

Cognitive behavioural therapy augmented with virtual reality exposure for treatment of social anxiety: A randomised clinical trial

Benjamin Amfred (✉ benjamin.alexander.thorup.amfred@regionh.dk)

Copenhagen Research Center for Mental Health - CORE <https://orcid.org/0000-0002-3064-8460>

Peter Bang

Copenhagen Research Center for Mental Health - CORE

Carsten Hjorthøj

Copenhagen Research Center for Mental Health - CORE

Clas Winding

Mental Health Center Copenhagen

Kirsten Møller

Mental Health Center Copenhagen

Morten Hvenegaard

Mental Health Center Copenhagen

Ulrik Krog Gausbøl

Mental Health Center Copenhagen

Ditte Sø

Mental Health Center Copenhagen

Nicole Rosenberg

Mental Health Center Copenhagen

Merete Nordentoft

Copenhagen Research Center for Mental Health - CORE

Study protocol

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Abstract

Background Social Anxiety Disorder (SAD) has high lifetime prevalence, early onset and long duration or chronicity. Cognitive Behavioural Therapy (CBT) has best evidence for treatment effect and planned exposure is considered one of the most effective elements of CBT in SAD. However, in vivo exposure can be difficult to access and control and is sometimes rejected by patients because they expect it to be too aversive. The use of virtual reality allows exposure to challenging situations in an immersive, but also protected, flexible and controlled environment. Methods The design is an investigator initiated randomized, assessor-blinded, parallel group and superiority designed clinical trial. 302 patients diagnosed with social anxiety disorder, will be included from two psychotherapeutic outpatient clinics at Mental Health Center Copenhagen. All patients will be offered a manual-based 14-week CBT group program, including eight sessions of exposure therapy. Patients will be randomised with concealed allocation sequence to CBT augmented with virtual reality exposure or CBT. Patients will be assessed at baseline, post treatment and at one-year follow-up by researchers blinded for treatment condition. The primary outcome will be social anxiety measured with Liebowitz Social Anxiety Scale. Secondary outcome measures will be depression, social functioning, and patient satisfaction. Exploratory outcomes will be substance and alcohol use, working alliance and quality of life. Discussion The SO REAL trial will be the hitherto largest trial investigating the use of virtual reality as augmentation of CBT and the results may guide future clinical treatments. Trials 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>

Background

Social anxiety disorder (also called social phobia)(SAD) is characterized by paying attention to oneself in an exaggerated manner and having marked fear of being evaluated negatively in specific or all situations, that imply interaction with others [1]. SAD has high lifetime prevalence, a pattern of early onset and long duration or chronicity [2]. Often the disorder has been untreated for decades due to a lack of recognition from surroundings and avoidance from the patients, causing severe problems in social adaptation and quality of life. Several meta-analyses have found that social anxiety disorder responds well to cognitive behavioural therapy (CBT) provided in individual as well as group format [3,4] although not as convincingly as other anxiety disorders [5]. However, knowledge about other elements of cognitive behavioural therapy, not least exposure, that are meant to provide this change is lacking [6]. Exposure therapy is considered one of the most effective elements in CBT, and the “gold standard” evidence-based technique for phobias.

Virtual reality exposure for SAD

Virtual Reality (VR) is a type of media that allows the creation of virtually mediated realities which are perceived as real or almost real, due to multisensory stimulation and blocking of real-world sensory input. The fact that the virtual reality user experiences the artificial environment as real opens numerous possibilities for psychological intervention. As a therapy tool, VR is most widely used and has shown the

best results through Virtual Reality Exposure (VRE) [7]. The use of VRE allows exposure to challenging situations in an immersive, but also protected, flexible and controlled virtual environment. This contrasts with in-vivo exposure which may be difficult to access and is sometimes rejected by patients because they consider it too aversive. Also, exposure in-vivo can be hard to organize logistically and challenging to control, especially in a group setting [8]. Using VRE can overcome or mitigate this problem by producing greater user acceptance and easy access to situations that would otherwise be too difficult to control or have unacceptable confidentiality risks. VRE is usually not used as an independent form of therapy, but rather a technological adjunct that can help the clinician to apply treatment more ecologically and effectively. VRE also allows the clinician to easily increase the level of difficulty of the exposure, e.g. patients can be exposed to more people or to more challenging social situations within the virtual environment. Based on this, VRE may improve efficacy and cost effectiveness of the treatment of social anxiety disorder.

Recent reviews and meta-analyses of VRE for anxiety disorders conclude that it is generally more effective than waitlist and placebo control and equally as effective as “gold-standard” treatment-as-usual controls [9–11]. However, for social anxiety disorder, there are only five trials published all with small sample sizes, the largest having 97 patients [8,12–15]. Thus, there is a scarcity of high quality randomized clinical trials evaluating integration of VRE in CBT. In addition, the four of the five published RCTs used VRE in an individual therapy format, and there are no established standards regarding the implementation of VRE into a group CBT setting. Lastly, none of these five studies evaluated the implementation of VRE in a naturalistic health care group setting with real-world patients. Consequently, there is a need for further investigation of methods and format for implementing VRE in such settings.

Aim and objectives:

The aim of the SO REAL-trial is to investigate the effect of cognitive behavioural therapy (CBT-In Vivo Exposure) versus cognitive behavioural therapy augmented with virtual reality exposure (CBT-Virtual Exposure) for patients diagnosed with social anxiety disorder.

In the SO REAL trial, the following hypotheses will be tested:

Primary hypothesis:

1. Post treatment, patients treated with cognitive behavioural therapy augmented with virtual reality exposure (CBT-In Virtuo) will have a lower level of social anxiety compared to the cognitive behavioural therapy groups with in vivo exposure (CBT-In Vivo), measured as the total score on the Liebowitz Social Anxiety Scale (LSAS) [16]. This measure assesses fear and avoidance of a range of social interactions and performance situations.

Secondary hypotheses:

1. One year after treatment, patients treated with CBT-In Virtuo will have lower levels of social anxiety symptoms compared to CBT-In Vivo.

2. Post treatment and one year after treatment, patients treated with CBT-In Virtuo will have lower levels of anxiety, depression and fear of negative evaluation compared to CBT-In Vivo.

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 [17]. As such, the SPIRIT Checklist and flowchart were used [see Additional file 1 and Fig. 1].

Recruitment

The SO REAL trial is a randomised, assessor-blinded, parallel-group superiority clinical trial, enrolling a total of 302 participants from outpatient facilities in the catchment area of Copenhagen. Patients are referred to treatment of social anxiety by their primary care physicians, psychiatrist or psychologist to Mental Health Centre Copenhagen. During intake all patients will be evaluated by experienced clinicians to be eligible for psychotherapeutic treatment as part of standard procedure in the psychotherapeutic clinic. After this clinical screening patients eligible for treatment will be approached and asked if they are interested in getting more information about the trial. If they accept, their contact details will be given to a research assistant, who will call and invite them for further assessment using Mini International Neuropsychiatric Interview. If eligibility is further confirmed, informed consent is collected. Patients are then randomised (1:1) to either CBT-*In Virtuo* or CBT-*In Vivo*, as described in further detail in the section Interventions. Patients, that cannot or will not participate in the study, will be offered treatment as usual. The recruitment and data collection process is outlined in Figure 2.

Inclusion criteria

Patients aged 18-75 years who provide written informed consent and fulfil diagnostic criteria for social anxiety disorder (ICD-code: F40.1) as well as the following:

- 1) Severity of social anxiety from moderate to severe degree (from cut-off 65 and up on the Liebowitz social anxiety scale).
- 2) Either not treated with antidepressants or unchanged doses of antidepressants for at least 4 weeks before inclusion and no change in antidepressants is anticipated.
- 3) Sufficient knowledge of the Danish language.

Exclusion criteria:

- 1) Alcohol or drug dependence.

Figure 1. Schedule of enrolment, interventions, and assessments.

Figure 2. Flowchart for inclusion, assessments, interventions and follow-up. All 302 patients will be included in the analyses.

Feasibility

The two psychotherapeutic clinics at mental Health Centre Copenhagen are responsible for treatment of all patients referred with social anxiety disorder in the catchment area of Mental Health Centre Copenhagen. Usually each of the clinics provide treatment for 75 patients every year. Thus, we anticipate that during a three-year recruitment period, 450 patients will be eligible for the trial, and we expect a high acceptance rate and a high follow-up rate, as the patients has already gone through a selection procedure in the central visitation unit at Mental Health Services in the Capital Region of Denmark.

Interventions

Therapeutic Intervention

The therapeutic intervention is manual-based cognitive behavioural CBT group therapy (CBT-group) adapted from the approach of Turk, C., L., Heimberg, R.G. & Magee, L. (2008)[18]. The treatment will consist of a total of 14 weekly two-hour group sessions performed in accordance with the manual to ensure a uniform and equal treatment for every patient throughout the study. Groups will consist of 8-9 patients, and every session will be led by two trained clinicians (e.g. psychologists or psychotherapists) with practical experience in CBT and *in vivo* exposure. In both conditions, the sessions dedicated to exposure is scheduled from the fifth to the twelfth sessions with approximately 30-90 min of exposure in each session. 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 behaviour 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 aim of the exposure is to develop new, non-threatening and adaptive responses to social situations by maximizing violations of expectancies of aversive events as well as minimizing safety behaviours.

In vivo exposure

The *in vivo* exposure will consist of guided within-group exposure (e.g. presentations) as well as exposure either inside or outside the clinic (e.g. asking for the time at the secretary's desk, spilling a beverage in the lunch room, being video recorded, dropping keys in public, yelling, dressing up or making improper requests in stores) with a focus on adjusting exposures to the needs of the group within the standardized treatment manual. For this reason, the *in vivo* exposure will not strictly match the *in virtuo* exposure.

In virtuo exposure

The patients receiving the *in virtuo* exposure will be immersed using an Oculus Go head-mounted display enabling viewing of 360° live recorded VR environments. Five exposure scenarios have been developed

based on general themes of the LSAS, patient feedback and clinical experience from a panel of clinicians. The five scenarios are as follows: 1) standing in line in a supermarket; 2) attending a party; 3) attending a formal meeting and giving a presentation; 4) small talking/debating in a canteen; and 5) entering an auditorium. Each scenario has four to six scenes of increasing difficulty as well as a neutral scene to familiarize patients with the VR setting. The neutral scene will also be used to reach within-session habituation for certain shorter scenes, where it would not otherwise be plausible. The aim is that all patients will work through all five scenarios during therapy, however, the order of the scenarios viewed will be chosen by the clinicians in order to accommodate the needs of the group. The last two *in virtuo* exposure sessions are devoted to individual work with one or two previously explored virtual environments closest to the patient's difficulties. Additionally, in the last two exposure sessions, the clinicians have the option of combining the *in virtuo* exposure with *in vivo* exposure (E.g. First going to the supermarket *in virtuo* and then to the actual supermarket).

Fidelity to treatment manual

The intervention is manual-based, which improves standardization of the treatment. Fidelity to the treatment manual will be assessed through a self-report questionnaire answered by the clinicians at three different timepoints throughout each group treatment. The questionnaire (and the timepoints whence it is delivered) is specifically designed to correspond to the treatment manual. This type of fidelity measurement, has been shown to be adequate for trials in which the effect of an add-on to treatment is tested [19].

The VR headsets will also record statistics regarding the use of the 360o films. This data illuminates the amount and type of use of the VR headsets and will also be matched to the individual patient. Throughout the study, this data will be used to measure the use of the VR films and how well it matches the guidelines proposed in the treatment manual.

Assessment

Diagnosis

Mini International Neuropsychiatric Interview (MINI), v. 7.0 for DSM-5 will be used to screen for diagnosis. Version 7.0 contains 17 modules for the major axis I psychiatric disorders in ICD-10 and DSM-IV-TR. Psychometric analyses of the MINI have demonstrated acceptable test-retest and inter-rater reliability. MINI is validated against CIDI for ICD-10 and SCID-P for DSM-IV. At the inclusion interview, all modules but P will be used to assess diagnostic eligibility (e.g. must have social anxiety disorder, may not have a psychotic disorder) and to detect comorbidity.

Adverse events

Unwanted negative side-effects induced by immersions in virtual reality (commonly referred to as cyber sickness) will be measured with the Simulator Sickness Questionnaire (SSQ) [20] administered after each VR exposure session.

The clinicians in charge of the treatment will register and deal with any adverse events, adverse reactions and report all serious adverse events and serious adverse reactions to the sponsor. Additional side effects or events will also be gathered from registers and patient files.

Data collection and management

See Figure 1 for an overview of data collection at baseline and follow-up. Self-reported data will be collected through surveys sent via REDCap (Research Electronic Data Capture). Assessors are trained in the interview instruments and will do regular co-ratings of live interviews. Interrater reliability of LSAS and secondary outcome measures will be calculated before the beginning of the trial. The interviewers will input data from the assessments directly into the electronic CRF (Case Report Form) using the data entry system REDCap [21]. 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 is 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 secured and locally. 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 special files. All data will be scrutinized in order to identify errors in data entry. Sponsor and the principal investigators ensure that data is stored at least 10 years after end of trial.

Outcomes and sample size calculation

Sample size calculations were performed on the primary outcome measure and a number of secondary outcome measures. Based on other studies using LSAS, we estimate SD to be 21. With $\alpha=0.05$, 80% power, and an expected standard deviation of 21, we will require 302 patients to detect the minimal relevant difference of 6.8 on the LSAS total score between the groups

Primary outcome:

The total score on the Liebowitz Social Anxiety Scale (LSAS) measured pre and post treatment. LSAS assesses anxiety level and avoidance of a range of situations typically feared by individuals with social anxiety. It has acceptable psychometric properties [16].

Secondary outcomes:

· Depressive symptoms measured pre treatment, post treatment and at follow-up as total scores on Hamilton Depression Rating Scale, 6 item version (HAM-D6) [22].

- Fear of negative evaluation measured pre treatment, post treatment and at follow-up with the Brief Version of the Fear of Negative Evaluation Scale [23].
- Work and Social Adjustment measured pre treatment, post treatment and at follow-up with the Work and Social Adjustment Scale (WSAS) [24].
- 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 [25].
- Quality of Life measured pre treatment, post treatment and at follow-up with the WHO Well-Being Index, 5 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 [26].
- Response (LSAS below 50 or a 15 points drop) and remission (LSAS below 25) of social anxiety symptoms measured post treatment and at follow-up.

Exploratory outcomes:

- Social functioning measured with Personal and Social Performance Scale (PSP) [27] pre treatment, post treatment and at one-year follow-up.
- Alcohol and substance use measured with Time Line Follow Back (TLFB) pre treatment, post treatment and at one-year follow-up.
- Self-belief of coping measured with General Self Efficacy (GSE) [28] pre treatment, post treatment and at one-year follow-up.
- Working alliance measured with Working Alliance Inventory post treatment [29].

Other measures:

- Unwanted negative side-effects induced by immersions in virtual reality (commonly referred to as cyber sickness) will be measured with the Simulator Sickness Questionnaire (SSQ) measured after the immersions.
- The experience of Social Presence as described by Lee (2004) [30] 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 concept of Presence because it has been theorized to be a critical element in the effective use of VRE for SAD [31].

Setting of assessment

Assessment will take place at the outpatient clinics where the patients also receive treatment. Self-report questionnaires (FNE, CSQ, WAI, WSAS, WHO-5) will be answered by following a link send to the patients email address, which the patients can access either on a personal device or on one of the clinics computers. MINI, LSAS, PSP, HAM-D6 and TLFB will be administered by trained researchers. After each session with VRE, *in-virtuo* specific questionnaires (Social Presence & Simulator Sickness Questionnaire) will be administered by the clinicians delivering the intervention.

Randomisation

Patients will be recruited from Mental Health Centre Copenhagen. Randomization ensues shortly after the inclusion and pre treatment interview. Randomization is done with a hidden allocation sequence and is centralized and handled with the randomization module in REDCap by a datamanager independent of the trial. Block sizes will be unknown to the researchers and clinicians. Factors for stratification are treatment site and severity of LSAS-SR with a cutoff score of 95. Individual randomization of the patients and allocation tables will be handled by external researchers with no affiliation with the project. An email of the assigned randomization of each patient will be sent to the team leaders organizing the logistics of the interventions in the Psychotherapeutic clinics. Assigned randomization of the patients will be stored by the research team datamanager. 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, the assessment will be performed by another researcher. Analysis and draft of conclusions will be performed by blinded researchers.

Statistical analyses

Analysis will all be from intention-to-treat. All included patients will also be included in the analyses. All tests 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. If the experimental groups are not significantly correlated to the outcome ($P>0.05$), no further analyses will be performed. If we find a significant correlation, a model adjusted for important prognostic covariates equal to the approach for continuous variables will be carried out.

Sensitivity analyses include an analysis of complete cases, removal of outliers (defined as standardized residuals greater than 3 standard deviations), a per protocol analysis defining patients not having a single contact as violating the protocol, and a second per protocol analysis including patients with at least 50% of intended out-patient contacts. The second per protocol analysis is likely to cause severe selection bias, as the outpatient treatment will include the patients with the highest level of motivation. Therefore, it is only considered meaningful to report negative results from this analysis. Positive, negative and inconclusive results, will all be published as soon as possible. All results will additionally be presented at international and national scientific and other relevant conferences.

Discussion

There are several strengths in the design of the SO-REAL trial. First, this will be the largest RCT to date assessing the use of VRE for social anxiety. Second, this will be the first study to assess the use of VRE in a naturalistic clinical group therapy setting. Third, the use of a treatment-as-usual control group means that effect sizes bias is minimized. Fourth, it employs observer-blinded assessment of outcomes. Additionally, the clinicians informing the patients of the trial will also be blinded as to which intervention the patient will receive. Moreover, data management, data analyses, and conclusions will be conducted and drawn blind to the intervention group. Fifth, the wide range of outcome measures in the trial allows the opportunity to assess outcome in areas of symptomatology, working alliance, treatment face validity, quality of life, social and personal functioning. Sixth, the use of intention-to-treat analysis means that results will more closely resemble the effects the intervention could have if implemented.

Practical challenges will be possible technical issues that might arise. Since the clinicians will not have knowledge with technical aspects of VR, troubleshooting technical issues 'on-the-go' might be difficult and/or time consuming.

Overall, we believe that the SO REAL trial will contribute with knowledge about the efficacy and feasibility of VRE for treating SAD in a naturalistic clinical setting and that the results of the trial may guide future application of VR technology in clinical settings across a wide breadth of use-cases.

Trial Status

Not yet begun inclusion. Inclusion to begin from February 4th, 2019. Inclusion expected to stop at February 4th, 2022. Protocol version 2, last revised 31.01.19.

List Of Abbreviations

SAD: Social Anxiety Disorder, VRE: Virtual Reality Exposure; CBT: Cognitive behavioural therapy; RCT: Randomised Controlled Trial.

Declarations

Funding

Professor Merete Nordentoft and Adj. Professor Nicole Rosenberg took the initiative to start the project. Merete Nordentoft submitted an application to Novo Nordisk Foundation and the SO REAL project was granted 5 million DKK. Merete Nordentoft and Nicole Rosenberg have no affiliation to the Novo Nordisk Foundation. Mental Health Centre Copenhagen supported the trial with in kind resources. The project is entirely independent from the Novo Nordisk Foundation and as such, 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 play any role in future publications that may derive from the project.

Availability of data and materials

The data that support the findings of this study are available from The Danish National Archives, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of The Danish National Archives.

Authors' contributions

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 revised the protocol, carried out the power calculations and will be responsible for supervising the statistical analyses. NR revised the protocol and was responsible for the non-experimental content of the CBT. CW, KM PB and BA directed the development of the VR films. CW, KM, UKG, DS, BA and PB developed the manual and guidelines for using VR therapeutically. MHP was responsible for outcome measures. PB and BA built the database, set up randomization, set up clinical procedures, developed the Social Presence Scale, will be responsible for all inclusion and outcome assessment, revised the protocol and developed fidelity measures.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Acknowledgements

N/A.

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. 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 treatment possibilities.

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Figures

Schedule of enrolment, interventions, and assessments.	STUDY PERIOD			
	Enrolment and allocation	Follow-up		
	TIMEPOINT	Pre-treatment	Post treatment	One-year
ENROLMENT:				
Eligibility screen	X			
Informed consent and inclusion	X			
Allocation	X			
INTERVENTIONS:				
CBT-In Vivo	←————→			
CBT-In Virtuo	←————→			
ASSESSMENT:				
Sociodemographic data (Age, gender, education)	X			
Mini International Neuropsychiatric Interview	X			
Liebowitz Social Anxiety Scale	X	X	X	
Hamilton Depression Rating Scale 5	X	X	X	
Substance and alcohol use measured Time Line Follow Back	X	X	X	
Fear of negative evaluation	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			
Stimulator Sickness Questionnaire	(During treatment for CBT-In virtuo) X			
Working Alliance Inventory (WAI)		X		

Figure 1

Schedule of enrolment, interventions, and assessments

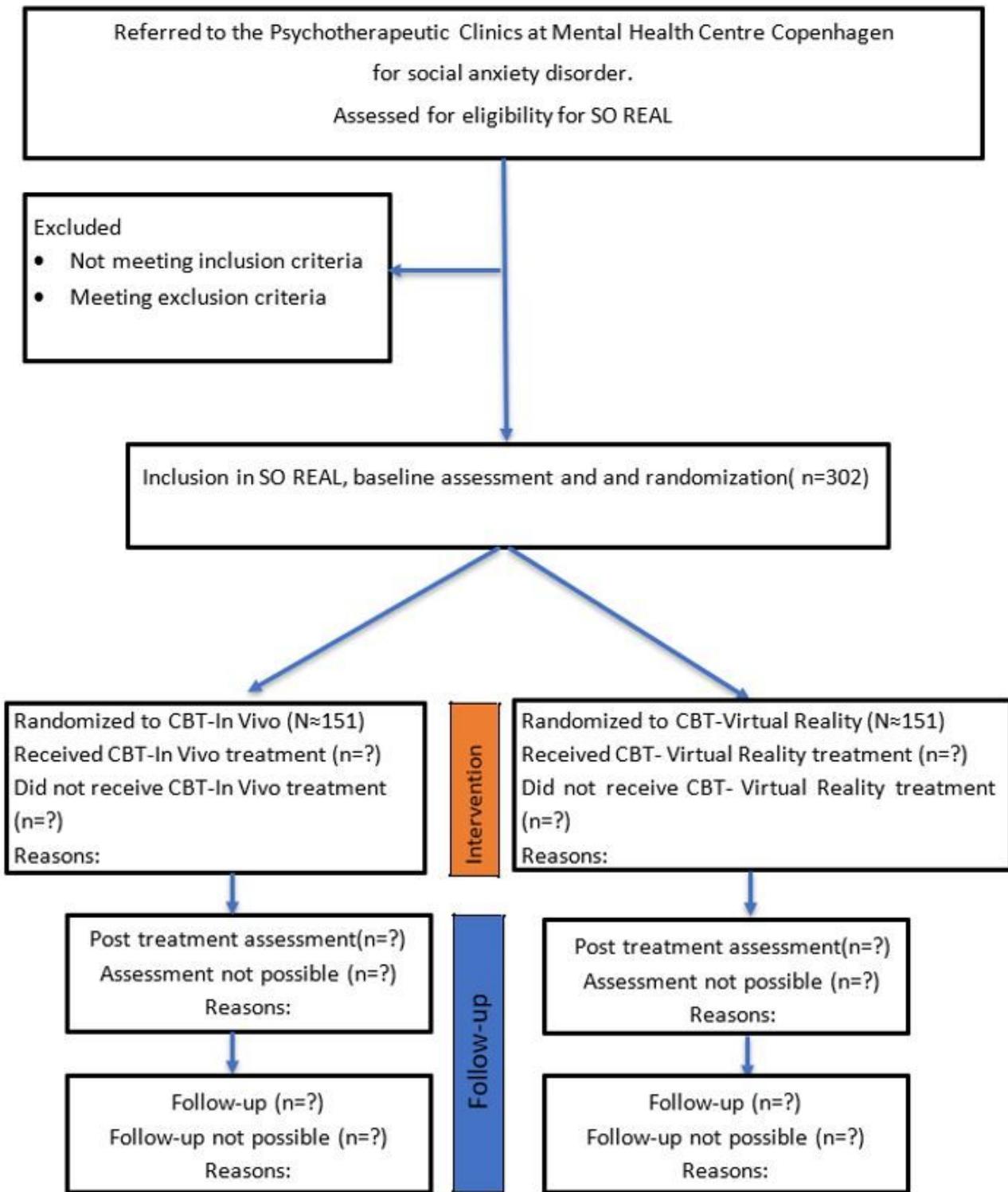


Figure 2

Flowchart for inclusion, assessments, interventions and follow-up. All 302 patients will be included in the analyses.

Supplementary Files

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