Virtual reality-assisted cognitive behavioural therapy for outpatients with alcohol use disorder (CRAVR): a protocol for a randomised controlled trial

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ABSTRACT

Introduction Alcohol use disorder (AUD) is a brain disorder linked to over 200 health conditions. Cognitive behavioural therapy (CBT) is considered the best practice in the treatment of AUD, but more than 60% of patients relapse within the first year after treatment. Psychotherapy combined with virtual reality (VR) has received increasing interest in the treatment of AUD. However, existing studies have primarily investigated the use of VR for cue reactivity. We therefore aimed to investigate the effect of VR-assisted CBT (VR-CBT).

Methods and analysis This is a single-site, assessor-blinded, randomised clinical trial being conducted at three outpatient clinics in Denmark. We will randomise 102 patients to 14 individual sessions of either manualised VR-CBT or CBT. The VR-CBT group will receive exposure to immersive high-risk VR scenarios from a pub, bar, party, restaurant, supermarket and at-home (30 videos) to activate high-risk-related beliefs and cravings for subsequent modification using CBT techniques. The treatment period is 6 months, and follow-up visits will be performed 3, 6, 9 and 12 months after inclusion. The primary outcome measure is the change in total alcohol consumption from baseline to 6 months after inclusion, measured with the Timeline Followback Method. Key secondary outcome measures include changes in the number of heavy drinking days, alcohol cravings, cognition, and symptoms of depression and anxiety.

Ethics and dissemination Approval has been obtained by the research ethics committee in the Capital Region of Denmark (H-20082136) and the Danish Data Protection Agency (P-2021-217). All patients will receive both oral and written information about the trial and written informed consent will be obtained from each patient before inclusion. The study results will be disseminated in peer-reviewed publications and conference presentations.

Trial registration number ClinicalTrials.gov, NCT05042180.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The present study is an assessor-blinded, randomised trial investigating long-term reduction in alcohol consumption and craving in patients with alcohol use disorder (AUD).

⇒ A total of 30 different 360° virtual reality (VR) high-risk scenarios distributed in 5 different locations are available for individualised exposure.

⇒ Cognitive behavioural therapy (CBT)-trained therapists with experience in treating AUD will perform all therapy sessions and receive supervision throughout the study period.

⇒ VR exposure is integrated into standard CBT, which makes it easily implemented in clinical settings.

⇒ It is a limitation that patients and therapists are unblinded; however, research staff remain blinded throughout the entire study period.

INTRODUCTION

Alcohol use disorder (AUD) is a chronic brain disorder linked to more than 200 health conditions and attributed to 3.3 million deaths each year globally. The disorder is characterised by periods of intake and loss of control, followed by periods of abstinence. Prolonged consumption of alcohol causes neuroadaptation that compromises cognitive functioning and has severe personal and interpersonal consequences. The treatment of choice includes pharmacological, social and psychotherapeutic interventions, but even when receiving complete treatment, more than 60% of patients experience relapse within the first year after being discharged. Thus, there is an urgent need to develop new treatment options for patients with AUD.
Cognitive behavioural therapy

Cognitivebehavioural therapy (CBT) is a time-limited, multissetion intervention based on the theory that psychological disorders are characterised by maladaptive behaviour and thinking derived from dysfunctional beliefs.\textsuperscript{5, 6} Individuals with AUD are thought to have specific beliefs activated under high-risk situations, including relapse-oriented, permissive, and anticipatory.\textsuperscript{5} According to the cognitive model of substance abuse, these beliefs are associated with specific thought patterns, ultimately resulting in behaviour toward relapse or continued substance abuse.\textsuperscript{5} CBT involves techniques to identify and modify such beliefs, patterns of thinking, and behavioural habits and improve coping skills to prevent continued abuse.\textsuperscript{5, 6} CBT interventions have proven effective in treating patients with AUD and are as efficacious as similar psychotherapeutic interventions that is, motivational interviewing and contingency management.\textsuperscript{7} However, the efficacy remains limited, and new treatment modalities with increased efficacy are necessary.

VR therapy

Technological advancement in conjunction with psychotherapy may improve the treatment of psychiatric disorders. Particularly, VR-assisted therapy has received increasing interest in clinical mental health research.\textsuperscript{3} VR technology is a computer-generated simulation where patients experience an immersive virtual environment. It has previously been used for skills training, mindfulness, and identifying behaviour and thought patterns in specific situations.\textsuperscript{9} For optimal immersion during VR simulation, it is considered essential that patients experience a sense of presence.\textsuperscript{10, 11} Lee defines the term ‘Presence’ as ‘a psychological state in which virtual objects are experienced as actual objects in either sensory or non-sensory ways’.\textsuperscript{12} It means that VR users react to virtual emotional stimuli similarly to real-life situations. The presence is generally achieved by stimulating the auditory and visual senses, allowing a high degree of interaction with the environment. VR has been used therapeutically in various ways, and promising results have been found for treating anxiety disorders, post-traumatic stress disorder, psychosis and eating and addictive disorders.\textsuperscript{13-17} Nevertheless, the research remains at an early stage.

VR exposure therapy (VRET)

In the field of AUD, VR has primarily been examined as a tool to test cue reactivity or deliver exposure therapy (ET).\textsuperscript{17} During ET, individuals are exposed to alcohol cues, for example, look, hold, smell, and taste, to elicit alcohol craving with subsequent retention from further consumption, that is, non-reinforced exposure.\textsuperscript{18} Based on classical conditioning, this method will weaken conditioned associations between cues, craving, and consumption in a process termed extinction.\textsuperscript{18} A meta-analysis from 2017 found minor effects of using classic ET for AUD.\textsuperscript{19} Treatment effects increased when combined with specific coping skill training, for example, thinking of the positive consequences of abstinence/moderation and the negative consequences of drinking.\textsuperscript{19} The limited efficacy of ET is suggested to be due to failure to extinguish the most salient conditioned cues, from spontaneous recovery when patients are re-exposure to the conditioned stimuli, for example, beer, pub, or when an extinguished conditioned response is reinstated because of exposure to an unconditioned stimulus, that is, cough medicine or benzodiazepines.\textsuperscript{18} In recent investigations, ET has been applied using VR (VRET).\textsuperscript{17} VR scenarios can expose patients to high-risk situations in a more confidential, flexible and controlled setting, often requiring less time compared with conventional in vivo sessions.\textsuperscript{9, 20, 21} VR exposure can easily be repeated, and cues can be individualised. A total of four reviews evaluating VRET in the treatment of addictive disorders have been published since 2014, and some of the studies suggest that VRET can reduce craving short-term.\textsuperscript{17, 22-24} However, the research field generally lacks methodological rigour with small sample sizes, few randomised studies, and a lack of long-term follow-up. Furthermore, no study has investigated the effect of VRET on long-term craving, alcohol consumption, or as an integrated part of CBT.

VR-assisted CBT (VR-CBT)

Contrary to CBT-based treatment for other mental disorders, exposure is currently not integrated as a standard part of CBT for AUD. This is most likely due to limited efficacy and logistical and confidential limitations. However, the recent technological improvements in VR have created new possibilities for bringing high-risk situations into a safe, confidential, and controllable clinical setting.

We hypothesise that VR exposure will reduce craving through non-reinforced exposure, and activate and reveal more ecologically valid high-risk-related beliefs, thought patterns, emotions and physiological responses compared with conventional CBT. This may contribute to greater insight and awareness of dysfunctional patterns for further modification using CBT. Since there is substantial evidence that emotional events are remembered more clearly, accurately and for more extended periods than neutral events, we hypothesise that the experience of VR-induced emotions during treatment sessions will further improve CBT interventions compared with conventional CBT.\textsuperscript{25} Thus, the present study may ultimately result in a novel treatment modality for patients with AUD: VR-CBT.

Primary hypothesis

► At 6 months post inclusion, patients randomised to VR-CBT will have a greater reduction in total alcohol consumption than patients randomised to conventional CBT, measured with the Timeline Followback (TLFB) Method.
Secondary hypothesis

► At 6 months post inclusion, patients randomised to VR-CBT will experience fewer heavy drinking days than patients receiving conventional CBT, measured by TLFB.
► At 6 months post inclusion, patients randomised to VR-CBT will experience less craving than patients receiving conventional CBT, measured by Penn Alcohol Craving Scale (PACS).

METHODS AND ANALYSIS

This article was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 explanation and elaboration: guidance for protocols of clinical trials. The SPIRIT checklist was followed.

Study design

The present study is an assessor-blinded, randomised, controlled, parallel, superiority-designed clinical trial designed to investigate the effect of VR-CBT versus conventional CBT in 102 patients diagnosed with AUD.

Recruitment

Patients will be recruited from three Novavi outpatient clinics in the Capital Region of Denmark and Region Zealand, Denmark. Patients can be referred from the hospital, general practitioner, commune, self-referred or elsewhere. Treatment is free of charge for everyone with a Danish Social Security Number. Each clinic has a medical doctor and therapeutically trained nurses and social workers that register patients into the treatment clinic. During registration, the clinical staff initiates abstinence treatment if indicated (benzodiazepines and vitamins) and informs all patients about the clinical trial (figure 1, day 1). The researchers are contacted to schedule an information meeting if the patient is interested. During the information meeting, all potentially eligible patients will be informed, verbally and in writing, on their rights and responsibilities while participating in the study (figure 1, day 2). The patients are informed that the trial’s primary aim is to investigate whether VR-CBT can reduce alcohol consumption and craving more than standard CBT and that VR-induced craving might increase the risk of relapse after treatment sessions.

Screening examinations will only be performed after the patient has agreed to participate and has signed the informed consent form (online supplemental material). At the time of screening, patients will undergo an interview to ensure that all inclusion and none of the exclusion criteria are met. Patients will also be asked about psychosocial factors in addition to treatment goals, motivation, alcohol history, previous treatment, family disposition, education, and civil status.

Inclusion criteria

► Informed oral and written consent.
► Diagnosed with AUD according to the criteria of the International Classification of Diseases 10th Revision (ICD-10).
► Age 18–70 years (both included).
► Heavy alcohol drinking is defined as having alcohol consumption over 60 g of alcohol per day (men) or...
48 g of alcohol per day (women) for at least 5 days in the past 30 days before inclusion, measured by the TLFB Method.

**Exclusion criteria**

- Severe neuropsychiatric disease, for example, a diagnosis of schizophrenia, paranoid psychosis, bipolar disorder, or substantial cognitive impairment.
- Any other active substance use defined as a Drug Use Disorders Identification Test (DUDIT) Score >6 (men) >2 (women) and fulfilling the criteria for a dependence of the substance according to the criteria of ICD-10 (except nicotine).
- Receiving any pharmacological treatment targeting AUD (ie, acamprosate, disulfiram, naltrexone, nalmefene) within the last 30 days.
- Insufficient Danish language skills to understand therapeutic sessions or informed consent.

**Intervention**

A total of 14 individual CBT sessions will be scheduled for each patient in both study arms and performed by therapeutically trained nurses. Treatment sessions have a duration of approximately 60 min and are based on a manualised protocol, which can be modified to individualise the treatment to each patient’s needs. Table 1 shows the proposed content for each CBT session, all carried out during the full course of treatment. Each session is structured similarly:

1. Mood check.
2. Set the agenda together.
3. Homework from the last session.
4. Today’s topic±VR exposure.

<table>
<thead>
<tr>
<th>Session</th>
<th>Topic</th>
<th>Homework</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Psychoeducation and the cognitive method</td>
<td>Identify high-risk situations and triggers</td>
</tr>
<tr>
<td>2</td>
<td>Problems and goals (including social relationships)</td>
<td>Identify problems and goals</td>
</tr>
<tr>
<td>3</td>
<td>Motivation</td>
<td>Identify the advantages and disadvantages of abuse versus change</td>
</tr>
<tr>
<td>4</td>
<td>Cognitive conceptualisation*</td>
<td>Craving registration</td>
</tr>
<tr>
<td>5</td>
<td>Cognitive analysis and reconstruction focusing on core beliefs,</td>
<td>Cognitive analysis and/or cognitive model of substance abuse</td>
</tr>
<tr>
<td>6</td>
<td>intermediate beliefs (rules, attitudes, assumptions), alcohol-related</td>
<td>Cognitive analysis and reconstruction</td>
</tr>
<tr>
<td>7</td>
<td>beliefs, automatic thoughts and possible changes in behaviour</td>
<td>Cognitive reconstruction</td>
</tr>
<tr>
<td>8</td>
<td>Cognitive analysis and reconstruction focusing on core beliefs,</td>
<td>Cognitive analysis and reconstruction</td>
</tr>
<tr>
<td>9</td>
<td>intermediate beliefs (rules, attitudes, assumptions), alcohol-related</td>
<td>Cognitive reconstruction</td>
</tr>
<tr>
<td>10</td>
<td>behavioural beliefs, automatic thoughts and possible changes in</td>
<td>Cognitive reconstruction</td>
</tr>
<tr>
<td></td>
<td>behaviour</td>
<td>Cognitive analysis and reconstruction</td>
</tr>
<tr>
<td>11</td>
<td>Behavioural experiment</td>
<td>Behavioural experiment</td>
</tr>
<tr>
<td></td>
<td>Practice relapse prevention</td>
<td>Relapse prevention</td>
</tr>
<tr>
<td></td>
<td>Identification of early warning signs</td>
<td>What to do in a crisis</td>
</tr>
<tr>
<td>12</td>
<td>Review reasons to maintain reduction or abstinence and warning signs</td>
<td>Identify advantages and disadvantages of abuse versus change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Practice coping strategies against craving</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behavioural experiment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cognitive analysis and reconstruction</td>
</tr>
<tr>
<td>13</td>
<td>Repeat topics from previous sessions</td>
<td>Relapse prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What to do in a crisis</td>
</tr>
<tr>
<td>14</td>
<td>Repeat topics from previous sessions</td>
<td>–</td>
</tr>
</tbody>
</table>

*Cognitive conceptualisation is used as a dynamic tool throughout the treatment period and is adjusted when discoveries are made during treatment.*
5. New homework.

To increase fidelity to the treatment manual, all therapists will register if they deviate from the proposed agenda. For further standardisation, therapists will register mood checks and whether they included the patient in preparation of the agenda, performed cognitive analysis and ensured a >75% chance of patients committing to the assigned homework. For patients randomised to VR-CBT, therapists will also register which VR videos patients have been exposed to, craving levels during exposure on a 10-point scale and side effects evaluated on Simulator Sickness Questionnaire (SSQ).

For patients randomised to VR-CBT, the first treatment session will be used to identify high-risk situations for individualisation of VR exposure. Based on the patient feedback during sessions, VR videos will be chosen from five available locations for individualisation. Locations have been selected based on Ghiță et al questioning 75 patients about the most triggering locations: (1) pub, (2) bar/party, (3) restaurant, (4) home and (5) supermarket.26 VR exposure is performed during sessions 2–14 and the number of videos in each session will be determined by the therapist and documented in manuals. Screenshots from the VR application and VR videos are shown in figure 2.

Each location contains six different situations with a gradually increasing number of alcohol-related cues and emotional triggers to induce thought, emotions, physiological reactions and increasing levels of craving. Videos of grades 5 and 6 have an interactive element, where actors (avatars) either ask the patient if he/she wants a beverage (patients are instructed to say no) or confronts the patient with an alcohol-related topic. The title and duration of all VR videos are shown in table 2.

When patients are exposed to VR high-risk scenarios during VR-CBT and experience craving or another reaction, patients are instructed to:
1. Stay in the scenario/video for non-reinforced exposure.
2. Practice coping strategies while craving occurs.
3. Perform cognitive analysis based on thoughts, emotions, and physiological reactions.

The therapist determines the usage of the above-mentioned CBT strategies. It is optional to freeze (pause) the video at any specific time, which may be beneficial for the CBT techniques mentioned above. After the CBT techniques are performed or if no reaction occurs, the next grade or another location is chosen to optimise the use of VR. Approximately 15 min of each session is allocated to VR exposure. Figure 3 shows the methodological use of VR videos in the CBT sessions.

Relapse
If patients relapse during the treatment period, the nurse will conduct a cognitive analysis during the following treatment session to identify the cause. In addition, the patient will be evaluated for withdrawal symptoms, and if indicated, the clinical staff will initiate abstinence treatment (benzodiazepines and vitamins). Relapse will not necessarily impact the CBT agenda outlined in table 1 but will be considered a source of new information and insight to be addressed during CBT sessions. However, if the relapse was caused by VR-induced craving, the study group will discuss whether the specific relapse should result in further participation or dropout.

Withdrawal criteria
Patients are free to withdraw from the trial at any time without providing a reason and without any impact on further treatment at the Novavi outpatient clinics. The reason for withdrawal will be registered only if the patient
wishes to inform the study personnel. Failure to comply with the clinical trial protocol, that is, if a patient misses more than five treatment sessions in total, will lead to exclusion from the trial. Registration of exclusion will contain information on the main reason.

VR scenarios and equipment
A total of 30 different high-risk videos have been produced using a GoPro Camera. All videos were filmed by movie producer and instructor Anne Heeno (AH) from the company TimestoryVR (www.timestoryvr.com), using professional actors and extras. The scenography and manuscripts were written in collaboration among Daniel Thaysen-Petersen, Irene Henriette Oestrich and AH. The head-mounted device, Oculus Quest V.2, will deliver high-resolution 360° videos using spatial sound. This equipment has been chosen since high-resolution and spatial sound optimises the sense of presence.27 Thus, different results must be expected when using equipment of a different quality. To navigate easily between different videos, an app has been developed in collaboration with researchers at Aalborg University, Denmark. Together with the therapist, patients can navigate through the app to find high-risk scenarios during treatment sessions. Before each video, a text and narrator prepare the patient for VR exposure by explaining what will happen during the video. Throughout all videos, patients may pause, replay or quit the video. Further information on the operationalisation of VR exposure during the CBT sessions is described in the section ‘Interventions’ and illustrated in figure 3.

VR-CBT education and supervision
To ensure a high competence level of the therapeutically trained nurses, all nurses in the clinical trial has at least a 1-year CBT course (theoretical and practical) in addition to a minimum of 1-year clinical experience with addiction treatment. Furthermore, all therapeutically trained nurses completed a VR-CBT education before study initiation and will receive supervision throughout the clinical trial. VR-CBT education was conducted by a clinical psychologist and specialist in CBT. The education consisted of seven workshops (7 hours each) with the following themes: (1) assessment and baseline, (2) exposure, self-control, coping and VR, (3) motivation, (4) addiction, consequences and craving, (5) the importance of thoughts, (6) coping strategies and (7) problem-solving, social skills and self-esteem. After the education, a pilot study was conducted for feasibility and for therapists to practice the use of VR-CBT. During the pilot study, each therapist performed three treatment sessions for one patient randomised to conventional CBT and one patient randomised to VR-CBT. Supervision was performed during the pilot study (7 hours) and

<table>
<thead>
<tr>
<th>Location</th>
<th>Pub</th>
<th>Bar/party</th>
<th>Restaurant</th>
<th>Home</th>
<th>Supermarket</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>In front of the pub (1:30 min)</td>
<td>Preparation at home (1:35 min)</td>
<td>Arrival at restaurant (1:39 min)</td>
<td>In the living room alone (1:26 min)</td>
<td>Home in front of refrigerator (1:30 min)</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Entering the pub (2:08 min)</td>
<td>Arrived outside the party (1:25 min)</td>
<td>Ordering food and drinks (3:53 min)</td>
<td>Alcohol commercial on TV (2:40 min)</td>
<td>Inside the supermarket (2:27 min)</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Getting beer in the bar (2:20 min)</td>
<td>Welcome speech (4:06 min)</td>
<td>Drinks are being served (3:23 min)</td>
<td>Alcohol emojis from a friend (2:21 min)</td>
<td>Beer and water department (1:59 min)</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Shots and singing (3:35 min)</td>
<td>At the bar before dinner (2:00 min)</td>
<td>Drinking problem is revealed (3:55 min)</td>
<td>Unexpected visit from friend (1:42 min)</td>
<td>Wine department (1:51 min)</td>
</tr>
<tr>
<td><strong>Grade 5</strong></td>
<td>Friend offers to buy alcohol (3:13 min)*</td>
<td>At the table with friends (2:49 min)*</td>
<td>Friend offers shots (3:52 min)*</td>
<td>Worried friend offers help (2:40 min)*</td>
<td>Free tasting samples (2:41 min)*</td>
</tr>
<tr>
<td><strong>Grade 6</strong></td>
<td>Friends want answers (4:32 min)*</td>
<td>Party in the bar (2:13 min)*</td>
<td>Friends want to go out (2:13 min)*</td>
<td>Drunk friend offers beer (1:51 min)*</td>
<td>Drunk guy at the liquor section (4:08 min)*</td>
</tr>
</tbody>
</table>

*Interactive element.

Figure 3 Virtual reality (VR)-assisted cognitivebehavioural therapy intervention.
will be conducted every second month during the clinical trial (3.5 hours/session).

Quantitative assessment
At inclusion, 3-month, 6-month, 9-month and 12-month follow-up (after inclusion), the following questionnaires will be performed either by a blinded assessor or by the unblinded patient:
- Blinded assessor evaluated:
  - Alcohol consumption using TLFB.28
  - The Clinical Institute Withdrawal Assessment of Alcohol Scale Revised (CIWA-Ar).29
  - Global Assessment of Functioning (GAF).30
  - Screen for Cognitive Impairment in Psychiatry (SCIP).31
- Unblinded patient reported:
  - Cue-induced craving before, during (maximum) and after each VR exposure evaluated on a Visual Analogue Scale (VAS) (0=no craving and 10=most intense imaginable craving).
  - PACS.32
  - Alcohol Use Disorders Identification Test (AUDIT).33
  - DUDIT.34
  - Beck Depression Inventory-II (BDI-II).35 36
  - Beck Anxiety Inventory (BAI).

Qualitative assessment
To determine potential side effects from VR and CBT, the following self-reported questionnaires are used unblinded.
- SSQ—during each VR-CBT session.37
- The Negative Effects Questionnaire—at 6-month and 12-month follow-up.38

In addition, a total of 15 patients and five therapists will be interviewed about the advantages and disadvantages of using VR in treatment sessions.
- Qualitative assessments of using VR-CBT (interviews).

Sample size calculation
The primary outcome measure (total alcohol consumption) was used for the sample size calculation. Based on data from the study by Johnson et al, where the reduction in the percentage of consumption was 60.3% in the intervention group and 32.7% in the control group, with an alpha of 5%, a power of 90% and an estimated SD of 34.5, the estimated sample size is of 68 patients (34 in each group).39 With an estimated dropout rate of 50%, a total of 102 patients (51 in each arm) are needed. The patients will be randomised into two groups with 51 patients in each group, using the randomisation module in Research Electronic Data Capture (REDCap).

Randomisation and blinding
The randomisation will be stratified in terms of age (two levels), gender (two levels) and baseline alcohol consumption (ie, number of heavy drinking days measured by TLFB, two levels) with block sizes of 4. The random allocation sequence will be uploaded in REDCap in accordance with REDCap’s user guide and reference manual. Patients and therapists are unblinded. Investigators performing assessments and data analysis will remain blinded until all patients have completed 12-month follow-ups. To maintain the blinding of investigators, therapists perform randomisation and the investigator’s randomisation rights are removed in REDCap during the entire trial. If a patient develops an adverse reaction that requires knowledge of the treatment, randomisation will be broken individually.

Statistical analysis
The analysis will be made by use of R software, with alpha set at 0.05 and two-sided testing. All analyses will be performed using the intention-to-treat principle on subjects, who were randomised and received at least one session of either VR-CBT or conventional CBT. Missing data will be imputed using multiple imputations, and a sensitivity analysis will be undertaken to evaluate and compare imputation results to complete case analysis. Multiple linear regression and logistic regression analysis will be used for the analysis, and data will be controlled for possible confounders; baseline alcohol consumption, social status, age, etc in addition to the treatment.

Endpoints
The primary endpoint is percentage reduction in total alcohol consumption, defined as reduction in grams of alcohol from baseline to the final treatment session (6-month follow-up), measured by TLFB. The secondary endpoints are percentage reduction in total alcohol consumption from baseline to 9-month and 12-month follow-up, as well as changes from baseline to 6-month, 9-month and 12-month follow-up for the number of heavy drinking days, defined as days with an excess intake of 60/48 g of alcohol per day (male/female) over the previous 30 days, AUDIT, DUDIT, PACS, SCIP, GAF, BAI, BDI-II, SSQ, cue-induced craving score (VAS) and CIWA-Ar. In addition, 15 patients and 5 therapists will be asked about the advantages and disadvantages of using VR in the treatment.

Trial status
Patient enrolment started in October 2021 and is continuing until 102 patients have been randomised and received the first treatment session.

Patient and public involvement
No patients were involved in the development of the intervention or in designing the study. When signing the informed consent, patients are offered to report their email addresses if they wish to be informed of the results of the study.

ETHICS AND DISSEMINATION
The study has been approved by the research ethics committee in the Capital Region of Denmark (H-20082136) and the Danish Data Protection Agency (P-2021-217). All patients will receive both oral and written information about the trial and written informed consent, patients are offered to report their email addresses if they wish to be informed of the results of the study.
consent will be obtained from each patient before inclusion (online supplemental material). The study is registered at ClinicalTrials.gov (NCT05042180). The protocol has version control and dates as identifiers. Any amendments must be approved by the above-mentioned authorities before implementation. The study results will be disseminated in peer-reviewed publications and conference presentations.

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Acknowledgements The authors thank the therapeutically trained project nurses from the Novavi clinics for their enormous efforts in providing therapy.

Contributors DT-P and AF-J made the first draft of the study protocol and statistical power calculations. A-CV, SWD, RN, AA, IHK, MM, BTA and SKHJ have made substantial contributions to the study design and the final version of the intervention. All authors contributed to the critical revision of the manuscript for important intellectual content and have approved the final manuscript.

Funding DT-P and AF-J initiated the project and were granted 1.672.812 DKK by the Novavi Foundation and 967.659 DKK by the TrygFonden (ID: 145842). DT-P and AF-J have no affiliation with either the Novavi Foundation or TrygFonden. The project is completely independent of the funding sources regarding study design, collection management, analysis, interpretation of data and writing of publications.

Competing interests AF-J has received an unrestricted research grant from Novo Nordisk A/S to investigate the effects of GLP-1 receptor stimulation on weight gain and metabolic disturbances in patients with schizophrenia treated with an antipsychotic. SWD is a consultant responsible for treatment at the Novavi Foundation.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel: Virtual Reality-Assisteret Eksponeringsterapi mod Alkoholafhængighed: Et Randomiseret Klinisk Forsøg (CRAVER studiet)

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: ________________________________________________________

Dato: _______________   Underskrift: ____________________________________________

Hvis der kommer nye væsentlige helbredsoplysninger frem om dig i forskningsprojektet vil du blive informeret. Vil du frabede dig information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, bedes du markere her: __________ (sæt x)

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:
Ja _____ (sæt x)    Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der afgiver information:

Dato: _______________   Underskrift: ____________________________________________

Projektidentifikation:
H-20082136, Version 3, 28. april 2021