [11].
87 However, in clinical practice, in-vivo exposure stimuli can be difficult to access and control and
88 patients or therapists sometimes reject the treatment, because they consider it too aversive or too
89 logistically demanding [12–14].

90 **Virtual Reality Exposure Therapy for Social Anxiety Disorder and Agoraphobia**

91 Virtual Reality (VR) technology allows the user to experience virtually mediated environments that
92 are perceived as real or almost real, due to multisensory stimulation and blocking of real-world
93 sensory input. Numerous possibilities for psychological intervention using VR are currently being
94 researched owing to its immersive quality [15,16]. As a therapy tool, VR is most widely used to

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4 95 perform Virtual Reality Exposure Therapy (VRET) [16,17], either as a standalone treatment, e.g.
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6 96 [18], or integrated into a CBT treatment e.g. [19].
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10 97 The use of VR allows flexible and controlled exposure to challenging situations in an immersive
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12 98 and safe environment. Therefore, using VRET can mitigate the challenges of in-vivo exposure
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14 99 therapy by producing greater user acceptance and access to situations that would otherwise be too
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17 100 difficult to control, too resource-intensive to find and/or have unacceptable confidentiality risks
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19 101 [15,19,20]. Based on this, VRET may improve the efficacy and cost-effectiveness of
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21 102 psychotherapeutic interventions for anxiety disorders.
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24 103 Recent reviews and meta-analysis of VRET either as a standalone treatment or combined with
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26 104 cognitive interventions, conclude that VRET is more effective than waitlist and placebo control and
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28
29 105 equally as effective as first-line treatment controls for anxiety disorders [21–23]. However, in one
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31 106 meta-analysis, the authors find significantly worse treatment effects of VRET for social anxiety
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34 107 disorder, when compared with control groups that received equal amounts of in-vivo exposure [24].
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36 108 It has been suggested that it is more difficult to produce VRET environments for social anxiety
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38 109 disorder, as compared to other phobic disorders because human interaction is complex and therefore
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41 110 difficult to realistically recreate [25] which may explain these results. Accordingly, the same meta-
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43 111 analysis found no significant difference in treatment efficacy for CBT with VRET vs CBT with in-
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45 112 vivo exposure for agoraphobia and specific phobia [24].
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48 113 In general, there is a scarcity of high-quality randomized clinical trials (RCT) evaluating the use of
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50 114 VRET for social anxiety disorder and agoraphobia [16,26,27]. For social anxiety disorder, there are
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53 115 five trials published, the largest having 97 participants [28,19,18,29,30]. For agoraphobia, there are
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55 116 six trials published, the largest having 80 participants [31–36]. All in all, the evidence-base for
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117 using VRET compared to in-vivo exposure for social anxiety disorder and agoraphobia remain
118 small. Therefore, larger studies that capitalize on the unique qualities of VRET are needed.

Virtual Reality Exposure in Group Therapy

120 VRET has never been investigated in a group format. Group therapy for social anxiety disorder and
121 agoraphobia is popular in outpatient settings because it has similar treatment efficacy [37–39] and is
122 proposed to have better cost-efficiency, compared to individual therapy [37,39]. However, the claim
123 of cost-efficiency for social anxiety disorder is disputed, at least in a UK mental healthcare setting
124 [40]. Beyond that, therapeutic interpersonal processes such as peer learning and modeling as been
125 suggested to be a distinct benefit of group therapy [41,42], though this has never been
126 systematically evaluated for mixed anxiety groups. A suggested drawback of group CBT compared
127 with individual CBT is that in-vivo exposure in group therapy is restrained by the logistics of
128 managing several patients simultaneously, leading to comparatively less individualized exposure
129 exercises [43,44].

130 The use of VRET in group therapy may therefore be especially beneficial, since it should allow for
131 individualized exposure, as well as a greater amount of exposure therapy because less time will be
132 spent on logistical issues (transport, planning, waiting, etc.), whilst at the same time retaining the
133 proposed benefits of the therapeutic interpersonal processes and cost-efficiency.

Treatment of social anxiety disorder and agoraphobia in the Danish mental health system

135 In the Danish mental health services, patients with social anxiety disorder or agoraphobia as their
136 primary diagnosis, are generally offered group CBT. To reduce wait time, patients with these
137 diagnoses are treated in the same therapy groups, generally referred to as “mixed anxiety groups” or
138 “phobia groups”. These mixed anxiety groups are considered to be as effective as diagnosis-specific
139 groups, due to the overlap in symptoms and diagnostic criteria [45], high degree of comorbidity

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4 140 [46], as well as recent evidence of the acceptable treatment efficacy of CBT-based transdiagnostic
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6 141 therapies [47].
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10 142 However, it is worth noting, that the pragmatic mixed anxiety group format has never been
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12 143 systematically evaluated and that the official treatment recommendation remain diagnoses specific
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14 144 CBT delivered in group or individually [48]. To maximize the study's clinical representitativenes, as
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16 145 defined by Shadish et al. [49], the treatment structure in the present study, including the comperator,
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18 146 will mimic the treatment offered by the Danish mental health services.
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22 147 **Aim and objectives:**

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25 148 In summary in-vivo exposure is considered effective, but can be challenging to perform. Virtual
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27 149 Reality Exposure therapy may alleviate these challenges. However, the usefulness of VRET for
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30 150 social anxiety disorder and agoraphobia remains unclear. Larger studies that capitalize on the
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32 151 benefits of VRET are needed. Group therapy may be one way to capitalize on the benefits of VRET
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34 152 because it could allow for more individualized exposure exercises. Mixed anxiety groups are
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37 153 commonly used in Danish mental healthcare to reduce wait time, but have not been systematically
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39 154 evaluated. The treatment, inclusion and exclusion criteria described in the present study match the
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41 155 eligibility criteria for treatment and treatment format of the Danish mental healthcare system to
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44 156 maximize transferability of results to clinical practice.
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47 157 Therefore, the SoREAL trial aims to evaluate the treatment efficacy of VRET in mixed anxiety
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49 158 CBT groups (CBT-in virtuo) compared to mixed anxiety CBT groups where exposure therapy is
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51 159 performed in-vivo (CBT-*in vivo*).
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54 160 Thus, in the SoREAL trial, the following hypotheses' will be tested:
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58 161 Primary hypothesis:
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4 162 1. Post-treatment, patients treated with CBT-*in virtuo* will have a lower level of anxiety
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7 163 symptoms compared to patients treated with CBT-*in vivo*, measured as total scores on the
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9 164 Liebowitz Social Anxiety Scale (LSAS) for patients with social anxiety disorder and the
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11 165 Mobility Inventory for Agoraphobia (MIA) for patients with agoraphobia converted to the
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13 166 percentage of maximum possible scores (POMP) and averaged within treatment arms.

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16 167 Secondary hypotheses:

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18 168 1. One year after treatment, patients treated with CBT-*in virtuo* will have lower levels of anxiety
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20 169 symptoms compared to patients treated with CBT-*in vivo*.
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23 170 2. Post-treatment and one year after treatment, patients treated with CBT-*in virtuo* will have lower
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25 171 levels of fear of negative evaluation compared to patients treated with CBT-*in vivo*.
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30 173 Overall, we believe that the SoREAL trial will contribute with knowledge about the efficacy and
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32 174 feasibility of VRE for treating social anxiety disorder and agoraphobia in a clinical outpatient
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34 175 setting. The results of this trial may guide future applications of VR in clinical settings across a
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36 176 wide breadth of use-cases.
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40 41 42 178 Methods and design

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45 179 This article was written in accordance with the SPIRIT (Standard Protocol Items:

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47 180 Recommendations for Interventional Trials) 2013 explanation and elaboration: guidance for
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49 181 protocols of clinical trials [50]. The SPIRIT Checklist was followed and the SPIRIT flowchart was
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52 182 used [See Additional file 1 and Figure 1].
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54 183 **Recruitment**

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56 184 The SoREAL trial is embedded directly into five outpatient clinics offering group CBT for social
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59 185 anxiety disorder and agoraphobia. These clinics are part of the Danish mental health care system.
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4 186 To be eligible for treatment in these clinics, patients must be referred by their primary care
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7 187 physicians to a Center for Visitation and Diagnosis in their area, where their symptomatology will
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9 188 be assessed. At the Center for Visitation and Diagnosis, they must be referred to one of the five
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11 189 outpatient clinics involved in the study. At the outpatient clinic, the patient will again be clinically
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13 190 assessed, and a diagnosis and treatment plan will be formulated. If social anxiety disorder and/or
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16 191 agoraphobia is considered the primary diagnosis for the patient, they will be asked if they are
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18 192 interested in getting more information about the trial. If they consent to it, their contact details will
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20 193 be given to a researcher, who will invite them to an interview concerning the study.
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25 195 Mini International Neuropsychiatric Interview (MINI), v. 7.0 for DSM-5 will be used to screen for
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27 196 diagnosis. Psychometric analyses of the MINI have demonstrated acceptable test-retest and inter-
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30 197 rater reliability [51,52]. Diagnostic screening is sufficient due to the thorough assessment from both
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32 198 Center for Visitation and Diagnostics and the outpatient clinics which must have confirmed social
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34 199 anxiety disorder or agoraphobia as the primary diagnosis of the patient, for the patient to be eligible
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36 200 for the study. If eligibility is confirmed, informed consent is acquired [See additional file 2, for a
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39 201 model consent form]. Patients that cannot or will not participate in the study will be offered
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41 202 treatment as usual, which is identical to the control group treatment. Inclusion and exclusion criteria
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43 203 were based on the eligibility criteria for receiving the treatment package in Danish outpatient
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46 204 clinics.

47 48 205 **Inclusion criteria**

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50 206 1) Fulfilling diagnostic criteria for social anxiety disorder and/or agoraphobia
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52 207 2) Age 18-75 years
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55 208 3) Sufficient knowledge of the Danish language
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57 209 4) Informed consent
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210 **Exclusion criteria**

211 1) Alcohol or drug dependence

212 **Feasibility**

213 Five psychotherapeutic outpatient clinics are involved in the study. All patients referred to these
214 clinics with the relevant diagnosis, who also agree to be contacted, will be invited to an interview
215 about their potential participation. Each of the clinics provides treatment for approximately 30
216 patients with social anxiety disorder and/or agoraphobia every year. Thus we anticipate that 450
217 patients will be eligible for the trial during a three-year recruitment period. We expect a high
218 eligibility rate, due to the previously mentioned assessment procedures the patients will have
219 completed. We also expect a high acceptance rate, due to the novel use of VR technology and the
220 use of a control group that is identical to the treatment they would be offered if they refused
221 participation. See Figure 2 for a flow diagram of the SoREAL trial.

222 **Treatment format**

223 The treatment for social anxiety disorder and Agoraphobia offered at the outpatient clinics must
224 follow the national guidelines for the treatment of these disorders. The guidelines are encapsulated
225 in specified “treatment packages”. For social anxiety disorder and agoraphobia, this package
226 contains:

- 227 • 1 hour of assessment
- 228 • 1 hour of individual therapy in preparation for group therapy
- 229 • 1 hour of psychometric testing
- 230 • 14 sessions of 2 hours of group therapy
- 231 • 1.5 hours of next of kin involvement
- 232 • 1 hour of pharmacological treatment planning with a psychiatrist
- 233 • 2.5 hours coordination with social services, relapse prevention and follow-up meetings

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4 234 Not all of this is necessary for every patient, but every patient can receive every part of the package,
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6 235 should they want to. The treatment in the present study must live up to the standards of the national
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9 236 guidelines. Patients are not allowed to be in any other form of psychotherapeutic treatment.
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13 238 The therapeutic intervention is manual-based cognitive-behavioral CBT group therapy adapted from
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16 239 the approach of Turk, Heimberg & Magee [53] and Graskie & Barlow [54] with worksheets from
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18 240 Arendt & Rosenberg [55] and inspiration from Bouchard et al. [56]. The treatment will consist of 14
19
20 241 weekly two-hour group sessions following the manual to ensure equal and uniform treatment for
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23 242 every patient throughout the study. The manual allows flexibility to ensure clinically representative
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25 243 conditions [49]. E.g. it is allowed to change the order of the sessions if it is considered beneficial for
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27 244 the group and multiple exercises are optional. However, the time dedicated to exposure is fixed in
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30 245 both groups. Concurrent psychopharmacological treatment is allowed in both intervention arms.
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34 247 Groups will consist of 8-9 patients with social anxiety disorder and/or agoraphobia as their primary
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36 248 diagnosis, and every session will be led by two trained clinicians (i.e. psychologists, psychiatrists or
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39 249 psychotherapists) with practical experience in CBT and *in vivo* exposure. Throughout the course of
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41 250 the study, the clinicians involved will treat both *CBT-in vivo* and *CBT-in virtuo* groups. Medical
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43 251 consultation, acute individual sessions, supplementary social counseling and physical therapy, are
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46 252 possible in both intervention arms. In both intervention arms, the sessions dedicated to exposure are
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48 253 scheduled from the fifth to the eleventh session with approximately 45 min of exposure in each
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50 254 session. From the fifth session and onwards, all patients in both interventions will have in-vivo
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53 255 exposure as homework. The cognitive therapy strategies used in the non-exposure sessions (first
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55 256 four and last two therapy sessions) are as follows; (a) introduction to CBT; (b) psychoeducation
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57 257 about anxiety and cognitive restructuring of dysfunctional assumptions and beliefs; (c) shifting self-
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4 258 focused attention and modifying cognitive distortions; (d) developing an understanding of safety
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6 259 behavior and the rationale of exposure; (f) evaluation, discussion and feedback on the use of
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9 260 patient-acquired techniques; and (d) relapse prevention. In both conditions, the exposure exercises
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11 261 aim to develop adaptive responses to anxiety-provoking situations, reinforce cognitive restructuring
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13 262 by framing exercises as behavioral experiments (though these were limited by the non-interactive
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16 263 medium), train attention exercises, train general cognitive strategies (e.g. identifying negative
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18 264 automatic thoughts) and train social skills. See Table 1 and Table 2 for an overview of the content
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20 265 of the CBT sessions for both conditions.
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281 *Table 1. Group Cognitive Behavioural Therapy Manual session overview for Social Anxiety Disorder and*
 282 *Agoraphobia*

Session	Content
Individual session	Case conceptualization. Psychoeducation on CBT. Treatment goal. Introduction to treatment setting.
1	Psychoeducation about anxiety. CBT anxiety model.
2	Psychoeducation about anxiety. Registration of thoughts, feelings, behavior and introduction to cognitive restructuring.
3	Psychoeducation and exercise: Cognitive bias, attention and self-focus. Repetition about Cognitive Restructuring. Attention exercises.
4	Psychoeducation about exposure therapy. Optionally, an introductory exposure exercise.
5	Exposure therapy.
6	Behavioral experiments in exposure exercises.
7	Repetition of the methods presented so far. Additional attention/mindfulness exercise linked to exposure.
8	Conversational skills and small-talk exposure exercises.
9	Introduction to Core beliefs. Additional exposure exercises.
10	Repetition of Core beliefs, resources and skills. Additional exposure exercises.
11	Exposure therapy, out of the clinic.
12	Repetition and evaluation of methods learned/used so far. Revising problem-goal list.
13	Evaluation, discussion and feedback on the different methods used by each patient.
14	Maintenance and relapse prevention; review of skills; review of progress and future goals; plan for continued exposures; relapse prevention strategies.

284 *Table 2. Group Cognitive Behavioural Therapy Manual session overview for Social Anxiety Disorder and*
 285 *Agoraphobia with Virtual Reality Exposure Therapy.*

Session	Content
Individual session	Case conceptualization. Psychoeducation on CBT. Treatment goal. Introduction to treatment setting.
1	Psychoeducation about anxiety. CBT anxiety model.
2	Psychoeducation about anxiety. Registration of thoughts, feelings, behavior and introduction to cognitive restructuring.
3	Psychoeducation and exercise: Cognitive bias, attention and self-focus. Repetition about Cognitive Restructuring. Attention exercises.
4	Psychoeducation about exposure therapy. Introduction to VRET.
5	VRET
6	Behavioral experiments in VRET
7	Repetition of the methods presented so far. Additional attention/mindfulness exercise linked to VRET.
8	Conversational skills and VRET.
9	Introduction to Core beliefs. Additional VRET exercises.
10	Repetition of Core beliefs, resources and skills. Additional VRET exercises.
11	VRET combined with in-vivo out-of-the-clinic exposure exercises.
12	Repetition and evaluation of methods learned/used so far. Revising problem-goal list.
13	Evaluation, discussion and feedback on the different methods used by each patient.
14	Maintenance and relapse prevention; review of skills; review of progress and future goals; plan for continued exposures; relapse prevention strategies.

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4 290 In the *in virtuo* condition, exposure will take place during 8 out of the 14 group sessions, as in the
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7 291 CBT-*in vivo* condition. Patients will be exposed to VR situations, which are relevant to them, and
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9 292 which they are motivated to engage in. Patients in CBT-*in virtuo* condition will be assigned *in vivo*
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11 293 exposure homework between sessions in the same way as the CBT-*in vivo* group.

13 294 **Fidelity to the treatment manual**

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16 295 The intervention is manual-based, which improves the standardization of the treatment. Fidelity to
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18 296 the treatment manual will be assessed through a self-report questionnaire answered by the clinicians
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20 297 at five different time points throughout each group treatment. The questionnaire (and the timepoints
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22
23 298 whence it is delivered) are designed to correspond to the treatment manual. This type of fidelity
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25 299 measurement has proved useful and adequate in trials where the effect of treatment is tested [57].

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27 300 The VR headsets will also record statistics of the use of the 360° films. This data shows which
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30 301 specific scenes were watched and how much and can be matched to the individual patient. This data
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32 302 will be used to keep track of the VR usage throughout the study to see how well it matches the
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34 303 treatment manual.

36 304 **Treatment completion and discontinuation**

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39 305 Criteria for *treatment completion*, *partial treatment* and *no treatment* were based on clinical
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41 306 guidelines for writing epicrisis as well as discussions within the research group.

- 43 307 • The attendance of ten or more group therapy sessions will be coded as 'treatment
44 308 completion'.
- 45
46 309 • The attendance of between four to nine group therapy sessions will be coded as 'partial
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48 310 treatment'.
- 49
50 311 • The attendance of less than four group therapy sessions will be coded as 'no treatment'.
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312 Treatment will be discontinued if participants do not show up to treatment three weeks in a row and
313 cannot be contacted after multiple attempts by the therapists. Participants that have their treatment
314 discontinued will still be included in the statistical analysis.

315 **Virtual reality equipment**

316 The patients receiving the *in virtuo* exposure will be immersed using an Oculus Go head-mounted
317 display, enabling viewing of 360° spherically camera recorded VR environments. The VR scenarios
318 will thus be high-resolution 360° stereoscopic films, that are played around the viewer. For audio,
319 the patients will use high-quality sound-blocking headphones. For ease of use, the individual videos
320 will be administered from an app that has been designed to be as intuitive to operate as possible.

321 The patient will only have to put on the headset, adjust the focus and choose the desired
322 environment by looking at it in the app. 360° video was chosen because it gives the most
323 photorealistic visuals, while also being the cheapest to produce. The downside is that it does not
324 allow direct user-interaction (e.g. the viewer cannot affect the environment in any way). To
325 circumvent this, there are multiple junctions throughout the films where the actors will talk directly
326 and unsolicited to the viewer (e.g. greetings, common questions) while also allowing time for the
327 viewer to respond. The actors respond in a generic way to the actions of the viewer. Unsolicited and
328 direct referral from a virtual environment seems to be an essential factor in triggering realistic
329 responses to it [58]. Though the non-interactability of the environment limits the flexibility of
330 behavioral experiments, it does not make them impossible. E.g., it is still possible to hypothesize
331 about internal states (e.g. “I will clam up if I have to present in front of people”) and identify and
332 challenge negative automatic thoughts.

333 **Virtual Reality scenarios**

334 13 VR exposure scenarios relevant for social anxiety disorder and Agoraphobia were chosen for the
335 *CBT-in virtuo* condition. The 13 scenarios are as follows:

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- 4 336 1) Standing in line in a supermarket
- 5
- 6 337 2) Being in a crowded shopping center
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- 8
- 9 338 3) Attending a party
- 10
- 11 339 4) Attending a formal meeting and giving a presentation
- 12
- 13 340 5) A job interview
- 14
- 15
- 16 341 6) Small talking/discussing in a university canteen with young adults
- 17
- 18 342 7) Small talking/discussing in a canteen in a work setting
- 19
- 20 343 8) Entering an auditorium
- 21
- 22
- 23 344 9) Leaving your apartment
- 24
- 25 345 10) Waiting for- and taking the bus
- 26
- 27 346 11) Crossing a bridge
- 28
- 29
- 30 347 12) Taking an elevator
- 31
- 32 348 13) Taking a commercial airplane
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36 350 Each scenario has four to six scenes of increasing difficulty as well as a neutral scene to familiarize

37

38 patients with the VR setting. All scenes skip to a looping version of a scene in the same

39 351 environment after being played, to allow patients to achieve within-session habituation if needed.

40

41 352 See additional file 3 for screenshots and descriptions of the individual scenes, as well as links to

42

43 353 view a selection of the scenes online. All identifiable persons depicted in the virtual environments

44

45 354 are paid actors.

46

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50 356 **Patient and Public Involvement: Development of virtual reality scenarios and manual**

51

52 357 The pilot phase was a continuous iterative process between the developers of the VR media, CBT-

53

54 trained clinicians and a panel of patients with social anxiety disorder and/or agoraphobia. The

55 358 process lasted approximately 16 months (12 for social anxiety disorder environments and 4 for

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4 360 agoraphobia) and consisted of regular meetings following each scenario's initial filming wherein the
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7 361 patients saw the VR scenario in question. Their experience (e.g. anxiety level provoked from the
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9 362 films, the validity of the scenarios) was then used as a starting point for a discussion of further
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11 363 development and alterations to the scenarios. Towards the end of the development of the scenarios
12
13 364 and application to launch them, two clinicians tested the usability of VRE in a group format. The
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15
16 365 clinicians and patients then gave further feedback on the films and the delivery of the exposure in
17
18 366 the group. This guided the initial draft for a group CBT manual with VRE for social anxiety
19
20 367 disorder and agoraphobia.

22 368 **Assessment**

24 369 *Diagnostics*

25 370 MINI version 7.0 for DSM-5 will be used to screen for diagnosis. At the inclusion interview, all
26
27 371 modules but P will be used to assess diagnostic eligibility. At the baseline interview, all modules
28
29 372 but P will be used to assess diagnosis and detect comorbidity. At the post-treatment interview, all
30
31 373 modules but P will be used to assess diagnosis and detect comorbidity. At the follow-up interview,
32
33 374 all modules but P will be used to assess diagnosis and detect comorbidity.

35 375 *Outcomes and sample size calculation*

36 376 We originally designed the trial around inclusion of only patients with social anxiety disorder,
37
38 377 basing the sample size calculation on the following parameters on the LSAS: With $\alpha=0.05$, 80%
39
40 378 power, and an expected standard deviation of 21, 302 patients would be required to detect the
41
42 379 minimal relevant difference of 6.8 on the LSAS total score between the groups.

43
44 380 Upon deciding to expand the diagnostic criteria for inclusion to also include patients with
45
46 381 agoraphobia, it was necessary to change our primary outcome measure. For patients with
47
48 382 agoraphobia, we primarily rate symptoms using MIA. To include both patients with social anxiety
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50 383 disorder and patients with agoraphobia, we thus decided to recalculate scores on these two scales to
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4 384 POMP as described below. Since the sample size calculation for LSAS was based on a Cohen's
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6 385 $d=0.33$, we also set the minimum clinically relevant difference on MIA, and by extension on the
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8
9 386 POMP, to $d=0.33$. Consequently, the required sample size remained unaffected by this change of
10
11 387 primary outcome measures and is thus still 302 patients. See Figure 3 for power calculations on
12
13 388 secondary outcomes.

15
16
17 389 Primary outcome:

18
19 390 Total scores on the LSAS for patients with social anxiety disorder and the MIA for patients with
20
21 391 Agoraphobia measured pre-treatment, post-treatment and at one-year follow-up converted to the
22
23 392 POMP and averaged within treatment arms. POMP calculations can bring differently measured
24
25 393 items to the same metric and do not change the multivariate distribution and covariance matrix of
26
27 394 the transformed variables. Therefore, scales transformed with the POMP method can be used to
28
29 395 examine mean-level differences between groups [59–61]. Using POMP transformed scores on two
30
31 396 different measures of phobic anxiety makes it possible to include patients with different primary
32
33 397 diagnoses in the same analysis, thus, avoiding the need for approximately double the number of
34
35 398 participants to reach a sufficient sample size. The downside of this method is that differences in the
36
37 399 sensitivity of the outcome measures and potential differences in treatment effect between patients
38
39 400 with social anxiety disorder and agoraphobia, which has been observed in diagnosis-specific
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41 401 treatment [62], are also averaged out, thus possibly skewing results.
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49 403 Social anxiety disorder symptom severity will be measured using a danish version of the LSAS.
50
51 404 LSAS assesses 24 situations typically feared by individuals with social anxiety disorder, rated on
52
53 405 anxiety and avoidance, divided into subscales of performance anxiety and social situations. It has
54
55 406 acceptable psychometric properties [63]. Agoraphobia symptom severity will be measured using a
56
57 407 danish version of the MIA. The MIA assesses avoidance of 26 situations typically feared by
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4 408 agoraphobic patients [64]. The MIA has demonstrated excellent psychometric properties and has
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6
7 409 been validated in multiple languages, including Swedish [65,66].
8

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11 411 Secondary outcomes:
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14 412 • Depressive symptoms measured pre-treatment, post-treatment and at follow-up as total scores
15
16 413 on the Hamilton Depression Rating Scale, 6 item version (HAM-6) [67]
17
- 18 414 • Fear of negative evaluation measured pre-treatment, post-treatment and at follow-up with the
19
20 415 Brief Version of the Fear of Negative Evaluation Scale (FNES) [68].
22
- 23 416 • Work and Social Adjustment measured pre-treatment, post-treatment and at follow-up with the
24
25 417 Work and Social Adjustment Scale (WSAS) [69, 70].
26
- 27
28 418 • User acceptability and satisfaction of treatment measured post-treatment with the Client
29
30 419 Satisfaction Questionnaire (CSQ). The CSQ is an 8-item scale loading to one factor of
31
32 420 satisfaction with mental health care service [71].
33
- 34
35 421 • Quality of Life measured pre-treatment, post-treatment and at follow-up with the WHO Well-
36
37 422 Being Index, five items (WHO-5). It is considered a very sensitive outcome measure as it does
38
39 423 not incorporate negative quality of life, i.e. distress, and has no ceiling effect [72].
40
- 41
42 424 • Treatment response on social anxiety disorder symptoms measured as LSAS below 50 or a 15
43
44 425 points drop.
45
- 46
47 426 • Treatment response on agoraphobia symptoms measured as MIA below 2 or a 0.5 points drop.
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- 49
50 427 • Remission of social anxiety disorder symptoms measured post-treatment and at follow-up as
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52 428 LSAS below 25 [73] and not qualifying for social anxiety disorder as measured using the MINI.
53
- 54
55 429 • Remission of agoraphobia symptoms measured post-treatment and at follow-up as MIA below
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57 430 1.5 and not qualifying for agoraphobia as measured using the MINI.
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4 431 Explorative outcomes:

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7 432 • Social functioning measured with Personal and Social Performance Scale [74] (PSP) pre-
8
9 433 treatment, post-treatment and at one-year follow-up.
10
11 434 • Substance and alcohol use measured with timeline followback [75] (TLFB) pre-treatment, post-
12
13 435 treatment and at one-year follow-up.
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15
16 436 • Self-belief of coping measured with General Self Efficacy [76] (GSE) pre-treatment, post-
17
18 437 treatment and at one-year follow-up.
19
20
21 438 • Working alliance measured with the Working Alliance Inventory [77] (WAI) post-treatment.
22
23 439 • Social anxiety symptoms in patients with social anxiety disorder, measured with the LSAS pre-
24
25 440 treatment, post-treatment and at one-year follow-up.
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27
28 441 • Agoraphobia symptoms in patients with agoraphobia, measured with the MIA pre-treatment,
29
30 442 post-treatment and at one-year follow-up.
31

32 443 Other measures:

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35 444 • Unwanted negative side-effects induced by immersions in VR (commonly referred to as
36
37 445 cybersickness) will be measured with the Simulator Sickness Questionnaire [78] (SSQ) at the
38
39 446 end of VRE sessions.
40
41
42 447 • Deterioration and adverse effects of psychotherapy on social anxiety disorder symptoms
43
44 448 measured post-treatment and at follow-up as a 6.8+ point increase in total LSAS score. Patients
45
46 449 who have deteriorated will be interviewed about their experiences in therapy.
47
48
49 450 • Deterioration and adverse effects of psychotherapy on Agoraphobia symptoms measured post-
50
51 451 treatment and at follow-up as a 0.3 point increase in total MIA score. Patients who have
52
53 452 deteriorated will be interviewed about their experiences in therapy.
54
55
56 453 • The experience of Social Presence, as described by Lee [79], will be measured after each VR
57
58 454 exposure session with a scale consisting of 9 questions rated on a 1-7 Likert scale. This scale
59
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4 455 was developed specifically for this trial because existing scales are too specific for the VR
5
6 456 equipment and content they were developed for. Social Presence is measured instead of the
7
8
9 457 more general construct of Presence, because it has been theorized to be a critical element in the
10
11 458 effective use of VRE for socially related fears [80,81].
12

13 459 14 15 16 460 **Data from medical report**

17
18 461 The following data will be retrieved from the participants' medical report with consent, only if the
19
20 462 participant cannot remember it:

- 21
22
23 463 1. Number of previous hospitalizations for mental health conditions or medical conditions.
- 24
25 464 2. Use of mental health services during the follow-up period
- 26
27 465 3. Current and previous psychopharmacological medication
- 28
29
30 466 4. Attendance rate of the CBT treatment.
31

32 467 33 34 468 **Setting of assessment**

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36
37 469 Assessment will take place at the outpatient clinics where the patients also receive treatment. Self-
38
39 470 report questionnaires (MIA, FNE, CSQ, WAI, WSAS, WHO-5) will be answered by following a
41
42 471 link sent to the patient's email address, which the patients can access either on a personal device or
43
44 472 on one of the clinic's computers. If preferred by the patient, the self-report questionnaires can be
45
46 473 filled out on printed copies of the scales while at the assessment interview. MINI, LSAS, PSP,
48
49 474 HAM-D6 and TLFB will be administered by trained researchers and research assistants. After each
50
51 475 session with VRE, specific questionnaires (Social Presence & Simulator Sickness Questionnaire)
52
53 476 will be administered by the clinicians delivering the intervention. If necessary, due to the global
54
55
56 477 COVID-19 pandemic, assessment interviews will be performed via telephone.
57

58 59 478 **Randomization** 60

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4 479 Randomization is performed by randomizing each therapy group, one week before the first
5
6
7 480 treatment session. This means that no patient is included while their treatment allocation is known.
8
9 481 The Randomization is done with a hidden allocation sequence generated from
10
11 482 www.sealedenvelope.com and is centralized and handled with the randomization module in
12
13
14 483 REDCap by a project manager uninvolved in the data collection. Block sizes will be unknown to
15
16 484 the outcome assessors and clinicians. The factor for stratification is the treatment site. Allocation
17
18 485 tables will be handled by external researchers with no affiliation with the project. An email of the
19
20
21 486 group's assigned randomization will be sent to the team leaders organizing the logistics of the
22
23 487 interventions in the Psychotherapeutic clinics. Assigned randomization of the groups will be stored
24
25 488 by the research team data manager. The randomization code will be stored at redcap.

27 489 **Blinding**

28
29
30 490 The assessors are blinded when interviewing at pre-treatment, post-treatment and at follow-up.
31
32 491 Should unblinding occur, another researcher will perform the assessment. Blinded researchers will
33
34 492 perform analysis and draft conclusions. There are no circumstances where unblinding of the
35
36
37 493 assessors is permissible.

39 40 494 **Data collection methods and management**

41
42 495 See Figure 1 for an overview of data collection. Self-reported data will be collected through surveys
43
44 496 send via REDCap (Research Electronic Data Capture) or filled out on paper. Assessors are trained
45
46
47 497 in the interview instruments and will do regular co-ratings of recorded interviews. Interrater
48
49 498 reliability of clinician-rated outcome measures will be calculated throughout the trial. The
50
51 499 interviewers will import data from the assessments directly into the electronic CRF (Case Report
52
53
54 500 Form) using the data entry system REDCap [82]. REDCap is an electronic data capture tool hosted
55
56 501 at CIMT (Center for IT, Medico and Telephony) in the Capital Region of Denmark. For non-self-
57
58 502 report measures, data will first be captured on paper and then entered electronically. REDCap
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4 503 complies with Danish legislation (the Act on Processing Personal Data) due to it having both
5
6 504 comprehensive user rights and access control management and a complete audit trail on all data
7
8
9 505 transactions. The data from individual patients are tied to a unique serial number. Assigned
10
11 506 researchers and GCP (Good Clinical Practice) monitors will be the only people who can access the
12
13 507 database. Non-electronic data will be stored locally in secure archives. Data will be exported from
14
15 508 REDCap without personal identifiers. Data will be exported to all well-known software packages:
16
17
18 509 (SPSS, SAS, Stata, R.) and stored on a secure network drive under the control of CIMT. A data
19
20 510 manager will ensure that all variables are correctly defined with variable and value labels. All
21
22 511 derived variables will be correctly defined, and algorithms will be kept in individual files. All data
23
24 512 will be scrutinized to identify errors in data entry. The sponsor and the principal investigators
25
26
27 513 ensure that data is stored at least ten years after the trial is ended.
28
29

30 514 **Statistical methods**

31
32 515 The analysis will all be from intention-to-treat. All included patients will also be included in the
33
34 516 analyses. All statistical tests of significance will be two-tailed. The primary outcome analysis will
35
36 517 be an intention-to-treat analysis. Missing data will be handled by multiple imputations (m=100). As
37
38 518 predictors in the imputation model, we will select variables if they are independent predictors of the
39
40 519 outcome or predictors of missing data ($P < 0.05$ in a univariate model). Each group will have
41
42 520 imputations done separately. Analysis of covariance will be used to calculate any significant results
43
44 521 between the two groups, using the baseline value and the stratification variables.
45
46 522 The continuous variables will be imputed with linear regression. Binary variables will be imputed
47
48 523 with binary logistic regression. Multinomial variables will be imputed with multinomial logistic
49
50 524 regression. Ordinal variables will be imputed with ordinal logistic regression. For every type of
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52 525 variable, we will perform 100 imputations.
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526 All distributions will be assessed for normality using visual inspection of histograms and Q-Q plots.

527 If not normally distributed, variables will be log-transformed, and if unsuccessful, a non-parametric
528 test will be used.

529 For dichotomous outcomes, we will perform multiple logistic regressions with treatment as usual as
530 reference and stratification variables as covariates after having imputed missing values using a
531 logistic regression model.

532 *Dissemination*

533 A trial protocol, including a plan for statistical procedures, has been published at
534 www.clinicaltrials.gov/ct2/show/NCT03845101. This will ensure that the SoREAL trial is
535 conducted and analyzed as planned. Possible deviations and reasons for those will be described in
536 publications. All data published will be verified for authenticity by controlling for internal
537 inconsistency. All results, positive, negative as well as inconclusive, will be published as quickly as
538 possible and still in concordance with Danish law on the protection of confidentially and personal
539 information. Results will be presented at national and international scientific conferences. Lastly,
540 results will be presented at relevant mental health centers in Denmark.

542 *Data monitoring and auditing:*

543 Like in GCP monitoring, an independent committee will check the following data for included
544 patients: Informed consent, inclusion and exclusion from intervention, serious adverse events and
545 severe adverse reactions. It will be checked whether there is a link between trial allocation and the
546 serious adverse events and severe adverse reactions.

548 *Safety:*

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4 549 In the clinical setting, the clinicians will register Adverse Events and Adverse Reactions and report
5
6 550 all Serious Adverse Events and Severe Adverse Reactions to the sponsor. Other events or side
7
8
9 551 effects will be collected from patient files and registers. International Conference on Harmonization
10
11 552 of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical
12
13 553 Practice guidelines define serious adverse events and serious adverse reactions. The patients in the
14
15
16 554 SoREAL trial are ensured by Danish law and the patient care regulation. Every patient in the
17
18 555 SoREAL trial will have access to their results of the trial if they wish to. The clinicians will not
19
20 556 have access to data collected from assessments done by the researchers.
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23 557

24 25 558 Trial status

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30 559 Inclusion began on February 4th, 2019. Inclusion is expected to stop on June 4th, 2023. Inclusion
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32 560 was delayed by approximately three months due to the COVID-19 pandemic.
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35 561 List of abbreviations

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40 562 VRET: Virtual Reality Exposure Therapy; CBT: Cognitive behavioral therapy; RCT: Randomised
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42 563 Controlled Trial. MINI: Mini international neuropsychiatric interview. VR: Virtual reality. LSAS:
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44 564 Liebowitz social anxiety scale. MIA: Mobility Inventory for Agoraphobia. POMP: Percentage of
45
46 565 Maximum Possible Score. PSP: Personal and social performance scale. TLFB: Timeline
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49 566 followback. FNE: Fear of negative evaluation scale. CSQ: Client satisfaction questionnaire. WAI:
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51 567 Working alliance inventory. WSAS: Work and social adjustment scale. HAMD-6: Hamilton
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53 568 depression scale, 6 item version.
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57 569 Declarations

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570 **Sponsor details**

571 Name: Merete Nordentoft.

572 Contact: merete.nordentoft@regionh.dk

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576 **Ethics approval and consent to participate**

577 The trial has obtained approval by the Regional Ethics Committee of Zealand (H-6-2013-015) and
578 the Danish Data Protection Agency (RHP-2014-009-02670). The trial is registered at
579 ClinicalTrial.gov as NCT03845101. The patients will receive information on the trial both verbally
580 and in written form. Written informed consent will be obtained from each patient before inclusion
581 in the trial. The consent form will be scanned and stored in the database system and the physical
582 copy will be destroyed. It is emphasized that participation in the trial is voluntary and that the
583 patient can withdraw his or her consent at any time without consequences for further and continued
584 treatment.

585 **Protocol amendments**

586 Changes in protocol will be reported to the trial registry by a researcher via the designated website,
587 to participants if it affects them in any way via email, to the ethical committee and Danish Data
588 Protection Agency via their online forms.

589 **Availability of data and materials**

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590 After completed analyses and publication, data will be transferred to The Danish National Archives
591 and made available for other researchers upon reasonable request and with permission of The
592 Danish National Archives.

593 **Additional file data**

594 Additional file 1. Format: docx. Title: SPIRIT 2013 Checklist. Description of data: Checklist of
595 recommended items to address in a clinical trial protocol and related documents.

596 Additional file 2. Format: docx. Title: Model Consent Form for the SoREAL Trial

597 Additional file 3. Format: docx. Title: Screenshots and descriptions of Virtual Reality Exposure
598 environments.

599 **Author contributions**

600 Authorship is this based on the Vancouver guidelines. All authors have read, revised and approved
601 the manuscript. MN and NR had the original idea for the trial. MN wrote the application for the
602 NovoNordic Foundation and is the PI of the trial. CH generated the allocation sequence, carried out
603 the power calculations and will be responsible for supervising the statistical analyses. NR was
604 responsible for the non-experimental content of the CBT. CW, KM, CS, PB and BTA directed the
605 development of the VR films. CW, KM, UKG, DS, PW, BTA and PB developed the manual and
606 guidelines for using VRET in group therapy. MHP was responsible for outcome measures. BTA
607 and PB developed the Social Presence Scale and fidelity measures. BTA set up randomization, built
608 and manage the database, and is responsible for all participant assessment, including training and
609 managing research assistants.

610 **Competing interests**

611 The authors declare that they have no competing interests.

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4 612 **Consent for publication**

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7 613 Not applicable.
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11 614 **Acknowledgments**

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14 615 N/A.
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17 616 **Funding**

18
19 617 MN and NR initiated the project. MN applied to Novo Nordisk Foundation, and the SoREAL trial
20
21 618 was granted 5.000.000 DKK [NNF17OC0027780]. MN and NR have no affiliation to the Novo
22
23 619 Nordisk Foundation. MN, PB and BTA applied to TrygFonden and the trial was granted an
24
25 620 additional 3.517.500 DKK [ID: 146169]. MN, PB and BTA have no affiliation to TrygFonden.
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29 621 The project is entirely independent of the Novo Nordisk Foundation and TrygFonden and therefore,
30
31 622 the funding body plays no role in the design of the study, the collection, analysis and interpretation
32
33 623 of data and in writing the manuscript. Nor will the Novo Nordisk Foundation or TrygFonden play
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35 624 any role in future publications that may derive from the project.
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39 625 **Protocol version and date**

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42 626 Protocol Version 5 – Revised 11.11.21
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628 **Figure legends**

629 Figure 1. Overview of data collection

630 Figure 2. Flow diagram of the SoREAL trial

631 Figure 3. Power calculation for secondary outcomes in the SoREAL trial

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For peer review only

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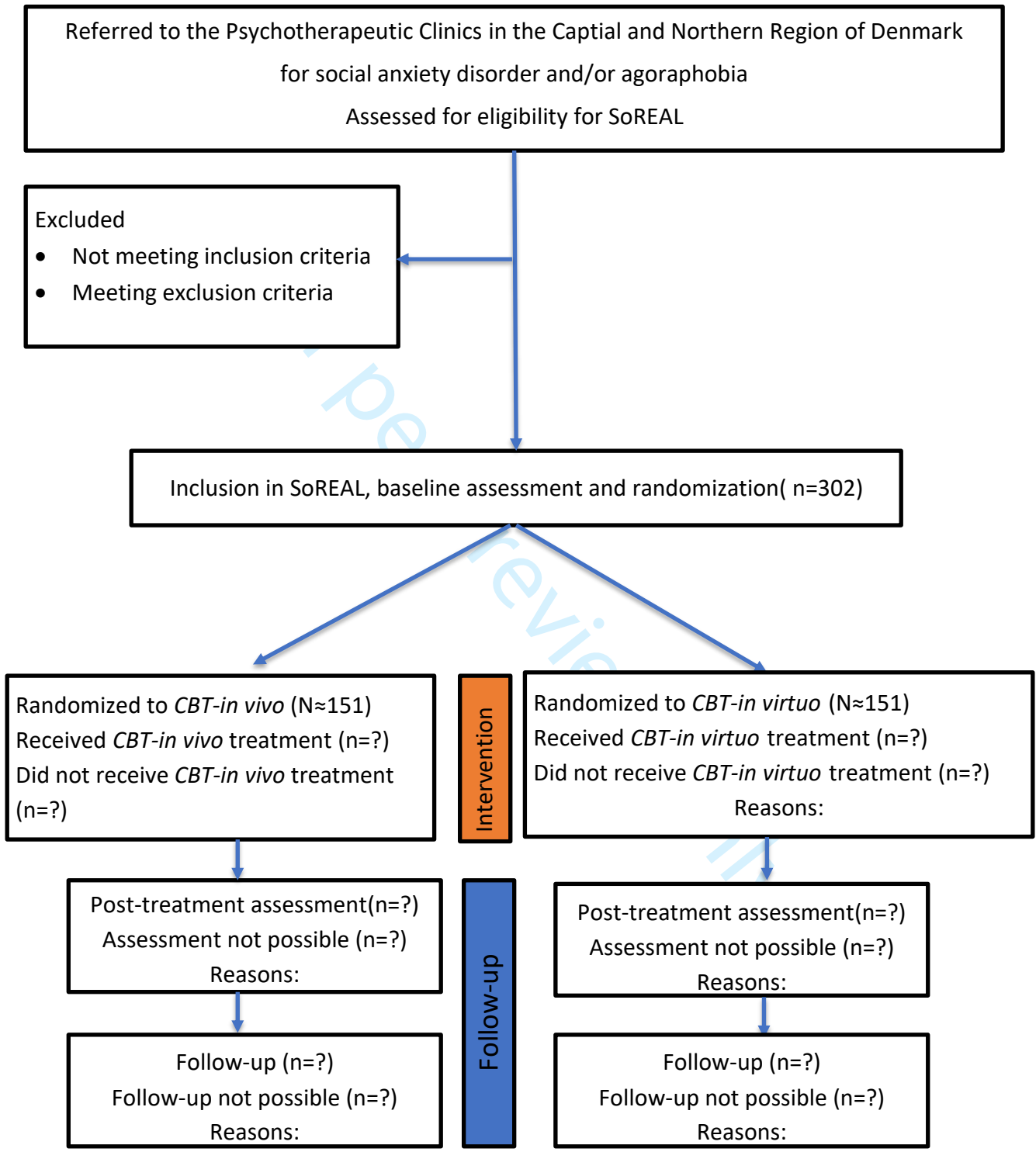
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Schedule of enrolment, interventions, and assessments.		STUDY PERIOD		
		Enrolment and allocation	Follow-up	
TIMEPOINT**		Baseline	Post-treatment	One-year
ENROLMENT:				
	ENROLMENT:	X		
	Eligibility screen	X		
	Informed consent and inclusion	X		
	Allocation	X		
INTERVENTIONS:				
	CBT-In vivo			
	CBT-In virtuo			
ASSESSMENTS:				
	Sociodemographic data (Interview + registries)	X		
	Diagnosis, using Mini International Neuropsychiatric Interview	X	X	X
	Liebowitz Social Anxiety Scale	X	X	X
	Agoraphobia Mobility Inventory	X	X	X
	Hamilton Depression Rating Scale 6	X	X	X
	Timeline Follow Back, Alcohol & Substance	X	X	X
	Fear of Negative Evaluation Scale	X	X	X
	Work and Social Adjustment Scale	X	X	X
	World Health Organization 5	X	X	X
	Personal and Social Performance Scale	X	X	X
	General Self Efficacy Scale	X	X	X
	Client Satisfaction Questionnaire		X	
	Social Presence Scale	(During treatment for CBT-In virtuo) X		
	Simulator Sickness Questionnaire	(During treatment for CBT-In virtuo) X		
	Working Alliance Inventory		X	

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Outcome	Lowest clinically relevant difference	Expected standard deviation	Calculated power	Reference
Fear of Negative Evaluation	4.5	10	97 %	[68]
Hamilton Depression Rating Scale, 6 items	1.6	4	93 %	[67]
Client Satisfaction Questionnaire	2	5	93 %	[70]
WHO Well-Being Index, 5 items	10	25	93 %	[71]
Work and Social Adjustment Scale	8	10	~100 %	[69,70]
Remission (LSAS<30)	20 % in control group vs. 35 % in the VR group		84%	[63,73]
Response (LSAS<50 or a 15 point drop)	65 % in control group vs. 80 % in VR group		84%	[63]
Remission (MIA<1.5)				
Response (MIA <2 or a 0.5 point drop)				



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3
	2b	All items from the World Health Organization Trial Registration Data Set	All items are accounted for in the protocol and in our registration.
Protocol version	3	Date and version identifier	Page 29
Funding	4	Sources and types of financial, material, and other support	Page 29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 28 & 1
	5b	Name and contact information for the trial sponsor	Page 27
	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	Page 29

1	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)	Except data management (see item 21a), none of the entities described here are relevant in the present trial. However, see item 5a for roles of protocol contributors.
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16	Introduction		
17			
18	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	Pages 4-7
19			
20			
21		6b Explanation for choice of comparators	Pages 6-7 & 18-22
22			
23	Objectives	7 Specific objectives or hypotheses	Pages 7-8
24			
25	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)	Page 2
26			
27			
28			
29	Methods: Participants, interventions, and outcomes		
30			
31	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	Pages 8-9
32			
33			
34	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)	Pages 9-10
35			
36			
37	Interventions	11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 10-18
38			
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1		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)	Pages 15-16 & 26
2				
3				
4		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 15
5				
6				
7		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Pages 10-11
8				
9	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	Pages 19 – 22
10				
11				
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14				
15	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)	See attached SPIRIT figure
16				
17				
18	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	Pages 18-19
19				
20				
21	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Pages 8-10
22				
23				
24	Methods: Assignment of interventions (for controlled trials)			
25				
26	Allocation:			
27				
28	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	Page 23
29				
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32				
33	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	Page 23
34				
35				
36				
37				
38	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pages 22-23
39				
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1	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 23
2				
3				
4		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 23
5				
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8	Methods: Data collection, management, and analysis			
9				
10	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pages 19-24 & Figure 3
11				
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15		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 21 & 22
16				
17				
18	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Pages 23-24
19				
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23	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 24-25
24				
25				
26		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A. We do not plan to perform subgroup or adjusted analyses.
27				
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32		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 24-25
33				
34				

Methods: Monitoring

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1	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 25
2				
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6		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A. We will not perform interim analyses.
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11	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 26
12				
13				
14	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 25
15				
16				
17				
18	Ethics and dissemination			
19				
20	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 27
21				
22				
23	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)	Page 27
24				
25				
26				
27	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 27
28				
29				
30				
31		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
32				
33				
34	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	Page 23-24
35				
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37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 28
38				
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1	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	Page 28
2				
3				
4	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
5				
6				
7	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	Page 25
8				
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11		31b	Authorship eligibility guidelines and any intended use of professional writers	Page 28
12				
13		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 28
14				
15				
16	Appendices			
17				
18	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary file 2
19				
20				
21				
22	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
23				
24				

*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.

Deltagerinformation - SoREAL

Forsøgets titel: SoREAL – Virtual Reality til behandling af angst

Vil du deltage i et forsøg, som samtidig er behandling?

Før du beslutter, om du vil deltage i forsøget, skal du fuldt ud forstå, hvad projektet går ud på, og hvorfor vi gennemfører dette. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Du vil blive inviteret til en samtale om forsøget, hvor denne deltagerinformation vil blive uddybet, og hvor du kan stille de spørgsmål, du må have. Du er velkommen til at tage et familiemedlem, en ven eller en bekendt med til samtalen.

Hvis du beslutter dig for at deltage i forsøget, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til betænkningstid, før du beslutter, om du vil underskrive samtykkeerklæringen.

Det er frivilligt at deltage i forsøget. Du kan når som helst og uden at angive en grund trække dit samtykke tilbage, uden at det vil få konsekvenser for din videre behandling

Formål med forsøget

I behandlingen af angst indgår øvelser hvor man udsætter sig for situationer, som man plejer at undgå. Dette kaldes eksponering. Forskning har vist, at det at blive udsat for og klare vanskelige situationer er et vigtigt element i effektiv behandling af angst. Eksponering i behandlingen sker sædvanligvis ved at man opsøger udfordrende situationer eller skaber dem i rollespil. I det forsøg som vi vil tilbyde dig at deltage i, afprøver vi om eksponering kan forbedres ved at bruge virtual reality. Det vil ske ved at man ser 360 graders film af en række af angstprovokende situationer. Filmene afspilles omkring dig i virtual reality briller, som optager hele dit synsfelt. Man har samtidigt hovedtelefoner på som blokerer for lyd fra virkeligheden. Derved vil filmene opleves meget virkelighedstro, og det vil virke som om man selv er tilstede i den situation, som filmen handler om.

Som deltager afgøres det ved lodtrækning om du bliver tilbudt den sædvanlige behandling, eller behandlingen hvor virtual reality indgår. Dette gøres for at have en kontrolgruppe at sammenligne den nye behandling med og for at minimere fejlkilder i resultaterne.

Det skal understreges, at kun nogle af eksponeringsøvelserne bliver erstattet med virtual reality øvelser, således vil alle der deltager stadig få noget eksponering i virkelige situationer.

Plan for forsøget

I psykiatrien i Danmark tilbydes patienter der lider af angst, 14 ugers gruppeterapi (14x2 timer, 1 gang pr. uge) – det såkaldte pakketilbud. Som et led i denne behandling indgår 8 sessioner hvor man arbejder med eksponering for vanskelige situationer. Alle forsøgsdeltagere vil i de 8 sessioner skulle arbejde med vanskelige situationer. Som deltager i dette forsøg afgøres det ved lodtrækning om disse situationer udføres i virkeligheden eller i virtual reality.

Som forsøgsdeltager inviteres du til deltagelse i et interview med en forsker forud for terapiens start, ved terapiens afslutning og et år efter terapiens start. Forskningsinterviewene vil dreje sig om symptomer på psykisk lidelse med fokus på angst og depression, livskvalitet, tilfredshed med behandlingen og eventuelle bivirkninger og inkluderer også besvarelse af en række spørgeskemaer. Til første forskningsinterview vil du yderligere blive tilbudt at gå med pulsar under hele behandlingsforløbet. Du vil efter hver terapisession med virtual reality eksponering blive bedt om at udfylde spørgeskemaer vedrørende din oplevelse af at bruge virtual reality udstyret.

Hvis du giver tilladelse til det vil der blive indhentet journaloplysninger om tidligere indlæggelser for psykiatriske eller somatiske tilstande, aktuel psykiatrisk behandling, aktuel og tidligere psykofarmakologisk behandling.

Hvis du ønsker at trække dig fra forskningsprojektet, vil det ikke få indflydelse på din øvrige behandling, og hvis du ønsker det, vil de oplysninger, som er indsamlet som del af forskningsprojektet, blive trukket ud af projektet, og dataindsamling og registrering vil herfra foregå som vanligt i sundhedsvæsenet. Det skal understreges at man i forbindelse med publikationer er sikret anonymitet.

Nytte ved forsøget

Vi ved aktuelt ikke, om behandling med virtual reality eksponering er mere eller mindre effektiv end den behandling, der sædvanligvis tilbydes. Hvis behandlingen med virtual reality eksponering er ligeså effektiv eller mere effektiv, kan det i fremtiden indgå systematisk i behandlingen af angst, og eventuelt komme til at være et træningstilbud, der kan supplere terapien uden for terapitimerne.

SoREAL 2018 - 2023

Bivirkninger, risici, komplikationer og ulemper

Der kan være bivirkninger ved forsøget i form af ubehag ved at bruge virtual reality briller, så som køresyge. Oplevelse af at blive rundtosset eller køresyg skyldes, at balanceevnen kan forstyrres af de sanseindtryk, som man får, når man har virtual reality udstyr på. Der er intet, der tyder på, at der er langvarige bivirkninger.

Der kan være risici ved forsøget, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer med dit helbred, mens forsøget står på. Hvis vi opdager bivirkninger, som vi ikke allerede har fortalt dig om, vil du naturligvis blive orienteret med det samme, og du vil skulle tage stilling til, om du ønsker at fortsætte i forsøget.

Andre behandlingsmuligheder

Alle der deltager i forsøget vil indgå i den øvrige behandling som sædvanligvis tilbydes til patienter som lider af angst.

Udelukkelse fra og afbrydelse af forsøg

Deltagelse i forsøget vil blive afbrudt, hvis deltagelse i gruppebehandlingen for angst afbrydes. Man vil fortsat blive tilbudt deltagelse i forskningsinterview.

Oplysninger om økonomiske forhold

Professor Merete Nordentoft har taget initiativ til projektet og har sammen med Nicole Rosenberg, Clas Winding, Kirsten Møller, Ruth Aharoni, Sebastian Swane og Carsten Hjorthøj indsendt en ansøgning til Novo Nordisk Fonden og har modtaget 5 millioner kr. til projektet.

Professor Merete Nordentoft, Benjamin Thorup Arnfred og Peter Bang har indsendt en ansøgning til TrygFonden og har modtaget yderligere 3.5 millioner kr. til projektet. Initiativtagerne til projektet har ingen økonomisk forbindelse med Novo Nordisk Fonden eller TrygFonden.

Adgang til forsøgsresultater

Forsøgets resultater vil blive sammenfattet i flere videnskabelige artikler. Vi forventer at kunne offentliggøre en artikel med projektets hovedresultater i 2023. I denne artikel vil vi præsentere resultaterne vedrørende effekten af de to sammenlignede behandlinger målt ved behandlingsafslutning og et år efter start i behandlingen.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i forsøget, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse.

SoREAL 2018 - 2023

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4 Hvis du vil vide mere om forsøget, er du meget velkommen til at kontakte:
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6

7 **Psykolog Benjamin T. Arnfred**
8

9 Mail: Benjamin.alexander.thorup.arnfred@regionh.dk
10
11

12 Telefon: +45 21 63 08 78
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14 Region Hovedstadens Psykiatri, Psykiatrisk Center København
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16 Kildegårdsvej 28, 2900 Hellerup
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Additional file 3 – Descriptions and screenshots of virtual environments used in the SoREAL trial.

All identifiable persons depicted are paid actors.

Environment 1 – Supermarket

Scene 0. Loop – Standing by the register. The supermarket is empty. [Link to YouTube](#)

Scene 1. 1:00 – Loop of scene 0. Standing in line. A man asks if you would use a ware separator. [Link to YouTube](#)

Scene 2. 1:39 – Loop of scene 0. Intimidating man cuts in line. Person in line is upset. You have forgotten to weigh your vegetables. [Link to YouTube](#)

Scene 3. 1:57 – Loop of scene 0. Your credit card is declined. Person in line is increasingly impatient and upset. [Link to YouTube](#)



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Scene 4. 0:50 – Loop of scene 0.
You win a prize for being
customer number 1.000.000.

[Link to YouTube](#)

Environment 2 – Presentation

Scene 0. Loop – Standing in
meeting room alone. [Link to](#)

[YouTube](#)

Scene 1. 2:20 – Loop of scene 0.
Meeting preparations with
colleague. [Link to YouTube](#)

Scene 2. 3:29 – Loop of scene 0.
Contact person arrives. Short
conversation. [Link to YouTube](#)

Scene 3. 2:35 – Loop of scene 0.
Two important meeting
participants arrive. [Link to](#)
[YouTube](#)



<p>1 2 3 4 5 6 7 8 9</p> <p>Scene 4. 2:01 – Loop of scene 0. The rest of the meeting participants arrive. Introductions to the group. Link to YouTube</p>	
<p>10 11 12 13 14 15 16 17</p> <p>Scene 5. 4:02 – Loop of scene 0. Presentation has technical difficulties. Partner leaves mid- presentation. Link to YouTube</p>	
<p>18 19 20 21 22 23</p> <p>Scene 6. 2:07 – Loop of scene 0. Scolding from the boss. Link to YouTube</p>	

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Environment 3 – Cafeteria

Scene 0. Loop – Sitting by table.

One person sits down nearby.

[Link to YouTube](#)

Scene 1. 3:04 – Loop of scene 0.

Someone small talks near you.

You are asked about parking.

Few people in the room. [Link to](#)

[YouTube](#)

Scene 2. 4:30 – Loop of scene 0.

More small talk. You are asked if there is room by the table. [Link](#)

[to YouTube](#)

Scene 3. 5:15 – Loop of scene 0.

You are in the middle of a discussion about art. [Link to](#)

[YouTube](#)

Scene 4. 5:11 – Loop of scene 0.

You are in the middle of a



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heated discussion about transgender issues. [Link to YouTube](#)

Environment 4 – Party

Scene 0. Loop – Arrived at door. Party audible inside.

Scene 1. 1:19 – Loop of scene 0. Guest arrives. Host opens door and greets guest. [Link to YouTube](#)

Scene 2. Loop – In kitchen with many partygoers. You are offered a shot of an alcoholic beverage. [Link to YouTube](#)

Scene 3. 3:35 – Loop of scene 2. Participate in drinking game in the kitchen. [Link to YouTube](#)

Scene 4. 3:37 – Loop of scene 2. In corner of room. Two guests



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have an intimate conversation
close by. [Link to YouTube](#)

Scene 5. 2:54 – Loop of scene 2.
On the dancefloor. A circle of
dancing revelers forms around
you. [Link to YouTube](#)

Environment 5 – Auditorium

Scene 0A. Loop. Sitting at a
lecture. [Link to YouTube](#)

Scene 0B. Loop. Waiting for
lecture to start. Few other
people. [Link to YouTube](#)

Scene 1. 1:14 – Loop of scene
0A. Arrived before class start to
empty auditorium. [Link to
YouTube](#)

Scene 2. 0:49 – Loop of scene
0A. Arrived exactly at the right
time. Few people in the
auditorium. [Link to YouTube](#)



<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46</p> <p>Scene 3. 1:02 – Loop of scene 0A. Arrived too late. Professor notes it as you enter. Link to YouTube</p> <p>Scene 4. 1:18 – Loop of scene 0A. Arrived much too late. Scolded in front of full auditorium by professor. Link to YouTube</p>	<p>For peer review only</p>
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Environment 6 – Job interview

A variety of relevant questions to be posed can be chosen by the patient such as “What are your weaknesses” etc., after the question a “listening loop” is played that allows the patient to talk while the two interviewers appear to listen.



**Environment 7 – Crossing a
bridge**

Scene 0A. Loop. Waiting in a
highway rest area.

Scene 0B. Loop. Waiting to get
picked up in sub-urban area.

Scene 1. 1:38 – Loop of scene 2.
Driving in sub-urban area.
Picking up other passengers.

Scene 2. Loop. Driving, no
conversation.

Scene 3. Loop. Crossing a bridge,
no conversation.

Scene 4. 4:25 -- Loop of scene 2.
Passenger gets carsick.

Scene 5. 5:27. Car breaks down
while crossing bridge.



**Environment 8 - Small
talking/discussing in a canteen
in a work setting**

Scene 0. Loop. At the buffet.

Scene 1. 1:00 – Loop of Scene 0.

Standing in line.

Scene 2. 3:00 – Loop of Scene 0.

In the middle of the canteen.

Scene 3. Loop. Eating with
colleagues. Small talk.


Scene 4. 2:00 – Loop of Scene 3.

Standing by table. Positive
mood.

Scene 5. 5:40 – Loop of Scene 3

Eating with colleagues. Negative
mood.



<p>Scene 6. 2:00 – Loop of Scene 0. Drops tray with food next to table.</p>	
<p>Environment 9 - Taking a commercial airplane</p> <p>Scene 0. 7:26. Taking a plane, from boarding to landing.</p> <p>It is possible to only play specific segments, e.g. “Turbulence” or “Boarding”.</p>	

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Environment 10 - Being in a crowded shopping center

Scene 0. Loop. At entrance to mall.

Scene 1. Loop. Inside mall, not crowded.

Scene 2. Loop. Inside mall, crowded.

Scene 4. Loop. Standing in line to toilet. One is out of order.



View only

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Environment 11 - Taking an elevator

Scene 0. Loop. Waiting for elevator.

Scene 1. Loop. Taking the elevator alone.

Scene 2. 1:45 – Loop of Scene 1. Taking the elevator with other people.

Scene 3. 6:30 – Loop of Scene 1. Elevator malfunctions with other people.

Scene 4. 6:20 – Loop of Scene 1 Elevator malfunctions with other people. You have a panic attack.



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Environment 12 - Waiting for-
and taking the bus

Scene 0. Loop. Waiting for bus.

Scene 1. 0:50 – Loop of Scene
2A. Bus arrives. Entering bus.

Scene 2A. Loop. In driving bus,
sitting.

Scene 2B. Loop. In driving bus,
standing.

Scene 3. 0:50 – Loop of Scene
2A. Baby driving in bus.

Scene 4. 2:00 – Loop of Scene
2A. Man speaks loudly on the
phone next to you.



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<p>Scene 5. 3:30 – Loop of Scene 2A. Drunk man enters bus and addresses you.</p>	
<p>Scene 6. 1:20 – Loop of Scene 2A. Elderly lady asks for your seat. You refuse.</p>	
<p>Scene 7. 2:00 – Loop of Scene 2A. Baby cries, man speaks loudly on phone and drunk man addresses you.</p>	

view only

Environment 13 - Leaving your
apartment

Scene 0. Loop. In entrance of
apartment.

Scene 1. Loop. On apartment
staircase outside apartment.

Scene 2. Loop. Standing in the
entrance to the apartment
building.

Scene 3. Loop. Standing in the
street outside apartment.



“—Loop of 0/1/2” indicates that the scene automatically jumps to that loop after finishin

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For peer review only