STUDY PROTOCOL

1. FULL TITLE

Virtual Reality Supported Therapy for the Negative Symptoms of Psychosis

2. TRIAL INFORMATION

Trial Identifiers

REC ID:	260511		
REC reference:	19/LO/0830		
Clinicaltrials.gov registration	NCT03995420		
Protocol Version Number:	1.2	Date:	30/09/2020

Sponsor

Name:	Professor Reza Razavi
Address:	King's College London, Room 5.31, James Clerk Maxwell Building, 57, Waterloo Road
Telephone:	02078483224
Fax:	
Email:	reza.razavi@kcl.ac.uk

Co-Sponsor

Name:	Dr Carol Cooley
Address:	R&D Governance Manager Joint R&D Office of South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience (IoPPN), R&D Office (POO5), Room W1.13, IoPPN Main Building, King's College London, De Crespigny Park, London SE5 8AF
Telephone:	Tel: 020 7848 0339
Email:	slam-ioppn.research@kcl.ac.uk

Chief Investigator

Name:	Dr Matteo Cella
Address:	Department of Psychology Institute of Psychiatry, Psychology & Neuroscience, De Crespigny Park, London SE5 8AF
Telephone:	020 7848 5001
Email:	matteo.cella@kcl.ac.uk

Name and address of Co-Investigator(s), Statistician, Therapy Service, Laboratories etc

Name:	Dr Lucia Valmaggia
Position/ Role:	Reader, Clinical Psychologist
Address:	Department of Psychology Institute of Psychiatry, Psychology & Neuroscience, De Crespigny Park, London SE5 8AF
Telephone:	02078485003
Fax:	
Email:	Lucia.valmaggia@klc.ac.uk

Name:	Prof Daniel Shal
Position/ Role:	Professor of Medical Statistics and Statistical Learning
Address:	Department of Biostatistics and Health Informatics Institute of Psychiatry, Psychology & Neuroscience, King's College London De Crespigny Park, London SE5 8AF
Telephone:	0207 848 0964
Fax:	
Email:	daniel.r.stahl@kcl.ac.uk

	Dr Daniel Robotham
Position/ Role:	Deputy Research Director, The McPin Foundation
Address:	The McPin Foundation 32-36 Loman Street London, SE1 0EH
Telephone:	020 7922 7875
Fax:	
Email:	danrobotham@mcpin.org

Study Synopsis

Study Title	**VIRTUAL REALITY SUPPORTED THERAPY FOR THE NEGATIVE SYMPTOMS OF PSYCHOSIS**
Protocol Short Title/ Acronym:	VR Therapy for Psychosis Negative Symptoms (V-NeST)
Study Phase If Not Mentioned In Title:	Feasibility
Sponsor Name:	Professor Reza Razavi
Chief Investigator:	Dr Matteo Cella
Clinicaltrials.gov registration	NCT03995420
REC Number:	260511
Medical Condition Or Disease Under Investigation:	Psychosis - Schizophrenia
Purpose of Clinical Trial:	The overall aim of this project is to test the feasibility and acceptability of a novel virtual reality assisted therapy, called V-NeST, to reduce the impact of negative symptoms on recovery in people with schizophrenia.
Primary Objective:	Assess recruitment and retention rates, including willingness to be randomised
Secondary Objective(s):	i) Assess recruitment and retention rates, including willingness to be randomised; ii) Test randomisation procedure; iii) Estimate variances for sample size

	calculations for later definitive RCT; iv) Check final research protocol.
Trial Design:	Feasibility, acceptability randomised controlled trial.
Endpoints:	Saturation
Sample Size:	30
Summary Of Eligibility Criteria:	Inclusion: 1- Service users under the care of NHS psychosis services, 2- aged over 18, 3- in a stable clinical condition, 4- with a documented episode of psychosis and/or a schizophrenia spectrum diagnosis according to DSM-5 and ICD-10 criteria. Exclusion: 1- Recent antipsychotic medication change (i.e. in the last 3 weeks), 2- moderate to severe learning disability, 3- insufficient English for therapy, 4- organic impairment, 5- high risk to Covid-19 complications
Intervention (Description, frequency, details of delivery)	Active Condition: V-NeST is a 12-session therapy using psychological intervention principles based on Cognitive Remediation and Cognitive Behavioural Therapy. Each therapy session will involve engaging with different VR based tasks where participants can experience virtual social interactions, passive and active recreational activities and job like scenarios. The therapy will be delivered with the support of a therapist once per week for 12 consecutive weeks. Each therapy session will last approximately 1-hour.
Comparator Intervention:	Control Condition: This is defined as multi-modal treatment and will consist of different therapies defined by the treating team. These will include regular contact with a care coordinator, medication management by a psychiatrist and potential access to psychosocial interventions (e.g. Occupational therapy) as considered appropriate by the clinical team.
Maximum Duration Of Treatment Of A Subject:	12 weeks (+/- 1 weeks)
Version And Date Of Final Protocol:	V1.1, 28/02/2019
Version And Date Of Protocol Amendments:	V 1.2, 30/09/2020

3. SCIENTIFIC ABSTRACT

Background: Negative symptoms are typically observed in people with schizophrenia and indicate a loss or reduction of a normal function (e.g. reduced motivation and affect display). Despite being important predictors of people's recovery the development of interventions for negative symptoms received only very limited attention. There are currently no evidenced based therapies for these symptoms.

Aims: To test the feasibility and acceptability of a novel virtual reality assisted therapy, called Virtual Reality Supported Therapy for the Negative Symptoms of Psychosis (V-NeST).

Methods: This is a single (rater) blind randomised study with two conditions; V-NeST plus treatment-as-usual (TAU) vs. TAU alone. The study will recruit thirty people with psychosis from NHS community care teams. Assessments will be at baseline and 3-month post-randomisation. We will also conduct a nested qualitative study to identify the key themes associated with the acceptability of the overall study and intervention. We will assess key feasibility parameters such as: consent and availability for screening; eligibility; availability for assessment, randomisation and treatment retention. Acceptability will be assessed by considering: therapy session attendance and drop-out; in-depth feedback from service users interviews; acceptability of the research procedures and measures. Participants will be assessed with measures of personal goal attainment, functioning levels, negative symptoms and reward sensitivity, the mechanism hypothesised to influence negative symptoms. Analyses will evaluate the feasibility and analyses of clinical outcomes will be focused on descriptive statistics and confidence intervals for treatment effects. We will estimate population variances of the main outcomes for future power calculations. A semi-structured interview will explore participants' experience of being recruited to the study, receiving V-NeST and identify barriers (and potential solutions) to treatment engagement. The interviews will be designed and conducted by an expert service-user researcher.

Timeline: We will complete this study in 24 months. We will spend the first six months completing the therapy and technology development procedures and all the regulatory aspects associated with the research. We will recruit 2.5 participants per month and complete recruitment by month 18 and complete therapy delivery by month 21 Analysis of the data will be completed by month 24. The results of this trial will allow us to plan the next study necessary to produce the evidence for this therapy efficacy. This will involve an application for further funding.

Dissemination: The results of this study will be disseminated in two academic peer-reviewed journal papers and presented at national and international scientific conferences. The results

will also be shared through the McPin Foundation, and with policy-makers and service commissioners.

Impact: Clinical services for people with psychosis have currently no recommended evidence-based interventions targeting negative symptoms. With a large proportion of service users experiencing these symptoms and these being largely responsible for poor functional outcomes clinical services can only partially fulfil their aim of supporting service users' recovery. This research aims to fill this gap by introducing a therapy designed to reduce negative symptoms and improve the recovery prospect of people with schizophrenia.

4. BACKGROUND AND RATIONALE

This project will test the feasibility and acceptability of a novel virtual reality assisted therapy to reduce the impact of negative symptoms on recovery in people with schizophrenia.

4.1 The Problem

Schizophrenia is the most severe form of psychosis, one of the most debilitating mental health conditions. Even with significant investments in both pharmacological and psychosocial interventions the majority of individuals affected by this illness will experience long term disability. It is estimated that only 1 in 10 people receiving this diagnosis will achieve full recovery (1). Negative symptoms are typically observed in people with schizophrenia and indicate a loss or reduction of a normal function. These include poor motivation, social withdrawal, difficulties in experiencing pleasure, blunted affect and reduced communication. Negative symptoms are prevalent in people with psychosis and it is estimated that for at least a third of the people receiving this diagnosis these symptoms are the main barrier to recovery (2). Despite their importance to illness prognosis and functioning, the development of interventions for negative symptoms received only very limited attention (3). There are currently no evidenced based pharmacological or psychological therapies for these symptoms and the UK NICE guidelines suggest considering offering art therapy and CBT for psychosis (CBTp) for the alleviation of negative symptoms (4). However, both these therapy approaches are not specifically designed to tackle the negative symptoms of schizophrenia. This is particularly true for CBTp which targets primarily hallucinations and delusions.

An issue that has significantly hampered therapy development for negative symptoms is the lack of a precise treatment target responsible for the emergence and maintenance of these symptoms. Recent research has begun to show consistently an association between reward processing abnormalities and negative symptoms in people with schizophrenia (5, 6). Studies found that difficulties in motivation and pleasure experience where associated with reduced sensitivity to feedback or reward learning.

4.2 The Mechanism

Reward learning (RL) is the term used to describe the cognitive processes responsible for calibrating our sensitivity to positive and negative feedback. RL is considered a key cognitive function in determining our behaviour as the capacity to correctly estimate the pleasure and the value of everyday situations is essential to human nature. We use this skill constantly to make decisions which define who we are and determine our role and function in society. Given its relevance RL has been the focus of a substantial body of basic research. We know that in human this process is mediated by the mesolimbic dopamine system, in particular by the ventral and dorsal striatum and ventral tegmental area and the nucleus accumbens (7, 8). Dopamine neurons in these areas have been found to respond to rewards but also, over time, learn to "fire" to predict reward (9). The affinity between the brain areas involved in this process and those considered responsible for a range of psychiatric conditions prompted the investigation of RL in mental health conditions. The consistent finding that RL abnormalities are found in many psychiatric disorders including schizophrenia (10-12) have prompted the United States National Institute of Mental Health to highlight RL as one of the core psychopathological processes of psychiatric conditions (13).

4.3 Linking the Mechanism to Clinical Practice

While the association between the biological substratum and RL related processes in schizophrenia is clear, limited research has, to date, explored how RL deficits may be linked to symptom dimensions and functional outcomes (14, 15). Emerging research is pointing at the association between RL deficits and negative symptoms (16, 17). Previous studies found that more feedback (either positive or negative) is necessary to modify behaviour (18), and showed that people with schizophrenia have impaired feedback sensitivity to learning from rewards, but that they maintain preserved learning from punishments, suggesting that this pattern could lead to motivational difficulties (19). Overcoming motivational issues is a longstanding challenge for effectively delivering interventions in people with psychosis (20). New treatments are needed that target feedback sensitivity and tackle motivational and RL problems, to produce a substantial improvement to the care prospect of people with psychosis.

4.4 Current Treatment Evidence

There are currently no pharmacological or psychosocial interventions designed to target RL problems. Contingency measures such as financial incentives are increasingly used to boost people's motivation (e.g 21). These approaches, however, circumvent RL difficulties by disproportionally increasing reward and, despite improving the likelihood of engaging for a short term in a specific therapy, they do not address the root of the problem limiting the potential of extending the therapy benefits to other areas.

One of our recent studies explored how components of a psychological therapy called Cognitive Remediation can impact RL deficits in people with psychosis (22). The result of this study suggested specific task practice and feedback management increases both sensitivity to positive and negative feedback in people with schizophrenia and that RL improvements were associated with negative symptoms reduction. The result of our recent studies also highlighted the importance of monitored task practice and real-time feedback suggesting that this approach can significantly reduce negative symptoms (22-24).

This evidence suggests that repeated task practice on tasks engaging motivation, controlled feedback and a focus on improving cognitive regulation processes (e.g. planning, monitoring, revision) can improve RL and reduce negative symptoms. However, people with negative symptoms often are extremely withdrawn from everyday life tasks; in-vivo work is very demanding for clinical services and cannot be controlled. This is why we propose to use Virtual Reality (VR) to overcome this barrier to effective therapy delivery. The proposed Virtual reality-

NEgative Symptom Therapy (V-NEST) will enable, for the first time, to reconstruct everyday situations that are difficult for people with negative symptoms. This will enable therapists to provide real-time feedback on everyday tasks and focus on improving cognitive regulation processing.

By controlling key variables of the everyday life environments V-NEST will provide multisensory stimulation and embodied interaction which cannot be achieved with any other method (25). Patients can practice real-time situations in a "safe" environment and receive real time positive feedback. The immersive and game like scenarios and the possibility to manipulate reward should improve reward learning and foster better engagement with therapy.

Doing actual everyday tasks and facing social situations often feels overwhelming for people with psychosis. V-NeST will enable a gradual introduction of these situations. In our previous research we have demonstrated that VR can enable people with psychosis to learn new skills and generalise them to real-life (26).

4.5 Why is this research needed?

Clinical services for people with psychosis have currently an array of effective therapies to tackle positive symptoms. However, there are no evidence-based interventions currently recommended targeting the negative symptoms of schizophrenia. With a large proportion of service users experiencing these symptoms and these being largely responsible for poor functional outcomes we believe clinical services are currently not best equipped to fulfil their aim of supporting service users' recovery. The proposed project aims to fill this gap by introducing a therapy designed to reduce the burden of negative symptoms and improve the recovery prospect of people with schizophrenia.

5. AIMS AND OBJECTIVES

The overall aim of this project is to test the feasibility and acceptability of a novel virtual reality assisted therapy, called V-NeST, to reduce the impact of negative symptoms on recovery in people with schizophrenia. The results will inform a later definitive trail by providing information on key parameters including *recruitment*, *retention*, *acceptability* and *treatment protocol*.

The project objectives are:

1) Assess recruitment and retention rates, including willingness to be randomised

2) Test randomisation procedure

3) Estimate variance for sample size calculations for later definitive RCT

4) Check final research protocol

5) Evaluate feasibility and acceptability of the novel VR assisted therapy

The hypothesis of the main trial, for which this is a feasibility study, will be: V-NeST plus treatment as usual (TAU) will achieve a sustained improvement in functioning levels compared to TAU alone.

V-NeST is a new VR augmented psychological therapy. Unlike existing psychological therapies, V-NeST uses VR alongside therapist contact to enable multisensory simulation and embodied interactions and real-time managed feedback. V-NeST uniquely targets negative symptoms difficulties for which there is currently no intervention provision in the NHS psychosis services. The work we conducted with service users and carers leading to this application suggested that an intervention tackling these difficulties will be much valued. We have involved service users and clinicians in the development stages of V-NeST which makes this intervention more likely to be an acceptable approach. To complete the development of V-NeST we will need to further tailor our existing VR scenarios. Before an efficacy study can be conducted this study will need to evaluate the therapy feasibility by addressing the following research questions:

1) Are the V-NeST therapy and research procedures appropriate, feasible and acceptable?

2) Can the study recruit, randomise and retain people in treatment according to target?

3) What is the sample size needed for the definitive trial?

4) What are the research and therapy resources needed, including training and supervision, for the final trial and future therapy implementation?

The following outputs will be used to answer the above research questions:

1) Evidence of the acceptability, feasibility of delivering the intervention and conducting the research assessment. A finalised treatment manual to guide and standardise the intervention procedures which can be used to evaluate fidelity.

2) Data on willingness to be recruited and randomised, take part in the therapy and drop-out rate. Date on eligible participants; willingness to be re-assessed after therapy.

3) Data on the standard deviation of the outcome measures to estimate the sample size for the definitive trial.

4) Information on research and therapy resources, including training and supervision, necessary for delivering V-NeST.

Information from this study will be used to support an application for funding for a definitive large scale RCT to test the efficacy of V-NeST to the Efficacy of Mechanism scheme (EME) or Health Technology Assessment (HTA) programme. The larger trial will be appropriately powered to evaluate both efficacy and the mechanistic component hypothesised to impact on negative symptoms (i.e. reward learning). As recommended by service users in consultations the primary outcome for this study will be an idiosyncratic measure of functioning levels (i.e. goal attainment scale) as this was considered capturing a valued outcome.

The result of the definitive trial will provide empirical data to support the implementation of this new treatment in psychosis services and this will contribute to improve the recovery prospect for people with psychosis.

6. RESEARCH PLAN AND METHODS

6.1 Study Design

This will be a single (rater) blind randomised feasibility study with two conditions; V-NeST plus treatment-as-usual (TAU) vs. TAU alone in people under the care of psychosis teams. Assessors, blind and independent to treatment group, will conduct all assessments at baseline and post-treatment (3-month).

6.2 Participants

Participants will be service users currently under the care of NHS psychosis services. Inclusion criteria will be: i) aged over 18; ii) in a stable clinical condition; iii) with a documented episode of psychosis and/or a diagnosis of schizophrenia.

Exclusion criteria will be: i) recent antipsychotic medication change (i.e. in the last 3 weeks); ii) moderate to severe learning disability; iii) Insufficient English for therapy; iv) Organic impairment; v) High risk for Covid-19 complications (or current or suspected Covid-19 symptoms).

6.3 Intervention

This study has 2 conditions: (i) Control condition (treatment-as-usual, TAU); (ii) Active condition (V-NeST plus TAU)

Control Condition: This is defined as multi-modal treatment and will consist of different therapies defined by the treating team. These will include regular contact with a care coordinator, medication management by a psychiatrist and potential access to psychosocial interventions (e.g. CBT or Occupational therapy) as considered appropriate by the clinical team.

Active Condition: V-NeST is a 12-session therapy using psychological intervention principles based on Cognitive Remediation and CBT. Each therapy session will involve engaging with different VR based tasks where participants can experience virtual social interactions, passive and active recreational activities and job like scenarios. The VR software will have a front-end experience in which the service user will be able to navigate the environment and a back-end system where the therapist can control the 3D environment, personalise the patient view and access the data to monitor and evaluate progress.

The VR environment will be based on a virtual social space (i.e. Virtual Café) which is already partially developed. Avatars (i.e. virtual humans) will be present in this space and it will be possible for participants to interact. The VR environment will present opportunities to engage in a range of different activities. We envisage some of these activities will be challenging for people experiencing negative symptoms. The activities in the VR environment will include:

i) *TV watching.* The virtual café will have an entertainment area. Here participants will be able to select from a series of TV programmes including sport, documentaries, news, music videos and movie clip. Participants will be able to select multiple clips or watch the same again.

ii) *Talk to virtual humans*. Participants will be able to engage in brief conversations with avatars. Different avatars will communicate using their unique personal interaction style (e.g. shy or talkative). Avatar communication content will be managed by the therapist in real time.

iii) *Videogames.* The virtual café will have a video games room. Here participants will be able to select and play a 3D video game.

iv) *Resting and doing nothing*. There will be a virtual sofa in a relaxing area where participants will be able to sit and relax in silence.

v) *Charity work*. The virtual café will have a room dedicated to voluntary work to help a charity. In this environment participants will be asked to perform some repetitive tasks (e.g. sorting out donated virtual books). Every task accomplished in this section will generate a £1 donation to a charity of the participant's choice.

Participants will be directed to complete these activities multiple times throughout different therapy sessions. For each of these activities they will receive **tailored feedback** and the

therapist will highlight some learning points. The tailored feedback will be provided in the way we believe to be most effective, with emphasis on positive feedback and as contingent as possible to the task. The therapist will also review how the feedback is appraised by the client with the aim to tailor it further and make it more relevant.

In the virtual environment service users will be asked to perform ratings of: **effort**, **pleasure** and **prospective pleasure**. These ratings alongside, other information collected by the software will be used to evaluate how core negative symptoms impact activity levels.

i) Social withdrawal will be estimated using: Time spent socialising and interacting with other avatars, number of social contacts, pleasure and effort rating during and after interactions, number of social interactions abandoned and number of self-initiated interactions.

ii) *Anhedonia* will be estimated using: difference between predicted and actual pleasure rating for the same activity; number of activities abandoned; time spent not doing any activity; time spend doing passive activities; difference between time spent in the most pleasurable and the least pleasurable activities.

iii) *Motivation* will be estimated using: number of activities abandoned; number of activities attempted, time spent in the activity with the highest difficulty / enjoyment ratio; difference between the time spent in the activity with the highest and the lowest difficulty level.

iv) *Alogia/affective flattening* will be estimated using*:* Quality and quantity of speech used; vocal intonation; prosody and expressivity during the virtual interactions; other non-verbal behaviour during the social interaction (e.g. looking at the avatar).

We aim to collect this information as this will give us an indication of how negative symptoms may interact and be modified by therapy procedures.

Termination: The intervention will be terminated if the client no longer wants to continue receiving the intervention. All instances of non-attendance will be monitored, investigated and where appropriate adverse events recorded. Family members and the clinical team will be informed.

Supervision: Therapists working on this project will receive weekly supervision from MC or LV who are both experienced clinical psychologists. Supervision will focus on clinical matter and maintaining therapy protocol fidelity.

Frequency and Duration: Each client will receive up to 12 weekly therapy sessions over a 3-month period. Each session will last approximately 1 hour.

Intervention Adherence and Compliance: We will monitor session attendance for all clients. Only participants who attend six or more therapy sessions will be considered in the analysis. All therapy activities and contact with the client (e.g. phone) will be recorded in clinical notes and monitored by the study supervisors.

Intervention records: Participants anonymised data, number and type of contact will be recorded through notes that will be entered in the project database which will be store safely on a KCL protected server. The trial therapist will record therapy attendance information and outcomes on SLAM's ePJs.

6.4 Sample Size and Recruitment

A sample size of 30 is considered adequate for obtaining reliable feasibility parameter estimates, including robust estimates of variance of main outcome for future sample size calculation (27, 28) . On the bases of previous similar research conducted on our site we have estimated for a dropout rate of 20% over the study period. This will allow this study to have completed data for at least 24 participants. Assuming an average recruitment rate of 2.5 cases per month it is estimated that the study will recruited to target in 12 months. We have successfully recruited at this rate in recent studies of psychological interventions in psychosis services (e.g. 29).

We will recruit across four Psychosis Early Intervention Services and four Psychosis Recovery Services in South London with a combined case load exceeding 1500 people and receiving approximately 50 new referrals every month. We have estimated that approximately 60% of the caseload will be eligible to participate in this study. Two of the applicants (i.e. MC and LV) work as clinicians in these Psychosis services and have successfully recruited for similar studies in this setting before. We have already discussed this study with the clinical teams and have full support for recruitment. Once in the position to start recruitment we plan to present the study in each of the four clinical teams and show the VR environment. We are also planning to present the study to the clinics' family and carers open evening.

6.5 Randomisation

Once identified by the clinical care team and consent for contact obtained, potential participants will be approached to arrange a baseline assessment. Following written consent, eligible

participants will be randomised to either V-NeST+TAU or TAU alone (with a 1:1 ratio). Randomisation will be performed using an online randomisation system set up by the Kings Clinical Trials Unit (CTU) at Kings College London. The trial statistician, DS, is an experience statistician from KCL department of Biostatistics and Health Informatics and will oversee the implementation of the randomisation process. The online randomisation system allows a study researcher to electronically submit study participants' details to the CTU. This will immediately generate a randomisation outcome message to the study CI. Blinding of allocation will be maintained for the research workers until all outcome measures for all participants have been collected. Blindness will be maintained using a range of measures (e.g. separate offices for therapist and researchers, protocols for answering phones, message taking and secretarial support, separate diaries and security for electronic randomisation information). The trial statistician will be also blind to the randomisation outcome.

6.6 Assessment

Assessments will be at baseline, and at 3 months post-randomisation.

6.6.1 Feasibility Evaluation

The feasibility of trial procedures will be examined using proportions and 95% CIs of: (i) availability and consent to be approached by a research therapist, (ii) consent and availability for screening, (iii) eligibility, (iv) availability for baseline assessment and randomisation, (v) treatment retention, and (vi) availability for follow-up assessment.

To examine the aims of the feasibility study we will use the following measures:

The primary outcome of the trial will be the degree to which participants achieve their personal goals, measured by the Goal Attainment Scale (GAS) (30) at post-therapy. The GAS is a method of scoring the extent to which participant's individual goals (set at baseline) are achieved during the intervention. In effect, each participant has their own outcome measure, but this is scored in a standardised way to allow statistical analysis. The goals are individually identified to suit the participant, and the levels are individually set around their current and expected levels of performance. The GAS has been adopted in several studies of psychosocial interventions in mental health (e.g. 31, 32, 33). It has been shown to be a reliable method of rating behaviours by self-report and has wide use in clinical practice.

In addition to the primary outcome participants will be also assessed with measures of:

1. **Functioning**: Functioning levels will be assessed with the Work and Social Adjustment Scale (WSAS) (34). This is a five-item scale self-assessed measure assessing individual's ability to perform everyday activities including work, home management, family and relationship interaction and social and private leisure activities.
2. **Symptoms**: Negative symptoms will be assessed with the Clinical Assessment Interview for Negative Symptoms (35). This is measure provides a detailed assessment of negative symptoms domains. It has been used widely in research in people with psychosis. Service users perception of negative symptoms will be assessed with the self-evaluation of negative symptoms scale (36). Psychotic symptoms will be assessed with the The Psychotic Symptom Rating Scales (PSYRATS) (37). This is one of the most widely used measures to assess symptoms in people with psychosis. Anxiety, depression and self-esteem will be measured with well validated questionnaire such as the Hospital Anxiety and Depression Scale (HADS) (38) and the Rosenberg self-esteem questionnaire (39) .
3. **Reward Learning and Motivation**: will be assessed with the Effort Expenditure for Reward Task (EEfRT) (40). This is a computer-based paradigm that assesses participant motivation to completed task of different difficulty levels under different reward conditions. The task has been developed for research in mental health and has been extensively used in people with psychosis.
4. **Cognition**: Working Memory will be assessed using the Digit Span test. This is well-established tests form a widely used battery, the Wechsler Adult Intelligence Scale (WAIS–III) (41). Processing speed will be assessed using the Trail Making Test (42). This is another well-validated and widely used test. Executive function will be measured using the short version of the Wisconsin Card Sorting Task (43). This is a widely used and well-validated task.

All participants will be asked to complete all assessment measures twice: at baseline and three months after. The study CI has routinely administered all the above measures to people with psychosis and is not aware of any issue in relation to their suitability, ease of use and acceptability in this service users' group.

6.6.2 Acceptability Evaluation

The objective of this evaluation is to inform the design of a definitive trial and help further refine the intervention and recruitment procedures by gathering in-depth feedback from service users who took part in the study. We will conduct a nested qualitative study to identify the key themes associated with the acceptability of the overall study and intervention. We will conduct semi-structured one-to-one interviews to explore participants' experience of being recruited to the study, receiving V-NeST and identify barriers (and potential solutions) to treatment

engagement. We aim to recruit and interview 12 study participants with different therapy engagement levels and clinical presentation after they have completed the therapy. This will allow exploring people's experiences of receiving the therapy but also the experiences of those who may have dropped-out or have found it difficult to engage in the study. The interviews questions were designed in collaboration with service-users and an expert qualitative researcher from the McPin foundation (Dr Robotham). The interviews use a topic guide adapted from similar evaluation projects we conducted in the past. Each interview will be audio-recorded and transcribed verbatim by a member of the research team. Transcripts will be analysed using Thematic Analysis. Emergent themes will be initially identified by a service users researcher and then reviewed and coded by a co-applicant (Dr Robotham) with further input by our service user researcher reference group at KCL.

6.6.3 Assessment of safety

We will record and consider adverse incidents: all deaths, suicide attempts, serious violent incidents, admissions to secure units and formal complaints about therapy. We will review all instances of patients attending A&E or being admitted to hospital in the period of the study. In case of an adverse incident the responsible clinical team, the trial management committee and the data monitoring and ethics committee (DMEC) will be informed. Appropriate actions in response to events will be determined on a case by case basis.

Therapists will record any notable events that might imply safety concerns. Any situations that the therapist feels might be concerning will be discussed in supervision, and if necessary, immediately reported to the Steering Committee. Safety will also be assessed from telephone calls with any participants who are experiencing significant symptoms. All incidents that qualify as adverse advents will be reported according to the study protocol.

6.6.4 Participant Withdrawal

All participants will have the right to revoke consent from the study at any time and this will be clearly stipulated at the time of consent. Withdrawal from the study can be at the request of the participant or at the discretion of the investigator. Withdrawn participants will be informed that they will no longer continue with the study protocol and that their withdrawal from the study will not influence their treatment within the service.

All outreach attempts will be documented throughout the intervention. Contact will be made with the family or a relevant member of the care team if appropriate. The intervention is terminated if patients no longer want to continue in their study participation.

The sponsor reserves the right to terminate the study at any stage for any reason, including funding considerations. Existing participants will be informed of the termination of the study and will be followed-up as part of the usual clinical management.

6.7 Covid-19 adaptations

Since the outbreak of Covid-19 in the UK in early 2020 the trial has revised procedures to minimise face-to-face contact with participants and where necessary to have face-to-face interactions make them safe. All screening and assessment procedures have been adapted to be completed remotely. A trial screening checklist was included to assess the risk of complication from Covid-19 consequences should the participant contract the infection (i.e. V-Nest Coronavirus Risk Assessment Matrix 30/10/2020). Participants scoring on the high-risk range on the checklist (i.e. 6 or above) will not be considered for the study as long as infection control measures are in place. All face-to-face therapy sessions will be conducted in line with the close operation protocol (V1.1 dated 30/09/2020). This protocol was developed in line with the sponsor (i.e. KCL) and NHS host (i.e. SLaM) infection control procedures.

7. STATISTICAL ANALYSIS

The main aims of the feasibility study will be delivered both via the continued monitoring of descriptive data and the analysis of data at the end treatment assessment. This will include reporting data in line with the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (44) showing attrition rates and loss to follow-up. Feasibility of trial procedures will be examined using proportions and 95% confidence intervals for rates of recruitment, consent, trial eligibility, treatment retention and availability for follow-up. Analyses of clinical outcomes will not be focused on statistical significance but will concentrate on descriptive statistics, and confidence intervals to assess the likely range of treatment effects. The primary outcome, goal

attainment, will be examined using an analysis of covariance approach (ANCOVA) with baseline measure as covariate (45). Estimates of population variances of the main outcomes for future power calculations will use the upper 80th percentile of confidence intervals around the estimates (46). A detailed statistical analysis plan will be produced prior to the examination of any of the outcome data.

8. DISSEMINATION

We are proposing to write at least two publications from academic peer-review journals detailing the results of this study. One paper will detail the results of the feasibility and acceptability study and a second paper will describe the results of the qualitative information. We will produce a manual with the therapy procedures and detailed information for clinicians on how to operate the VR system. These resources will be important for future studies of this therapy. We will also present the results of this study to relevant conferences, meetings and to the clinical teams who took part in the study.

The results will be presented at national and international scientific conferences. If appropriate, social media will be used to increase dissemination to a wider audience and regular updates will be uploaded on the VR-Lab website. The results will also be shared through the McPin Foundation and our funder NIHR.

9. PROJECT TIMETABLE

Milestones Stage 1 (Initial 6 months): (i) obtaining ethics and research governance approvals; (ii) publicising the study to senior managers, clinicians and service users in the sites participating in the study; (iii) all therapy procedures to be finalised ahead of ethics and R&D application; (iv) VR adaptation work agreed; (v) VR adaptation will be completed and tested.

Milestones Stage 2 (month 6-8): (i) RA recruited and in post and the process of publicising the study will continue; (ii) Training will be provided for the RA in undertaking assessments and for the therapist in delivering the intervention; (iii) begin recruitment.

Milestone Stage 3 (Months 7to 18): (i) Study recruitment at the rate 2.5 per month.

Milestone Stage 4 (Months 7 to 21): (i) Therapy delivered to all participants.

Milestones Stage 5 (Months 16 to 18): (i) Final assessments (by month 22); (ii) Qualitative interviews will be completed by month 18; (iii) Analysis of the qualitative and quantitative data will be completed by month 21; (iv) manuscripts drafting completed by month 24.

See below for project timeline.

Project Timeline

Virtual Reality Supported Therapy for the Negative Symptoms of Psychosis (V-NeST)

	Month																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Ethics R&D																								
Therapy and VR refinment																								
RA in post (14 months)							1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
Recruitment (2.5 per month)							2	5	7	10	12	15	17	20	22	25	27	30						
Participants in Therapy (group N)							2	5	7	8	7	8	7	8	7	8	7	8	5	2	3			
Feedback interviews (participant N)										3			3		3			3						
Qualitative analysis																								
Traial Analysis																								
TSC/DMEC meeting																								

10. PROJECT MANAGEMENT

10.1 Structure

MC and LV will be responsible for monitoring all research procedures, recruitment, staff training, data monitoring and management and report writing. MC and LV will supervise the research worker during the study. The *Trail Management Group* (MC, LV, DS and DR) will meet bimonthly throughout the trial to monitor progress and achievements.

An independent *Data Monitoring and Ethics Committee (DMEC)* will monitor data collection and analysis, safety, confidentiality and adherence to LREC protocols. The DMEC will meet twice per year and will include the study CI, and independent statistician and a clinician. A

protocol for monitoring adverse events will be employed and reviewed by the DMEC. ~~A~~longside the DMC a *Trial Steering Committee (TSC)* will also meet twice per year to review the study progress and implement the DMEC recommendations. The TSC will be chaired by an independent clinical academic and include an independent statistician, two independent PPI member, an independent clinician and the trial statistician (DS), CI (MC) and co-I (LV). MC and LV will have the responsibility to fulfil all the research governance arrangements and liaise with the NHS.

11. ETHICS, CONSENT AND DATA MANAGEMENT

11.1 Ethics

We will seek ethical approval from an NHS ethic committee. We will also make the necessary application for confirmation of capacity and capability and R&D approval to the South London and Maudsley NHS Foundation Trust. Patient Information Sheet and the research procedures will be reviewed by our patient advisory group at KCL ahead of ethics and R&D approval submission.

The project will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with the UK policy framework for health and social care research.

This protocol and related documents will be submitted for review to an NHS Research Ethics Committee (REC).

The Chief Investigator (CI) will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor. The CI will ensure that REC Favourable Opinion, HRA approval, and Trust Confirmation of Capacity and Capability will be in place before recruiting from the Trust. Should it be necessary to add research sites at a later stage, the sponsor will be approached to review an amendment for submission to the HRA, and Confirmation of Capacity and Capability will be obtained from the new NHS sites before starting recruitment from research sites.

11.2 Obtaining Consent

Consents will be taken by research workers who will be given prior training in this process. All study participants will be provided with a written information sheet and a written consent form for the study. All participants will have been judged to be capable of providing informed consent. At first appointment potential participants will be presented with a patient information

and they will be reassured that there is no obligation to take part and that not participating will not affect their treatment in any way. It will be emphasised that they may wish to contact others before making up their mind and that there is no hurry to do so. Two copies of consent form will be signed by the participant and the research worker. The original form is to be given to the participant and while the second copy will be retained by the research worker to be stored securely on KCL premises and separately from the anonymised research data. It will be made explicit to participants both verbally and on the information sheet and consent form that they have the right to withdraw at any time from the study without giving a reason and without this affecting their care.

11.3 Data Collection

Research assessment data will be collected by the project research workers under the supervision of MC and LV. Data will be collected on paper files and on King's College London computers and stored according to the data protection act. Interviews will be recorded on voice recorders and transcribed by the interviewer (omitting all personal identifiable information). Once transcribed the audio recordings will be destroyed. Information on therapy attendance will be collected by the study therapist and stored on paper and electronic records. The VR software will also produce a report in electronic format which will be stored on King's College London computers.

11.4 Data Management

All researchers and team members will have a contract with KCL and SLAM. All researchers will be trained and will be familiar with current laws, rules and protocol (governed by the NHS, university ethics guidelines and UK GDPR) regarding consent, anonymity and data storage. Prior to providing consent to participating in the study, participants will be made fully aware of how their study data will be handled and who will have access to it. Data will be stored in KCL facilities. All data will be stored on university password-protected computers. Computer data storage will comply with the Data Protection Act and will be anonymised. All identifiable data (e.g. email addresses and telephone numbers) will be kept separately from the research data which will be stored under participants' IDs. Only research workers directly involved in the study will know the passwords. Paper/hard copies of the consent forms and paper and pencil assessments will be stored in locked filing cabinets at the university. Consent forms will be kept separately from the research data (which will be stored under participants' IDs).

12. PATIENT AND PUBLIC INVOLVMENT

We have engaged, and we are consulting mental health service users and carers to improve our study feasibility and the development of this application. We have received feedback from the Service User Advisory Group (SUAG) and the Biomedical Research Centre (BRC) PPI group on the suitability of the VR and technology-based procedures. We aim to continue to engage in this process and we have the involvement of two service users to provide regular feedback on the new methodology. We have also the support of the BRC Young People Mental Health Network. We have identified a young person from this network who will be able to support the therapy development. We have also taken advantage of a KCL based group of service users (FAST-R) who have provided feedback on our ethics application, forms (e.g. PIS) and study protocol ahead of submission. Via the McPin foundation we will involve service users in the analysis of the qualitative data. Two service users will be part of this study Trial Steering committee.

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