BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051147
Article Type:	Protocol
Date Submitted by the Author:	26-May-2021

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Keywords:	Anxiety disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, PSYCHIATRY

Title page

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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Abstract

Introduction Anxiety disorders have a high lifetime prevalence, early-onset, and long duration or chronicity. Exposure therapy is considered one of the most effective elements in cognitive behavioral therapy (CBT) for anxiety, but *in vivo* exposure can be challenging to access and control, and is sometimes rejected by patients because they consider it too aversive. Virtual reality allows flexible and controlled exposure to challenging situations in an immersive and protected environment. **Aim** The SoREAL-trial aims to investigate the effect of group cognitive-behavioral therapy (*CBT-in vivo*) versus group cognitive behavioral therapy with virtual reality exposure (*CBT-in virtuo*) for patients diagnosed with social anxiety disorder and/or agoraphobia, in mixed groups. **Methods & Analysis** The design is an investigator-initiated randomized, assessor-blinded, parallel-group and superiority-designed clinical trial. Three hundred two patients diagnosed with social anxiety disorder and/or agoraphobia will be included from the regional mental health centers of Copenhagen and North Sealand and the Northern Region of Denmark. All patients will be offered a manual-based 14-week cognitive behavioral group treatment program, including eight sessions with exposure therapy. Therapy groups will be centrally randomized with concealed allocation sequence to either CBT-*in virtuo* or CBT-*in vivo*. Patients will be assessed at baseline, post-treatment and one-year follow-up by treatment blinded researchers and research assistants. The primary outcome will be diagnosis-specific symptoms measured with the Liebowitz Social Anxiety Scale for patients with social anxiety disorder and the Mobility Inventory for Agoraphobia for patients with agoraphobia. Secondary outcome measures will include depression symptoms, social functioning, and patient satisfaction. Exploratory outcomes will be substance and alcohol use, working alliance and quality of life. **Ethics and dissemination:** The trial has been approved by the research ethics committee in the Capital Region of Denmark. All results, positive, negative as well as inconclusive, will be published as quickly as possible and still in concordance with Danish law on the protection

of confidentially and personal information. Results will be presented at national and international scientific conferences. **Trial registration:** The project was registered at clinicaltrials.gov on 02/19/2019 as NCT03845101. Can be found online at https://clinicaltrials.gov/ct2/show/NCT03845101

Article Summary

Strengths and limitations of this study

- The present study will be the first large randomized clinical trial to investigate virtual reality exposure therapy for social anxiety disorder and agoraphobia in group therapy.
- The present study is very closely integrated with clinical practice, making results highly transferable to similar real-life settings.
- Mixing patients with social anxiety disorder and agoraphobia in the same therapy groups have never been investigated systematically, which may confound the interpretation of results.
- Because the study is embedded in an outpatient hospital setting, the intervention was designed to be flexible. This increases the ecological validity but also the risk of systematic bias in treatment administration.

Keywords

Virtual Reality Exposure Therapy, Social Anxiety Disorder, Agoraphobia, Cognitive Behavioral Therapy, Randomized Clinical Trial.

Word Count

Background

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

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

Virtual Reality Exposure Therapy for Social Anxiety Disorder and Agoraphobia

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

perform Virtual Reality Exposure Therapy (VRET) [16,17], either as a standalone treatment, e.g. [18], or integrated into a CBT treatment e.g. [19].

The use of VR allows flexible and controlled exposure to challenging situations in an immersive and safe environment. Therefore, using VRET can mitigate the challenges of in-vivo exposure therapy by producing greater user acceptance and access to situations that would otherwise be too difficult to control, too resource-intensive to find and/or have unacceptable confidentiality risks [15,19,20]. Based on this, VRET may improve the efficacy and cost-effectiveness of psychotherapeutic interventions for anxiety disorders.

Recent reviews and meta-analysis of VRET either as a standalone treatment or combined with cognitive interventions, conclude that VRET is more effective than waitlist and placebo control and equally as effective as first-line treatment controls for anxiety disorders [21–23]. However, in one meta-analysis, the authors find significantly worse treatment effects of VRET for social anxiety disorder, when compared with control groups that received equal amounts of in-vivo exposure [24]. It has been suggested that it is more difficult to produce VRET environments for social anxiety disorder, as compared to other phobic disorders because human interaction is complex and therefore difficult to realistically recreate [25] which may explain these results. Accordingly, the same meta-analysis found no significant difference in treatment efficacy for CBT with VRET vs CBT with in-vivo exposure for agoraphobia and specific phobia [24].

In general, there is a scarcity of high-quality randomized clinical trials (RCT) evaluating the use of VRET for social anxiety disorder and agoraphobia [16,26,27]. For social anxiety disorder, there are five trials published, the largest having 97 participants [28,19,18,29,30]. For agoraphobia, there are six trials published, the largest having 80 participants [31–36]. All in all, the evidence-base for

using VRET compared to in-vivo exposure for social anxiety disorder and agoraphobia remain small. Therefore, larger studies that capitalize on the unique qualities of VRET are needed.

Virtual Reality Exposure in Group Therapy

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

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

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

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

[46], as well as recent evidence of the acceptable treatment efficacy of CBT-based transdiagnostic therapies [47].

However, it is worth noting, that the pragmatic mixed anxiety group format has never been systematically evaluated and that the official treatment recommendation remain diagnoses specific CBT delivered in group or individually [48]. To maximize the study's clinical representitativenes, as defined by Shadish et al. [49], the treatment structure in the present study, including the comperator, will mimic the treatment offered by the Danish mental health services.

Aim and objectives:

In summary in-vivo exposure is considered effective, but can be challenging to perform. Virtual Reality Exposure therapy may alleviate these challenges. However, the usefulness of VRET for social anxiety disorder and agoraphobia remains unclear. Larger studies that capitalize on the benefits of VRET are needed. Group therapy may be one way to capitalize on the benefits of VRET because it could allow for more individualized exposure exercises. Mixed anxiety groups are commonly used in Danish mental healthcare to reduce wait time, but have not been systematically evaluated. The treatment, inclusion and exclusion criteria described in the present study match the eligibility criteria for treatment and treatment format of the Danish mental healthcare system to maximize transferability of results to clinical practice.

Therefore, the SoREAL trial aims to evaluate the treatment efficacy of VRET in mixed anxiety CBT groups (CBT-in virtuo) compared to mixed anxiety CBT groups where exposure therapy is performed in-vivo (CBT-*in vivo*).

Thus, in the SoREAL trial, the following hypotheses' will be tested:

Primary hypothesis:

1. Post-treatment, patients treated with CBT-*in virtuo* will have a lower level of anxiety symptoms compared to patients treated with CBT-*in vivo*, measured as total scores on the Liebowitz Social Anxiety Scale (LSAS) for patients with social anxiety disorder and the Mobility Inventory for Agoraphobia (MIA) for patients with agoraphobia converted to the percent of maximum possible scores (POMP) and averaged within treatment arms.

Secondary hypotheses:

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

Overall, we believe that the SoREAL trial will contribute with knowledge about the efficacy and feasibility of VRE for treating social anxiety disorder and agoraphobia in a clinical outpatient setting. The results of this trial may guide future applications of VR in clinical settings across a wide breadth of use-cases.

Methods and design

This article was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 explanation and elaboration: guidance for protocols of clinical trials [50]. The SPIRIT Checklist was followed and the SPIRIT flowchart was used [See Additional file 1 and Figure 1].

Recruitment

The SoREAL trial is embedded directly into five outpatient clinics offering group CBT for social anxiety disorder and agoraphobia. These clinics are part of the Danish mental health care system.

To be eligible for treatment in these clinics, patients must be referred by their primary care physicians to a Center for Visitation and Diagnosis in their area, where their symptomatology will be assessed. At the Center for Visitation and Diagnosis, they must be referred to one of the five outpatient clinics involved in the study. At the outpatient clinic, the patient will again be clinically assessed, and a diagnosis and treatment plan will be formulated. If social anxiety disorder and/or agoraphobia is considered the primary diagnosis for the patient, they will be asked if they are interested in getting more information about the trial. If they consent to it, their contact details will be given to a researcher, who will invite them to an interview concerning the study.

Mini International Neuropsychiatric Interview (MINI), v. 7.0 for DSM-5 will be used to screen for diagnosis. Psychometric analyses of the MINI have demonstrated acceptable test-retest and inter-rater reliability [51,52]. Diagnostic screening is sufficient due to the thorough assessment from both Center for Visitation and Diagnostics and the outpatient clinics which must have confirmed social anxiety disorder or agoraphobia as the primary diagnosis of the patient, for the patient to be eligible for the study. If eligibility is confirmed, informed consent is acquired. Patients that cannot or will not participate in the study will be offered treatment as usual, which is identical to the control group treatment. Inclusion and exclusion criteria were based on the eligibility criteria for receiving the treatment package in Danish outpatient clinics.

Inclusion criteria

1) Fulfilling diagnostic criteria for social anxiety disorder (ICD-code: F40.1) and/or Agoraphobia (ICD-code: 40.0)
2) Age 18-75 years
3) Sufficient knowledge of the Danish language
4) Informed consent

Exclusion criteria

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

Feasibility

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

Treatment format

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

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

Not all of this is necessary for every patient, but every patient can receive every part of the package, should they want to. The treatment in the present study must live up to the standards of the national guidelines. Patients are not allowed to be in any other form of psychotherapeutic treatment.

The therapeutic intervention is manual-based cognitive-behavioral CBT group therapy adapted from the approach of Turk, Heimberg & Magee [53] and Graske & Barlow [54] with worksheets from Arendt & Rosenberg [55] and inspiration from Bouchard et al. [56]. The treatment will consist of 14 weekly two-hour group sessions following the manual to ensure equal and uniform treatment for every patient throughout the study. The manual allows flexibility to ensure clinically representative conditions [49]. E.g. it is allowed to change the order of the sessions if it is considered beneficial for the group and multiple exercises are optional. However, the time dedicated to exposure is fixed in both groups. Concurrent psychopharmacological treatment is allowed in both intervention arms.

Groups will consist of 8-9 patients with social anxiety disorder and/or agoraphobia as their primary diagnosis, and every session will be led by two trained clinicians (i.e. psychologists, psychiatrists or psychotherapists) with practical experience in CBT and *in vivo* exposure. Throughout the course of the study, the clinicians involved will treat both *CBT-in vivo* and CBT-*in virtuo* groups. Medical consultation, acute individual sessions, supplementary social counseling and physical therapy, are possible in both intervention arms. In both intervention arms, the sessions dedicated to exposure are scheduled from the fifth to the eleventh session with approximately 45 min of exposure in each session. From the fifth session and onwards, all patients in both interventions will have in-vivo exposure as homework. The cognitive therapy strategies used in the non-exposure sessions (first four and last two therapy sessions) are as follows; (a) introduction to CBT; (b) psychoeducation about anxiety and cognitive restructuring of dysfunctional assumptions and beliefs; (c) shifting self-

focused attention and modifying cognitive distortions; (d) developing an understanding of safety behavior and the rationale of exposure; (f) evaluation, discussion and feedback on the use of patient-acquired techniques; and (d) relapse prevention. In both conditions, the exposure exercises aim to develop adaptive responses to anxiety-provoking situations, reinforce cognitive restructuring by framing exercises as behavioral experiments (though these were limited by the non-interactive medium), train attention exercises, train general cognitive strategies (e.g. identifying negative automatic thoughts) and train social skills. See Table 1 and Table 2 for an overview of the content of the CBT sessions for both conditions.

Table 1. Group Cognitive Behavioural Therapy Manual session overview for Social Anxiety Disorder and 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.

Table 2. Group Cognitive Behavioural Therapy Manual session overview for Social Anxiety Disorder and 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.

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

Fidelity to the treatment manual

The intervention is manual-based, which improves the standardization of the treatment. Fidelity to the treatment manual will be assessed through a self-report questionnaire answered by the clinicians at five different time points throughout each group treatment. The questionnaire (and the timepoints whence it is delivered) are designed to correspond to the treatment manual. This type of fidelity measurement has proved useful and adequate in trials where the effect of treatment is tested [57]. The VR headsets will also record statistics of the use of the 360º films. This data shows which specific scenes were watched and how much and can be matched to the individual patient. This data will be used to keep track of the VR usage throughout the study to see how well it matches the treatment manual.

Treatment completion and discontinuation

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

- The attendance of ten or more group therapy sessions will be coded as 'treatment completion'.
- The attendance of between four to nine group therapy sessions will be coded as 'partial treatment'.
- The attendance of less than four group therapy sessions will be coded as 'no treatment'.

Treatment will be discontinued if participants do not show up to treatment three weeks in a row and cannot be contacted after multiple attempts by the therapists. Participants that have their treatment discontinued will still be included in the statistical analysis.

Virtual reality equipment

The patients receiving the *in virtuo* exposure will be immersed using an Oculus Go head-mounted display, enabling viewing of 360° spherically camera recorded VR environments. The VR scenarios will thus be high-resolution 360° stereoscopic films, that are played around the viewer. For audio, the patients will use high-quality sound-blocking headphones. For ease of use, the individual videos will be administered from an app that has been designed to be as intuitive to operate as possible. The patient will only have to put on the headset, adjust the focus and choose the desired environment by looking at it in the app. 360° video was chosen because it gives the most photorealistic visuals, while also being the cheapest to produce. The downside is that it does not allow direct user-interaction (e.g. the viewer cannot affect the environment in any way). To circumvent this, there are multiple junctions throughout the films where the actors will talk directly and unsolicited to the viewer (e.g. greetings, common questions) while also allowing time for the viewer to respond. The actors respond in a generic way to the actions of the viewer. Unsolicited and direct referral from a virtual environment seems to be an essential factor in triggering realistic responses to it [58]. Though the non-interactability of the environment limits the flexibility of behavioral experiments, it does not make them impossible. E.g., it is still possible to hypothesize about internal states (e.g. “I will clam up if I have to present in front of people”) and identify and challenge negative automatic thoughts.

Virtual Reality scenarios

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

1) Standing in line in a supermarket
2) Being in a crowded shopping center
3) Attending a party
4) Attending a formal meeting and giving a presentation
5) A job interview
6) Small talking/discussing in a university canteen with young adults
7) Small talking/discussing in a canteen in a work setting
8) Entering an auditorium
9) Leaving your apartment
10) Waiting for- and taking the bus
11) Crossing a bridge
12) Taking an elevator
13) Taking a commercial airplane

Each scenario has four to six scenes of increasing difficulty as well as a neutral scene to familiarize patients with the VR setting. All scenes skip to a looping version of a scene in the same environment after being played, to allow patients to achieve within-session habituation if needed. See additional file 2 for screenshots and descriptions of the individual scenes. All identifiable persons depicted in the virtual environments are paid actors.

Patient and Public Involvement: Development of virtual reality scenarios and manual

The pilot phase was a continuous iterative process between the developers of the VR media, CBT-trained clinicians and a panel of patients with social anxiety disorder and/or agoraphobia. The process lasted approximately 16 months (12 for social anxiety disorder environments and 4 for agoraphobia) and consisted of regular meetings following each scenario's initial filming wherein the

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

Assessment

Diagnostics

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

Outcomes and sample size calculation

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

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

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

Primary outcome:

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

Social anxiety disorder symptom severity will be measured using a danish version of the LSAS. LSAS assesses 24 situations typically feared by individuals with social anxiety disorder, rated on anxiety and avoidance, divided into subscales of performance anxiety and social situations. It has acceptable psychometric properties [63]. Agoraphobia symptom severity will be measured using a danish version of the MIA. The MIA assesses avoidance of 26 situations typically feared by

agoraphobic patients [64]. The MIA has demonstrated excellent psychometric properties and has been validated in multiple languages, including Swedish [65,66].

Secondary outcomes:

- Depressive symptoms measured pre-treatment, post-treatment and at follow-up as total scores on the Hamilton Depression Rating Scale, 6 item version (HAM-6) [67]
- Fear of negative evaluation measured pre-treatment, post-treatment and at follow-up with the Brief Version of the Fear of Negative Evaluation Scale (FNES) [68].
- Work and Social Adjustment measured pre-treatment, post-treatment and at follow-up with the Work and Social Adjustment Scale (WSAS) [69].
- User acceptability and satisfaction of treatment measured post-treatment with the Client Satisfaction Questionnaire (CSQ). The CSQ is an 8-item scale loading to one factor of satisfaction with mental health care service [70].
- Quality of Life measured pre-treatment, post-treatment and at follow-up with the WHO Well-Being Index, five items (WHO-5). It is considered a very sensitive outcome measure as it does not incorporate negative quality of life, i.e. distress, and has no ceiling effect [71].
- Treatment response on social anxiety disorder symptoms measured as LSAS below 50 or a 15 points drop.
- Treatment response on agoraphobia symptoms measured as MIA below 2 or a 0.5 points drop.
- Remission of social anxiety disorder symptoms measured post-treatment and at follow-up as LSAS below 25 and not qualifying for social anxiety disorder as measured using the MINI.
- Remission of agoraphobia symptoms measured post-treatment and at follow-up as MIA below 1.5 and not qualifying for agoraphobia as measured using the MINI.

Explorative outcomes:

- Social functioning measured with Personal and Social Performance Scale [72] (PSP) pre-treatment, post-treatment and at one-year follow-up.
- Substance and alcohol use measured with timeline followback [73] (TLFB) pre-treatment, post-treatment and at one-year follow-up.
- Self-belief of coping measured with General Self Efficacy [74] (GSE) pre-treatment, post-treatment and at one-year follow-up.
- Working alliance measured with the Working Alliance Inventory [75] (WAI) post-treatment.
- Social anxiety symptoms in patients with social anxiety disorder, measured with the LSAS pre-treatment, post-treatment and at one-year follow-up.
- Agoraphobia symptoms in patients with agoraphobia, measured with the MIA pre-treatment, post-treatment and at one-year follow-up.

Other measures:

- Unwanted negative side-effects induced by immersions in VR (commonly referred to as cybersickness) will be measured with the Simulator Sickness Questionnaire [76] (SSQ) at the end of VRE sessions.
- Deterioration and adverse effects of psychotherapy on social anxiety disorder symptoms measured post-treatment and at follow-up as a 6.8+ point increase in total LSAS score. Patients who have deteriorated will be interviewed about their experiences in therapy.
- Deterioration and adverse effects of psychotherapy on Agoraphobia symptoms measured post-treatment and at follow-up as a 0.3 point increase in total MIA score. Patients who have deteriorated will be interviewed about their experiences in therapy.
- The experience of Social Presence, as described by Lee [77], will be measured after each VR exposure session with a scale consisting of 9 questions rated on a 1-7 Likert scale. This scale

was developed specifically for this trial because existing scales are too specific for the VR equipment and content they were developed for. Social Presence is measured instead of the more general construct of Presence, because it has been theorized to be a critical element in the effective use of VRE for socially related fears [78,79].

Data from medical report

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

1. Number of previous hospitalizations for mental health conditions or medical conditions.
2. Use of mental health services during the follow-up period
3. Current and previous psychopharmacological medication
4. Attendance rate of the CBT treatment.

Setting of assessment

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

Randomization

Randomization is performed by randomizing each therapy group, one week before the first treatment session. This means that no patient is included while their treatment allocation is known. The Randomization is done with a hidden allocation sequence generated from www.sealedenvelope.com and is centralized and handled with the randomization module in REDCap by a project manager uninvolved in the data collection. Block sizes will be unknown to the outcome assessors and clinicians. The factor for stratification is the treatment site. Allocation tables will be handled by external researchers with no affiliation with the project. An email of the group's assigned randomization will be sent to the team leaders organizing the logistics of the interventions in the Psychotherapeutic clinics. Assigned randomization of the groups will be stored by the research team data manager. The randomization code will be stored at redcap.

Blinding

The assessors are blinded when interviewing at pre-treatment, post-treatment and at follow-up. Should unblinding occur, another researcher will perform the assessment. Blinded researchers will perform analysis and draft conclusions.

Data collection methods and management

See Figure 1 for an overview of data collection. Self-reported data will be collected through surveys send via REDCap (Research Electronic Data Capture) or filled out on paper. Assessors are trained in the interview instruments and will do regular co-ratings of recorded interviews. Interrater reliability of clinician-rated outcome measures will be calculated throughout the trial. The interviewers will import data from the assessments directly into the electronic CRF (Case Report Form) using the data entry system REDCap [80]. REDCap is an electronic data capture tool hosted at CIMT (Center for IT, Medico and Telephony) in the Capital Region of Denmark. For non-self-report measures, data will first be captured on paper and then entered electronically. REDCap complies with Danish legislation (the Act on Processing Personal Data) due to it having both

comprehensive user rights and access control management and a complete audit trail on all data transactions. The data from individual patients are tied to a unique serial number. Assigned researchers and GCP (Good Clinical Practice) monitors will be the only people who can access the database. Non-electronic data will be stored locally in secure archives. Data will be exported from REDCap without personal identifiers. Data will be exported to all well-known software packages: (SPSS, SAS, Stata, R.) and stored on a secure network drive under the control of CIMT. A data manager will ensure that all variables are correctly defined with variable and value labels. All derived variables will be correctly defined, and algorithms will be kept in individual files. All data will be scrutinized to identify errors in data entry. The sponsor and the principal investigators ensure that data is stored at least ten years after the trial is ended.

Statistical methods

The analysis will all be from intention-to-treat. All included patients will also be included in the analyses. All statistical tests of significance will be two-tailed. The primary outcome analysis will be an intention-to-treat analysis. Missing data will be handled by multiple imputations (m=100). As predictors in the imputation model, we will select variables if they are independent predictors of the outcome or predictors of missing data ($P<0.05$ in a univariate model). Each group will have imputations done separately. Analysis of covariance will be used to calculate any significant results between the two groups, using the baseline value and the stratification variables.

The continuous variables will be imputed with linear regression. Binary variables will be imputed with binary logistic regression. Multinomial variables will be imputed with multinomial logistic regression. Ordinal variables will be imputed with ordinal logistic regression. For every type of variable, we will perform 100 imputations.

All distributions will be assessed for normality using visual inspection of histograms and Q-Q plots. If not normally distributed, variables will be log-transformed, and if unsuccessful, a non-parametric test will be used.

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

Dissemination

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

Data monitoring and auditing:

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

Safety:

In the clinical setting, the clinicians will register Adverse Events and Adverse Reactions and report all Serious Adverse Events and Severe Adverse Reactions to the sponsor. Other events or side effects will be collected from patient files and registers. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice guidelines define serious adverse events and serious adverse reactions. The patients in the SoREAL trial are ensured by Danish law and the patient care regulation. Every patient in the SoREAL trial will have access to their results of the trial if they wish to. The clinicians will not have access to data collected from assessments done by the researchers.

Trial status

Inclusion began on February 4th, 2019. Inclusion is expected to stop on June 4th, 2023. Inclusion was delayed by approximately three months due to the COVID-19 pandemic.

List of abbreviations

VRET: Virtual Reality Exposure Therapy; CBT: Cognitive behavioral therapy; RCT: Randomised Controlled Trial. MINI: Mini international neuropsychiatric interview. VR: Virtual reality. LSAS: Liebowitz social anxiety scale. MIA: Mobility Inventory for Agoraphobia. POMP: Percentage of Maximum Possible Score. PSP: Personal and social performance scale. TLFB: Timeline followback. FNE: Fear of negative evaluation scale. CSQ: Client satisfaction questionnaire. WAI: Working alliance inventory. WSAS: Work and social adjustment scale. HAMD-6: Hamilton depression scale, 6 item version.

Declarations

Sponsor details

Name: Merete Nordentoft.

Contact: merete.nordentoft@regionh.dk

Ethics approval and consent to participate

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

Protocol amendments

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

Availability of data and materials

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

Additional file data

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

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

Author contributions

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

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Acknowledgments

N/A.

Funding

MN and NR initiated the project. MN applied to Novo Nordisk Foundation, and the SoREAL trial was granted 5.000.000 DKK [NNF17OC0027780]. MN and NR have no affiliation to the Novo Nordisk Foundation. MN, PB and BTA applied to TrygFonden and the trial was granted an additional 3.517.500 DKK [ID: 146169]. MN, PB and BTA have no affiliation to TrygFonden.

The project is entirely independent of the Novo Nordisk Foundation and TrygFonden and therefore, the funding body plays no role in the design of the study, the collection, analysis and interpretation of data and in writing the manuscript. Nor will the Novo Nordisk Foundation or TrygFonden play any role in future publications that may derive from the project.

Protocol version and date

Protocol Version 4 – Revised 02.03.21

Figure legends

Figure 1. Overview of data collection

Figure 2. Flow diagram of the SoREAL trial

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

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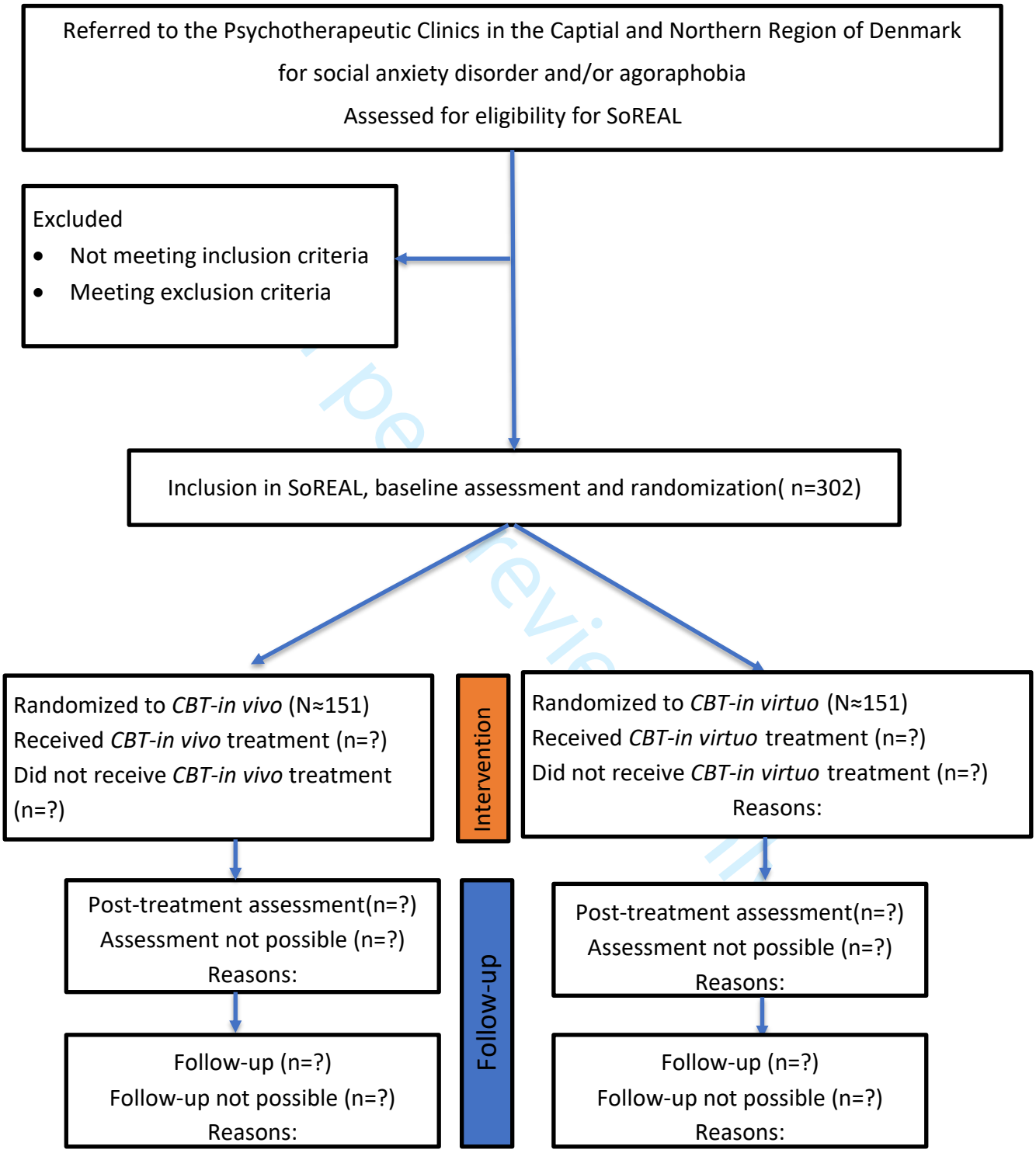
Schedule of enrolment, interventions, and assessments.	STUDY PERIOD		
	Enrolment and allocation	Follow-up	
TIMEPOINT**	Baseline	*Post-treatment*	*One-year*
ENROLMENT:	X		
Eligibility screen	X		
Informed consent and inclusion	X		
Allocation	X		
INTERVENTIONS:			
CBT-In vivo	←	—	→
CBT-In virtuo	←	—	→
ASSESSMENTS:			
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	



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 Questionaire	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

	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
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4-7, Line 66-149
	6b	Explanation for choice of comparators	Page 6-7, Line 128-139
Objectives	7	Specific objectives or hypotheses	Page 8, Line 155-164
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, Line 29-30
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 8, Line 177-178
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)	Page 9-10, Line 188-204
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 10-18, Line 216-358
	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)	Page 16, Line 305-307 & page 26 line 539-546

	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
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 10-11, Line 216-238
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
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 8-9, Line 177-186 & page 10, line 206-214
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 23, Line 472-474
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
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.

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
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 23-24, line 485-503; Page 19 – 22, Line 381-468 ; Figure 3
	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
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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 25, line 533-536

	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
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 27, line 567
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
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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 28, line 599.
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
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

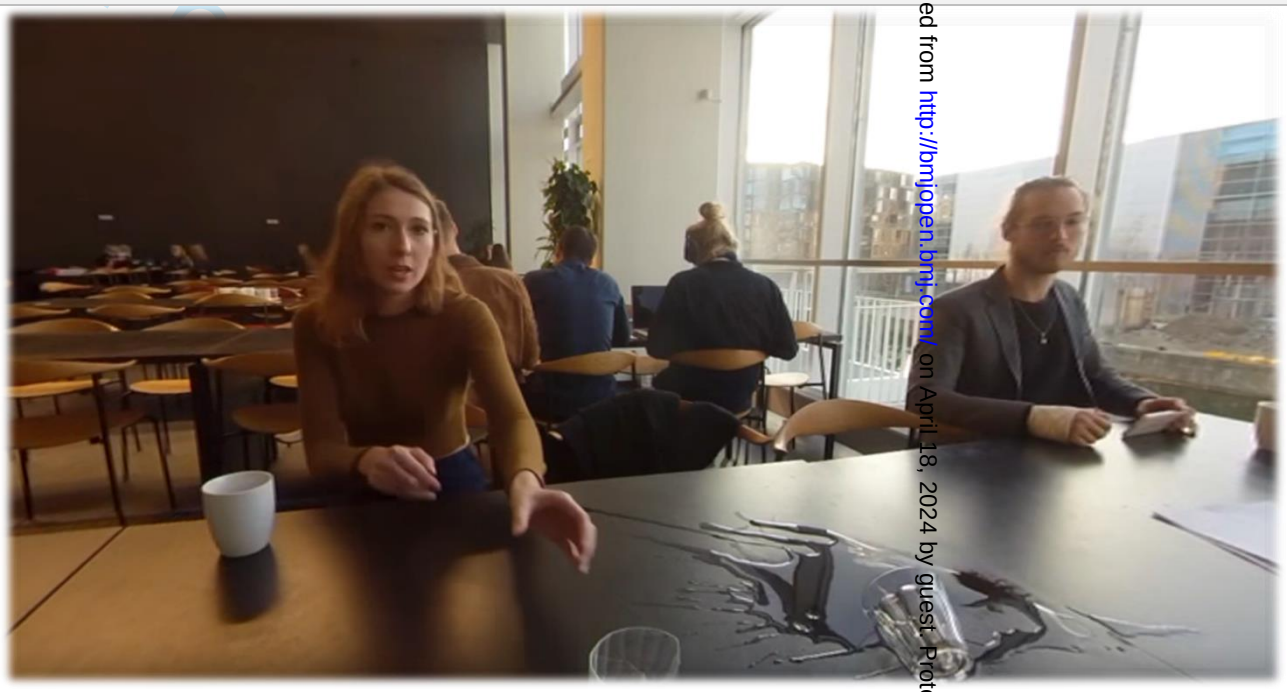
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 25, line 523-530
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 28, line 580-582
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A. Can be send on inquiry.
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

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

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.	

Scene 4. 0:50 – Loop of scene 0. You win a prize for being customer number 1.000.000.	
Environment 2 – Presentation Scene 0. Loop – Standing in meeting room alone. Scene 1. 2:20 – Loop of scene 0. Meeting preparations with colleague. Scene 2. 3:29 – Loop of scene 0. Contact person arrives. Short conversation. Scene 3. 2:35 – Loop of scene 0. Two important meeting participants arrive. Scene 4. 2:01 – Loop of scene 0. The rest of the meeting participants arrive. Introductions to the group.	

Scene 5. 4:02 – Loop of scene 0. Presentation has technical difficulties. Partner leaves mid-presentation. Scene 6. 2:07 – Loop of scene 0. Scolding from the boss.	
Environment 3 – Cafeteria Scene 0. Loop – Sitting by table. One person sits down nearby. Scene 1. 3:04 – Loop of scene 0. Someone small talks near you. You are asked about parking. Few people in the room. Scene 2. 4:30 – Loop of scene 0. More small talk. You are asked if there is room by the table.	

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.	

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.	

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.	

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.	

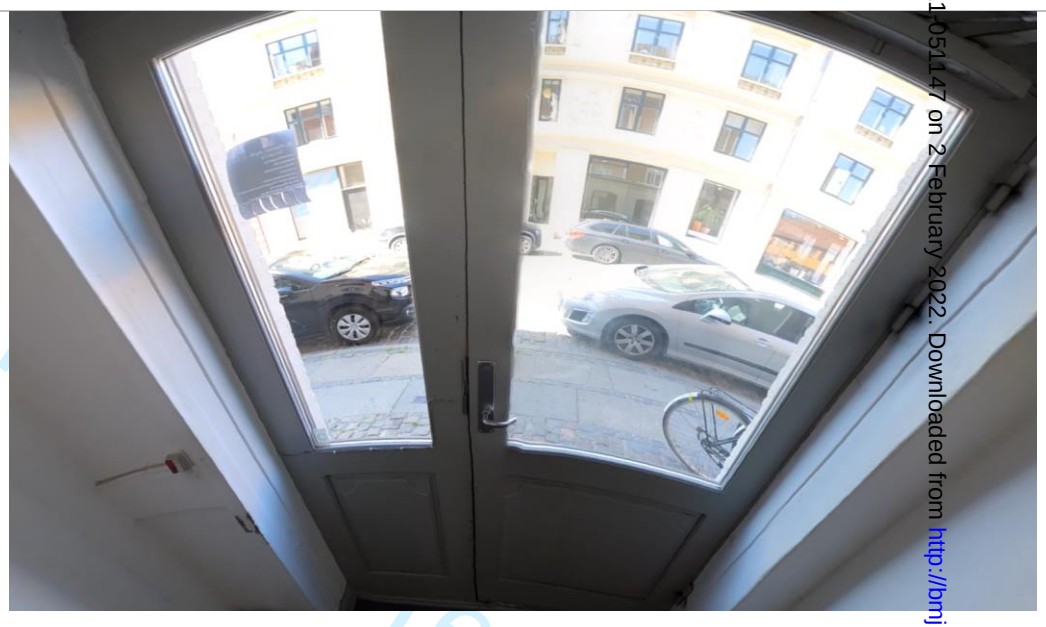
Scene 6. 2:00 – Loop of Scene 0. Drops tray with food next to table.	
Environment 9 - Taking a commercial airplane Scene 0. 7:26. Taking a plane, from boarding to landing. It is possible to only play specific segments, e.g. “Turbulence” or “Boarding”.	

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.	

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.	

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.	

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

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.

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:	*BMJ Open*
Manuscript ID	bmjopen-2021-051147.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Nov-2021

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice
Keywords:	Anxiety disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, PSYCHIATRY

Title page

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

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Keywords

Virtual Reality Exposure Therapy, Social Anxiety Disorder, Agoraphobia, Cognitive Behavioral Therapy, Randomized Clinical Trial.

Word Count: 6.603

Abstract

Introduction Anxiety disorders have a high lifetime prevalence, early-onset, and long duration or chronicity. Exposure therapy is considered one of the most effective elements in cognitive behavioral therapy (CBT) for anxiety, but *in vivo* exposure can be challenging to access and control, and is sometimes rejected by patients because they consider it too aversive. Virtual reality allows flexible and controlled exposure to challenging situations in an immersive and protected environment. **Aim** The SoREAL-trial aims to investigate the effect of group cognitive-behavioral therapy (*CBT-in vivo*) versus group cognitive behavioral therapy with virtual reality exposure (*CBT-in virtuo*) for patients diagnosed with social anxiety disorder and/or agoraphobia, in mixed groups. **Methods & Analysis** The design is an investigator-initiated randomized, assessor-blinded, parallel-group and superiority-designed clinical trial. Three hundred two patients diagnosed with social anxiety disorder and/or agoraphobia will be included from the regional mental health centers of Copenhagen and North Sealand and the Northern Region of Denmark. All patients will be offered a manual-based 14-week cognitive behavioral group treatment program, including eight sessions with exposure therapy. Therapy groups will be centrally randomized with concealed allocation sequence to either CBT-*in virtuo* or CBT-*in vivo*. Patients will be assessed at baseline, post-treatment and one-year follow-up by treatment blinded researchers and research assistants. The primary outcome will be diagnosis-specific symptoms measured with the Liebowitz Social Anxiety Scale for patients with social anxiety disorder and the Mobility Inventory for Agoraphobia for patients with agoraphobia. Secondary outcome measures will include depression symptoms, social functioning, and patient satisfaction. Exploratory outcomes will be substance and alcohol use, working alliance and quality of life. **Ethics and dissemination:** The trial has been approved by the research ethics committee in the Capital Region of Denmark. All results, positive, negative as well as inconclusive, will be published as quickly as possible and still in concordance with Danish law on the protection

of confidentially and personal information. Results will be presented at national and international scientific conferences. **Trial registration:** The project was registered at clinicaltrials.gov on 02/19/2019 as NCT03845101. Can be found online at https://clinicaltrials.gov/ct2/show/NCT03845101

Article Summary

Strengths and limitations of this study

- The present study will be the first large randomized clinical trial to investigate virtual reality exposure therapy for social anxiety disorder and agoraphobia in group therapy.
- The present study is very closely integrated with clinical practice, making results highly transferable to similar real-life settings.
- Mixing patients with social anxiety disorder and agoraphobia in the same therapy groups have never been investigated systematically, which may confound the interpretation of results.
- Because the study is embedded in an outpatient hospital setting, the intervention was designed to be flexible. This increases the ecological validity but also the risk of systematic bias in treatment administration.

Background

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

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

Virtual Reality Exposure Therapy for Social Anxiety Disorder and Agoraphobia

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

perform Virtual Reality Exposure Therapy (VRET) [16,17], either as a standalone treatment, e.g. [18], or integrated into a CBT treatment e.g. [19].

The use of VR allows flexible and controlled exposure to challenging situations in an immersive and safe environment. Therefore, using VRET can mitigate the challenges of in-vivo exposure therapy by producing greater user acceptance and access to situations that would otherwise be too difficult to control, too resource-intensive to find and/or have unacceptable confidentiality risks [15,19,20]. Based on this, VRET may improve the efficacy and cost-effectiveness of psychotherapeutic interventions for anxiety disorders.

Recent reviews and meta-analysis of VRET either as a standalone treatment or combined with cognitive interventions, conclude that VRET is more effective than waitlist and placebo control and equally as effective as first-line treatment controls for anxiety disorders [21–23]. However, in one meta-analysis, the authors find significantly worse treatment effects of VRET for social anxiety disorder, when compared with control groups that received equal amounts of in-vivo exposure [24]. It has been suggested that it is more difficult to produce VRET environments for social anxiety disorder, as compared to other phobic disorders because human interaction is complex and therefore difficult to realistically recreate [25] which may explain these results. Accordingly, the same meta-analysis found no significant difference in treatment efficacy for CBT with VRET vs CBT with in-vivo exposure for agoraphobia and specific phobia [24].

In general, there is a scarcity of high-quality randomized clinical trials (RCT) evaluating the use of VRET for social anxiety disorder and agoraphobia [16,26,27]. For social anxiety disorder, there are five trials published, the largest having 97 participants [28,19,18,29,30]. For agoraphobia, there are six trials published, the largest having 80 participants [31–36]. All in all, the evidence-base for

using VRET compared to in-vivo exposure for social anxiety disorder and agoraphobia remain small. Therefore, larger studies that capitalize on the unique qualities of VRET are needed.

Virtual Reality Exposure in Group Therapy

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

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

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

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

[46], as well as recent evidence of the acceptable treatment efficacy of CBT-based transdiagnostic therapies [47].

However, it is worth noting, that the pragmatic mixed anxiety group format has never been systematically evaluated and that the official treatment recommendation remain diagnoses specific CBT delivered in group or individually [48]. To maximize the study's clinical representitativenes, as defined by Shadish et al. [49], the treatment structure in the present study, including the comperator, will mimic the treatment offered by the Danish mental health services.

Aim and objectives:

In summary in-vivo exposure is considered effective, but can be challenging to perform. Virtual Reality Exposure therapy may alleviate these challenges. However, the usefulness of VRET for social anxiety disorder and agoraphobia remains unclear. Larger studies that capitalize on the benefits of VRET are needed. Group therapy may be one way to capitalize on the benefits of VRET because it could allow for more individualized exposure exercises. Mixed anxiety groups are commonly used in Danish mental healthcare to reduce wait time, but have not been systematically evaluated. The treatment, inclusion and exclusion criteria described in the present study match the eligibility criteria for treatment and treatment format of the Danish mental healthcare system to maximize transferability of results to clinical practice.

Therefore, the SoREAL trial aims to evaluate the treatment efficacy of VRET in mixed anxiety CBT groups (CBT-in virtuo) compared to mixed anxiety CBT groups where exposure therapy is performed in-vivo (CBT-*in vivo*).

Thus, in the SoREAL trial, the following hypotheses' will be tested:

Primary hypothesis:

1. Post-treatment, patients treated with CBT-*in virtuo* will have a lower level of anxiety symptoms compared to patients treated with CBT-*in vivo*, measured as total scores on the Liebowitz Social Anxiety Scale (LSAS) for patients with social anxiety disorder and the Mobility Inventory for Agoraphobia (MIA) for patients with agoraphobia converted to the percentage of maximum possible scores (POMP) and averaged within treatment arms.

Secondary hypotheses:

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

Overall, we believe that the SoREAL trial will contribute with knowledge about the efficacy and feasibility of VRE for treating social anxiety disorder and agoraphobia in a clinical outpatient setting. The results of this trial may guide future applications of VR in clinical settings across a wide breadth of use-cases.

Methods and design

This article was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 explanation and elaboration: guidance for protocols of clinical trials [50]. The SPIRIT Checklist was followed and the SPIRIT flowchart was used [See Additional file 1 and Figure 1].

Recruitment

The SoREAL trial is embedded directly into five outpatient clinics offering group CBT for social anxiety disorder and agoraphobia. These clinics are part of the Danish mental health care system.

To be eligible for treatment in these clinics, patients must be referred by their primary care physicians to a Center for Visitation and Diagnosis in their area, where their symptomatology will be assessed. At the Center for Visitation and Diagnosis, they must be referred to one of the five outpatient clinics involved in the study. At the outpatient clinic, the patient will again be clinically assessed, and a diagnosis and treatment plan will be formulated. If social anxiety disorder and/or agoraphobia is considered the primary diagnosis for the patient, they will be asked if they are interested in getting more information about the trial. If they consent to it, their contact details will be given to a researcher, who will invite them to an interview concerning the study.

Mini International Neuropsychiatric Interview (MINI), v. 7.0 for DSM-5 will be used to screen for diagnosis. Psychometric analyses of the MINI have demonstrated acceptable test-retest and inter-rater reliability [51,52]. Diagnostic screening is sufficient due to the thorough assessment from both Center for Visitation and Diagnostics and the outpatient clinics which must have confirmed social anxiety disorder or agoraphobia as the primary diagnosis of the patient, for the patient to be eligible for the study. If eligibility is confirmed, informed consent is acquired [See additional file 2, for a model consent form]. Patients that cannot or will not participate in the study will be offered treatment as usual, which is identical to the control group treatment. Inclusion and exclusion criteria were based on the eligibility criteria for receiving the treatment package in Danish outpatient clinics.

Inclusion criteria

1) Fulfilling diagnostic criteria for social anxiety disorder and/or agoraphobia
2) Age 18-75 years
3) Sufficient knowledge of the Danish language
4) Informed consent

Exclusion criteria

1) Alcohol or drug dependence

Feasibility

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

Treatment format

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

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

Not all of this is necessary for every patient, but every patient can receive every part of the package, should they want to. The treatment in the present study must live up to the standards of the national guidelines. Patients are not allowed to be in any other form of psychotherapeutic treatment.

The therapeutic intervention is manual-based cognitive-behavioral CBT group therapy adapted from the approach of Turk, Heimberg & Magee [53] and Graske & Barlow [54] with worksheets from Arendt & Rosenberg [55] and inspiration from Bouchard et al. [56]. The treatment will consist of 14 weekly two-hour group sessions following the manual to ensure equal and uniform treatment for every patient throughout the study. The manual allows flexibility to ensure clinically representative conditions [49]. E.g. it is allowed to change the order of the sessions if it is considered beneficial for the group and multiple exercises are optional. However, the time dedicated to exposure is fixed in both groups. Concurrent psychopharmacological treatment is allowed in both intervention arms.

Groups will consist of 8-9 patients with social anxiety disorder and/or agoraphobia as their primary diagnosis, and every session will be led by two trained clinicians (i.e. psychologists, psychiatrists or psychotherapists) with practical experience in CBT and *in vivo* exposure. Throughout the course of the study, the clinicians involved will treat both *CBT-in vivo* and CBT-*in virtuo* groups. Medical consultation, acute individual sessions, supplementary social counseling and physical therapy, are possible in both intervention arms. In both intervention arms, the sessions dedicated to exposure are scheduled from the fifth to the eleventh session with approximately 45 min of exposure in each session. From the fifth session and onwards, all patients in both interventions will have in-vivo exposure as homework. The cognitive therapy strategies used in the non-exposure sessions (first four and last two therapy sessions) are as follows; (a) introduction to CBT; (b) psychoeducation about anxiety and cognitive restructuring of dysfunctional assumptions and beliefs; (c) shifting self-

focused attention and modifying cognitive distortions; (d) developing an understanding of safety behavior and the rationale of exposure; (f) evaluation, discussion and feedback on the use of patient-acquired techniques; and (d) relapse prevention. In both conditions, the exposure exercises aim to develop adaptive responses to anxiety-provoking situations, reinforce cognitive restructuring by framing exercises as behavioral experiments (though these were limited by the non-interactive medium), train attention exercises, train general cognitive strategies (e.g. identifying negative automatic thoughts) and train social skills. See Table 1 and Table 2 for an overview of the content of the CBT sessions for both conditions.

Table 1. Group Cognitive Behavioural Therapy Manual session overview for Social Anxiety Disorder and 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.

Table 2. Group Cognitive Behavioural Therapy Manual session overview for Social Anxiety Disorder and 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.

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

Fidelity to the treatment manual

The intervention is manual-based, which improves the standardization of the treatment. Fidelity to the treatment manual will be assessed through a self-report questionnaire answered by the clinicians at five different time points throughout each group treatment. The questionnaire (and the timepoints whence it is delivered) are designed to correspond to the treatment manual. This type of fidelity measurement has proved useful and adequate in trials where the effect of treatment is tested [57]. The VR headsets will also record statistics of the use of the 360º films. This data shows which specific scenes were watched and how much and can be matched to the individual patient. This data will be used to keep track of the VR usage throughout the study to see how well it matches the treatment manual.

Treatment completion and discontinuation

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

- The attendance of ten or more group therapy sessions will be coded as 'treatment completion'.
- The attendance of between four to nine group therapy sessions will be coded as 'partial treatment'.
- The attendance of less than four group therapy sessions will be coded as 'no treatment'.

Treatment will be discontinued if participants do not show up to treatment three weeks in a row and cannot be contacted after multiple attempts by the therapists. Participants that have their treatment discontinued will still be included in the statistical analysis.

Virtual reality equipment

The patients receiving the *in virtuo* exposure will be immersed using an Oculus Go head-mounted display, enabling viewing of 360° spherically camera recorded VR environments. The VR scenarios will thus be high-resolution 360° stereoscopic films, that are played around the viewer. For audio, the patients will use high-quality sound-blocking headphones. For ease of use, the individual videos will be administered from an app that has been designed to be as intuitive to operate as possible. The patient will only have to put on the headset, adjust the focus and choose the desired environment by looking at it in the app. 360° video was chosen because it gives the most photorealistic visuals, while also being the cheapest to produce. The downside is that it does not allow direct user-interaction (e.g. the viewer cannot affect the environment in any way). To circumvent this, there are multiple junctions throughout the films where the actors will talk directly and unsolicited to the viewer (e.g. greetings, common questions) while also allowing time for the viewer to respond. The actors respond in a generic way to the actions of the viewer. Unsolicited and direct referral from a virtual environment seems to be an essential factor in triggering realistic responses to it [58]. Though the non-interactability of the environment limits the flexibility of behavioral experiments, it does not make them impossible. E.g., it is still possible to hypothesize about internal states (e.g. “I will clam up if I have to present in front of people”) and identify and challenge negative automatic thoughts.

Virtual Reality scenarios

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

1) Standing in line in a supermarket
2) Being in a crowded shopping center
3) Attending a party
4) Attending a formal meeting and giving a presentation
5) A job interview
6) Small talking/discussing in a university canteen with young adults
7) Small talking/discussing in a canteen in a work setting
8) Entering an auditorium
9) Leaving your apartment
10) Waiting for- and taking the bus
11) Crossing a bridge
12) Taking an elevator
13) Taking a commercial airplane

Each scenario has four to six scenes of increasing difficulty as well as a neutral scene to familiarize patients with the VR setting. All scenes skip to a looping version of a scene in the same environment after being played, to allow patients to achieve within-session habituation if needed. See additional file 3 for screenshots and descriptions of the individual scenes, as well as links to view a selection of the scenes online. All identifiable persons depicted in the virtual environments are paid actors.

Patient and Public Involvement: Development of virtual reality scenarios and manual

The pilot phase was a continuous iterative process between the developers of the VR media, CBT-trained clinicians and a panel of patients with social anxiety disorder and/or agoraphobia. The process lasted approximately 16 months (12 for social anxiety disorder environments and 4 for

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

Assessment

Diagnostics

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

Outcomes and sample size calculation

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

Upon deciding to expand the diagnostic criteria for inclusion to also include patients with agoraphobia, it was necessary to change our primary outcome measure. For patients with agoraphobia, we primarily rate symptoms using MIA. To include both patients with social anxiety disorder and patients with agoraphobia, we thus decided to recalculate scores on these two scales to

POMP as described below. Since the sample size calculation for LSAS was based on a Cohen's d=0.33, we also set the minimum clinically relevant difference on MIA, and by extension on the POMP, to d=0.33. Consequently, the required sample size remained unaffected by this change of primary outcome measures and is thus still 302 patients. See Figure 3 for power calculations on secondary outcomes.

Primary outcome:

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

Social anxiety disorder symptom severity will be measured using a danish version of the LSAS. LSAS assesses 24 situations typically feared by individuals with social anxiety disorder, rated on anxiety and avoidance, divided into subscales of performance anxiety and social situations. It has acceptable psychometric properties [63]. Agoraphobia symptom severity will be measured using a danish version of the MIA. The MIA assesses avoidance of 26 situations typically feared by

agoraphobic patients [64]. The MIA has demonstrated excellent psychometric properties and has been validated in multiple languages, including Swedish [65,66].

Secondary outcomes:

- Depressive symptoms measured pre-treatment, post-treatment and at follow-up as total scores on the Hamilton Depression Rating Scale, 6 item version (HAM-6) [67]
- Fear of negative evaluation measured pre-treatment, post-treatment and at follow-up with the Brief Version of the Fear of Negative Evaluation Scale (FNES) [68].
- Work and Social Adjustment measured pre-treatment, post-treatment and at follow-up with the Work and Social Adjustment Scale (WSAS) [69, 70].
- User acceptability and satisfaction of treatment measured post-treatment with the Client Satisfaction Questionnaire (CSQ). The CSQ is an 8-item scale loading to one factor of satisfaction with mental health care service [71].
- Quality of Life measured pre-treatment, post-treatment and at follow-up with the WHO Well-Being Index, five items (WHO-5). It is considered a very sensitive outcome measure as it does not incorporate negative quality of life, i.e. distress, and has no ceiling effect [72].
- Treatment response on social anxiety disorder symptoms measured as LSAS below 50 or a 15 points drop.
- Treatment response on agoraphobia symptoms measured as MIA below 2 or a 0.5 points drop.
- Remission of social anxiety disorder symptoms measured post-treatment and at follow-up as LSAS below 25 [73] and not qualifying for social anxiety disorder as measured using the MINI.
- Remission of agoraphobia symptoms measured post-treatment and at follow-up as MIA below 1.5 and not qualifying for agoraphobia as measured using the MINI.

Explorative outcomes:

- Social functioning measured with Personal and Social Performance Scale [74] (PSP) pre-treatment, post-treatment and at one-year follow-up.
- Substance and alcohol use measured with timeline followback [75] (TLFB) pre-treatment, post-treatment and at one-year follow-up.
- Self-belief of coping measured with General Self Efficacy [76] (GSE) pre-treatment, post-treatment and at one-year follow-up.
- Working alliance measured with the Working Alliance Inventory [77] (WAI) post-treatment.
- Social anxiety symptoms in patients with social anxiety disorder, measured with the LSAS pre-treatment, post-treatment and at one-year follow-up.
- Agoraphobia symptoms in patients with agoraphobia, measured with the MIA pre-treatment, post-treatment and at one-year follow-up.

Other measures:

- Unwanted negative side-effects induced by immersions in VR (commonly referred to as cybersickness) will be measured with the Simulator Sickness Questionnaire [78] (SSQ) at the end of VRE sessions.
- Deterioration and adverse effects of psychotherapy on social anxiety disorder symptoms measured post-treatment and at follow-up as a 6.8+ point increase in total LSAS score. Patients who have deteriorated will be interviewed about their experiences in therapy.
- Deterioration and adverse effects of psychotherapy on Agoraphobia symptoms measured post-treatment and at follow-up as a 0.3 point increase in total MIA score. Patients who have deteriorated will be interviewed about their experiences in therapy.
- The experience of Social Presence, as described by Lee [79], will be measured after each VR exposure session with a scale consisting of 9 questions rated on a 1-7 Likert scale. This scale

was developed specifically for this trial because existing scales are too specific for the VR equipment and content they were developed for. Social Presence is measured instead of the more general construct of Presence, because it has been theorized to be a critical element in the effective use of VRE for socially related fears [80,81].

Data from medical report

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

1. Number of previous hospitalizations for mental health conditions or medical conditions.
2. Use of mental health services during the follow-up period
3. Current and previous psychopharmacological medication
4. Attendance rate of the CBT treatment.

Setting of assessment

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

Randomization

Randomization is performed by randomizing each therapy group, one week before the first treatment session. This means that no patient is included while their treatment allocation is known. The Randomization is done with a hidden allocation sequence generated from www.sealedenvelope.com and is centralized and handled with the randomization module in REDCap by a project manager uninvolved in the data collection. Block sizes will be unknown to the outcome assessors and clinicians. The factor for stratification is the treatment site. Allocation tables will be handled by external researchers with no affiliation with the project. An email of the group's assigned randomization will be sent to the team leaders organizing the logistics of the interventions in the Psychotherapeutic clinics. Assigned randomization of the groups will be stored by the research team data manager. The randomization code will be stored at redcap.

Blinding

The assessors are blinded when interviewing at pre-treatment, post-treatment and at follow-up. Should unblinding occur, another researcher will perform the assessment. Blinded researchers will perform analysis and draft conclusions. There are no circumstances where unblinding of the assessors is permissible.

Data collection methods and management

See Figure 1 for an overview of data collection. Self-reported data will be collected through surveys send via REDCap (Research Electronic Data Capture) or filled out on paper. Assessors are trained in the interview instruments and will do regular co-ratings of recorded interviews. Interrater reliability of clinician-rated outcome measures will be calculated throughout the trial. The interviewers will import data from the assessments directly into the electronic CRF (Case Report Form) using the data entry system REDCap [82]. REDCap is an electronic data capture tool hosted at CIMT (Center for IT, Medico and Telephony) in the Capital Region of Denmark. For non-self-report measures, data will first be captured on paper and then entered electronically. REDCap

complies with Danish legislation (the Act on Processing Personal Data) due to it having both comprehensive user rights and access control management and a complete audit trail on all data transactions. The data from individual patients are tied to a unique serial number. Assigned researchers and GCP (Good Clinical Practice) monitors will be the only people who can access the database. Non-electronic data will be stored locally in secure archives. Data will be exported from REDCap without personal identifiers. Data will be exported to all well-known software packages: (SPSS, SAS, Stata, R.) and stored on a secure network drive under the control of CIMT. A data manager will ensure that all variables are correctly defined with variable and value labels. All derived variables will be correctly defined, and algorithms will be kept in individual files. All data will be scrutinized to identify errors in data entry. The sponsor and the principal investigators ensure that data is stored at least ten years after the trial is ended.

Statistical methods

The analysis will all be from intention-to-treat. All included patients will also be included in the analyses. All statistical tests of significance will be two-tailed. The primary outcome analysis will be an intention-to-treat analysis. Missing data will be handled by multiple imputations (m=100). As predictors in the imputation model, we will select variables if they are independent predictors of the outcome or predictors of missing data ($P<0.05$ in a univariate model). Each group will have imputations done separately. Analysis of covariance will be used to calculate any significant results between the two groups, using the baseline value and the stratification variables.

The continuous variables will be imputed with linear regression. Binary variables will be imputed with binary logistic regression. Multinomial variables will be imputed with multinomial logistic regression. Ordinal variables will be imputed with ordinal logistic regression. For every type of variable, we will perform 100 imputations.

All distributions will be assessed for normality using visual inspection of histograms and Q-Q plots. If not normally distributed, variables will be log-transformed, and if unsuccessful, a non-parametric test will be used.

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

Dissemination

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

Data monitoring and auditing:

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

Safety:

In the clinical setting, the clinicians will register Adverse Events and Adverse Reactions and report all Serious Adverse Events and Severe Adverse Reactions to the sponsor. Other events or side effects will be collected from patient files and registers. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice guidelines define serious adverse events and serious adverse reactions. The patients in the SoREAL trial are ensured by Danish law and the patient care regulation. Every patient in the SoREAL trial will have access to their results of the trial if they wish to. The clinicians will not have access to data collected from assessments done by the researchers.

Trial status

Inclusion began on February 4th, 2019. Inclusion is expected to stop on June 4th, 2023. Inclusion was delayed by approximately three months due to the COVID-19 pandemic.

List of abbreviations

VRET: Virtual Reality Exposure Therapy; CBT: Cognitive behavioral therapy; RCT: Randomised Controlled Trial. MINI: Mini international neuropsychiatric interview. VR: Virtual reality. LSAS: Liebowitz social anxiety scale. MIA: Mobility Inventory for Agoraphobia. POMP: Percentage of Maximum Possible Score. PSP: Personal and social performance scale. TLFB: Timeline followback. FNE: Fear of negative evaluation scale. CSQ: Client satisfaction questionnaire. WAI: Working alliance inventory. WSAS: Work and social adjustment scale. HAMD-6: Hamilton depression scale, 6 item version.

Declarations

Sponsor details

Name: Merete Nordentoft.

Contact: merete.nordentoft@regionh.dk

Ethics approval and consent to participate

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

Protocol amendments

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

Availability of data and materials

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

Additional file data

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

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

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

Author contributions

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

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Acknowledgments

N/A.

Funding

MN and NR initiated the project. MN applied to Novo Nordisk Foundation, and the SoREAL trial was granted 5.000.000 DKK [NNF17OC0027780]. MN and NR have no affiliation to the Novo Nordisk Foundation. MN, PB and BTA applied to TrygFonden and the trial was granted an additional 3.517.500 DKK [ID: 146169]. MN, PB and BTA have no affiliation to TrygFonden.

The project is entirely independent of the Novo Nordisk Foundation and TrygFonden and therefore, the funding body plays no role in the design of the study, the collection, analysis and interpretation of data and in writing the manuscript. Nor will the Novo Nordisk Foundation or TrygFonden play any role in future publications that may derive from the project.

Protocol version and date

Protocol Version 5 – Revised 11.11.21

Figure legends

Figure 1. Overview of data collection

Figure 2. Flow diagram of the SoREAL trial

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

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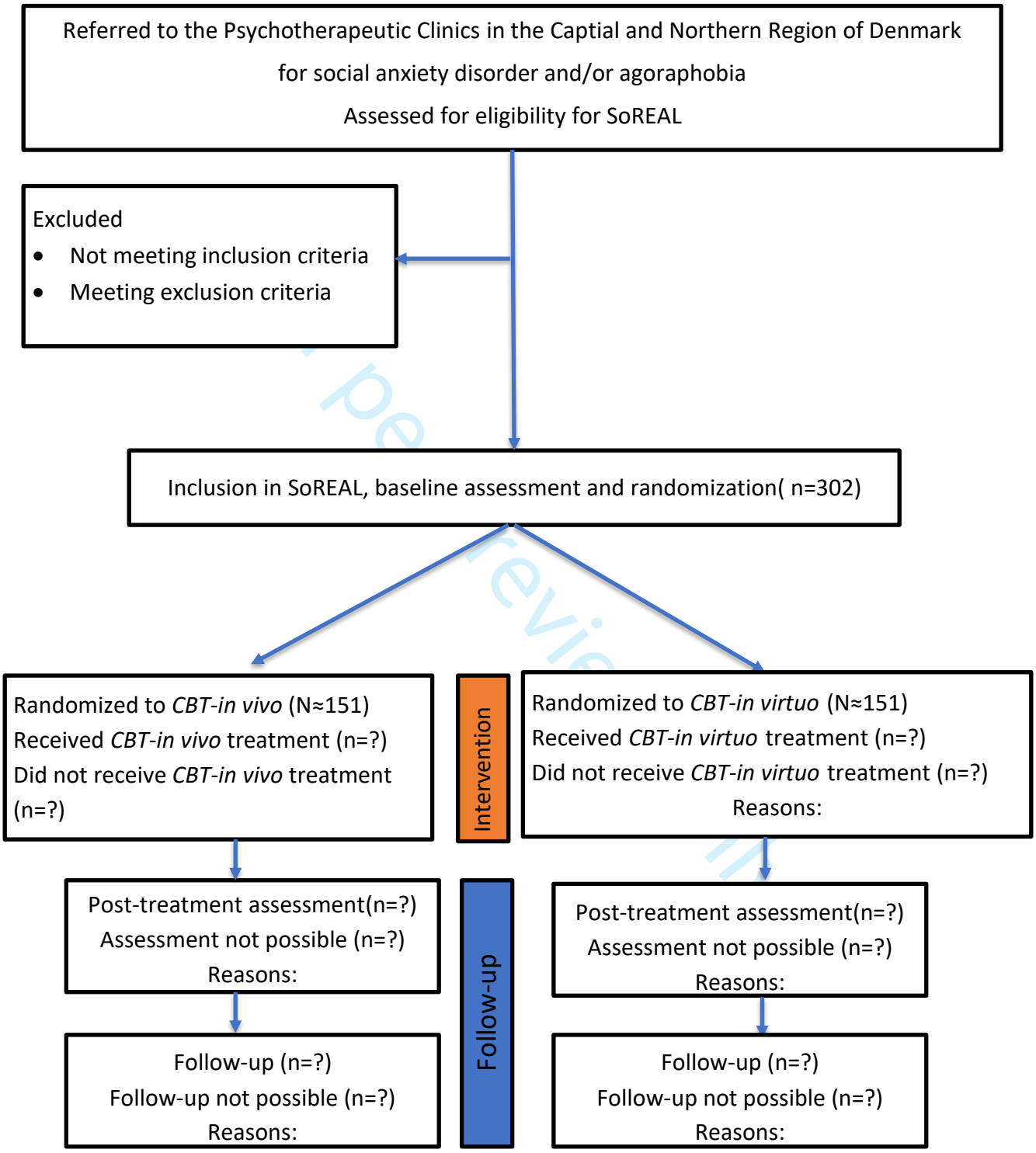
Schedule of enrolment, interventions, and assessments.	STUDY PERIOD		
	Enrolment and allocation	Follow-up	
TIMEPOINT**	Baseline	*Post-treatment*	*One-year*
ENROLMENT:	X		
Eligibility screen	X		
Informed consent and inclusion	X		
Allocation	X		
INTERVENTIONS:			
CBT-In vivo	←	—	→
CBT-In virtuo	←	—	→
ASSESSMENTS:			
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	



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 Questionaire	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)				

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

	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.
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pages 4-7
	6b	Explanation for choice of comparators	Pages 6-7 & 18-22
Objectives	7	Specific objectives or hypotheses	Pages 7-8
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Pages 8-9
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 10-18

	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Pages 10-11
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
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
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Pages 8-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 23
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pages 22-23

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 23
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 23
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pages 19-24 & Figure 3
	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
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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A. We do not plan to perform subgroup or adjusted analyses.
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 24-25
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 25
	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.
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 27
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
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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 28

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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 28
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 28
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary file 2
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

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

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 angstprovokendere 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 pulsur 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 sundhedsvæsnet. 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.

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.

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

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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	

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	

Scene 4. 2:01 – Loop of scene 0. The rest of the meeting participants arrive. Introductions to the group. Link to YouTube Scene 5. 4:02 – Loop of scene 0. Presentation has technical difficulties. Partner leaves mid-presentation. Link to YouTube Scene 6. 2:07 – Loop of scene 0. Scolding from the boss. Link to YouTube	

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	

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	

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	

Scene 3. 1:02 – Loop of scene 0A. Arrived too late. Professor notes it as you enter. Link to YouTube Scene 4. 1:18 – Loop of scene 0A. Arrived much too late. Scolded in front of full auditorium by professor. Link to YouTube	

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.	

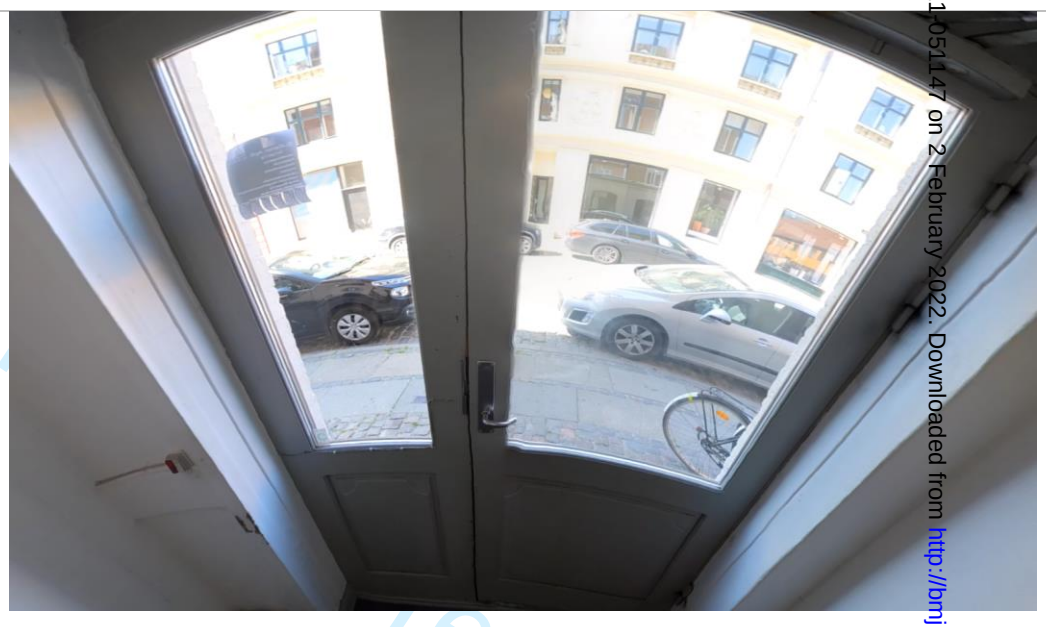
Scene 6. 2:00 – Loop of Scene 0. Drops tray with food next to table.	
Environment 9 - Taking a commercial airplane Scene 0. 7:26. Taking a plane, from boarding to landing. It is possible to only play specific segments, e.g. “Turbulence” or “Boarding”.	

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.	

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.	

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.	

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

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