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EFFECT OF ENVIRONMENTAL ENRICHMENT ON RELAPSE RATES IN PATIENTS WITH SEVERE ALCOHOL USE DISORDER: PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Introduction Alcohol use disorder (AUD) ranks among the most prevalent psychiatric disorders worldwide. Yet, current treatments remain insufficient to treat AUD, with more than half of patients relapsing within weeks after treatment. In animal models, exposure to environmental enrichment (EE) has been shown to be a promising approach to reduce craving and relapse. However, controlled, multimodal EE is difficult to transpose to humans. To address this gap, this study aims at assessing the effectiveness of exposure to a newly designed EE protocol during inpatient treatment in reducing relapse to alcohol use. Our EE will combine several promising enrichment factors identified in the literature—physical activity, cognitive stimulation, mindfulness and virtual reality (VR).

Methods and analysis A randomised controlled trial involving 135 participants presenting with severe AUD and undergoing two weeks of inpatient treatment will be conducted. Patients will be randomised to an intervention group or a control group. The intervention will consist of six 40-minute sessions of EE spread over nine days. During the first 20 minutes of these sessions, patients will practise mindfulness in multisensory VR, in virtual environments designed to practise mindfulness and use it to regulate craving induced by virtual cues or stress. During the remaining 20 minutes, participants will practise indoor cycling combined with cognitive training exercises. The control group will undergo standard inpatient management. Relapse will be assessed at two weeks, one month and three months after discharge from the hospital using the Timeline Followback questionnaire on alcohol consumption, a breathalyser and a blood test. Relapse will be defined as drinking at least five drinks per occasion or drinking at least five times a week. It is predicted that the group receiving the EE intervention will have a lower relapse rate than the control group. An intention-to-treat analysis will be performed to test this hypothesis.

Keywords: *alcohol use disorder, relapse, craving, environment, mindfulness, virtual reality, exercise, cognition*

Ethics and dissemination

All participants have to give written informed consent to the investigator. This study is approved by the Ethics Committee Nord Ouest IV of Lille (reference number 2022-A01156-37). Results will be disseminated through presentations, peer-reviewed journals and seminar conferences.

Trial registration number

NCT05577741

ARTICLE SUMMARY

Strengths and limitations of the study

- This study is the first to attempt to transpose the complex EE used in animal models to humans for the treatment of AUD.
- Our EE protocol is designed to target the main triggers of relapse, which are stress and cue reactivity.
- Repeated assessments and follow-up during the period of vulnerability for alcohol-dependent patients allow a robust evaluation of the outcomes.
- The EE used for this intervention does not include specific forms of social stimulation.
- Neither the participants nor the therapist can be blinded to the treatment, as this trial includes complex behavioural interventions.

INTRODUCTION

Alcohol use disorder (AUD) is one of the most prevalent psychiatric disorders, affecting 107 million people worldwide [1,2]. It is associated with high morbidity and mortality, causing three million deaths per year [2]. Relapse is the most significant obstacle to rehabilitation. Despite the existence of several treatments, 85% of patients treated for AUD relapse, even after long periods of abstinence [3]. In particular, the first three months of abstinence constitute the period of greatest vulnerability [4], and more than half of patients will consume their first drink (lapse) within two weeks [5]. Craving is one of the main predictors of relapse [6-9] and is elicited by drug use, drug-associated environmental cues and stress [10-12]. It is therefore necessary to manage craving, through therapy allowing patients to better handle daily stress and cue exposure.

Environmental enrichment

Environmental enrichment (EE) is a promising experimental paradigm to reduce craving and the risk of relapse. The role of the environment in the adoption and continuation of addictive behaviour is well demonstrated [13-21]; however, environment as a determinant of drug-related behaviour presents an opportunity for intervention [21]. Several preclinical studies have found that EE combining different types of stimulation can prevent the development and maintenance of addictive behaviours. EE combines complex social, cognitive and physical stimulation (a large cage, new toys, a racing wheel) that aim to improve sensory, cognitive and motor functions. In several experimental models of addiction (and for different types of drugs), housing addicted animals in an EE space during a period of abstinence led to extinction of the addictive behaviour and a reduced risk of relapse compared to control animals housed in standard cages [18,22,23]. This non-pharmacological strategy would prevent relapse by altering the stress response and drug-seeking behaviour, resulting in decreased brain reactivity to cues [14,17-19].

Some human studies have examined the effect of different aspects of EE, such as physical activity, cognitive or social stimulation, separately on addiction [18]. However, no study has integrated these different components into a model of EE to provide multimodal stimulation. Yet, preclinical studies suggest that cognitive and physical stimulation can induce additive or complementary action leading to greater neurogenesis when combined, which can produce better therapeutic results [24].

Environmental components in the treatment of addiction

Different components of EE have already shown promising results in humans. Physical exercise has positive effects on methamphetamine [25], alcohol [26] and nicotine addiction [27-30]. In particular, several studies have shown the positive effect of exercise on stress, mood and craving in alcohol-dependent patients, suggesting that physical activity could be effective in treating addiction [31]. Regarding cognitive stimulation, studies that integrated cognitive training of several cognitive functions (attention, memory, executive functions) have revealed positive effects on different types of addiction, improving cognition, well-being and the compulsive aspect of craving [32-35]. A recent review highlights the potential of combining cognitive exercises with alternative interventions such as mindfulness that can impact both non-cognitive and cognitive processes, particularly executive functions known to be strongly impaired in alcohol-dependent patients [24]. Mindfulness practice allows to train attentional reorientation, metacognition, inhibitory control, emotion regulation and interoception. Thus, mindfulness serves as cognitive–behavioural training that promotes well-being while targeting addiction mechanisms [36,37]. A number of studies suggest that mindfulness interventions allow the reduction of craving, drug consumption and the relapse rate in tobacco and alcohol addiction [38,39]. Furthermore, some authors have found that among the methods used in training executive functions, mindfulness and physical activity are particularly promising, facilitating a general improvement in tasks other than those used for training [40]. An intervention combining these different techniques could therefore be more effective in training the deregulated cognitive and affective processes involved in addiction.

Virtual reality (VR) is also increasingly used in medical protocols to enrich the environment of patients presenting with various cognitive disorders [41,42]. VR allows exposing patients to different levels of enrichment and stimulation in secure and controlled environments. Moreover, VR helps promote patients' well-being and stimulates them at the cognitive level. Another benefit is that VR can simulate proximal and contextual cues of risky situations for patients (being in a bar or at a party with people drinking and offering alcohol) [43,44]. Several studies have shown that exposure to cues in VR is particularly effective in inducing craving. Therefore, VR is increasingly used for addiction treatment, mainly in cue exposure protocols, to try to extinguish the stimulus (cue) response (drug consumption) association [45,46]. In addition, an interesting feature of VR is that it can be used to induce stress [47,48], a known trigger of craving and relapse, which has not been targeted by exposure protocols in addictology. VR could therefore allow patients to practise regulating their cravings induced by cues or stress in a secure setting, preparing them for a return to everyday life.

Furthermore, VR could facilitate mindfulness practice. Indeed, practicing mindfulness can be complicated for beginners, who may have difficulty staying focused [49]. In particular, many alcohol-dependent patients have comorbidities, such as depression; these can lead to a loss of motivation that can make active participation on the part of the patient more difficult. One study showed that VR, as a very immersive technology, could compensate for these difficulties by facilitating the allocation of attentional resources to the virtual environment (VE), thus reducing distracting thoughts [50]. The combination of VR and mindfulness can therefore be an interesting EE tool. Practising mindfulness in VEs that induce craving through cues or stress could be particularly useful in training patients to cope with these situations.

Aims of the study

The main aim of this study is to assess the effectiveness of exposure to EE combining physical activity, cognitive activity and mindfulness in VR to prevent AUD relapse. The randomised control trial will allocate half of the patients to a control group that will receive only the standard

treatment for AUD and half to an intervention group that will receive several sessions of EE in addition to the standard treatment. We hypothesise that the relapse rate in the group receiving the EE intervention will be lower than in the control group at two weeks, one month and three months after discharge from the hospital. We also expect the EE intervention to induce a greater decrease in patients' craving and drug-seeking behaviour than standard treatment. It is predicted that the EE intervention will improve patients' mindfulness skills. Finally, we believe the decrease in the relapse rate and craving should be moderated by inter-individual differences in terms of the perceived richness of the daily environment. The more the daily environment is perceived as rich, the more effective the EE intervention should be in reducing the relapse rate, craving and drug-seeking behaviour.

METHODS AND ANALYSIS

Trial design

This study is a randomised, controlled, non-blinded trial with two parallel arms comparing an EE intervention group to a control group following standard care. Participants will be randomised at a 1/1 ratio to one of two groups. Both groups will complete a battery of tests and questionnaires on the first day of their inclusion and on the tenth day to evaluate craving and mindfulness skills before and after the EE intervention. Follow-ups will be conducted at two weeks, one month and three months after discharge from the hospital to assess relapse. In addition to these measurement sessions, the intervention group will carry out six EE sessions during the inpatient period.

Study setting

This monocentric study will take place in the laboratories of the Pierre Deniker Intersectoral Clinical Research Unit in Psychiatry at the Henri Laborit University Hospital Centre (CHL) in Poitiers, France.

Participants

One hundred and thirty-five patients undergoing inpatient alcohol treatment will be recruited from the Calliope Addiction Unit at the CHL. Calculation of the sample size is reported in the sample size section.

The inclusion criteria are as follows: patients aged 18–65 hospitalised for alcohol addiction at the CHL in an open ward for at least 48 hours with severe AUD according to the DSM-5 classification; benefiting from social security personally or through a third party in accordance with French law on research involving humans; and having signed the informed consent form after having received written information. The exclusion criteria are as follows: disabling cognitive impairment; susceptibility to cybersickness; cardiological pathologies that could compromise the participation of the patient (detected by an ECG); advanced pulmonary, renal or hepatic diseases or any unstable and serious medical conditions that could compromise the participation of the patient (subject to the judgment of a doctor); hypertension; ataxia; uncompensated or unstable psychiatric pathology; pregnancy; breastfeeding; simultaneous participation in another trial; any other current addiction except addiction to tobacco and benzodiazepines; being an employee of the investigator or of the clinical study site; being a patient protected by law; not covered by state health insurance; and being unable to complete the questionnaire based on the opinion of the investigator.

Randomisation

Patients are randomised 1:1 to either the control or intervention group. A block randomisation is used with a bloc size of 4, using an allocation sequence generated from Rstudio by the associate biostatistician.

Intervention

The intervention consists of six sessions of exposure to EE spread over nine days (depending on the inclusion date). The EE is produced using two innovative tools combining different types of stimulation:

1) The practice of mindfulness in multisensory VR

A total of six VEs have been developed in collaboration with Sensiks (Amsterdam, Netherlands) using Unity software. An Oculus headset and two joysticks are used to interact with the VEs. To mimic real life and guarantee the participant's immersion, the following interactions are possible in the VEs using the joysticks: moving around the environment by teleportation, catching and throwing virtual objects and ordering a virtual drink using a menu. For each VE, mindfulness instructions are broadcast to enable guided mindfulness while exploring the environments. The mindfulness instructions have been pre-recorded by a therapist specialising in therapeutic relaxation and can be found in the appendix. These instructions take into account the VE presented and guide the participant through the scenario.

Description of the VEs (Figure 1):

Environments 1 and 2 represent relaxing natural places: a virtual forest for the former and a sandy beach for the latter. In these VEs, the participants can catch and throw natural objects (flowers, mushrooms, shells).

Environments 3 and 4 feature places with cues associated with alcohol consumption: bottles of alcohol and avatars drinking in an appropriate context. Mindfulness instructions guide the participant through the following scenario. After a walk down a virtual street, the participant has to buy a bottle of water in a store and then order a coffee in a bar. The participant can grab objects (bottle of alcohol, cigarettes, coins) and buy or order a drink using a virtual menu presenting several choices of alcohol or soft drinks. The scenario for VE 4 is a virtual party in a house. Some avatars dance, smoke and drink alcohol in the living room, and others sit and chat or play cards. The session consists of the participant sitting with them and then going to the kitchen to get a bottle of water. Interactions with objects are the same as in environment 3 (possibility to grab bottles of alcohol, cigarettes or decorative objects), and a menu allows selecting a drink from the fridge, including a glass of water, wine, beer or fruit juice.

Environments 5 and 6 present stressful contexts. The scenario for VE 5 consists of a virtual parachute jump. The participant is immersed in a virtual airplane environment with avatars showing signs of stress (frequently looking right, left or out the window; shaky hands; leaning forward), and they have to jump after them. The participant cannot move freely or grab objects in this environment. The scenario unfolds gradually for 20 minutes. After the jump, the participant falls into a void, their parachute opens and they gradually descend. At the end of the session, the participant is at ground level. For VE 6, the scene takes place in a virtual airplane environment in which there is turbulence. The participant can explore the plane by teleporting. An announcement warning of turbulence is broadcast, and the participant is teleported into a seat and can no longer move. The turbulence consists of shaking of the plane, and there is a

thunderstorm, falling luggage and avatars expressing fear (looking right and left, holding their heads in their hands, screaming and sobbing). Once the turbulence has subsided, the participant can grab a book or a bottle of water using the joystick.

These VR sessions take place in a multisensory cabin that allows enriching the experience by potentiating the immersion and the experience of mindfulness. This cabin enables a more embodied and realistic experience by generating sounds, smells, air and heat (Figure 2). This device (the Sensory reality pod) was designed by Sensiks as a modular framework that includes electronic modules and programmable actuators to generate the defined stimulations at the desired times. The modules and actuators are linked through a central device. The cabin also includes software and a database to program, store and share multisensory experiences. The VR cabin measures 119x119x224 cm. This tool provides a multisensory experience that adapts to the VE presented. The appropriate smells (notably forest, beach, alcohol, tobacco, coffee, gasoline), sounds, airflow and heat are programmed for each VE and evolve according to the exploration of the environment or as the session progresses (e.g. when moving in the sun in the VE, heaters are switched on).

For each of the six sessions, patients complete 20 minutes of guided mindfulness while exploring a VE. The first two sessions aim to teach participants the practice of mindfulness through immersion in relaxing environments (VEs 1 and 2). Next, to train the patients to better control craving induced by cues, they are gradually exposed to VEs containing cues meant to arouse the desire to consume alcohol (VEs 3 and 4). The aim is to get used to being confronted with cues without it precipitating consumption by learning to regulate cue-induced craving through mindfulness. Finally, to train the patients to regulate stress, a powerful inducer of craving and relapse [12], they are gradually exposed to environments that can induce stress (VEs 5 and 6). Mindfulness instructions guide the patient to regulate stress and stress-induced craving. During VR mindfulness sessions, patients' cardiac and respiratory activity is monitored using a breathing belt and a heartbeat ear clip.

2) Performing cognitive exercises while cycling

The second tool used for this intervention is the Vélo-cognitif (cognitive bike) (Figure3), specially designed by RevLim to practise a cognitive and physical dual task. This tool combines an exercise bike and a touch pad offering cognitive training games. The bike has different levels of resistance. The cognitive exercises are designed by HappyNeuron, a network of scientific experts specialising in cognitive training. These exercises include training in inhibition, attention, memory and visuo-spatial skills through playful games of various difficulty levels. By simultaneously stimulating motor skills and cognition, this tool offers a playful activity in which the participants are able to see themself progressing and which could reduce stress through physical activity [51]. In a pilot study using the cognitive bike with patients suffering from substance use disorder, most patients reported having enjoyed the activity [52]. This tool could therefore help improve well-being and quality of life by providing a rewarding activity while retraining executive functions.

Control group

Patients in the control group are treated according to the standard protocol used at the Laborit Psychiatric Hospital. This consists of a clinical and biological examination performed by a health professional following the patient's admission to hospital. A treatment for withdrawal symptoms (benzodiazepines) is then administered under medical supervision. The patient benefits from individual medical and psychological monitoring. Workshops and therapeutic meetings are offered.

Measures

Primary outcome

The primary outcome is the proportion of individuals who relapsed two weeks after inpatient period. Relapse is defined as drinking at least five drinks per occasion or drinking at least five times a week [53,54]. Maintenance of abstinence and relapse are assessed using the Alcohol Timeline Followback assessment method [55]. Relapse is also assessed using biological indicators—a breathalyser, and a blood test for the measurements of carbohydrate deficient transferrin (CDT) and gamma-glutamyl transpeptidase (GGT). CDT is a glycoprotein synthesised by the liver and is a specific marker indicating the presence of alcohol in the blood. Elevated CDT levels suggest recent high alcohol consumption, particularly if other liver-associated enzymes (such as GGT) are elevated [56].

Secondary outcomes

Mid-term relapse

Relapse is assessed using the same measures at one month and three months.

Craving

- Explicit craving, defined as the conscious desire to consume alcohol, is assessed in two ways:
    - Subjective craving during the past week is assessed using the Obsessive Compulsive Drinking Scale (OCDS) questionnaire [57], which measures an individual's alcohol consumption and attempts to control it over the past week.
    - Craving induced by cues is assessed using the craving induction protocol of Fox et al. [58]. This protocol induces craving through personalised cues, which consist of a short text written by the patient. This text should describe a memory of a situation of strong craving that led to consumption and should detail the context, the physical sensations and the state of mind during that scene. This half-page script is recorded by the experimenter, and then the audio is played to the patient during a second session. The patient indicates his level of craving before and after listening to the script on a visual analogue scale ranging from 0 to 10, where 0 represents no desire to consume and 10 represents an extremely strong craving.
- To obtain a more objective assessment in relation to the automatic component of craving and drug-seeking behaviour, we also use three implicit measures:

- Identification with the drug is assessed using a standard Implicit Association Test [59]. This test measures whether alcohol is more strongly associated with the self or others using images referring to alcohol or neutral images as target categories and words referring to the self or others as attribute categories (example: 'me', 'I', 'myself', 'mine' or 'they', 'them', 'their', 'others') [59].
- A test of the seeking for alcohol-related stimuli based on the task of Moeller et al. [60] and adapted to alcohol is used. This test allows evaluating the preference for the drug among other reinforcers via four categories of images (drug, pleasant, unpleasant and neutral). There is a choice of four decks of cards, face down, each containing a majority of one of the image categories. A large image of the selected deck is presented on the screen for 2000 milliseconds, and then the subjects can select one of the decks again. A pseudo-randomisation described in [61] aims at reducing awareness of the identity of the deck while allowing a preference to be established. We adapted this task to alcohol addiction using images related to alcohol consumption (a glass of beer, a glass of wine, people drinking in a bar, etc.).
- Attentional bias towards alcohol is assessed using the task of Soleymani et al. [62], a visual research test for alcohol-related stimuli (eye tracking). This task consists of freely viewing several sets of 16 images of alcoholic and non-alcoholic drinks, while an eye-tracker records the location of the first fixation and the total fixation time for each image. The strength of the attentional bias is determined by these two parameters.

Mindfulness

- Mindfulness skills acquisition is measured using the Five Facets Mindfulness questionnaire [63, 64]. This questionnaire assesses the tendency to be in a state of mindfulness in daily life based on five facets of mindfulness: observation (being attentive to one's internal/external states), description (being able to verbalise one's internal experiences), action with awareness (not automatic), non-judgment of internal and external experience (posture of acceptance, non-evaluative) and non-reactivity (detachment, non-response to internal states). We use the 15-item version of the questionnaire [65,66].
- The development of mindfulness skills is also assessed during mindfulness sessions using heart rate, respiratory rate and salivary cortisol measurements. These measures allow us to monitor the patient's attention to instructions, the stress induced by the environments and whether mindfulness can effectively regulate this stress. These measurements also allow the calculation of heart rate variability associated with self-regulation skills, which is commonly used in research on mindfulness-based interventions [67,68,69].

Richness of daily environment

We evaluate the effect of inter-individual differences in terms of the richness of the daily environment on the response to treatment. Inter-individual differences are assessed using the Measurement of the Perception of a Stimulating Environment Questionnaire (MPSEQ) (Chatard A, Barillot L, Besnier M, et al. Measurement of the Perception of a Stimulating

Environment Questionnaire, unpublished). Composed of 13 items, this questionnaire evaluates to what extent the individual perceives their environment as stimulating. Each item is a declarative statement referring to the stimulations, activities or satisfaction and entertainment that the person perceives or realises in their life (example: 'My immediate environment is rich in sensations and stimulation of all kinds'). The individual expresses the extent to which they agree or disagree with each statement using a scale ranging from 1 to 7, with 1 corresponding to completely disagree and 7 to completely agree.

Study schedule

Table 1
Study schedule of enrolment and assessments by time points (Tn).
S1, S2, S3, S4, S5 and S6 refer to the 6 different EE sessions of the intervention.

	Enrolment	**Intervention**						**Post-intervention**	**Follow-ups**		
Time point	**T0**	**T1**						**T2**	**T3**	**T4**	**T5**
		S1	S2	S3	S4	S5	S6				
Eligibility screening	X										
Informed consent	X										
Group allocation	X										
Primary outcome											
TLFB									X	X	X
Breathalyser									X	X	X
Blood test								X	X	X	X
Secondary outcomes											
OCDS	X								X	X	X
Craving induced by cues	X							X			
IAT	X							X			
Alcohol seeking	X			X	X	X	X	X			
Alcohol attentional bias	X							X			
MPSEQ	X										
FFMQ	X		X					X			
Salivary cortisol	X					X	X				

Potential participants are invited to a 15-minute informative meeting. Eligibility screening is conducted, and patients are invited to participate after being provided a description of the study. A pre-test in the VR cabin is offered to the patients to allow them to get acquainted with VR and to check that they do not shows signs of cybersickness.

Patients are reconvened (T0), and if they wish to participate in the study and if they meet all the eligibility criteria they sign the consent form and are randomly assigned to one of two groups. They complete baseline measures of their craving and salivary cortisol and complete questionnaires about their initial mindfulness skills and their perception of the richness of their daily environment (Table 1).

Intermediate measures take place for participants undergoing the intervention (T1). The acquisition of mindfulness skills is assessed after the second session of intervention. After sessions 3, 4, 5 and 6 meant to train participants to regulate their craving, they complete the Test of the seeking for alcohol-related stimuli. Salivary cortisol is measured after session 5 and session 6, which are expected to induce stress in the patient.

On the tenth day of inclusion or after completing the intervention (depending on the group) (T2), participants are seen again for a measurement session during which craving and mindfulness skills are assessed. A blood test is performed to obtain a baseline measurement of CDT and GGT. Relapse is assessed in both groups according to the method described in the measures section at two weeks (T3), one month (T4) and three months (T5) after T2.

Sample size

Sample size calculation is done using G*Power software to have 80% power ($1 - \beta$) to find a significant effect ($p < 0.05$) with an average Cohen's effect size of d=0.50 or f=0.25 [70]. With a Cohen's d of 0.50, we will have an 80% chance of detecting a significant difference ($p< .05$) between the two groups at least equal to 25%. The hypothesis will therefore be confirmed if the relapse rate in the intervention group is at least 25% lower than that of the control group.

The power analysis determined that 112 participants will be needed. However, due to the large number of dropouts among alcohol-dependent patients and the intention-to-treat analysis that we plan to perform, we expect to need a margin of 20% in terms of recruitment, that is, 135 participants. We therefore estimate a priori that an additional 23 participants will be needed to be able to assess the primary outcome (relapse at two weeks after T2) and to draw conclusions from our results.

Data analysis

An intention-to-treat analysis will be conducted using Rstudio® software. A descriptive analysis of the study population will be performed. Qualitative variables will be expressed as a percentage. Quantitative variables will be expressed as mean and standard deviation or as median and interquartile range. A value of $p<0.05$ will be considered statistically significant. An exploratory study of the data structure will be conducted using principal component

analysis. All participant data will be used for the efficacy analysis. Missing data will be replaced using imputation with interim values.

The initial comparability resulting from the randomisation will be checked using tests appropriate to the distribution (parametric or non-parametric) and type (quantitative/qualitative) of the variables studied. We will use analyses of variance (ANOVA) taking into account the experimental conditions.

The primary and secondary outcomes will be analysed using a parametric test (or non-parametric depending on the distribution) for comparison of means comparing the differences according to the groups (inter-participant), with a unilateral alpha risk of 5 %. A parametric (or non-parametric depending on the distribution) test for comparison of means will also be used to compare the differences before and after the intervention and before and during the intervention for the intervention group (intra-participant), with a unilateral alpha risk of 5%. If significant differences are observed, correlation analyses will be conducted to identify the factors that may explain this difference.

DISCUSSION

This study aims at finding new non-pharmacological alternatives to promote long-term abstinence and reduce the incidence of relapse, which could greatly improve the health and well-being of people suffering from AUD. To this end, we will evaluate the effectiveness of EE sessions in reducing relapses in patients receiving treatment for AUD. This study is the first attempt to transpose the EE approach described in preclinical studies that combines different types of stimulation to humans. Our study should inform about the potential of this strategy to treat addiction and about the necessary components of EE for humans. EE provides rewarding stimulations as alternatives to drug taking while training the cognitive and affective processes deregulated in AUD. It should therefore provide learning that can be reused in daily life in stressful or cue-exposure situations [18].

In terms of study limitations, it is possible that the acceptability of VR and mindfulness can play a role in the effectiveness of the intervention. We have chosen to exclude people who show a cybersickness type of discomfort with VR. Regarding mindfulness, repeated measures of mindfulness skills should help to control for this acceptability bias. Another limitation is that we chose to induce stress through VR during the last two EE sessions, even though stress is supposed to be the opposite of EE and can therefore interfere with the enrichment procedure. However, the sessions are considered to be part of EE because they provide cognitive training in regulating stress through mindfulness. Another possible weakness of the EE in this study is that it does not include social stimulation, while several animal studies have shown that social stimulation is an important component of EE, and social support in humans is an important part of addiction treatment [18]. Therefore, further studies are needed to investigate a model of EE that includes social stimulation. Finally, it will be important in the future to perform parametric studies to investigate whether more or fewer EE sessions can increase or decrease the benefits of this EE protocol.

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FOOTNOTES

Competing interests statement.

None declared.

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Authors' contributions

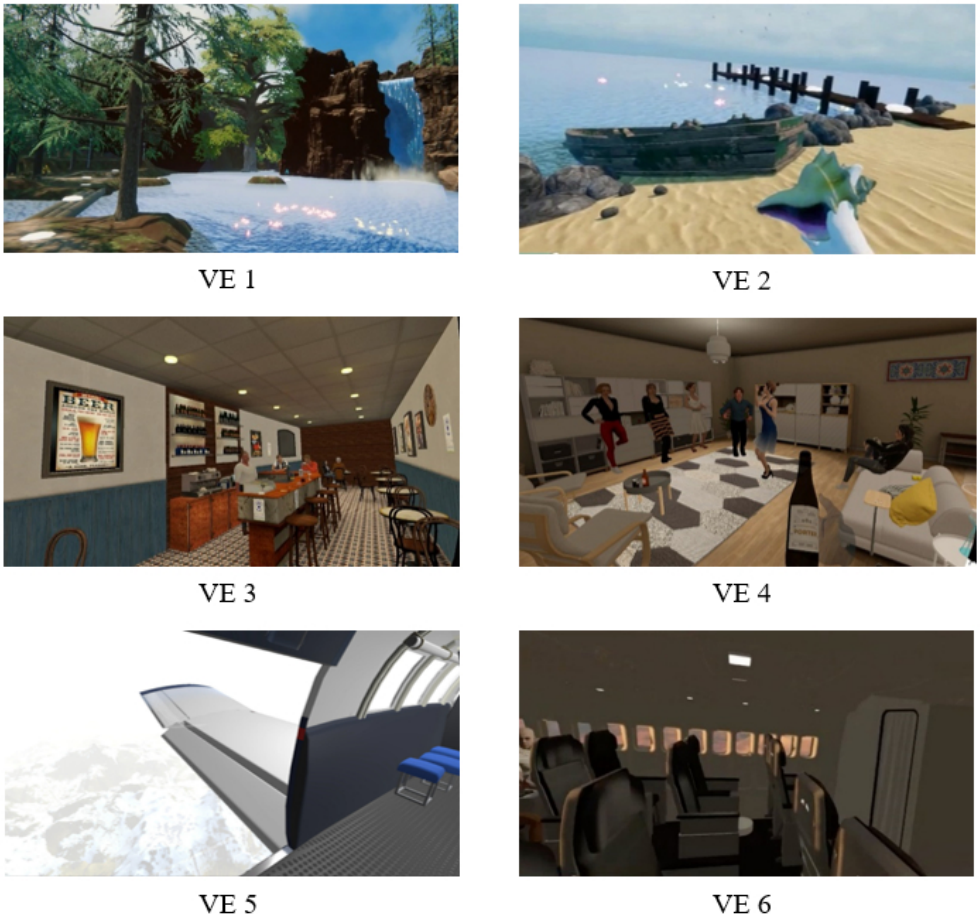
AC, NJ and MS were responsible for identifying the research question and designing the study protocol. MB, LB and CC contributed to the development of the protocol and study design. LB wrote the first draft of this manuscript, which was revised and modified by all authors.

Figure legends:

Figure 1. Virtual environments presented: forest (VE 1), beach (VE 2), bar (VE 3), party (VE 4), parachute jump (VE 5), plane (VE 6)

Figure 2. Sensory reality pod: Device created by Sensiks containing programmable actuators to generate different types of stimulation using heaters, an odour diffusion module connected to bottles containing fragrances, an audio system and fans

Figure 3. Vélo-cognitif (cognitive bike) consisting of an exercise bike to which a digital touch pad is attached to allow cognitive exercises to be performed while pedalling



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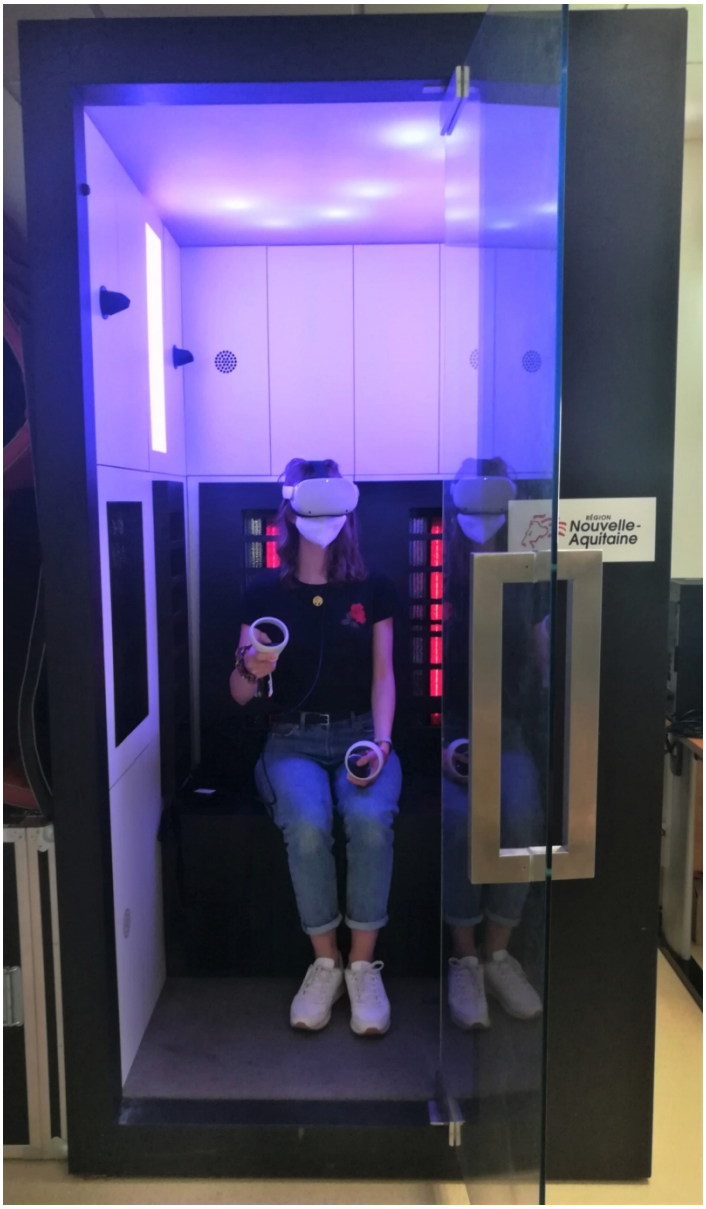
382x368mm (47 x 47 DPI)



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818x1399mm (72 x 72 DPI)

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752x834mm (72 x 72 DPI)

Mindfulness instructions for mindfulness practice in virtual environments (VEs)

- **VE1: Immersion in a forest**

  First of all, go and discover this environment.

  Your senses are a precious help. Observe the scenery of this forest, the luminosity, the smells, the possible sounds, in a global way

  To immerse yourself in this place, stop for a few moments. Close your eyes. Pay attention only to the sounds that are present. From the most distant (perhaps the wind blowing in the distance) to the closest (your breathing). Observe, without judging...

  Observe if this causes things to happen to you: for example, do you have any thoughts? Observe them passing and let them go as they came. Sensations (e.g. tension in the body? tingling? a feeling of lightness...)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came, that is, without trying to hold them back, and without trying to make them go: their departure is gradual, passive.

  To finish, I suggest that you focus your attention on a specific object, for example a leaf, a mushroom, a flower... whatever feels good to you... Choose what makes you happy.

  Approach this object and give it your full attention.

  Without judgement, observe its colours, its shape. Does it have a scent? Does it make sounds when you bring it close to your ear? Take a few moments to observe...

  When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

  Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste.

  We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE2**: **Walking along a beach**

  First of all, discover the environment.

  Your five senses are of great help. Observe the beach, the colours, the possible smells, the sounds

To immerse yourself in this place, stop for a few moments. Close your eyes. Pay attention only to the sounds that are present. From the most distant (perhaps the wind blowing in the distance, the sound of the waves) to the closest (your breathing). Observe, without judging...

Observe if this causes things to happen to you: for example, do you have thoughts? Observe them passing and let them go as they came. Sensations (e.g. tension in the body? tingling? a feeling of lightness...)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came, that is to say, without trying to hold them back, and without trying to make them go away: their departure is done gradually, passively.

Finally, I suggest that you focus your attention on a particular object, for example a shell, something that seems good to you... Choose what you like. Approach it and give it your full attention.

Without judgment, observe its colours, its shape. Does it have a scent? Does it make sounds when you bring it close to your ear? Take a few moments to observe...

When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE3: Walking down the street, buying something in a shop, then ordering a coffee in a bar**

First of all, make this new environment your own.

Your five senses are a great help. Observe your surroundings. Observe the street you are on, the landscape, the smells of the city, the sounds.

You can go into the shop near you to buy a bottle of water. Focus on the elements around you. The sounds, from the most distant (perhaps the music in the shop, conversations) to the closest (your breathing). Observe, without judging...

You are going to walk towards the exit. Once outside, you see a café in front of you. Walk slowly towards it and enter it.

Continue to focus on your sensations, the wind caressing your face, the sounds of the street. As you enter the café, observe whether this causes anything to happen to you: for example, do you have any sensations (e.g. tension in your body? tingling?)?

Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

You are going to sit at the counter and order a coffee. Focus on the smells and sounds of conversation around you. Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste or not. Once again, without judging, welcoming things as they are. To finish, I suggest that you focus your attention on a particular object, for example a cup of coffee, which seems good to you... Choose what pleases you. Approach it and give it your full attention.

Without judgment, observe its colours, its shape. Does it smell? Does it make sounds when you bring it close to your ear? Take a few moments to observe...

When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste or not. Once again, without judging, welcoming things as they are.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE4**: **Party in a house with other people who smoke and drink alcohol**

First of all, get used to this new environment.

Your five senses are of great help. Observe your surroundings. Observe the house you are in, the rooms, the smells in the house, the sounds.

Walk around the house and focus on the elements around you. The sounds, from the most distant (perhaps the music in the house, conversations) to the closest (your breathing). Observe, without judging...

Let any sensations, thoughts or emotions within you quietly and passively subside. You let it happen... Without trying to change your breathing, without trying to hold anything back... You let the sensations that may be present happen, until they disappear by themselves. You let it happen.

Go to the table and sit down with the other people. Observe if this causes things to happen in you: for example, do you have any sensations (e.g. tension in the body? tingling?)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them

back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

You get up and go to the kitchen. Look in the fridge for a bottle of water. Focus on the smells and sounds of conversation around you. Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste.

Go back to your seat and continue to focus on the sounds and smells. Observe whether this causes you to do something: for example, do you have any sensations (e.g. tension in the body? tingling?)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Accept it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

To finish, I suggest that you focus your attention on a particular object, for example a plate, a flower, something that seems good to you... Choose what you like. Approach it and focus your attention on this object.

Without judgment, observe its colours, its shape. Does it have a scent? Does it make sounds when you bring it close to your ear? Take a few moments to observe... When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste or not. Once again, without judging, welcoming things as they are.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE5: A parachute jump**

First of all, get used to this new environment.

Your five senses are a great help. Observe your environment, around you. Observe the cabin you are in, the landscape, the sounds.

Before approaching the edge, you can focus on yourself. Close your eyes. Pay attention only to the sounds that are present. From the most distant (perhaps the wind blowing in the distance) to the closest (your breathing). Observe, without judging...

The jumping will now begin. Try to keep the calmness you have achieved. Let the sensations come to you without trying to anticipate them.

Continue to focus on your sensations, the wind caressing your face... Observe if this causes things to happen to you: for example, do you have any sensations (e.g. tension in your body? tingling?)? Welcome them, without judging. Let them come and go as

they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

Perhaps you notice an increase in your heart rate, your heart beating faster..., or tensions in your body, muscles that stiffen...

You let it happen, without judgment. Let it happen, without trying to control anything. Let these sensations pass, the emotions that come, as they have come. Let it happen, passively, so that they leave quietly as they came. You let it happen..., without trying to modify your breathing. You let it happen, in confidence, quietly.

Continue to observe and feel your environment. Try to perceive again the elements around you, the noises, perhaps the wind

Let all sensations, thoughts and emotions in you quietly and passively subside. You let it happen... Without trying to change your breathing, without trying to hold anything inside you... You let the sensations that may be present happen, until they disappear by themselves. You let it happen. The parachute will now open. In the same way, observe if these sensations are pleasant for you, if they leave an imprint in you, a pleasant taste or not. Once again, without judging, welcoming things as they are.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE6: Flying with turbulence**

First of all, get used to this new environment.

Your five senses are of great help. Observe your surroundings. Observe the cabin you are in, the landscape through the window, the smells, the sounds. Take time to explore the cabin. As the captain announces, turbulence will start in the plane. You can return to your seat. Close your eyes and let the sensations come to you without trying to anticipate them.

Continue to focus on your sensations, the ventilation of the cabin on your face, the sounds of your surroundings.

The belt signals come on and you hear thunder in the distance. Observe if this causes things to happen to you: for example, do you have any sensations (e.g. tension in your body? tingling?)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

Perhaps you notice an increase in your heart rate, your heart beating faster..., or tensions in your body, muscles that tighten...

You let it happen, without judgment. Let it happen, without trying to control anything. Let these sensations pass, the emotions that come, as they have come. Let it happen, passively, so that they go away quietly as they came. You let it happen..., without trying to modify your breathing. You let it happen, in confidence, quietly.

Around you, you observe the luggages falling and the elements falling over. Focus on the way it makes you feel. Accept it and let it go without chasing it or holding it back. Perhaps you notice an increase in your heart rate, your heart beating faster..., or tension in your body, muscles tightening...

You let it happen, without judgment. Let it happen, without trying to control anything. Let these sensations pass, the emotions that come, as they have come. Let it happen, passively, so that they go away quietly as they came. You let it happen..., without trying to modify your breathing. You let it happen, in confidence, quietly.

The plane calms down again and the turbulence goes away. Continue to observe and feel your surroundings during the turbulence. Observe if these sensations are pleasant for you, if they leave an imprint on you, a pleasant sensation or not. Again, without judging, welcoming things as they are.

Let all sensations, thoughts or emotions in you quietly and passively subside. You let it happen... Without trying to change your breathing, without trying to hold anything inside you... You let the sensations that may be present happen, until they disappear by themselves. You let it happen. To finish, I suggest that you focus your attention on a particular object, for example a book, something that seems good to you... Choose what you like.

Approach it and give it your full attention. Without judgment, observe its colours, its shape. Does it smell? Does it make sounds when you bring it close to your ear? Take a few moments to observe... When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste or not. Once again, without judging, welcoming things as they are.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2-3
	2b	Specific objectives or hypotheses	3-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	X
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	X
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	X
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	X
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	X

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	X
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	X
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	X
	13b	For each group, losses and exclusions after randomisation, together with reasons	X
Recruitment	14a	Dates defining the periods of recruitment and follow-up	X
	14b	Why the trial ended or was stopped	X
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	X
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	X
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	X
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	X
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	X
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	X
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	X
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	X
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	X
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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EFFECT OF ENVIRONMENTAL ENRICHMENT ON RELAPSE RATES IN PATIENTS WITH SEVERE ALCOHOL USE DISORDER: PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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EFFECT OF ENVIRONMENTAL ENRICHMENT ON RELAPSE RATES IN PATIENTS WITH SEVERE ALCOHOL USE DISORDER: PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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EFFECT OF ENVIRONMENTAL ENRICHMENT ON RELAPSE RATES IN PATIENTS WITH SEVERE ALCOHOL USE DISORDER: PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

ABSTRACT

Introduction Alcohol use disorder (AUD) ranks among the most prevalent psychiatric disorders worldwide. Despite current treatments, more than half of patients relapse within weeks after treatment. In animal models, exposure to environmental enrichment (EE) has been shown to be a promising approach to reduce relapse. However, controlled, multimodal EE is difficult to transpose to humans. To address this gap, this study aims at assessing the effectiveness of exposure to a newly designed EE protocol during AUD treatment in reducing relapse to alcohol use. Our EE will allow an enhancement of the standard intervention, and will combine several promising enrichment factors identified in the literature—physical activity, cognitive stimulation, mindfulness and virtual reality (VR).

Methods and analysis A randomised controlled trial involving 135 participants receiving treatment for severe AUD will be conducted. Patients will be randomised to an intervention enhancement group or a control group. The enhanced intervention will consist of six 40-minute sessions of EE spread over nine days. During the first 20 minutes of these sessions, patients will practise mindfulness in multisensory VR, in virtual environments designed to practise mindfulness and use it to regulate craving induced by virtual cues or stress. Then, participants will practise indoor cycling combined with cognitive training exercises. The control group will undergo standard management for AUD. The primary outcome is relapse assessed at two weeks after the tenth day of inclusion, using a questionnaire and biological indicators. Relapse will be defined as drinking at least five drinks per occasion or drinking at least five times a week. It is predicted that the group receiving the EE intervention will have a lower relapse rate than the control group. The secondary outcomes are relapse at one month and three months after the tenth day of inclusion, craving and drug seeking behaviour, mindfulness skills acquisition, and the effect of the intervention enhancement on the perceived richness of the daily environment, assessed by questionnaires and neuropsychological tasks.

Ethics and dissemination
All participants have to give written informed consent to the investigator. This study is approved by the Ethics Committee Nord Ouest IV of Lille (reference number 2022-A01156-37). Results will be disseminated through presentations, peer-reviewed journals and seminar conferences. All information on ethical considerations and open science practices can be accessed at https://osf.io/b57uj/

Trial registration number
ClinicalTrials.gov: NCT05577741

Keywords: *alcohol use disorder, relapse, craving, environment, mindfulness, virtual reality, exercise, cognition*

ARTICLE SUMMARY

Strengths and limitations of the study

- This study is the first to attempt to transpose the complex EE used in animal models to humans for the treatment of AUD.
- Our EE protocol is designed to target the main triggers of relapse, which are stress and cue reactivity.
- Repeated assessments and follow-up during the period of vulnerability for alcohol-dependent patients allow a robust evaluation of the outcomes.
- The EE used for this intervention does not include specific forms of social stimulation.
- Neither the participants nor the therapist can be blinded to the treatment, as this trial includes complex behavioural interventions.

INTRODUCTION

Alcohol use disorder (AUD) is one of the most prevalent psychiatric disorders, affecting 107 million people worldwide [1,2]. It is associated with high morbidity and mortality, causing three million deaths per year [2]. Relapse is the most significant obstacle to rehabilitation. Despite the existence of several treatments, 85% of patients treated for AUD relapse, even after long periods of abstinence [3]. In particular, the first three months of abstinence constitute the period of greatest vulnerability [4], and more than half of patients will consume their first drink (lapse) within two weeks [5]. Craving is one of the main predictors of relapse [6-9] and is triggered by drug use, drug-associated environmental cues and stress [10-12]. It is therefore necessary to manage craving, through therapy allowing patients to better handle daily stress and cue exposure.

Environmental enrichment

Environmental enrichment (EE) is a promising experimental paradigm to reduce craving and the risk of relapse. The role of the environment in the development and continuation of addictive behaviour is well demonstrated [13-21]. In addition, environmental conditions during periods of abstinence represent an interesting opportunity for intervention [21]. Preclinical studies have found that EE combining different types of stimulation can prevent the development and maintenance of addictive behaviours. EE combines complex social, cognitive and physical stimulation (a large cage, new toys, a racing wheel) that aim to improve sensory, cognitive and motor functions. In animal models of addiction (and for different types of drugs), housing addicted individuals in an EE during a period of abstinence led to extinction of the addictive behaviour and a reduced risk of relapse compared to control animals housed in standard cages [18,22,23]. This non-pharmacological strategy would prevent relapse by altering the stress response and drug-seeking behaviour, resulting in decreased brain reactivity to cues [14,17-19]. Behavioral and neurobiological evidence suggest that modulation of the reactivity to stress plays a major role in the effects of EE [24,25].

Human studies have examined the effect of different aspects of EE, such as physical activity, cognitive or social stimulation, separately on addiction [18]. However, no study has integrated these different components into a model of EE to provide multimodal stimulation. Yet, preclinical studies suggest that cognitive and physical stimulation can induce additive or complementary action leading to greater neurogenesis when combined, which can produce better therapeutic results [26].

Environmental components in the treatment of addiction

Different components of EE have already shown promising results in humans. Physical exercise has positive effects on methamphetamine [27], alcohol [28] and nicotine addiction [29-32]. In particular, several studies have shown positive effects of exercise on stress, mood and craving in alcohol-dependent patients, suggesting that physical activity could be effective in treating addiction [33]. Regarding cognitive stimulation, studies that integrated cognitive training of several cognitive functions (attention, memory, executive functions) have revealed positive effects on different types of addiction, improving cognition, well-being and the compulsive aspect of craving [34-37]. Interestingly, there exist commercial solutions such as the cognitive bike (vélo-cognitif) that allow performing at the same time physical and cognitive exercise in comfortable, easy and safe conditions that are adapted to hospital settings. A recent review highlights the potential of combining cognitive exercises with alternative interventions such as mindfulness that can impact both non-cognitive and cognitive processes, particularly executive functions known to be strongly impaired in alcohol-dependent patients [26]. Mindfulness practice allows training attentional reorientation, metacognition, inhibitory control, emotion regulation and interoception. Thus, mindfulness serves as cognitive–behavioural training that promotes well-being while targeting emotional regulation and addiction mechanisms [38,39]. Many studies have shown positive effects of mindfulness practice on stress levels [40,41]. In particular, the Mindfulness Based Stress Reduction programme is widely used to improve stress regulation by teaching people to practice mindfulness in stressful situations [42]. Furthermore, a number of studies suggest that mindfulness interventions allow the reduction of craving, drug consumption and the relapse rate in tobacco and alcohol addiction [43,44]. In addition, some authors have found that among the methods used in training executive functions, mindfulness and physical activity are particularly promising, facilitating a general improvement in tasks other than those used for training [45]. An intervention combining these different techniques could therefore be more effective in training the deregulated cognitive and affective processes involved in addiction [26].

Virtual reality (VR) is increasingly used in medical protocols to enrich the environment of patients suffering from various cognitive disorders [46,47]. VR allows exposing patients to different levels of enrichment and stimulation in secure and controlled environments. Moreover, VR helps promote patients' well-being and stimulates them at the cognitive level [48]. Another benefit is that VR can simulate proximal and contextual cues of risky situations for patients (being in a bar or at a party with people drinking and offering alcohol) [49,50]. Several studies have shown that exposure to cues in VR is particularly effective in inducing craving [51-53]. Therefore, VR is increasingly used for addiction treatment, mainly in cue exposure protocols, to try to extinguish the stimulus (cue) response (drug consumption) association [54,55]. In addition, an interesting feature of VR is that it can be used to induce stress [56,57], a known trigger of craving and relapse [12]. VR could therefore allow patients to practise regulating their cravings induced by cues or stress in a secure setting, preparing them for a return to everyday life.

VR could facilitate mindfulness practice. Indeed, practicing mindfulness can be complicated for beginners, who may have difficulty staying focused [58]. In particular, many alcohol-dependent patients have comorbidities, such as depression [59,60]; these can lead to a loss of motivation that can make active participation on the part of the patient more difficult. One study showed that VR, as a very immersive technology, could compensate for these difficulties by facilitating the allocation of attentional resources to the virtual environment (VE), thus reducing distracting thoughts [61]. The combination of VR and mindfulness can therefore be an interesting tool to provide EE in humans. Practising mindfulness in VEs that induce craving through cues or stress could be particularly useful in training patients to learn how to cope with these situations in their real life.

Aims of the study

The main aim of this study is to assess the effectiveness of exposure to EE combining physical activity, cognitive activity using cognitive bikes and mindfulness in VR to prevent AUD relapse. Our randomised control trial will allocate half of the patients to a control group that will receive only the standard treatment for AUD and half to an intervention enhancement group that will receive several sessions of EE in addition to the standard treatment. We hypothesise that the relapse rate in the group receiving the EE intervention will be lower than in the control group at two weeks, one month and three months after the intervention or the tenth day of inclusion. We also expect the EE intervention to induce a greater decrease in patients' craving and drug-seeking behaviour than standard treatment. It is predicted that the EE intervention will improve patients' mindfulness skills. Finally, we believe that the intervention, by providing alternative rewarding stimuli to drug taking, should encourage a change in behaviour [24] and thus in lifestyle (modification of one's environment), and should therefore increase the perceived richness of the daily environment

METHODS AND ANALYSIS

Trial design

This study is a randomised, controlled, non-blinded trial with two parallel arms comparing an EE intervention group to a control group following standard care. Participants will be randomised at a 1/1 ratio to one of two groups. Both groups will complete a battery of tests and questionnaires on the first day of their inclusion and on the tenth day to evaluate craving and mindfulness skills before and after the EE intervention. Follow-ups will be conducted at two weeks, one month and three months after the intervention or the tenth day of inclusion to assess relapse. In addition to these measurement sessions, the intervention enhancement group will carry out six EE sessions.

Study setting

This study will take place in the laboratories of the Pierre Deniker Intersectoral Clinical Research Unit in Psychiatry at the Henri Laborit University Hospital Centre (CHL) in Poitiers, France. The study will end as soon as the number n= 135 participants is reached or at the end of the 2-year inclusion period.

Participants

One hundred and thirty-five patients undergoing alcohol treatment will be recruited from the Calliope Addiction Unit at the CHL, or from the University Hospital of Poitiers. The base rate of relapse at this site is estimated to be about 50% at one month and 60% at three months [62] . Calculation of the sample size is reported in the sample size section.

The inclusion criteria are as follows: patients aged 18–65 treated for alcohol addiction at the CHL in an open ward or at the University Hospital of Poitiers for at least 48 hours with severe AUD according to the DSM-5 classification; benefiting from social security personally or through a third party in accordance with French law on research involving humans; and having signed the informed consent form after having received written information. The exclusion criteria are as follows: disabling cognitive impairment; susceptibility to cybersickness; cardiological pathologies that could compromise the participation of the patient (detected by an ECG); advanced pulmonary or renal diseases or any unstable and serious medical conditions that could compromise the participation of the patient (subject to the judgment of a doctor); hypertension; ataxia; uncompensated or unstable psychiatric pathology; pregnancy; breastfeeding; simultaneous participation in another trial; any other current addiction except addiction to tobacco, THC and benzodiazepines; being an employee of the investigator or of the clinical study site; being a patient protected by law; not covered by state health insurance; and being unable to complete the questionnaire based on the opinion of the investigator.

Randomisation

Patients are randomised 1:1 to either the control or intervention EE enhancement group. A block randomisation is used with a bloc size of 4, using an allocation sequence generated from Rstudio by a biostatistician.

Intervention

The enhanced intervention consists of six sessions of exposure to EE spread over nine days (depending on the inclusion date). These sessions take place in addition to the standard intervention and are planned with the patient so as not to interfere with other activities (workshops or therapeutic meetings). The EE is produced using two innovative tools combining different types of stimulation:

1) *The practice of mindfulness in multisensory VR*

A total of six VEs have been developed in collaboration with Sensiks (Amsterdam, Netherlands) using Unity software. An Oculus headset and two joysticks are used to interact with the VEs. To mimic real life and guarantee the participant's immersion, the following interactions are possible in the VEs using the joysticks: moving around the environment by teleportation, catching and throwing virtual objects and ordering a virtual drink using a menu. Teleportation consists of pointing the joystick at predetermined points in the environments, represented by white circles on the ground. When the user points to one of the circles, he/she is immediately teleported to that location, thus limiting the risk of cybersickness due to vection. For each VE, mindfulness instructions are broadcast to enable guided mindfulness while exploring the environments. The mindfulness instructions have been pre-recorded by a therapist specialising in therapeutic relaxation and can be found in supplementary file 1. These instructions take into account the VE presented and guide the participant through the scenario.

Description of the VEs (Figure 1):

Environments 1 and 2 represent relaxing natural places: a virtual forest for the former and a sandy beach for the latter. In these VEs, the participants can catch and throw natural objects (flowers, mushrooms, shells).

Environments 3 and 4 feature places with cues associated with alcohol consumption: bottles of alcohol and avatars drinking in an appropriate context. Mindfulness instructions guide the participant through the following scenario. After a walk down a virtual street, the participant has to buy a bottle of water in a store and then order a coffee in a bar. The participant can grab objects (bottle of alcohol, cigarettes, coins) and buy or order a drink using a virtual menu presenting several choices of alcohol or soft drinks. The scenario for VE 4 is a virtual party in a house. Some avatars dance, smoke and drink alcohol in the living room, and others sit and chat or play cards. The session consists of the participant sitting with them and then going to the kitchen to get a bottle of water. Interactions with objects are the same as in environment 3 (possibility to grab bottles of alcohol, cigarettes or decorative objects), and a menu allows selecting a drink from the fridge, including a glass of water, wine, beer or fruit juice.

Environments 5 and 6 present stressful contexts. The scenario for VE 5 consists of a virtual parachute jump. The participant is immersed in a virtual airplane environment with avatars showing signs of stress (frequently looking right, left or out the window; shaky hands; leaning forward), and they have to jump after them. The participant cannot move freely or grab objects in this environment. The scenario unfolds gradually for 20 minutes. After the jump, the participant falls into a void, their parachute opens and they gradually descend. At the end of the session, the participant is at ground level. For VE 6, the scene takes place in a virtual airplane environment in which there is turbulence. The participant can explore the plane by teleporting. An announcement warning of turbulence is broadcast, and the participant is teleported into a seat and can no longer move. The turbulence consists of shaking of the plane, and there is a thunderstorm, falling luggage and avatars expressing fear (looking right and left, holding their heads in their hands, screaming and sobbing). Once the turbulence has subsided, the participant can grab a book or a bottle of water using the joystick.

The VR sessions take place in a multisensory cabin that allows enriching the experience by potentiating the immersion and the experience of mindfulness. This cabin enables a more embodied and realistic experience by generating sounds, smells, air and heat (Figure 2). This device (the Sensory reality pod) was designed by Sensiks as a modular framework that includes electronic modules and programmable actuators to generate the defined stimulations at the desired times. The modules and actuators are linked through a central device. The cabin also includes software and a database to program, store and share multisensory experiences. The VR cabin measures 119x119x224 cm. This tool provides a multisensory experience that adapts to the VE presented. The appropriate smells (notably forest, beach, alcohol, tobacco, coffee, gasoline), sounds, airflow and heat are programmed for each VE and evolve according to the exploration of the environment or as the session progresses (e.g. when moving in the sun in the VE, heaters are switched on).

For each of the six sessions, patients complete 20 minutes of guided mindfulness while exploring a VE. The first two sessions aim to teach participants the practice of mindfulness through immersion in relaxing environments (VEs 1 and 2). Next, to train the patients to better control craving induced by cues, they are gradually exposed to VEs containing cues meant to arouse the desire to consume alcohol (VEs 3 and 4). The aim is to get used to being confronted with cues without it precipitating consumption by learning to regulate cue-induced craving through mindfulness. Finally, to train the patients to regulate stress, a powerful inducer of craving and relapse [12], they are gradually exposed to environments that can induce stress (VEs 5 and 6). Mindfulness instructions guide the patient to regulate stress and stress-induced craving. The goal of this stress induction is for patients to learn to better regulate their stress in daily life, thus reducing their risk of relapse. During VR mindfulness

sessions, patients' cardiac and respiratory activity is monitored using a breathing belt and a heartbeat ear clip.

2) Performing cognitive exercises while cycling

The second tool used for this intervention is the cognitive bike (Vélo-cognitif, Figure 3), designed by RevLim to practise a cognitive and physical dual task. This tool combines an exercise bike and a touch pad offering cognitive training games. The bike has different levels of resistance. The cognitive exercises are designed by HappyNeuron, a network of scientific experts specialising in cognitive training. These exercises include training in inhibition, attention, memory and visuo-spatial skills through playful games of various difficulty levels. By simultaneously stimulating motor skills and cognition, this tool offers a playful activity in which the participants are able to see themself progressing and which could reduce stress through physical activity [63]. In a pilot study using the cognitive bike with patients suffering from alcohol use disorder, most patients reported having enjoyed the activity [64]. This tool could therefore help improve well-being and quality of life by providing a rewarding physical activity while exercising executive functions.

Control group

Patients in the control group are treated according to the standard protocol used at the Laborit Psychiatric Hospital. This consists of a clinical and biological examination performed by a health professional following the patient's admission to hospital. A treatment for withdrawal symptoms (benzodiazepines) is then administered under medical supervision. The patient benefits from individual medical and psychological monitoring. Workshops and therapeutic meetings are offered.

Measures

Primary outcome

The primary outcome is the proportion of individuals who relapsed two weeks after the tenth day of inclusion. Relapse has been defined as drinking at least five drinks per occasion or drinking at least five times a week [65,66]. Maintenance of abstinence and relapse are usually assessed using the Alcohol Timeline Followback (TLFB) assessment method [67]. However, this method relies on verbal reports and may thus be sensitive to underreporting. Relapse is also assessed using biological indicators—a breathalyser, and a blood test for the measurements of carbohydrate deficient transferrin (CDT) and gamma-glutamyl transpeptidase (GGT). CDT is a glycoprotein synthesised by the liver and is a specific marker indicating the presence of alcohol in the blood. Elevated CDT levels suggest recent high alcohol consumption, particularly if other liver-associated enzymes (such as GGT) are elevated [68]. These measures will be used as combined indicators of relapse in order to corroborate the patient's report and to objectify the relapse, to avoid a possible reporting bias. Indeed, underestimation of consumption is frequent, and may be related to low insight or social desirability bias [62,69,70], hence it is of interest to combine subjective with objective indicators of relapse. In this clinical trial, we will consider that a relapse occurred if at least one of the three indicators points to a relapse: 1) if in the TLFB the patient indicates consumption at least 5 times a week or at least 5 drinks per occasion; 2) if there is a significant increase in CDT and GGT since the day 10 blood test; or 3) if the breathalyser is positive. We will consider patients as non-relapsers if none of these indicators (TLFB, CDT and GGT, breathalyser) are positive.

Secondary outcomes

1. Mid-term relapse

Relapse is assessed using the same measures at one month and three months.

2. Craving

- Explicit craving, defined as the conscious desire to consume alcohol, is assessed in two ways:
  - Subjective craving during the past week is assessed using the Obsessive Compulsive Drinking Scale (OCDS) questionnaire [71], which measures an individual's alcohol consumption and attempts to control it over the past week.
  - Craving induced by cues is assessed using the craving induction protocol of Fox et al. [72]. This protocol induces craving through personalised cues, which consist of a short text written by the patient. This text should describe a memory of a situation of strong craving that led to consumption and should detail the context, the physical sensations and the state of mind during that scene. This half-page script is recorded by the experimenter, and then the audio is played to the patient during a second session. The patient indicates his level of craving before and after listening to the script on a visual analogue scale ranging from 0 to 10, where 0 represents no desire to consume and 10 represents an extremely strong craving.
- To obtain a behavioral assessment in relation to the automatic component of craving and drug-seeking behaviour, we also use three implicit measures (that will be combined into a single score of implicit craving):
  - Identification with the drug is assessed using a standard Implicit Association Test [73]. This test measures whether alcohol is more strongly associated with the self or others using images referring to alcohol or neutral images as target categories and words referring to the self or others as attribute categories (example: 'me', 'I', 'myself', 'mine' or 'they', 'them', 'their', 'others') [73].
  - A test of the seeking for alcohol-related stimuli based on the probabilistic image choice task of Moeller et al. [74] and adapted to alcohol is used. This test allows evaluating the preference for the drug among other reinforcers via four categories of images (drug, pleasant, unpleasant and neutral). There is a choice of four decks of cards, face down, each containing a majority of one of the image categories. A large image of the selected deck is presented on the screen for 2000 milliseconds, and then the subjects can select one of the decks again. A pseudo-randomisation described in [75] aims at reducing awareness of the identity of the deck while allowing a preference to be established. We adapted this task to alcohol addiction using images related to alcohol consumption (a glass of beer, a glass of wine, people drinking in a bar, etc.).
  - Attentional bias towards alcohol is assessed using the task of Soleymani et al. [76], a visual research test for alcohol-related stimuli (eye tracking). This task consists of freely viewing several sets of 16 images of alcoholic and non-alcoholic drinks, while an eye-tracker records the location of the first fixation

and the total fixation time for each image. The strength of the attentional bias is determined by these two parameters.

3. Mindfulness

- Mindfulness skills acquisition is measured using the Five Facets Mindfulness questionnaire [77,78]. This questionnaire assesses the tendency to be in a state of mindfulness in daily life based on five facets of mindfulness: observation (being attentive to one's internal/external states), description (being able to verbalise one's internal experiences), action with awareness (not automatic), non-judgment of internal and external experience (posture of acceptance, non-evaluative) and non-reactivity (detachment, non-response to internal states). We use the 15-item version of the questionnaire [79,80].
- The development of mindfulness skills is also assessed during mindfulness sessions using heart rate, respiratory rate and salivary cortisol measurements. These measures allow us to monitor the patient's attention to instructions, the stress induced by the environments and whether mindfulness can effectively regulate this stress. These measurements also allow the calculation of heart rate variability associated with self-regulation skills, which is commonly used in research on mindfulness-based interventions [81-83].

4. Richness of daily environment

We evaluate the effect of the intervention on the perceived richness of the daily environment. The perceived richness of the daily environment is assessed using the Measurement of the Perception of a Stimulating Environment Questionnaire (MPSEQ) (Chatard A, Barillot L, Besnier M, et al. Measurement of the Perception of a Stimulating Environment Questionnaire, unpublished, supplementary file 2). Composed of 13 items, this questionnaire evaluates to what extent the individual perceives their environment as stimulating. Each item is a declarative statement referring to the stimulations, activities or satisfaction and entertainment that the person perceives or realises in their life (example: 'My immediate environment is rich in sensations and stimulation of all kinds'). The individual expresses the extent to which they agree or disagree with each statement using a scale ranging from 1 to 7, with 1 corresponding to completely disagree and 7 to completely agree.

Study schedule

Table 1
Study schedule of enrolment and assessments by time points (Tn).
S1, S2, S3, S4, S5 and S6 refer to the 6 different EE sessions of the enhanced intervention.

	Enrolment	Enhanced intervention						Post-intervention	Follow-ups		
Time point	**T0**	**T1**						**T2**	**T3**	**T4**	**T5**
		S1	S2	S3	S4	S5	S6				
Eligibility	X										

screening									
Informed consent	X								
Group allocation	X								
Primary outcome									
TLFB							X	X	X
Breathalyser							X	X	X
Blood test						X	X	X	X
Secondary outcomes									
OCDS	X						X	X	X
Craving induced by cues	X					X			
IAT	X					X			
Alcohol seeking	X					X			
Alcohol attentional bias	X					X			
MPSEQ	X					X	X	X	X
FFMQ	X		X			X			
Salivary cortisol	X			X	X				

Potential participants are invited to a 15-minute informative meeting. Eligibility screening is conducted, and patients are invited to participate after being provided a description of the study. A pre-test in the VR cabin is offered to the patients to allow them to get acquainted with VR and to check that they do not shows signs of cybersickness.

Patients are reconvened (T0), and if they wish to participate in the study and if they meet all the eligibility criteria they sign the consent form and are randomly assigned to one of two groups. They complete baseline measures of their craving and salivary cortisol and complete questionnaires about their initial mindfulness skills and their perception of the richness of their daily environment (Table 1).

Intermediate measures take place for participants undergoing the intervention enhancement (T1). The acquisition of mindfulness skills is assessed after the second session of intervention enhancement. Salivary cortisol is measured after session 5 and session 6, which are expected to induce stress in the patient.

On the tenth day of inclusion or after completing the enhanced intervention (depending on the group) (T2), participants are seen again for a measurement session during which craving and mindfulness skills are assessed. A blood test is performed to obtain a baseline measurement of CDT and GGT. Relapse is assessed in both groups according to the method described in the measures section at two weeks (T3), one month (T4) and three months (T5) after T2.

Sample size

The required sample size was computed to have 80% statistical power to detect a significant reduction of relapse rate of at least 25% on our primary outcome (with $p < .05$, two-tailed). We considered a 25% reduction in relapse rate as the smallest effect size of interest in our study. This effect size seems realistic to us and appears to be the smallest effect size of clinical interest given the investment of material and human time in this intervention. The smallest effect size of interest is the smallest effect that (1) researchers personally care about, (2) is theoretically interesting, or (3) has practical relevance [84]. The relapse rate on our site is about 50% on average after one month [62]. This is consistent with other studies in which nearly half of the patients relapsed in the weeks following hospital discharge for alcohol withdrawal [85-86]. With a relapse rate of 50% after one month, there is significant potential to reduce the relapse rate by 25%. It is quite possible that the intervention will have a much smaller effect size. However, if the relapse rate is not reduced by at least 25%, the intervention would be considered to have no efficacy or too low to be of clinical relevance.

The a-priori power analysis for sample size indicates that the required sample size is 116 for our primary outcome. However, we will include 135 patients to compensate for possible missing data. For the secondary outcomes (craving, mindfulness skills, perceived richness of the daily environment) this sample size ($N = 135$) provides adequate power ($1- ß = .82$) to detect a medium effect size or a larger effect size (Cohen's $d > .50$, with $p < .05$ (two-sided).

Data analysis

Data analysts will be blind to the condition: the condition will be letter coded rather than explicitly "control" or "intervention". All analyses will be conducted using both Rstudio® and SPSS 23.0® software. A descriptive analysis of the study population will be performed. Qualitative variables will be expressed as a proportion with 95% confidence interval. Quantitative variables will be expressed as mean and standard deviation or as median and interquartile range. A value of $p<0.05$ (two-tailed) will be considered statistically significant. In intention-to-treat analyses, missing data will be simulated using a multiple-imputation technique with interim values.

The initial comparability resulting from the randomisation will be checked using tests appropriate to the distribution (parametric or non-parametric) and type (quantitative/qualitative) of the variables studied.

The primary outcome (relapse at two weeks) will be analysed using an independent sample proportion test (Chi-square) comparing the differences according to the groups with a two-tailed alpha risk of 5%. The difference between the two groups for relapse at one month and three months (secondary outcomes) will be analysed in the same way. An independent sample t-test (Student's t-test) will be used on the other secondary outcomes (craving, mindfulness skills and perceived richness of the daily environment) to compare the differences before and after the enhanced intervention, and before and during the enhanced intervention for the intervention enhancement group (within-participant), with a two-tailed alpha risk of 5%.

ETHICS AND DISSEMINATION

All participants have to give written informed consent to the investigator. This study is approved by the Ethics Committee Nord Ouest IV of Lille (reference number 2022-A01156-37). Results will be disseminated through presentations, peer-reviewed journals and seminar conferences. All information on ethical considerations and open science practices can be accessed at https://osf.io/b57uj/

PATIENT AND PUBLIC INVOLVEMENT

Patients or public were not involved in the design or conduct of the study.

DISCUSSION

This study aims at evaluating the effectiveness of exposure to EE sessions in reducing relapse in patients receiving treatment for AUD. This study is the first attempt to transpose the EE approach described in preclinical studies [24] combining different types of stimulation to humans. Our study should inform about the potential of this strategy to treat addiction by promoting long-term abstinence and reducing the incidence of relapse. Our EE provides rewarding stimulations as alternatives to drug taking while training the cognitive and emotional processes deregulated in AUD [64] and provide skills that can be reused in daily life in stressful or cue-exposure situations to resist craving and avoid relapse [18].

In terms of study limitations, it is possible that the acceptability of VR and mindfulness [87-90] can play a role in the effectiveness of the intervention enhancement. We have chosen to exclude people who show a cybersickness type of discomfort in the VR. Regarding mindfulness, repeated measures of mindfulness skills should help to control for this acceptability bias. Another limitation is that we chose to induce stress through VR during the last two EE sessions, even though stress is supposed to be a sort of functional opposite of EE and can therefore interfere with the enrichment procedure [24,25]. However, the sessions may be considered to be part of EE because they provide cognitive training to learn regulating stress through mindfulness. Another possible weakness of the EE in this study is that it does not include additional social stimulation compared to standard treatment, while several animal studies have shown that social stimulation is an important component of EE [24], and social support in humans is an important part of addiction treatment [18]. Therefore, further studies are needed to investigate whether a protocol of EE that includes more specific forms social stimulation would be more effective than the present one. Finally, it will be important in the future to perform parametric studies to investigate whether more or fewer EE sessions can increase or decrease the benefits of this EE protocol.

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FOOTNOTES

Competing interests statement.

None declared.

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Authors' contributions

AC, NJ and MS were responsible for identifying the research question and designing the study protocol. MB, LB and CC contributed to the development of the protocol and study design. LB wrote the first draft of this manuscript, which was revised and modified by all authors.

Figure legends:

Figure 1. Virtual environments presented: forest (VE 1), beach (VE 2), bar (VE 3), party (VE 4), parachute jump (VE 5), plane (VE 6)

Figure 2. Sensory reality pod: Device created by Sensiks containing programmable actuators to generate different types of stimulation using heaters, an odour diffusion module connected to bottles containing fragrances, an audio system and fans. The authors (including the person pictured in the figure) declare that this photograph was illustrated by one of the co-authors, and grant permission and give their consent to BMJ open for the use of this photograph for publication, including print or web-based publications. The authors understand that with their authorization the photograph can never be revoked.

Figure 3. Vélo-cognitif (cognitive bike) consisting of an exercise bike to which a digital touch pad is attached to allow cognitive exercises to be performed while pedalling. The authors (including the person pictured in the figure) declare that this photograph was illustrated by one of the co-authors, and grant permission and give their consent to BMJ open for the use of this photograph for publication, including print or web-based publications. The authors understand that with their authorization the photograph can never be revoked.

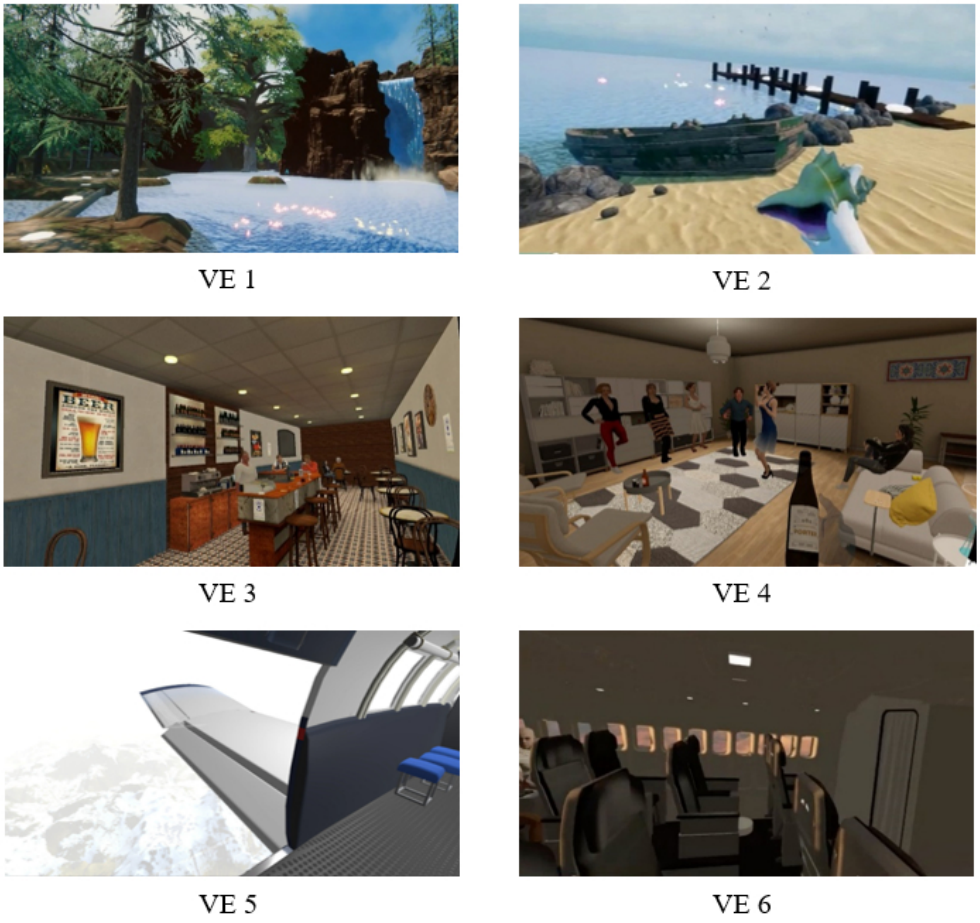

Figure 1. Virtual environments presented: forest (VE 1), beach (VE 2), bar (VE 3), party (VE 4), parachute jump (VE 5), plane (VE 6)

382x368mm (47 x 47 DPI)

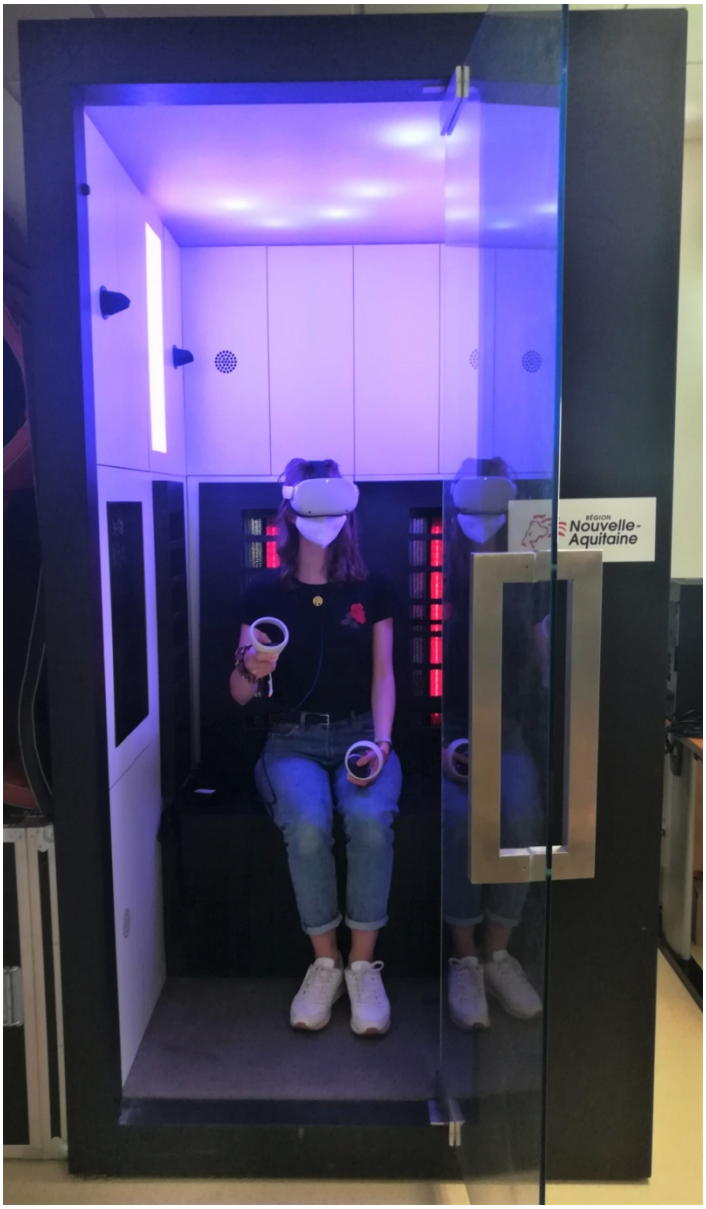

Figure 2. Sensory reality pod: Device created by Sensiks containing programmable actuators to generate different types of stimulation using heaters, an odour diffusion module connected to bottles containing fragrances, an audio system and fans

818x1399mm (72 x 72 DPI)

Figure 3. Vélo-cognitif (cognitive bike) consisting of an exercise bike to which a digital touch pad is attached to allow cognitive exercises to be performed while pedalling

752x834mm (72 x 72 DPI)

Mindfulness instructions for mindfulness practice in virtual environments (VEs)

- **VE1: Immersion in a forest**

  First of all, go and discover this environment.

  Your senses are a precious help. Observe the scenery of this forest, the luminosity, the smells, the possible sounds, in a global way

  To immerse yourself in this place, stop for a few moments. Close your eyes. Pay attention only to the sounds that are present. From the most distant (perhaps the wind blowing in the distance) to the closest (your breathing). Observe, without judging...

  Observe if this causes things to happen to you: for example, do you have any thoughts? Observe them passing and let them go as they came. Sensations (e.g. tension in the body? tingling? a feeling of lightness...)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came, that is, without trying to hold them back, and without trying to make them go: their departure is gradual, passive.

  To finish, I suggest that you focus your attention on a specific object, for example a leaf, a mushroom, a flower... whatever feels good to you... Choose what makes you happy.

  Approach this object and give it your full attention.

  Without judgement, observe its colours, its shape. Does it have a scent? Does it make sounds when you bring it close to your ear? Take a few moments to observe...

  When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

  Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste.

  We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE2**: **Walking along a beach**

  First of all, discover the environment.

  Your five senses are of great help. Observe the beach, the colours, the possible smells, the sounds

To immerse yourself in this place, stop for a few moments. Close your eyes. Pay attention only to the sounds that are present. From the most distant (perhaps the wind blowing in the distance, the sound of the waves) to the closest (your breathing). Observe, without judging...

Observe if this causes things to happen to you: for example, do you have thoughts? Observe them passing and let them go as they came. Sensations (e.g. tension in the body? tingling? a feeling of lightness...)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came, that is to say, without trying to hold them back, and without trying to make them go away: their departure is done gradually, passively.

Finally, I suggest that you focus your attention on a particular object, for example a shell, something that seems good to you... Choose what you like. Approach it and give it your full attention.

Without judgment, observe its colours, its shape. Does it have a scent? Does it make sounds when you bring it close to your ear? Take a few moments to observe...

When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE3: Walking down the street, buying something in a shop, then ordering a coffee in a bar**

First of all, make this new environment your own.

Your five senses are a great help. Observe your surroundings. Observe the street you are on, the landscape, the smells of the city, the sounds.

You can go into the shop near you to buy a bottle of water. Focus on the elements around you. The sounds, from the most distant (perhaps the music in the shop, conversations) to the closest (your breathing). Observe, without judging...

You are going to walk towards the exit. Once outside, you see a café in front of you. Walk slowly towards it and enter it.

Continue to focus on your sensations, the wind caressing your face, the sounds of the street. As you enter the café, observe whether this causes anything to happen to you: for example, do you have any sensations (e.g. tension in your body? tingling?)?

Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

You are going to sit at the counter and order a coffee. Focus on the smells and sounds of conversation around you. Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste or not. Once again, without judging, welcoming things as they are. To finish, I suggest that you focus your attention on a particular object, for example a cup of coffee, which seems good to you... Choose what pleases you. Approach it and give it your full attention.

Without judgment, observe its colours, its shape. Does it smell? Does it make sounds when you bring it close to your ear? Take a few moments to observe...

When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste or not. Once again, without judging, welcoming things as they are.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE4**: **Party in a house with other people who smoke and drink alcohol**

First of all, get used to this new environment.

Your five senses are of great help. Observe your surroundings. Observe the house you are in, the rooms, the smells in the house, the sounds.

Walk around the house and focus on the elements around you. The sounds, from the most distant (perhaps the music in the house, conversations) to the closest (your breathing). Observe, without judging...

Let any sensations, thoughts or emotions within you quietly and passively subside. You let it happen... Without trying to change your breathing, without trying to hold anything back... You let the sensations that may be present happen, until they disappear by themselves. You let it happen.

Go to the table and sit down with the other people. Observe if this causes things to happen in you: for example, do you have any sensations (e.g. tension in the body? tingling?)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them

back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

You get up and go to the kitchen. Look in the fridge for a bottle of water. Focus on the smells and sounds of conversation around you. Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste.

Go back to your seat and continue to focus on the sounds and smells. Observe whether this causes you to do something: for example, do you have any sensations (e.g. tension in the body? tingling?)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Accept it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

To finish, I suggest that you focus your attention on a particular object, for example a plate, a flower, something that seems good to you... Choose what you like. Approach it and focus your attention on this object.

Without judgment, observe its colours, its shape. Does it have a scent? Does it make sounds when you bring it close to your ear? Take a few moments to observe... When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste or not. Once again, without judging, welcoming things as they are.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE5: A parachute jump**

First of all, get used to this new environment.

Your five senses are a great help. Observe your environment, around you. Observe the cabin you are in, the landscape, the sounds.

Before approaching the edge, you can focus on yourself. Close your eyes. Pay attention only to the sounds that are present. From the most distant (perhaps the wind blowing in the distance) to the closest (your breathing). Observe, without judging...

The jumping will now begin. Try to keep the calmness you have achieved. Let the sensations come to you without trying to anticipate them.

Continue to focus on your sensations, the wind caressing your face... Observe if this causes things to happen to you: for example, do you have any sensations (e.g. tension in your body? tingling?)? Welcome them, without judging. Let them come and go as

they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

Perhaps you notice an increase in your heart rate, your heart beating faster..., or tensions in your body, muscles that stiffen...

You let it happen, without judgment. Let it happen, without trying to control anything. Let these sensations pass, the emotions that come, as they have come. Let it happen, passively, so that they leave quietly as they came. You let it happen..., without trying to modify your breathing. You let it happen, in confidence, quietly.

Continue to observe and feel your environment. Try to perceive again the elements around you, the noises, perhaps the wind

Let all sensations, thoughts and emotions in you quietly and passively subside. You let it happen... Without trying to change your breathing, without trying to hold anything inside you... You let the sensations that may be present happen, until they disappear by themselves. You let it happen. The parachute will now open. In the same way, observe if these sensations are pleasant for you, if they leave an imprint in you, a pleasant taste or not. Once again, without judging, welcoming things as they are.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

- **VE6: Flying with turbulence**

First of all, get used to this new environment.

Your five senses are of great help. Observe your surroundings. Observe the cabin you are in, the landscape through the window, the smells, the sounds. Take time to explore the cabin. As the captain announces, turbulence will start in the plane. You can return to your seat. Close your eyes and let the sensations come to you without trying to anticipate them.

Continue to focus on your sensations, the ventilation of the cabin on your face, the sounds of your surroundings.

The belt signals come on and you hear thunder in the distance. Observe if this causes things to happen to you: for example, do you have any sensations (e.g. tension in your body? tingling?)? Welcome them, without judging. Let them come and go as they came. An emotion (fear, anger, sadness, surprise, disgust, joy...)? Welcome it, without judgement. Take them into account as they are, in the present moment, without judgment. Then let them go as they came. Let them go..., without trying to hold them back, and without trying to make them go away: their departure happens gradually, passively. Let it happen...

Perhaps you notice an increase in your heart rate, your heart beating faster..., or tensions in your body, muscles that tighten...

You let it happen, without judgment. Let it happen, without trying to control anything. Let these sensations pass, the emotions that come, as they have come. Let it happen, passively, so that they go away quietly as they came. You let it happen..., without trying to modify your breathing. You let it happen, in confidence, quietly.

Around you, you observe the luggages falling and the elements falling over. Focus on the way it makes you feel. Accept it and let it go without chasing it or holding it back. Perhaps you notice an increase in your heart rate, your heart beating faster..., or tension in your body, muscles tightening...

You let it happen, without judgment. Let it happen, without trying to control anything. Let these sensations pass, the emotions that come, as they have come. Let it happen, passively, so that they go away quietly as they came. You let it happen..., without trying to modify your breathing. You let it happen, in confidence, quietly.

The plane calms down again and the turbulence goes away. Continue to observe and feel your surroundings during the turbulence. Observe if these sensations are pleasant for you, if they leave an imprint on you, a pleasant sensation or not. Again, without judging, welcoming things as they are.

Let all sensations, thoughts or emotions in you quietly and passively subside. You let it happen... Without trying to change your breathing, without trying to hold anything inside you... You let the sensations that may be present happen, until they disappear by themselves. You let it happen. To finish, I suggest that you focus your attention on a particular object, for example a book, something that seems good to you... Choose what you like.

Approach it and give it your full attention. Without judgment, observe its colours, its shape. Does it smell? Does it make sounds when you bring it close to your ear? Take a few moments to observe... When you take this time, observe if you have thoughts, sensations, emotions... Without judgement. Taste the present moment... The "here and now".

Observe if these sensations are pleasant to you, if they leave an imprint on you, a pleasant taste or not. Once again, without judging, welcoming things as they are.

We are coming to the end of this experience, thank you for participating and see you soon for the next discovery together.

Measurement of the Perception of a Stimulating Environment Questionnaire (MPSEQ)

(Chatard A, Barillot L, Besnier M, et al. Measurement of the Perception of a Stimulating Environment Questionnaire, unpublished)

Please indicate your degree of agreement with the statements below using the following response scale: 1 = Strongly disagree; 2 = Disagree; 3 = Somewhat disagree; 4 = Neither agree nor disagree; 5 = Somewhat agree; 6 = Agree; 7 = Strongly agree

1. My immediate environment is rich in sensations and stimuli of all kinds ___
2. Often, I tell myself that my life is not very exciting ___
3. I practice many physical and/or sports activities ___
4. My physical and/or sports activities are a source of personal development ___
5. I have a rich inner life ___
6. I play and/or listen to a lot of music ___
7. I watch a lot of exiting and stimulating films and documentaries ___
8. I have a lot of friends and social connections ___
9. My social relationships are rich and stimulating ___
10. I do many diverse and varied activities ___
11. I have a passion in life (ex: a hobby) ___
12. I live in a stimulating environment ___
13. I have the impression that my daily environment is boring, that it is always the same ___

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
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 1**
	2b	All items from the World Health Organization Trial Registration Data Set__ Please see: https://clinicaltrials.gov/ct2/show/record/NCT05577741
Protocol version	3	Date and version identifier__ **Please see:** https://osf.io/b57uj/ **(Additional information file)**
Funding	4	Sources and types of financial, material, and other support__ **Page 19**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors__ **Page 19**
	5b	Name and contact information for the trial sponsor__ **Page 19**
	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 19**
	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)__ **Please see:** https://osf.io/b57uj/ **(Additional information file)**
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 2-4**
	6b	Explanation for choice of comparators__ **Page 4**
Objectives	7	Specific objectives or hypotheses__ **Page 4**

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 4**

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 4**
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 5**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered__ **Page 5-7, Page 9-10**
	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)__**X**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)__ **X**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial__ **X**
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 7-9**
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)__ **Page 9-10**
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 11**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size__ **Page 4**

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 5**
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 5**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions__ **Page 5**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how__ **Page 11**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial__**X**
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 7-9**
	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__ **Please see:** https://osf.io/b57uj/ **(CPP file p.56)**
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 11**
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 11**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)__**X**

	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 12**
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__ **Please see:** https://osf.io/b57uj/ **(Additional information file)**
	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__ **Please see:** https://osf.io/b57uj/ **(CPP file p.51)**
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__ **Please see:** https://osf.io/b57uj/ **(CPP file p.54)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor__ **Please see:** https://osf.io/b57uj/ **(CPP file p.57)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval__**Page 12**
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)__ **Please see:** https://osf.io/b57uj/ **(CPP file p.60)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)__ **Please see:** https://osf.io/b57uj/ **(CPP file p.61)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable__**X**
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__ **Please see:** https://osf.io/b57uj/ **(CPP file p.53 and 57)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site__**Page 18**

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__ **Please see:** https://osf.io/b57uj/ **(CPP file p.61)**
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__ **Please see:** https://osf.io/b57uj/ **(CPP file p.60)**
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 12**
	31b	Authorship eligibility guidelines and any intended use of professional writers__**X**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code__Please see our data sharing plan at: https://clinicaltrials.gov/ct2/show/record/NCT05577741
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates__ **Please see:** https://osf.io/b57uj/
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__**X**

*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.