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Automated virtual reality (VR) cognitive therapy for patients with psychosis: study protocol for a single-blind parallel group randomised controlled trial (gameChange)

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Automated virtual reality (VR) cognitive therapy for patients with psychosis: study protocol for a single-blind parallel group randomised controlled trial (gameChange)

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ABSTRACT

Introduction: Many patients with psychosis experience everyday social situations as anxiety-provoking. The fears can arise, for example, from paranoia, hallucinations, social anxiety, or negative-self beliefs. The fears lead patients to withdraw from activities, and this isolation leads to a cycle of worsening physical and mental health. Breaking this cycle requires highly active treatment directly in the troubling situations so that patients learn that they can safely and confidently enter them. However patients with psychosis seldom receive such life-changing interventions. To solve this problem we have developed an automated psychological treatment delivered in Virtual Reality (VR). It allows patients to experience computer simulations of the situations that they find anxiety-provoking. A virtual coach guides patients, using cognitive techniques, in how to overcome their fears. Patients are willing to enter VR simulations of anxiety-provoking situations because they know the simulations are not real, but the learning made transfers to the real world.

Methods and analysis: 432 patients with psychosis and anxious avoidance of social situations will be recruited from National Health Service (NHS) secondary care services. In the gameChange trial, they will be randomised (1:1) to the six-session VR cognitive treatment added to treatment as usual or treatment as usual. Assessments will be conducted at 0, 6 (post-treatment), and 26 weeks by a researcher blind to allocation. The primary outcome is avoidance and distress in real-life situations, using a behavioural assessment task, at six weeks. The secondary outcomes are psychiatric symptoms, activity levels, and quality of life. All main analyses will be intention-to-treat. Moderation and mediation will be tested. An economic evaluation will be conducted.

Ethics and dissemination: The trial has received ethical approval from the NHS Health Research Authority (19/SC/0075). A key output will be a high-quality automated VR treatment for patients to overcome anxious avoidance of social situations.

Registration: ISRCTN17308399

Keywords: schizophrenia; psychosis; cognitive therapy; virtual reality; treatment.

Strengths and limitations of this study

- A multi-centre randomized controlled trial of 432 patients with psychosis being seen in National Health Service mental health trusts, which will be the largest trial of VR used to treat a mental health condition.
- Automated delivery of the VR intervention meaning high treatment fidelity and a highly scalable treatment that could greatly increase access to psychological therapy.
- Mediation built into the treatment design can test whether the treatment works as hypothesized.
- The control condition is treatment as usual meaning that it cannot be definitively established which VR treatment elements produce clinical change.
- It is impossible to blind patients to the treatment allocation, which could introduce bias into the treatment effect estimation.

BACKGROUND

Rationale

Too many patients with psychosis, despite standard treatment, become isolated and inactive, with negative effects on both mental and physical health. Approximately 80% of patients with schizophrenia experience an episode of depression (1). Physical activity levels in patients with schizophrenia are reduced on average by approximately two thirds (2). Over 90% of patients with schizophrenia are unemployed and spend “less time in functional but also in social and leisure activities and more time resting and ‘doing nothing’ compared to the general population” (3). Life expectancy is on average 14.5 years shorter (4), due to largely preventable conditions such as high blood pressure, diabetes, and heart disease. Partly this physical ill health reflects unhealthy lifestyles including inactivity.

Our view is that a substantial part of this inactivity arises from avoidance due to anxiety. In a clinical assessment study of 1800 patients with non-affective psychosis attending NHS mental health services, two-thirds of the patients had levels of anxious avoidance equivalent to patients diagnosed with agoraphobia (5). The anxiety in patients with psychosis can arise from a number of sources: fears that others will harm them, voices telling them of danger, social anxiety fears of humiliation and rejection, and negative beliefs about the self that cause a lack of confidence and a sense of vulnerability. But withdrawal from activities because of anxiety need not be inevitable. Appropriate treatment, as seen in the anxiety disorders (6), can produce excellent outcomes. Such treatment involves identifying fearful thoughts and the safety-seeking (or defence) behaviours that maintain those cognitions by preventing receipt and processing of disconfirmatory evidence. The thoughts must then be tested in behavioural experiments in the troubling situations while the defence behaviours are dropped (7). However, there is a dearth of therapists to carry out this skilled work for patients with schizophrenia. It is well-recognised that there is considerable under-provision of psychological therapy for patients with schizophrenia (8). There is the additional problem that the sometimes very fearful beliefs of patients with psychosis mean that they can be much less likely to engage in behavioural experiments in the real world before their fears have been lessened by other means. Our solution is the provision of automated psychological therapy using Virtual Reality (VR).

Virtual reality (interactive computer-generated environments) has been used since the early 1990's to treat anxiety (9). Meta-analyses indicate that VR treatments for anxiety disorders can produce large treatment effects (10) that generalise to the real world (11). Previous uses of VR for mental health problems have depended on a therapist providing the psychological therapy (12). In a trial of one hundred patients with a fear of heights, we have shown that the provision of cognitive therapy can be automated using VR by the incorporation of a virtual coach (13). The treatment effect sizes in this trial

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2 were very large (effect size Cohen's $d=2.0$; the number of patients needed to treat (NNT) to at least halve
3 fear of heights was 1.3), and better than expected from face-to-face therapy. Automated treatment has
4 the potential to be scalable, removing a key cause of the highly limited access to psychological therapy
5 for patients with psychosis.
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10 VR may also be especially suited to the difficulties of patients with psychosis. Patients with strong fears
11 are much more likely to test out their fear expectations in VR because they know it is a simulation but
12 the learning that they make then transfers to the real world. VR treatment can also include engaging
13 tasks that make the treatment experience much more pleasurable. A graded approach can easily be
14 applied in VR, allowing the individual to repeatedly experience the situations they find difficult and make
15 new learning. Our view is that VR treatments have the potential to be faster, more efficacious, and
16 appealing to patients than traditional face-to-face approaches. We conducted a first test of VR to treat
17 persecutory delusions in patients with psychosis (14). Just thirty minutes in graded VR environments,
18 with the psychological advice provided by a therapist, led to a large reduction in distress in real-world
19 situations (e.g. going into a shop). VR has been shown to be safe to use with patients with psychosis (15).
20 A recent randomised controlled trial of over one hundred patients with psychosis showed that 16 one-
21 hour sessions with VR environments and a therapist who administered CBT techniques led at follow-up
22 to a moderate increase in time spent with other people as assessed by an experience sampling method
23 (16). In the THRIVE trial our team is currently testing a four-session automated VR cognitive treatment
24 for patients specifically with persecutory delusions (ISRCTN12497310) (17).
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36 In the gameChange project (www.gameChangeVR.com), we have recently developed - using a socially-
37 inclusive design process - a new automated VR cognitive treatment for patients for psychosis having
38 difficulties being in everyday social situations due to anxiety. It is designed to be easy to use, engaging
39 for patients and staff, and delivered with the latest consumer equipment. Therefore this VR treatment
40 has the potential to be widely implemented in treatment services. Psychological treatment that involves
41 direct coaching in the situations that trouble patients with psychosis is rarely available in mental health
42 services. Therefore we set out to determine the *in toto* effects of adding the VR treatment to treatment
43 as usual. This entails a test that randomises patients to receive the VR treatment in addition to usual care
44 or to usual care. We aim to determine the clinical effects on real-world performance, activity levels,
45 psychiatric symptoms, and quality of life.
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56 **Aims and hypotheses**

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2 The primary research question we aim to test is: Does automated VR cognitive treatment added to
3 treatment as usual, compared to treatment as usual alone, lead to a post-treatment reduction in real
4 world avoidance and distress for patients with psychosis attending NHS mental health services?
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8 Our primary hypothesis is that:
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11 1. Compared to treatment as usual, VR cognitive therapy added to treatment as usual will reduce
12 avoidance and distress of real world situations (post treatment).
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15 Our secondary hypotheses are:
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18 1. Compared to treatment as usual, VR cognitive therapy added to treatment as usual will reduce
19 psychiatric symptoms (paranoia, anxious avoidance, depression, suicidal ideation), increase activity, and
20 improve quality of life (post-treatment).
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23 2. Treatment effects will be maintained at follow-up.
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26 3. The mediators of VR treatment will be safety beliefs, threat cognitions, and defence behaviours.
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29 4. Treatment effects will be moderated by the occurrence of negative auditory hallucinations in social
30 situations, hopelessness, appearance concerns, and threat cognitions.
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33 We also include a health economic evaluation of the VR treatment. It will focus on determining the cost
34 of the VR treatment using a microcosting approach, performing a within-trial cost-effectiveness analysis,
35 and extrapolating the within-trial results to a 10 years horizon using a state-transition model.
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43 **METHODS AND ANALYSIS**

44 45 46 47 48 **Trial design and flow chart**

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51 The design is a multicentre, parallel group randomised controlled trial with single blind assessment to
52 test whether the automated VR cognitive treatment added to treatment as usual, compared to
53 treatment as usual alone, leads to a post-treatment reduction in real world distress and avoidance for
54 patients with psychosis attending NHS mental health services. Treatment as usual will be measured but
55 remain unchanged in both groups. Assessments will be carried out at 0 (baseline), 6 (post treatment),
56 and 26 (follow-up) weeks by a researcher blind to treatment allocation. A summary of the trial design
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3 can be seen in Figure 1. The trial is prospectively registered with the ISRCTN registry: ISRCTN17308399.
4 There is a Data Monitoring and Ethics Committee (DMEC).
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18 **Randomisation, blinding, and code-breaking**

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20 Participants will be randomised once they have completed the baseline assessment. Participants will be
21 allocated to one of the trial arms using a 1:1 allocation ratio. Randomisation will be carried out by a
22 validated online system, Sortition, designed by the University of Oxford Primary Care Clinical Trials Unit.
23 Randomisation using a permuted blocks algorithm, with randomly varying block size, will be stratified by
24 site (Bristol/Manchester/Newcastle/Nottingham/Oxford) and service type (in-patient/early
25 intervention/community mental health team).
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30 The research assessors will be blinded to group allocation, but the patients and staff member present
31 will not be (they cannot be blinded to whether psychological intervention is delivered or received). If an
32 allocation is revealed between assessment sessions, this is logged by the trial coordinator and re-blinding
33 will occur using another assessor.
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41 **Participants**

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43 The trial participants will be patients with psychosis and self-reported difficulties going outside among
44 other people due to anxiety. The principal method of recruitment will be via seeking referrals to the trial
45 from the relevant clinical teams (adult community mental health teams; early intervention services, and
46 inpatient units) in the participating mental health trusts. The trial centres will be Bristol, Manchester,
47 Newcastle, Nottingham, Oxford, with recruitment from local NHS mental health trusts. With the approval
48 of the clinical team, patients interested in taking part will then be approached by the research team,
49 given information about the trial, and screening conducted. Our Lived Experience Advisory Panel (LEAP)
50 have also emphasised the importance of patients of the participating trusts self-initiating referral to the
51 trials, in order to minimise the chances that particular patients are overlooked by clinical teams or the
52 clinician was not present at a referral meeting. Hence we will also advertise the study and patients within
53 participating trusts will be able to self-refer for a screening to take part in the study. However, in all
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instances we will also seek to confirm that a member of the clinical team gives approval for a patient to enter the trial. Informed consent will be obtained from all patients before participation.

Inclusion criteria:

- Adults aged 16 years or older;
- Attending a NHS mental health trust for the treatment of psychosis;
- Clinical diagnosis of schizophrenia spectrum psychosis (F20-29) or an affective diagnosis with psychotic symptoms (F31.2, 31.5, 32.3, 33.3) (ICD-10) (18);
- Having self-reported difficulties going outside their home primarily due to anxiety that they would like treated;
- And participant is willing and able to give informed consent for participation in the trial.

Exclusion criteria:

- Unable to attempt an Oxford-Behavioural Assessment Task (O-BAT) (the primary outcome measure) at baseline (e.g. due to being unpermitted to leave a psychiatric ward);
- Photosensitive epilepsy;
- Significant visual, auditory, or balance impairment;
- Current receipt of another intensive psychological therapy (or about to start it within the 6 week trial therapy window);
- Insufficient comprehension of English;
- In forensic settings or Psychiatric Intensive Care Unit (PICU);
- Organic syndrome;
- Primary diagnosis of alcohol or substance disorder or personality disorder;
- Significant learning disability;
- Or current active suicidal plans.

Assessments

Basic demographic and clinical data will be collected (e.g. age, gender, ethnicity, clinical diagnosis, medication use). The primary outcome, avoidance and distress of everyday situations as measured by the Oxford-Behavioural Avoidance Task (O-BAT) (adapted from 14), will be measured at baseline, six weeks, and 26 weeks. The O-BAT comprises a personalised hierarchy of five real world situations that the patient finds difficult due to anxiety. The person then tries to carry out the hierarchy, rating anxiety at each step achieved, and stopping when they decide the anxiety is too great. This therefore produces an avoidance score (0-5, with higher scores indicating lower avoidance) and a distress score (0-10, with

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higher scores indicating greater distress) for each level. Secondary outcomes will also be assessed as all three time-points. Anxious avoidance (AMI-A (19) and self-report version of the O-BAT (20)), suicidal ideation (Columbia Suicide Severity Rating Scale) (21), overall paranoia (R-GPTS) (22, 23), paranoia worries (Paranoia Worries Questionnaire) (24), and levels of depression (PHQ-9) (25) will be assessed. Activity levels will be assessed using actigraphy (over 7 days), complemented with a time-budget assessing meaningful activity (26). The EQ-5D-5L (27) and ReQoL (28) will assess quality of life. Additionally, quality of life will be assessed using the Questionnaire about the Process of Recovery (QPR) (29). For mediation, we will assess, at all time-points, threat cognitions and use of defence behaviours (CDBQ) (30) and strength of safety, vulnerability and threat anticipation beliefs (31). Moderators will be assessed at baseline only by a brief assessment of negative hallucinations when outside (32), the Beck Hopelessness Scale (33), the Body-Esteem Scale for Adolescents and Adults (34), and the Cognition and Defence Behaviours Questionnaire (30). We will record service use, and other relevant health economic data, using the Client Service Receipt Inventory (35). A summary of the measures is provided in Table 1.

Insert Table 1 about here

The VR psychological treatment

The gameChange VR treatment is a virtual-reality application recommended for adults (16+) who have anxieties when outside in everyday social situations. This software is intended to reduce anxieties around other people and therefore to help participants feel safer and more comfortable around people. The aim for the outcome is that patients feel more able to go outside into everyday situations. The treatment was programmed by the University of Oxford spin-out company Oxford VR (www.oxfordvr.org). The treatment will be a CE marked Class I Active Medical Device- Z301 (Standalone Software), in conformity with the essential requirements and provisions of the EC Directive 93/42/EEC (Medical Devices).

A mental health professional, most likely a peer support worker, will be in the room when the treatment is given. This person will help the patient put on the VR headset and start the programme. The staff member will also encourage the person to apply the learning from VR into the real world. The applications will run through the Steam software application on a laptop computer connected to a head-

1
2 mounted display and accessories. All hardware is already commercially available and has not been
3 modified for the trial. Satisfaction will be assessed after completion of the last treatment session using a
4 modified version of the Client Satisfaction Questionnaire (36).
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8 The VR Cognitive Therapy (VRCT/gameChange treatment) aims for patients to test their fear
9 expectations around other people in order to relearn safety. The treatment is not designed as exposure
10 therapy (participants are not asked to remain in situations until anxiety reduces) but as repeated
11 behavioural experiment tests (to learn that they are safer than they had thought). The treatment is
12 designed to be delivered in approximately 6 sessions of thirty minutes. Three sessions will be considered
13 the minimum (adherent) dose of therapy. However participants can proceed at their own pace, meaning
14 that a fewer or greater number of sessions is allowed. The participant typically stands, and is able to walk
15 a few paces in the scenarios. A virtual coach guides the person through the treatment, including
16 encouraging the dropping of defence behaviours, and elicits feedback to tailor the progression of the
17 treatment. When first entering VR, the patient goes into the coach's virtual office and is guided in how to
18 use VR (i.e. the basic functions). At the beginning of the first session, the virtual coach explains the
19 rationale behind the treatment, and the participant selects which one of six virtual reality situations that
20 they would like to begin in. The six virtual reality scenarios are a: café, GP waiting room, pub, bus, street
21 scene, and newsagent. Each scenario has five levels of difficulty (e.g. the number and proximity of people
22 in the social situation increases) and participants work their way through each level of difficulty. There
23 are (therapeutic) game type tasks within a number of the levels (that are designed to help the person
24 drop defence behaviours and make new learning). The participant can choose a different scenario in
25 each session or repeat a previous situation. Throughout the sessions, participants' responses to
26 questions from the virtual coach are given by means of gripping a virtual globe. Belief ratings are
27 repeated within VR at the beginning and end of each treatment session. Figure 2 provides a summary of
28 the treatment design.
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57 **Control condition**

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2 Participants who are allocated to the control arm will continue to receive their usual care. No additional
3 interventions will be offered by the research team. Treatment as usual for the participants within this
4 trial will typically consist of long term prescription of psychiatric medications, and meetings with a
5 mental health practitioner. Treatment as usual will vary across individuals and mental health trusts. We
6 will collect detailed data on treatment as usual (which will also inform the health economic evaluation).
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16 A trial standard operational procedure has been written for adverse events. We will record the
17 occurrence of any serious adverse events reported to us and also check each patient's medical notes at
18 the end of their participation in the trial. An adverse event is defined by the ISO14155:2011 guidelines
19 for medical device trials as serious if it: a) results in death or, b) is a life-threatening illness or injury or, c)
20 requires hospitalisation or prolongation of existing hospitalisation or, d) results in persistent or
21 significant disability or incapacity or, e) medical or surgical intervention is required to prevent any of the
22 above, f) leads to foetal distress, foetal death or consists of a congenital anomaly or birth defect or, g) is
23 otherwise considered medically significant by the investigator.
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31 Life threatening in the definition of a serious adverse event (SAE) refers to an event in which the subject
32 was at risk of death at the time of the event; it does not refer to an event that hypothetically might have
33 caused death if it were more severe. A planned hospitalization for a pre-existing condition, without a
34 serious deterioration in health, is not considered to be a serious adverse event. The sorts of serious
35 adverse events that can typically happen to this participant group include: deaths, suicide attempts,
36 serious violent incidents, and admissions to hospital.
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42 We will also record any adverse device effects from the VR treatment, which includes adverse events
43 resulting from insufficient or inadequate instructions for use, deployment, installation, or operation, or
44 any malfunction of the software. It also includes any event resulting from user error or intentional
45 misuse.
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51 52 **Analysis**

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54 A full statistical analysis plan will be drafted prior to recruitment beginning and approved before any
55 analysis. We will report data in line with the CONSORT 2010 Statement (37) showing attrition rates and
56 loss to follow-up. The primary analyses will be carried out using the intention-to-treat principle. That is,
57 after randomisation, participants will be analysed according to their allocated intervention arm
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2 irrespective of what intervention they actually receive, and with data available from all participants
3 included in the analysis including those who do not complete therapy.
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6 We will test the primary hypothesis for between-group difference in the primary outcome (O-BAT at 6
7 weeks) using a linear mixed effects model which models the response at 6 weeks, and 26 weeks, with
8 baseline outcome measure, stratification variables, and treatment assignment as fixed effects, with a
9 patient specific random intercept. An interaction between time and randomised group will be fitted as a
10 fixed effect to allow estimation of treatment effect at all time points. The linear mixed effects model will
11 account for missing data assuming data are missing-at-random (MAR). Standard residual diagnostics will
12 be assessed for the appropriateness of the model. $P < 0.05$ will be used as the level of statistical
13 significance. Similar mixed effect models will be used to analyse secondary outcomes. We will recruit
14 around 432 participants into this trial, with 216 in each arm. This sample size takes into consideration a
15 maximum attrition rate of 20%, and provide 90% power to detect a difference of around 8 (standard
16 deviation =23) in O-BAT anxiety score (using the 0-100 scaling from Freeman et al, 2016), from
17 randomisation to 6 weeks (i.e. standardised effect size of 0.35) at 5% level of significance (2-sided).
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27 The mediation analysis will investigate putative mediational factors using modern causal inference
28 methods. This involves using parametric regression models to test for mediation of VRCT on outcome
29 through the putative mediators. Analyses will adjust for baseline measures of the mediator, outcomes,
30 and possible measured confounders. We will include repeated measurement of mediators and outcomes
31 to account for classical measurement error and baseline confounding. The identified moderator variables
32 (negative auditory hallucinations, hopelessness, appearance concerns, and social phobia) will be
33 considered for moderation of the intervention effect on the primary outcome.
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40 A microcosting approach will be used to inform the cost per patient of the VR treatment. The within-trial
41 health economic analysis will describe and compare the costs and outcomes of the two trial arms.
42 Incremental cost per activity gained (primary outcome) will be estimated and the costs and remaining
43 outcomes (utilities, psychiatric symptoms, and wellbeing) assessed separately. This will be informed by a
44 health economics statistical plan written prior to the economic analysis. The health economics will use an
45 NHS and social care services perspective with resource utilisation valued using national cost datasets and
46 EQ-5D-5L data converted into utilities using the UK tariffs. A broader perspective including lost earnings,
47 patient out-of-pocket costs, and criminal justice costs will also be considered. A state-transition model
48 will be developed to extrapolate the within-trial analysis and estimate the incremental costs per quality-
49 adjusted life years (QALYs) gained from using the VR treatment, supported by the trial data, literature
50 reviews, and discussions with clinical experts. Uncertainty around the incremental cost-effectiveness
51 ratio will be reported using the cost-effectiveness plane and the cost-effectiveness acceptability curve.
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60 The maximum reimbursable price of the VR treatment conditional on the willingness to pay per QALY will

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be determined. We will then estimate the affordability to the NHS of a decision to implement the VR treatment. This will take the form of budget impact analysis using a time horizon of 3 years to be consistent with NICE, informed by the results of the trial health economics analysis.

Patient and public involvement

The project has had extensive PPI. Principally this has occurred via The McPin Foundation, a charity that exists to “transform mental health research by putting the lived experience of people affected by mental health problems at the heart of research methods and the research agenda”. A grant-holder is from The McPin Foundation. Three other people with lived experience commented on the grant application and a focus group of people with lived experience was convened so that they could try VR and comment upon the application.

Following the award of the grant there has been considerable PPI. A Lived Experience Advisory Panel (LEAP) has been formed to advise and shape the development of the treatment, the trial protocol, and implementation into services. The LEAP comprises 12 individuals with lived experience of psychosis drawn from each of the study sites (Bristol, Manchester, Newcastle, Nottingham, Oxford). For the protocol they have advised on: the choice of outcome measures, recruitment methods, the format of recruitment materials, and the content and wording of study materials. The LEAP have also reviewed and commented on the trial protocol document. In addition to the LEAP, we have also worked with people with lived experience from each of the trial sites to develop the VR treatment. A number of workshops were held. Through these workshops, people have contributed to the selection of the VR scenarios, the therapeutic tasks within the scenarios, and style of VR coach. These workshops entailed people with lived experience sharing their ideas, reviewing design concepts, and testing these out within VR. In addition to these workshops, there has been weekly input from a smaller group of individuals with lived experience to gain prompt feedback on details of design. There has been detailed user testing of the VR treatment during software development.

PPI will continue throughout the trial. First, LEAP meetings will occur over the course of the trial. The LEAP will advise on any difficulties that occur in the trial. The LEAP will also contribute to the dissemination strategy. Second, there will be a qualitative evaluation of the VR treatment, with the interviews carried out by researchers with lived experience. This work will be run by The McPin Foundation. Third, a McPin staff member sits on fortnightly gameChange review meetings and on the Research Steering Committee (RSC) comprised of senior team members.

Ethics and dissemination

The trial has received Health Research Authority (HRA) and Health and Care Research Wales (HCRW) approval (IRAS 256895, The gameChange trial). The trial received ethical approval from the NHS South Central - Oxford B Research Ethics Committee (19/SC/0075). The results of the trial will be published in a peer-reviewed journal and made open access. An anonymised version of the main outcome data will be available from the trial team on reasonable request after publication of the main results paper.

Trial status

The trial is due to start patient recruitment in July 2019. Recruitment will be for a year until July 2020, with final outcome data collected by January 2021. A trial paper with the outcome results should be submitted for publication around April 2021.

Funding

The trial is funded by the NHS National Institute of Health Research (NIHR) invention for innovation (i4i) programme (Project II-C7-0117-20001). It is also supported by the NIHR Oxford Health Biomedical Research Centre.

Competing interests

DF is a founder and chief clinical officer of Oxford VR, a University of Oxford spin-out company, which has programmed the gameChange treatment, is a collaborator in the research, and will commercialise the treatment. DF holds equity in Oxford VR.

Authors' contributions

DF is the chief investigator, conceived the project, had overall responsibility for the treatment and trial design, and drafted the trial protocol. DC, MC, JG, CH, TK, JM, JL, FW, and L-MY contributed to the overall study design. FW, SL, TK, TC, and DC, contributed to the treatment design. TK, TC, HA, and DR have been responsible for PPI. JM, SB, MC, AB, and DR have advised on treatment implementation. LM-Y is responsible for the statistical analysis. JL and MC are responsible for the health economic analysis. AR and AG contributed to the VR programming and support of the hardware. SL and LR are co-ordinating

1
2 the trial. The trial site leads are DF/FW (Oxford), AM (Manchester), RD (Newcastle), EO'R (Nottingham),
3
4 KC (Bristol). All authors commented on the trial protocol.
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For peer review only

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Table 1. Summary of objectives and assessment measures

	Objectives	Outcome Measures
Primary	Test whether the virtual reality treatment leads to reduction in avoidance and distress in everyday situations.	Oxford - Behavioural Assessment Task (O-BAT).
Secondary	1. Test clinical improvements by treatment type in activity levels, psychiatric symptoms, quality of life.	Activity levels: Actigraphy, time-budget measure. Psychiatric symptoms: Agoraphobia Mobility Inventory-Avoidance, Self-report O-BAT, Revised Green et al Paranoid Thoughts Scale, Paranoia Worries Questionnaire, PHQ-9, Columbia-Suicide Severity Rating Scale. Quality of life: EQ-5D-5L, ReQoL, Questionnaire on the Progress of Recovery.
	2. Determine the cost-effectiveness of the virtual reality treatment.	Client Service Receipt Inventory.
	3. Test mediation of treatment effects by changes in safety beliefs, threat cognitions, and defence (safety-seeking) behaviours.	Cognition and Defence Behaviours Questionnaire and strength of safety beliefs, vulnerability belief, and threat anticipation.
	4. Test moderation of treatment effects (negative auditory hallucinations when outside, hopelessness, appearance concerns, and threat cognitions).	Hallucinations scale; Beck Hopelessness Scale; Body-Esteem Scale for Adolescents and Adults; Cognition and Defence Behaviours Questionnaire.
	5. Assess patient satisfaction with the VR therapy.	Modified version of the Client Satisfaction Questionnaire.

Figure 1. Trial flow diagram

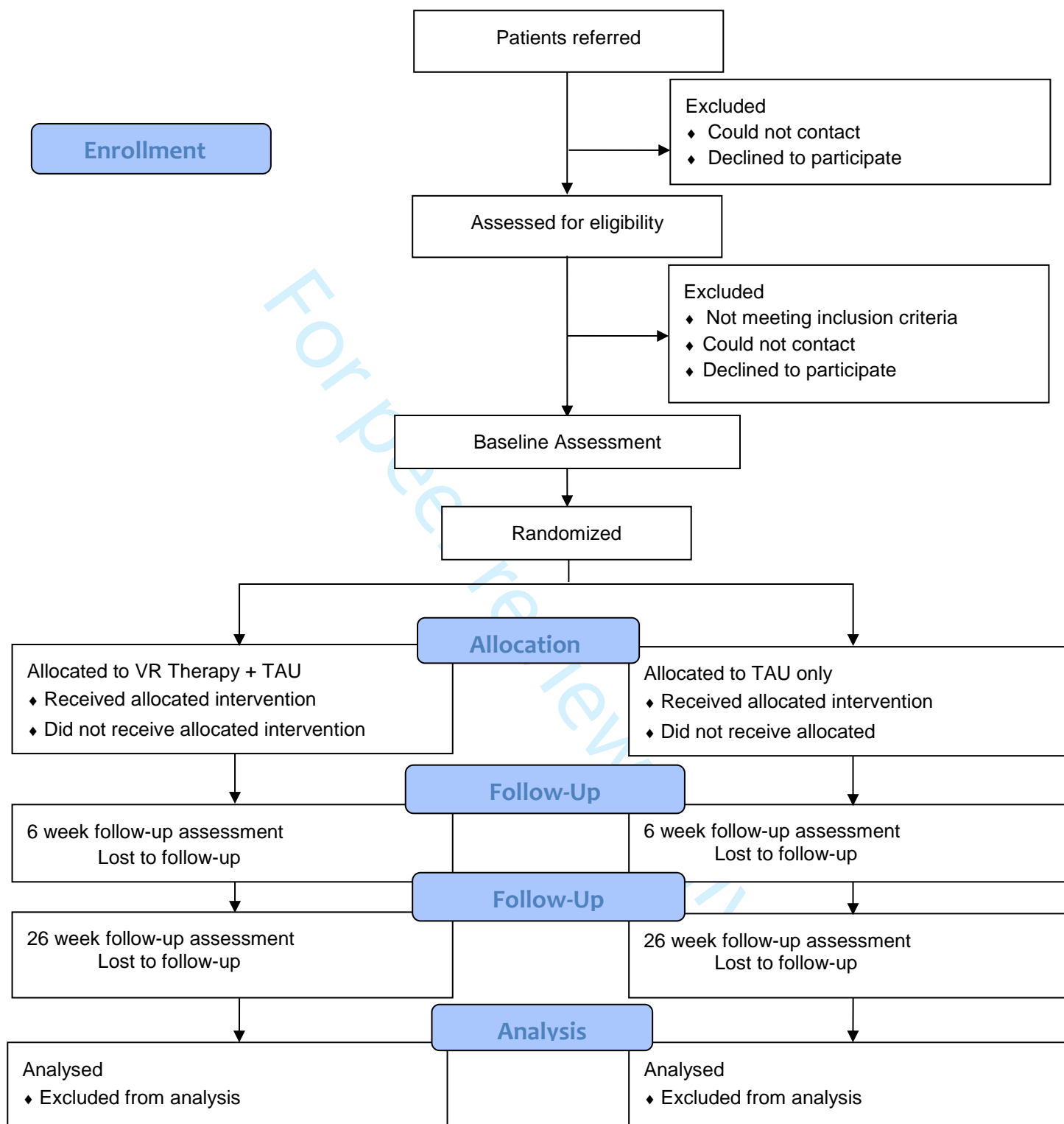
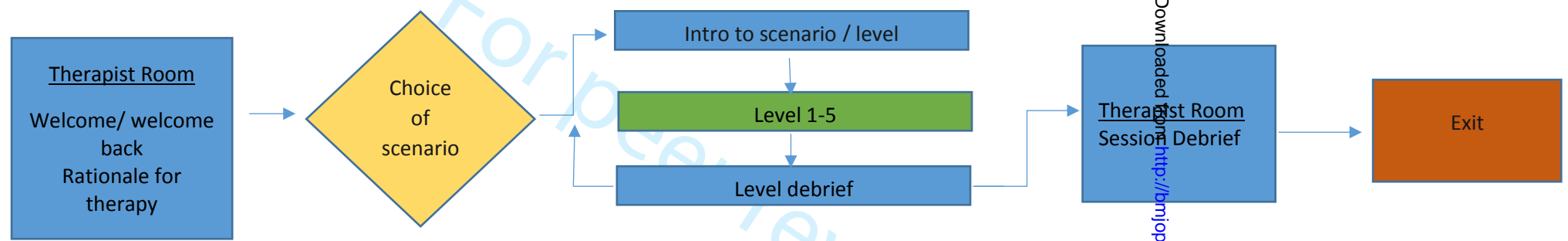


Figure 2. The structure of the VR treatment.



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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

1	Roles and	#5b	Name and contact information for the trial sponsor	n
2	responsibilities:			
3	sponsor contact			
4	information			
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6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n
8	responsibilities:		collection, management, analysis, and interpretation of	
9	sponsor and funder		data; writing of the report; and the decision to submit the	
10			report for publication, including whether they will have	
11			ultimate authority over any of these activities	
12				
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15	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n
16	responsibilities:		centre, steering committee, endpoint adjudication	
17	committees		committee, data management team, and other individuals	
18			or groups overseeing the trial, if applicable (see Item 21a	
19			for data monitoring committee)	
20				
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22				
23				
24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	4-5
27	rationale		undertaking the trial, including summary of relevant	
28			studies (published and unpublished) examining benefits	
29			and harms for each intervention	
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33	Background and	#6b	Explanation for choice of comparators	5
34	rationale: choice of			
35	comparators			
36				
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38	Objectives	#7	Specific objectives or hypotheses	6
39				
40				
41	Trial design	#8	Description of trial design including type of trial (eg,	6
42			parallel group, crossover, factorial, single group),	
43			allocation ratio, and framework (eg, superiority,	
44			equivalence, non-inferiority, exploratory)	
45				
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47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
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53				
54	Study setting	#9	Description of study settings (eg, community clinic,	7,8
55			academic hospital) and list of countries where data will be	
56			collected. Reference to where list of study sites can be	
57				
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		obtained	
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2	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)	8
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9	Interventions: description	#11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
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14	Interventions: modifications	#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)	n
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21	Interventions: adherence	#11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n
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27	Interventions: concomitant care	#11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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31	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	8,9
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42	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)	6
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49	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	12
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55	Recruitment	#15 Strategies for achieving adequate participant enrolment to reach target sample size	7
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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	7
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	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n

Methods: Data collection, management, and analysis

Data collection plan	#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	n
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		protocol	
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3	Data collection plan:	#18b	n
4	retention	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	
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9	Data management	#19	n
10		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	
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17	Statistics: outcomes	#20a	11
18		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	
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23	Statistics: additional analyses	#20b	11
24		Methods for any additional analyses (eg, subgroup and adjusted analyses)	
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27	Statistics: analysis population and missing data	#20c	12
28		Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
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33	Methods: Monitoring		
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36	Data monitoring: formal committee	#21a	6
37		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	
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46	Data monitoring: interim analysis	#21b	n
47		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	
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51	Harms	#22	11
52		Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
53			
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58	Auditing	#23	n
59		Frequency and procedures for auditing trial conduct, if	
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any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
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)	n
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	n
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n
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	n
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n
Dissemination policy: trial results	#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	n
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	n

1 authorship professional writers
 2
 3 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full protocol, 14
 4 reproducible research participant-level dataset, and statistical code
 5

6 Appendices

7
 8 Informed consent [#32](#) Model consent form and other related documentation n
 9 materials given to participants and authorised surrogates
 10
 11

12 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of n
 13 biological specimens for genetic or molecular analysis in
 14 the current trial and for future use in ancillary studies, if
 15 applicable
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19 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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Automated virtual reality (VR) cognitive therapy for patients with psychosis: study protocol for a single-blind parallel group randomised controlled trial (gameChange)

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Automated virtual reality (VR) cognitive therapy for patients with psychosis: study protocol for a single-blind parallel group randomised controlled trial (gameChange)

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ABSTRACT

Introduction: Many patients with psychosis experience everyday social situations as anxiety-provoking. The fears can arise, for example, from paranoia, hallucinations, social anxiety, or negative-self beliefs. The fears lead patients to withdraw from activities, and this isolation leads to a cycle of worsening physical and mental health. Breaking this cycle requires highly active treatment directly in the troubling situations so that patients learn that they can safely and confidently enter them. However patients with psychosis seldom receive such life-changing interventions. To solve this problem we have developed an automated psychological treatment delivered in Virtual Reality (VR). It allows patients to experience computer simulations of the situations that they find anxiety-provoking. A virtual coach guides patients, using cognitive techniques, in how to overcome their fears. Patients are willing to enter VR simulations of anxiety-provoking situations because they know the simulations are not real, but the learning made transfers to the real world.

Methods and analysis: 432 patients with psychosis and anxious avoidance of social situations will be recruited from National Health Service (NHS) secondary care services. In the gameChange trial, they will be randomised (1:1) to the six-session VR cognitive treatment added to treatment as usual or treatment as usual. Assessments will be conducted at 0, 6 (post-treatment), and 26 weeks by a researcher blind to allocation. The primary outcome is avoidance and distress in real-life situations, using a behavioural assessment task, at six weeks. The secondary outcomes are psychiatric symptoms, activity levels, and quality of life. All main analyses will be intention-to-treat. Moderation and mediation will be tested. An economic evaluation will be conducted.

Ethics and dissemination: The trial has received ethical approval from the NHS Health Research Authority (19/SC/0075). A key output will be a high-quality automated VR treatment for patients to overcome anxious avoidance of social situations.

Registration: ISRCTN17308399

Keywords: schizophrenia; psychosis; cognitive therapy; virtual reality; treatment.

Strengths and limitations of this study

- A multi-centre randomized controlled trial of 432 patients with psychosis being seen in National Health Service mental health trusts, which will be the largest trial of VR used to treat a mental health condition.
- Automated delivery of the VR intervention meaning high treatment fidelity and a highly scalable treatment that could greatly increase access to psychological therapy.
- Mediation built into the treatment design can test whether the treatment works as hypothesized.
- The control condition is treatment as usual meaning that it cannot be definitively established which VR treatment elements produce clinical change.
- It is impossible to blind patients to the treatment allocation, which could introduce bias into the treatment effect estimation.

BACKGROUND

Rationale

Too many patients with psychosis, despite standard treatment, become isolated and inactive, with negative effects on both mental and physical health. Approximately 80% of patients with schizophrenia experience an episode of depression (1). Physical activity levels in patients with schizophrenia are reduced on average by approximately two thirds (2). Over 90% of patients with schizophrenia are unemployed and spend “less time in functional but also in social and leisure activities and more time resting and ‘doing nothing’ compared to the general population” (3). Life expectancy is on average 14.5 years shorter (4), due to largely preventable conditions such as high blood pressure, diabetes, and heart disease. Partly this physical ill health reflects unhealthy lifestyles including inactivity.

Our view is that a substantial part of this inactivity arises from avoidance due to anxiety. In a clinical assessment study of 1800 patients with non-affective psychosis attending NHS mental health services, two-thirds of the patients had levels of anxious avoidance equivalent to patients diagnosed with agoraphobia (5). The anxiety in patients with psychosis can arise from a number of sources: fears that others will harm them, voices telling them of danger, social anxiety fears of humiliation and rejection, and negative beliefs about the self that cause a lack of confidence and a sense of vulnerability. But withdrawal from activities because of anxiety need not be inevitable. Appropriate treatment, as seen in the anxiety disorders (6), can produce excellent outcomes. Such treatment involves identifying fearful thoughts and the safety-seeking (or defence) behaviours that maintain those cognitions by preventing receipt and processing of disconfirmatory evidence. The thoughts must then be tested in behavioural experiments in the troubling situations while the defence behaviours are dropped (7). However, there is a dearth of therapists to carry out this skilled work for patients with schizophrenia. It is well-recognised that there is considerable under-provision of psychological therapy for patients with schizophrenia (8). There is the additional problem that the sometimes very fearful beliefs of patients with psychosis mean that they can be much less likely to engage in behavioural experiments in the real world before their fears have been lessened by other means. Our solution is the provision of automated psychological therapy using Virtual Reality (VR).

Virtual reality (interactive computer-generated environments) has been used since the early 1990's to treat anxiety (9). Meta-analyses indicate that VR treatments for anxiety disorders can produce large treatment effects (10) that generalise to the real world (11). Previous uses of VR for mental health problems have depended on a therapist providing the psychological therapy (12). In a trial of one hundred patients with a fear of heights, we have shown that the provision of cognitive therapy can be automated using VR by the incorporation of a virtual coach (13). The treatment effect sizes in this trial

1
2 were very large (effect size Cohen's $d=2.0$; the number of patients needed to treat (NNT) to at least halve
3 fear of heights was 1.3), and better than expected from face-to-face therapy. Automated treatment has
4 the potential to be scalable, removing a key cause of the highly limited access to psychological therapy
5 for patients with psychosis.
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10 VR may also be especially suited to the difficulties of patients with psychosis. Patients with strong fears
11 are much more likely to test out their fear expectations in VR because they know it is a simulation but
12 the learning that they make then transfers to the real world. VR treatment can also include engaging
13 tasks that make the treatment experience much more pleasurable. A graded approach can easily be
14 applied in VR, allowing the individual to repeatedly experience the situations they find difficult and make
15 new learning. Our view is that VR treatments have the potential to be faster, more efficacious, and
16 appealing to patients than traditional face-to-face approaches. We conducted a first test of VR to treat
17 persecutory delusions in patients with psychosis (14). Just thirty minutes in graded VR environments,
18 with the psychological advice provided by a therapist, led to a large reduction in distress in real-world
19 situations (e.g. going into a shop). VR has been shown to be safe to use with patients with psychosis (15).
20 A recent randomised controlled trial of over one hundred patients with psychosis showed that 16 one-
21 hour sessions with VR environments and a therapist who administered CBT techniques led at follow-up
22 to a moderate increase in time spent with other people as assessed by an experience sampling method
23 (16). In the THRIVE trial our team is currently testing a four-session automated VR cognitive treatment
24 for patients specifically with persecutory delusions (ISRCTN12497310) (17).
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36 In the gameChange project (www.gameChangeVR.com), we have recently developed - using a socially-
37 inclusive design process - a new automated VR cognitive treatment for patients for psychosis having
38 difficulties being in everyday social situations due to anxiety. It is designed to be easy to use, engaging
39 for patients and staff, and delivered with the latest consumer equipment. Therefore this VR treatment
40 has the potential to be widely implemented in treatment services. Psychological treatment that involves
41 direct coaching in the situations that trouble patients with psychosis is rarely available in mental health
42 services. Therefore we set out to determine the *in toto* effects of adding the VR treatment to treatment
43 as usual. This entails a test that randomises patients to receive the VR treatment in addition to usual care
44 or to usual care. We aim to determine the clinical effects on real-world performance, activity levels,
45 psychiatric symptoms, and quality of life.
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56 **Aims and hypotheses**

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2 The primary research question we aim to test is: Does automated VR cognitive treatment added to
3 treatment as usual, compared to treatment as usual alone, lead to a post-treatment reduction in real
4 world avoidance and distress for patients with psychosis attending NHS mental health services?
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8 Our primary hypothesis is that:
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11 1. Compared to treatment as usual, VR cognitive therapy added to treatment as usual will reduce
12 avoidance and distress of real world situations (post treatment).
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15 Our secondary hypotheses are:
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18 1. Compared to treatment as usual, VR cognitive therapy added to treatment as usual will reduce
19 psychiatric symptoms (paranoia, anxious avoidance, depression, suicidal ideation), increase activity, and
20 improve quality of life (post-treatment).
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23 2. Treatment effects will be maintained at follow-up (6 months).
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26 3. The mediators of VR treatment will be safety beliefs, threat cognitions, and defence behaviours.
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29 4. Treatment effects will be moderated by the occurrence of negative auditory hallucinations in social
30 situations, hopelessness, appearance concerns, and threat cognitions.
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33 We also include a health economic evaluation of the VR treatment. It will focus on determining the cost
34 of the VR treatment using a microcosting approach, performing a within-trial cost-effectiveness analysis,
35 and extrapolating the within-trial results to a 10 years horizon using a state-transition model.
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43 **METHODS AND ANALYSIS**

44 45 46 47 48 **Trial design and flow chart**

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51 The design is a multicentre, parallel group randomised controlled trial with single blind assessment to
52 test whether the automated VR cognitive treatment added to treatment as usual, compared to
53 treatment as usual alone, leads to a post-treatment reduction in real world distress and avoidance for
54 patients with psychosis attending NHS mental health services. Treatment as usual will be measured but
55 remain unchanged in both groups. Assessments will be carried out at 0 (baseline), 6 (post treatment),
56 and 26 (follow-up) weeks by a researcher blind to treatment allocation. A summary of the trial design
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3 can be seen in Figure 1. The trial is prospectively registered with the ISRCTN registry: ISRCTN17308399.
4 There is a Data Monitoring and Ethics Committee (DMEC).
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18 **Randomisation, blinding, and code-breaking**

19 Participants will be randomised once they have completed the baseline assessment. Participants will be
20 allocated to one of the trial arms using a 1:1 allocation ratio. Randomisation will be carried out by a
21 validated online system, Sortition, designed by the University of Oxford Primary Care Clinical Trials Unit.
22 Randomisation using a permuted blocks algorithm, with randomly varying block size, will be stratified by
23 site (Bristol/Manchester/Newcastle/Nottingham/Oxford) and service type (in-patient/early
24 intervention/community mental health team).
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30 The research assessors will be blinded to group allocation, but the patients and staff member present
31 will not be (they cannot be blinded to whether psychological intervention is delivered or received). If an
32 allocation is revealed between assessment sessions, this is logged by the trial coordinator and re-blinding
33 will occur using another assessor.
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41 **Participants**

42 The trial participants will be patients with psychosis and self-reported difficulties going outside among
43 other people due to anxiety. The principal method of recruitment will be via seeking referrals to the trial
44 from the relevant clinical teams (adult community mental health teams; early intervention services, and
45 inpatient units) in the participating mental health trusts. The trial centres will be Bristol, Manchester,
46 Newcastle, Nottingham, Oxford, with recruitment from local NHS mental health trusts. With the approval
47 of the clinical team, patients interested in taking part will then be approached by the research team,
48 given information about the trial, and screening conducted. Our Lived Experience Advisory Panel (LEAP)
49 have also emphasised the importance of patients of the participating trusts self-initiating referral to the
50 trials, in order to minimise the chances that particular patients are overlooked by clinical teams or the
51 clinician was not present at a referral meeting. Hence we will also advertise the study and patients within
52 participating trusts will be able to self-refer for a screening to take part in the study. However, in all
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instances we will also seek to confirm that a member of the clinical team gives approval for a patient to enter the trial. Informed consent will be obtained from all patients before participation.

Inclusion criteria:

- Adults aged 16 years or older;
- Attending a NHS mental health trust for the treatment of psychosis;
- Clinical diagnosis of schizophrenia spectrum psychosis (F20-29) or an affective diagnosis with psychotic symptoms (F31.2, 31.5, 32.3, 33.3) (ICD-10) (18);
- Having self-reported difficulties going outside their home primarily due to anxiety that they would like treated;
- And participant is willing and able to give informed consent for participation in the trial.

Exclusion criteria:

- Unable to attempt an Oxford-Behavioural Assessment Task (O-BAT) (the primary outcome measure) at baseline (e.g. due to being unpermitted to leave a psychiatric ward);
- Photosensitive epilepsy;
- Significant visual, auditory, or balance impairment;
- Current receipt of another intensive psychological therapy (or about to start it within the 6 week trial therapy window);
- Insufficient comprehension of English;
- In forensic settings or Psychiatric Intensive Care Unit (PICU);
- Organic syndrome;
- Primary diagnosis of alcohol or substance disorder or personality disorder;
- Significant learning disability;
- Or current active suicidal plans.

Assessments

Basic demographic and clinical data will be collected (e.g. age, gender, ethnicity, clinical diagnosis, medication use). The primary outcome, avoidance and distress of everyday situations as measured by the Oxford-Behavioural Avoidance Task (O-BAT) (adapted from 14), will be measured at baseline, six weeks, and 26 weeks. The O-BAT comprises a personalised hierarchy of five real world tasks that the patient finds difficult due to anxiety. The person then tries to carry out the hierarchy, rating anxiety at each step achieved, and stopping when they decide the anxiety is too great. This therefore produces an avoidance score (0-5, with higher scores indicating lower avoidance) and a distress score (0-10, with

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higher scores indicating greater distress) for each level. All assessors receive training in administering the O-BAT and the manual. The initial O-BAT for each participant is reviewed by a clinician. A detailed assessment of social avoidance is first carried out using both a semi-structured interview and a self-report measure of social avoidance, the SR-OBAT (19). This identifies the everyday situations and tasks that are anxiety-provoking for the participant, and provides a predicted level of distress for each. Based on this, the five-step personalized hierarchy is developed. A hierarchy can be constructed within one or a number of feared situations (e.g. standing on the front door step for three minutes, standing outside the front gate for three minutes, walking down the local street, walking to the local shop, buying something in the shop). The hierarchy is set up so that it is likely that the patient may only complete a small number of steps at baseline. Secondary outcomes will also be assessed at all three time-points. Anxious avoidance (AMI-A (20) and self-report version of the O-BAT (19)), suicidal ideation (Columbia Suicide Severity Rating Scale) (21), overall paranoia (R-GPTS) (22, 23), paranoia worries (Paranoia Worries Questionnaire) (24), and levels of depression (PHQ-9) (25) will be assessed. Activity levels will be assessed using actigraphy (over 7 days), complemented with a time-budget assessing meaningful activity (26). The EQ-5D-5L (27) and ReQoI (28) will assess quality of life. Additionally, quality of life will be assessed using the Questionnaire about the Process of Recovery (QPR) (29). For mediation, we will assess, at all time-points, threat cognitions and use of defence behaviours (CDBQ) (30) and strength of safety, vulnerability and threat anticipation beliefs (31). Moderators will be assessed at baseline only by a brief assessment of negative hallucinations when outside (32), the Beck Hopelessness Scale (33), the Body-Esteem Scale for Adolescents and Adults (34), and the Cognition and Defence Behaviours Questionnaire (30). We will record service use, and other relevant health economic data, using the Client Service Receipt Inventory (35). A summary of the measures is provided in Table 1.

Insert Table 1 about here

The VR psychological treatment

The gameChange VR treatment is a virtual-reality application recommended for adults (16+) who have anxieties when outside in everyday social situations. This software is intended to reduce anxieties around

1
2 other people and therefore to help participants feel safer and more comfortable around people. The aim
3 for the outcome is that patients feel more able to go outside into everyday situations. The treatment was
4 programmed by the University of Oxford spin-out company Oxford VR (www.oxfordvr.org). The
5 treatment is a CE marked Class I Active Medical Device- Z301 (Standalone Software), in conformity with
6 the essential requirements and provisions of the EC Directive 93/42/EEC (Medical Devices).
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11 A mental health professional, most likely a peer support worker or psychology assistant, will be in the
12 room when the treatment is given. This person will help the patient put on the VR headset and start the
13 programme. The staff member will also encourage the person to apply the learning from VR into the real
14 world through the setting up of homework tasks to be carried out between sessions. The applications
15 will run through the Steam software application on a laptop computer connected to a head-mounted
16 display and accessories. All hardware is already commercially available and has not been modified for the
17 trial. Satisfaction will be assessed after completion of the last treatment session using a modified version
18 of the Client Satisfaction Questionnaire (36).
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26 The VR Cognitive Therapy (VRCT/gameChange treatment) aims for patients to test their fear
27 expectations around other people in order to relearn safety. The treatment is not designed as exposure
28 therapy (participants are not asked to remain in situations until anxiety reduces) but as repeated
29 behavioural experiment tests (to learn that they are safer than they had thought). The treatment is
30 designed to be delivered in approximately 6 sessions of thirty minutes. Three sessions will be considered
31 the minimum (adherent) dose of therapy. However participants can proceed at their own pace, meaning
32 that a fewer or greater number of sessions is allowed. The participant typically stands, and is able to walk
33 a few paces in the scenarios. A virtual coach guides the person through the treatment, including
34 encouraging the dropping of defence behaviours, and elicits feedback to tailor the progression of the
35 treatment. When first entering VR, the patient goes into the coach's virtual office and is guided in how to
36 use VR (i.e. the basic functions). At the beginning of the first session, the virtual coach explains the
37 rationale behind the treatment, and the participant selects which one of six virtual reality situations that
38 they would like to begin in. The six virtual reality scenarios are a: café, GP waiting room, pub, bus, street
39 scene, and newsagent. Each scenario has five levels of difficulty (e.g. the number and proximity of people
40 in the social situation increases) and participants work their way through each level of difficulty. There
41 are (therapeutic) game type tasks within a number of the levels (that are designed to help the person
42 drop defence behaviours and make new learning). The participant can choose a different scenario in
43 each session or repeat a previous situation (and level). Throughout the sessions, participants' responses
44 to questions from the virtual coach are given by means of gripping a virtual globe. Belief ratings are
45 repeated within VR at the beginning and end of each treatment session. Figure 2 provides a summary of
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1
2 the treatment design. A video about the gameChange treatment can be viewed here:
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4 <https://www.youtube.com/watch?v=D31wodNAMZA&feature=youtu.be>
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19 **Control condition**

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21 Participants who are allocated to the control arm will continue to receive their usual care. No additional
22 interventions will be offered by the research team. Treatment as usual for the participants within this
23 trial will typically consist of long term prescription of psychiatric medications, and meetings with a
24 mental health practitioner. Treatment as usual will vary across individuals and mental health trusts. We
25 will collect detailed data on treatment as usual (which will also inform the health economic evaluation).
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32 **Adverse events**

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34 A trial standard operational procedure has been written for adverse events. We will record the
35 occurrence of any serious adverse events reported to us and also check each patient's medical notes at
36 the end of their participation in the trial. An adverse event is defined by the ISO14155:2011 guidelines
37 for medical device trials as serious if it: a) results in death or, b) is a life-threatening illness or injury or, c)
38 requires hospitalisation or prolongation of existing hospitalisation or, d) results in persistent or
39 significant disability or incapacity or, e) medical or surgical intervention is required to prevent any of the
40 above, f) leads to foetal distress, foetal death or consists of a congenital anomaly or birth defect or, g) is
41 otherwise considered medically significant by the investigator.
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50 Life threatening in the definition of a serious adverse event (SAE) refers to an event in which the subject
51 was at risk of death at the time of the event; it does not refer to an event that hypothetically might have
52 caused death if it were more severe. A planned hospitalization for a pre-existing condition, without a
53 serious deterioration in health, is not considered to be a serious adverse event. The sorts of serious
54 adverse events that can typically happen to this participant group include: deaths, suicide attempts,
55 serious violent incidents, and admissions to hospital.
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2 We will also record any adverse device effects from the VR treatment, which includes adverse events
3 resulting from insufficient or inadequate instructions for use, deployment, installation, or operation, or
4 any malfunction of the software. It also includes any event resulting from user error or intentional
5 misuse.
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10 11 12 **Analysis**

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15 A full statistical analysis plan will be drafted prior to recruitment beginning and approved before any
16 analysis. We will report data in line with the CONSORT 2010 Statement (37) showing attrition rates and
17 loss to follow-up. The primary analyses will be carried out using the intention-to-treat principle. That is,
18 after randomisation, participants will be analysed according to their allocated intervention arm
19 irrespective of what intervention they actually receive, and with data available from all participants
20 included in the analysis including those who do not complete therapy. The outcome analyses will be
21 conducted by statisticians in the University of Oxford Primary Care Clinical Trials Unit.
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27 We will test the primary hypothesis for between-group difference in the primary outcome (O-BAT at 6
28 weeks) using a linear mixed effects model which models the response at 6 weeks, and 26 weeks, with
29 baseline outcome measure, stratification variables, and treatment assignment as fixed effects, with a
30 patient specific random intercept. An interaction between time and randomised group will be fitted as a
31 fixed effect to allow estimation of treatment effect at all time points. The linear mixed effects model will
32 account for missing data assuming data are missing-at-random (MAR). Standard residual diagnostics will
33 be assessed for the appropriateness of the model. $P < 0.05$ will be used as the level of statistical
34 significance. Similar mixed effect models will be used to analyse secondary outcomes. We will recruit
35 around 432 participants into this trial, with 216 in each arm. This sample size takes into consideration a
36 maximum attrition rate of 20%, and provide 90% power to detect a difference of around 8 (standard
37 deviation = 23) in O-BAT anxiety score (using the 0-100 scaling from Freeman et al, 2016 (14)), from
38 randomisation to 6 weeks (i.e. standardised effect size of 0.35) at 5% level of significance (2-sided).
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48 The mediation analysis will investigate putative mediational factors using modern causal inference
49 methods. This involves using parametric regression models to test for mediation of VRCT on outcome
50 through the putative mediators. Analyses will adjust for baseline measures of the mediator, outcomes,
51 and possible measured confounders. We will include repeated measurement of mediators and outcomes
52 to account for classical measurement error and baseline confounding. The identified moderator variables
53 (negative auditory hallucinations, hopelessness, appearance concerns, and social phobia) will be
54 considered for moderation of the intervention effect on the primary outcome.
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2 A microcosting approach will be used to inform the cost per patient of the VR treatment. The within-trial
3 health economic analysis will describe and compare the costs and outcomes of the two trial arms.
4 Incremental cost per activity gained (primary outcome) will be estimated and the costs and remaining
5 outcomes (utilities, psychiatric symptoms, and wellbeing) assessed separately. This will be informed by a
6 health economics statistical plan written prior to the economic analysis. The health economics will use an
7 NHS and social care services perspective with resource utilisation valued using national cost datasets and
8 EQ-5D-5L data converted into utilities using the UK tariffs. A broader perspective including lost earnings,
9 patient out-of-pocket costs, and criminal justice costs will also be considered. A state-transition model
10 will be developed to extrapolate the within-trial analysis and estimate the incremental costs per quality-
11 adjusted life years (QALYs) gained from using the VR treatment, supported by the trial data, literature
12 reviews, and discussions with clinical experts. Uncertainty around the incremental cost-effectiveness
13 ratio will be reported using the cost-effectiveness plane and the cost-effectiveness acceptability curve.
14 The maximum reimbursable price of the VR treatment conditional on the willingness to pay per QALY will
15 be determined. We will then estimate the affordability to the NHS of a decision to implement the VR
16 treatment. This will take the form of budget impact analysis using a time horizon of 3 years to be
17 consistent with NICE, informed by the results of the trial health economics analysis.
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33 **Patient and public involvement**

34 The project has had extensive PPI. Principally this has occurred via The McPin Foundation, a charity that
35 exists to “transform mental health research by putting the lived experience of people affected by mental
36 health problems at the heart of research methods and the research agenda”. A grant-holder is from The
37 McPin Foundation. Three other people with lived experience commented on the grant application and a
38 focus group of people with lived experience was convened so that they could try VR and comment upon
39 the application.
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45 Following the award of the grant there has been considerable PPI. A Lived Experience Advisory Panel
46 (LEAP) has been formed to advise and shape the development of the treatment, the trial protocol, and
47 implementation into services. The LEAP comprises 12 individuals with lived experience of psychosis
48 drawn from each of the study sites (Bristol, Manchester, Newcastle, Nottingham, Oxford). For the
49 protocol they have advised on: the choice of outcome measures, recruitment methods, the format of
50 recruitment materials, and the content and wording of study materials. The LEAP have also reviewed and
51 commented on the trial protocol document. In addition to the LEAP, we have also worked with people
52 with lived experience from each of the trial sites to develop the VR treatment. A number of workshops
53 were held. Through these workshops, people have contributed to the selection of the VR scenarios, the
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2 therapeutic tasks within the scenarios, and style of VR coach. These workshops entailed people with
3 lived experience sharing their ideas, reviewing design concepts, and testing these out within VR. In
4 addition to these workshops, there has been weekly input from a smaller group of individuals with lived
5 experience to gain prompt feedback on details of design. There has been detailed user testing of the VR
6 treatment during software development.
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11 PPI will continue throughout the trial. First, LEAP meetings will occur over the course of the trial. The
12 LEAP will advise on any difficulties that occur in the trial. The LEAP will also contribute to the
13 dissemination strategy. Second, there will be a qualitative evaluation of the VR treatment, with the
14 interviews carried out by researchers with lived experience. This work will be run by The McPin
15 Foundation. Third, a McPin staff member sits on fortnightly gameChange review meetings and on the
16 Research Steering Committee (RSC) comprised of senior team members.
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25 **Ethics and dissemination**

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27 The trial has received Health Research Authority (HRA) and Health and Care Research Wales (HCRW)
28 approval (IRAS 256895, The gameChange trial). The trial received ethical approval from the NHS South
29 Central - Oxford B Research Ethics Committee (19/SC/0075). The results of the trial will be published in a
30 peer-reviewed journal and made open access. An anonymised version of the main outcome data will be
31 available from the trial team on reasonable request after publication of the main results paper.
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39 **Trial status**

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41 The trial is due to start patient recruitment in July 2019. Recruitment will be for a year until July 2020,
42 with final outcome data collected by January 2021. A trial paper with the outcome results should be
43 submitted for publication around April 2021.
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50 **Funding**

51
52 The trial is funded by the NHS National Institute of Health Research (NIHR) invention for innovation (i4i)
53 programme (Project II-C7-0117-20001). It is also supported by the NIHR Oxford Health Biomedical
54 Research Centre.
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Competing interests

DF is a founder and chief clinical officer of Oxford VR, a University of Oxford spin-out company, which has programmed the gameChange treatment, is a collaborator in the research, and will commercialise the treatment. DF holds equity in Oxford VR.

Authors' contributions

DF is the chief investigator, conceived the project, had overall responsibility for the treatment design and the trial design, and drafted the trial protocol. DC, MC, JG, CH, TK, JM, JL, FW, and L-MY contributed to the overall study design. FW, SL, TK, TC, and DC, contributed to the treatment design. TK, TC, HA, and DR have been responsible for PPI. JM, SB, MC, AB, and DR have advised on treatment implementation. LM-Y is responsible for the statistical analysis. JL and MC are responsible for the health economic analysis. AR and AG contributed to the VR programming and support of the hardware. SL and LR are co-ordinating the trial. The trial site leads are DF/FW (Oxford), AM (Manchester), RD (Newcastle), EO'R (Nottingham), KC (Bristol). All authors commented on the trial protocol.

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Table 1. Summary of objectives and assessment measures

	Objectives	Outcome Measures
Primary	Test whether the virtual reality treatment leads to reduction in avoidance and distress in everyday situations.	Oxford - Behavioural Assessment Task (O-BAT).
Secondary	1. Test clinical improvements by treatment type in activity levels, psychiatric symptoms, quality of life.	Activity levels: Actigraphy, time-budget measure. Psychiatric symptoms: Agoraphobia Mobility Inventory-Avoidance, Self-report O-BAT, Revised Green et al Paranoid Thoughts Scale, Paranoia Worries Questionnaire, PHQ-9, Columbia-Suicide Severity Rating Scale. Quality of life: EQ-5D-5L, ReQoL, Questionnaire on the Progress of Recovery.
	2. Determine the cost-effectiveness of the virtual reality treatment.	Client Service Receipt Inventory.
	3. Test mediation of treatment effects by changes in safety beliefs, threat cognitions, and defence (safety-seeking) behaviours.	Cognition and Defence Behaviours Questionnaire and strength of safety beliefs, vulnerability belief, and threat anticipation.
	4. Test moderation of treatment effects (negative auditory hallucinations when outside, hopelessness, appearance concerns, and threat cognitions).	Hallucinations scale; Beck Hopelessness Scale; Body-Esteem Scale for Adolescents and Adults; Cognition and Defence Behaviours Questionnaire.
	5. Assess patient satisfaction with the VR therapy.	Modified version of the Client Satisfaction Questionnaire.

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2 Figure 1. Trial flow diagram.
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4 Figure 2. The structure of the VR treatment.
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For peer review only

Figure 1. Trial flow diagram

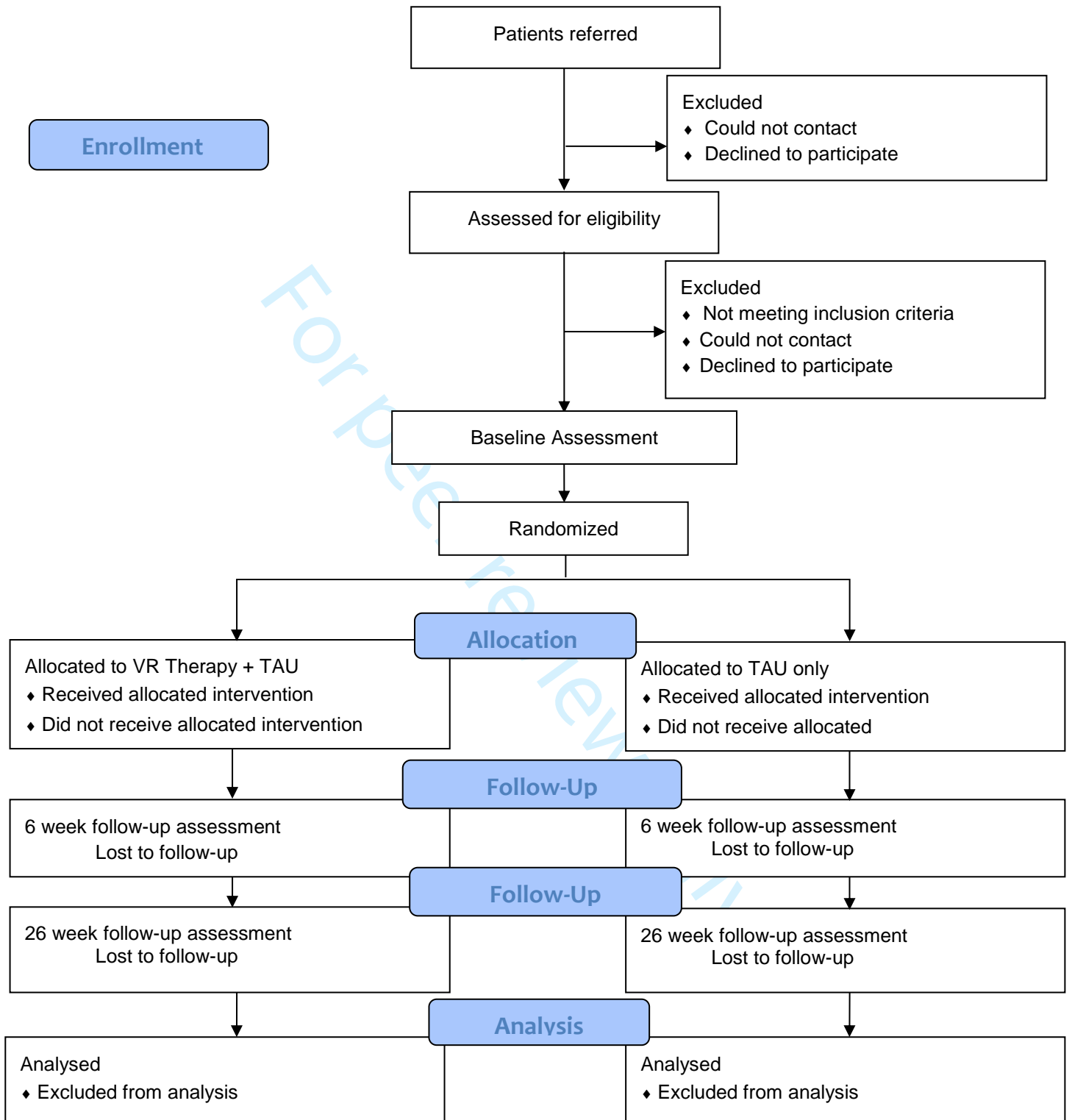
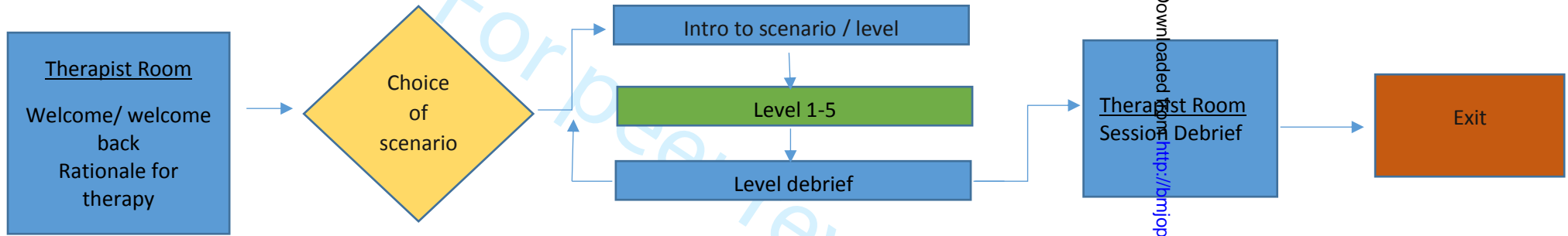


Figure 2. The structure of the VR treatment.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

1	Roles and	#5b	Name and contact information for the trial sponsor	n
2	responsibilities:			
3	sponsor contact			
4	information			
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6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n
8	responsibilities:		collection, management, analysis, and interpretation of	
9	sponsor and funder		data; writing of the report; and the decision to submit the	
10			report for publication, including whether they will have	
11			ultimate authority over any of these activities	
12				
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15	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n
16	responsibilities:		centre, steering committee, endpoint adjudication	
17	committees		committee, data management team, and other individuals	
18			or groups overseeing the trial, if applicable (see Item 21a	
19			for data monitoring committee)	
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	4-5
27	rationale		undertaking the trial, including summary of relevant	
28			studies (published and unpublished) examining benefits	
29			and harms for each intervention	
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32				
33	Background and	#6b	Explanation for choice of comparators	5
34	rationale: choice of			
35	comparators			
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38	Objectives	#7	Specific objectives or hypotheses	6
39				
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41	Trial design	#8	Description of trial design including type of trial (eg,	6
42			parallel group, crossover, factorial, single group),	
43			allocation ratio, and framework (eg, superiority,	
44			equivalence, non-inferiority, exploratory)	
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48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
53				
54	Study setting	#9	Description of study settings (eg, community clinic,	7,8
55			academic hospital) and list of countries where data will be	
56			collected. Reference to where list of study sites can be	
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		obtained	
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2	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)	8
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9	Interventions: description	#11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9,10
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14	Interventions: modifications	#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)	n
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21	Interventions: adherence	#11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n
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27	Interventions: concomitant care	#11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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31	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	8,9
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42	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)	6
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49	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	12
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55	Recruitment	#15 Strategies for achieving adequate participant enrolment to reach target sample size	7
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1 Methods:

2 Assignment of 3 interventions (for 4 controlled trials) 5 6

7 Allocation: sequence 8 generation	#16a	Method of generating the allocation sequence (eg, 9 computer-generated random numbers), and list of any 10 factors for stratification. To reduce predictability of a 11 random sequence, details of any planned restriction (eg, 12 blocking) should be provided in a separate document that 13 is unavailable to those who enrol participants or assign 14 interventions 15	7
16 Allocation 17 concealment 18 mechanism	#16b	Mechanism of implementing the allocation sequence (eg, 19 central telephone; sequentially numbered, opaque, sealed 20 envelopes), describing any steps to conceal the sequence 21 until interventions are assigned 22	7
23 Allocation: 24 implementation	#16c	Who will generate the allocation sequence, who will enrol 25 participants, and who will assign participants to 26 interventions 27	7
28 Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, 29 trial participants, care providers, outcome assessors, data 30 analysts), and how 31	7
32 Blinding (masking): 33 emergency unblinding	#17b	If blinded, circumstances under which unblinding is 34 permissible, and procedure for revealing a participant's 35 allocated intervention during the trial 36	n

37 Methods: Data 38 collection, 39 management, and 40 analysis

41 Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, 42 and other trial data, including any related processes to 43 promote data quality (eg, duplicate measurements, 44 training of assessors) and a description of study 45 instruments (eg, questionnaires, laboratory tests) along 46 with their reliability and validity, if known. Reference to 47 where data collection forms can be found, if not in the 48	n
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		protocol	
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3	Data collection plan:	#18b	Plans to promote participant retention and complete
4	retention		follow-up, including list of any outcome data to be
5			collected for participants who discontinue or deviate from
6			intervention protocols
7			
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9	Data management	#19	Plans for data entry, coding, security, and storage,
10			including any related processes to promote data quality
11			(eg, double data entry; range checks for data values).
12			Reference to where details of data management
13			procedures can be found, if not in the protocol
14			
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16			
17	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
18			outcomes. Reference to where other details of the
19			statistical analysis plan can be found, if not in the protocol
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23	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and
24	analyses		adjusted analyses)
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26			
27	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-
28	population and		adherence (eg, as randomised analysis), and any
29	missing data		statistical methods to handle missing data (eg, multiple
30			imputation)
31			
32			
33	Methods: Monitoring		
34			
35			
36	Data monitoring:	#21a	Composition of data monitoring committee (DMC);
37	formal committee		summary of its role and reporting structure; statement of
38			whether it is independent from the sponsor and competing
39			interests; and reference to where further details about its
40			charter can be found, if not in the protocol. Alternatively,
41			an explanation of why a DMC is not needed
42			
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46	Data monitoring:	#21b	Description of any interim analyses and stopping
47	interim analysis		guidelines, including who will have access to these interim
48			results and make the final decision to terminate the trial
49			
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51	Harms	#22	Plans for collecting, assessing, reporting, and managing
52			solicited and spontaneously reported adverse events and
53			other unintended effects of trial interventions or trial
54			conduct
55			
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58	Auditing	#23	Frequency and procedures for auditing trial conduct, if
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any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
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)	n
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	n
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n
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	n
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n
Dissemination policy: trial results	#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	n
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	n

1 authorship professional writers
 2
 3 Dissemination policy: [#31c](#) Plans, if any, for granting public access to the full protocol, 14
 4 reproducible research participant-level dataset, and statistical code
 5

6 Appendices

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 8 Informed consent [#32](#) Model consent form and other related documentation n
 9 materials given to participants and authorised surrogates
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12 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage of n
 13 biological specimens for genetic or molecular analysis in
 14 the current trial and for future use in ancillary studies, if
 15 applicable
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 17
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19 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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 21 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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