VIRTUAL REALITY FOR TREATING AGORAPHOBIA AND AGORAPHOBIC AVOIDANCE

[MT725]

FINAL PROTOCOL

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Final Protocol

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PROJECT TITLE

Virtual reality for treating agoraphobia and agoraphobic avoidance.

1.1 Plain English Summary

Agoraphobia/agoraphobic avoidance is an anxiety disorder where people have a fear of particular places and situations, such as open or crowded places, or places from which escape seems difficult. Symptoms of agoraphobia vary across individuals, but can include physical symptoms (e.g. rapid heartbeat and breathing, chest pain, dizziness), cognitive symptoms (e.g. about how others will react, worries about the consequences of having a panic attack), and behavioural symptoms (e.g. not leaving home, avoiding certain situations).[1]

This assessment considers whether virtual reality (VR) therapies are beneficial and safe to use for people (16+ years of age) with agoraphobia and agoraphobic avoidance, and whether these technologies represent good value for money for the National Health Service (NHS). Based upon the final scope, four virtual reality enabled therapies will be compared with alternative treatment options offered by the NHS.

1.2 Decision Problem

1.2.1 Purpose

The topic has been identified by NICE for early value assessment (EVA). The objective of an EVA is to identify promising technologies in health and social care where there is significant need and enable earlier conditional access while informing further evidence generation. The evidence developed will demonstrate if the expected benefits of the technologies are realised and inform a final NICE evaluation and decision on the routine use of the technologies in the NHS.

1.2.2 The interventions

This EVA is on virtual reality (VR) for agoraphobia and agoraphobic avoidance, delivered with the support of a mental health worker or as part of face-to-face therapy or teletherapy. The interventions would be offered in addition to standard care for any co-occurring mental health conditions. Four interventions will be covered. They are:

- Amelia VR (Amelia Virtual Care, AVC) – a VR platform designed to be used as a tool by therapists to support the treatment of mental health disorders. It is delivered under the guidance of a therapist in clinical settings or remotely using AVC's smartphone app. It also offers a homework feature with virtual mindfulness and relaxation sessions. AVC helps therapists to facilitate the delivery of evidence-based treatment including gradual exposure, mindfulness-based cognitive therapy and desensitisation. AVC has over 100 virtual environments that can be configured and personalised to a patient's needs using a simple control panel.

- gameChange (Oxford VR) – designed to treat agoraphobia and agoraphobic avoidance in people with psychosis. It delivers VR cognitive therapy and is compatible with a range of VR equipment that use 6 degrees of freedom tracking. This includes the HTC Vive, Meta Quest and Pico Neo headsets. The treatment includes repeated behavioural experiments using the headset to simulate different real-life situations (including visiting a café, shop, pub, street, doctor's office and bus) to help people test their fear expectations. It is delivered in around 6 weekly 30-minute sessions. Treatment is facilitated by a virtual coach to support the use of techniques and assist people to overcome their difficulties. It should also be supported by a mental health worker either remotely or in the room during sessions to help people maximise their learning from gameChange in the real world. It may be used with outpatients in clinics or at home.

- Invirto (Invirto) – offers app-based cognitive behavioural therapy (CBT) content and exposure exercises in VR using a VR headset. The programme includes psychoeducation via the app, interoceptive exposure, situational exposure with VR, anxiety diary, monitoring and progress reports, and relaxation and mindfulness exercises. Its programme for agoraphobia includes over 15 situational exposure scenarios such as driving a car, using an elevator, public transport and shopping. These are prepared and followed up as behavioural experiments in the app. Invirto also has programmes for panic disorder and social phobia.

- XR Therapeutics (XRT) – offers VR treatment to help reduce anxieties and to treat phobias including agoraphobia. It is designed to be combined with face-to-face CBT and

allows therapists to tailor digital scenes to a person's individual needs. Treatment can be adapted in real time allowing therapists to manage the rate of exposure and the intensity of situations. Digital scenes can also be personalised in line with a person's background and cultural preferences. XRT does not require the use of a VR headset. VR technology is used to project digital scenes onto a curved white screen to recreate situations such as being in a supermarket in a safe setting.

1.2.3 Care pathways

The NHS recommends a stepped care approach for treating agoraphobia and any underlying panic disorder.[2] The first step involves recognition and accurate diagnosis, including identification of any comorbidities. Treatment may encourage self-help techniques and lifestyle changes such as exercise to help people relieve and manage their symptoms. People may be offered individual guided self-help, which is based on cognitive-behavioural therapy (CBT) and delivered with the support of a therapist. If needed or preferred, more intensive treatments should be offered such as CBT or applied relaxation.

The NICE clinical guideline on the management of generalised anxiety disorder and panic disorder in adults recommends that people with moderate to severe panic disorder with or without agoraphobia should be offered CBT or an antidepressant.[3] Clinical advice during the scoping workshop for this appraisal, however, suggested that not all people with agoraphobia or agoraphobic avoidance would, in practice, receive psychological therapies. This may be particularly true for people with serious mental illness (SMI) and those for whom agoraphobia is secondary to another condition, and who therefore may be ineligible for Increasing Access to Psychological Therapies (IAPT) services. This means that for some people, typical treatment could be antidepressants or antipsychotics (if appropriate), simple contact and monitoring with services or self-management.

VR for treating agoraphobia and agoraphobic avoidance would be offered after clinical assessment and diagnosis. It would be an alternative or addition to standard care psychological interventions for agoraphobia. The place in the care pathway depends on the specific disorder and comorbidities, healthcare professional assessment and clinical judgement, the content of the intervention, patient preferences and risk, and the level of support needed to deliver the intervention.

More details about the scope and the place of VR in the agoraphobia and agoraphobic avoidance care pathway for the purposes of this EVA can be found on the Final Scope document on the NICE website.[4]

1.2.4 Population

People aged 16 years and over with agoraphobia or agoraphobic avoidance. Agoraphobic avoidance includes people with symptoms comparable to those for agoraphobia, but where people have not received a formal clinical diagnosis of agoraphobia. For this reason, a formal diagnosis of agoraphobia will not be required for inclusion in the report.

1.2.5 Comparators

Comparators will include the following, either alone or in combination:

- Guided self-help
- Cognitive behavioural therapy (CBT)
- Exposure therapy
- Applied relaxation
- Antidepressants licensed for the treatment of panic disorder
- Oral antipsychotic medication
- Simple contact and monitoring with services

1.2.6 Healthcare settings

Outpatient clinics, inpatient settings or home-based care

1.2.7 Outcomes to be examined

Intermediate measures for consideration may include:

- Patient choice and preferences
- Acceptability and satisfaction
- Accessibility and digital access
- Intervention adherence and completion
- Intervention-related adverse events
- Device-related adverse events

Clinical outcomes for consideration may include:

- Change in agoraphobia symptoms
- Change in other psychological symptoms
- Global functioning and work and social adjustment
- Rates of recovery, time to recovery
- Rates of relapse or deterioration, time to relapse or deterioration

Patient-reported outcomes for consideration may include:

- Health-related quality of life
- Recovering quality of life
- Patient experience
- Social contact

1.2.8 Sub-groups to be examined

If the evidence allows other subgroups that may be considered include people with:

- psychosis who have agoraphobia or agoraphobic avoidance,
- agoraphobia or agoraphobic avoidance that occurs with other mental health problems including, but not limited to, anxiety disorders, mood disorders and severe mental illness,
- recurring or longer-term agoraphobia or agoraphobic avoidance,
- high or severe agoraphobic avoidance,
- varying levels of digital literacy or access,
- a greater interest in and willingness to try VR,
- protected characteristics.

1.3 Objective

The purpose of the EVA is to summarise and critically appraise existing evidence on the clinical effectiveness and cost-effectiveness of VR therapies for people with agoraphobia and agoraphobic avoidance. A review will be conducted to identify relevant evidence for the included interventions in the target population. Where feasible, a de novo economic model

will also be developed to provide an early view of the potential cost-effectiveness of the included interventions. The following objectives are proposed:

1.3.1 Clinical Effectiveness

- Identify and assess evidence relating to the use and clinical effectiveness of the included technologies as it pertains to the scope
- Report on any potential safety issues
- Report the evidence gaps, highlighting what data may need to be collected to inform these gaps
- If evidence is included that is not directly related to the scope, outline the potential generalisability and limitations of the evidence

1.3.2 Cost-Effectiveness

- Identify and assess economic evidence relating to the use of the included technologies within the scope
- Subject to sufficient evidence, develop a conceptual economic model related to the scope, that can be used to inform future research and data collection
- Report available model inputs and evidence gaps
- Report on the technologies' costs and effects, and an early assessment of whether there is a *prima facie* case for their use to be a cost-effective alternative to standard care in the NHS.

1.4 Evidence review

A review to identify evidence for the clinical and cost-effectiveness of included interventions will be undertaken following the general principles published by the Centre for Reviews and Dissemination (CRD) at the University of York.[5] A systematic literature review (SLR) to comprehensively search for all relevant evidence for the appraisal is beyond the scope of an EVA. However, the review methods, including the literature search strategy and evidence synthesis, will be high quality and conducted in a transparent manner, with the aim to produce a comprehensive overview of the relevant literature. Based on initial scoping searches, the EAG does not expect there to be a large body of evidence for the included technologies, and that this evidence base should be identified through our planned searches. However, if the evidence base identified is large, the EAG will prioritise the inclusion of

evidence that is of the best quality and most pertinent to the objectives of the EVA. If technologies have little evidence in line with the scope, the EAG will consider including potentially relevance evidence, identified through the EAG's existing searches, that is broadly relevant but does not adhere strictly to the scope, for example in terms of the population or comparator.

At study commencement the EAG or NICE will request the manufacturers supply any evidence they wish to be considered and reviewed by the EAG.

1.4.1 Search strategy

Searches for clinical and cost-effectiveness will be conducted in one strategy, without any study type filters, to reduce screening burden. An exemplar search strategy for MEDLINE is provided in Appendix 1.

The search process will comprise the interrogation of the following main elements:

- Electronic databases, including MEDLINE (inc In-Process and PubMed-not-MEDLINE records), EMBASE, APA PsycInfo and Cochrane.
- Economics sources, such as NHS EED, ScHARR HUD and CEA Registry.
- Manufacturer websites.
- The WHO International Clinical Trials Registry Platform (ICTRP) and the US National Library of Medicines registry at clinicaltrials.gov.
- MHRA field safety notices and the MAUDE database will be searched for adverse events.
- In addition, any industry submissions to NICE, as well as any relevant systematic reviews identified by the search strategy, will be scrutinised to identify additional relevant studies.
- Relevant clinical guidelines from NICE, SIGN and INAHTA, especially for economic modelling

In addition to the above searches, a targeted search of the broader literature on people with agoraphobia or agoraphobic avoidance will be undertaken to identify the evidence base on HRQoL (i.e. health state utility values), resource use and costs for treatment and side-effects (UK studies only if available), and the methods available for the modelling of agoraphobia or agoraphobic avoidance to inform cost-effectiveness analyses. The search strategies

employed will be reported, and findings from these explorative searches will be presented in summary format, using a tabular approach and narrative text.

1.4.2 Clinical evidence to be included

This assessment will look across a range of evidence types including RCTs and real-world evidence. Systematic reviews meeting the inclusion criteria will also be included. Studies may report either quantitative or qualitative evidence. The following evidence types will be excluded:

- Animal models
- Pre-clinical and biological studies
- Narrative reviews, editorials, opinions
- Meeting abstracts, for studies where full-text papers are available. If studies are only available as meeting abstracts, inclusion will depend on sufficient information being available to offer meaningful critique.
- Studies not available in the English language.

1.4.3 Economic evidence to be included

Full economic evaluations, costing studies and studies reporting health related quality of life measures that inform either the design of the EAG's own analysis or provide a source of input data will be included where they meet the inclusion criteria set out for the review of clinical effectiveness (see section 1.2). Priority will be given to more recent studies and those with a UK NHS setting.

1.4.4 Study selection

The abstracts and titles of references retrieved by the searches will be screened against the inclusion criteria for relevance. Full publications of potentially relevant studies will be obtained. The retrieved articles will be assessed for inclusion by one reviewer and a minimum of 10% will be independently checked by a second reviewer, using the pre-specified inclusion/exclusion criteria. Discrepancies will be resolved by discussion, with the involvement of a third reviewer, where necessary. Duplicate papers will be deleted.

1.4.5 Quality assessment strategy

Formal risk of bias assessment will not be conducted, as it is not required in the EVA process. Discussion will be included in the EAG report on potential biases in key studies and how the risk of bias could affect key outcomes. The report will explicitly detail the potential sources of bias such as the main confounding factors and will comment on the generalisability of the results to clinical practice in the NHS.

1.4.6 Data extraction strategy

Data will be extracted from included studies into a bespoke database by one reviewer and a minimum of 10% will be checked by a second reviewer. Discrepancies will be resolved by discussion, with the involvement of a third reviewer if necessary. Data points to be extracted include information about the study reference and design, the population and intervention characteristics, relevant outcomes and their measurement.

1.4.7 Methods of analysis / synthesis

Clinical data will be tabulated and narratively synthesised.

Methods and findings from included economic evaluations will be summarised in a tabular format and synthesised in a narrative review. Economic evaluations carried out from the perspective of the UK NHS and Personal Social Services (PSS) perspective will be presented in greater detail.

Key sources of risk of bias will be discussed. The generalisability of findings to clinical practice in the NHS will be considered.

1.5 Economic modelling

If data allows, an economic model will be constructed either by adapting an existing model or developing a new model using available evidence and following guidance on good practice in conduct and reporting of decision analytic modelling for HTA.[6-8] If data do not allow construction of a model, the EAG will describe the appropriate characteristics of the model that would be required (e.g. structure, setting, input parameters and ideal sources of data).

The structure of any model will be determined on the basis of research evidence and clinical expert advice (from specialist committee members) about:

- appropriate assumptions to make where no suitable data are identified for effectiveness for some of the interventions,

- appropriate assumptions to make if there are data gaps in the information available to populate resource use or quality of life information per health state.

All assumptions applied in the modelling framework will be clearly stated. All data inputs and their source will be clearly identified.

Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:

- Intervention delivery costs
  - Licencing costs of the technologies
  - Healthcare professional training
  - Costs of the standalone VR headsets
  - Healthcare professional grade and time for intervention delivery
- Cost of other resource use (e.g. associated with managing anxiety, adverse events or complications):
  - GP or mental health team appointments

Where appropriate, and if data allows, sensitivity analyses will be undertaken to explore uncertainty. These may include one-way and multi-way sensitivity analyses, use of probabilistic sensitivity analyses (PSA), and value of information analyses where modelling permits. The use of PSA involves sampling of parameter inputs from distributions that characterise uncertainty in the mean estimate of the parameter. PSA is used to characterise uncertainty in a range of parameter inputs simultaneously, to consider the combined implications of uncertainty in parameters. Value of Information analysis helps identify where future research can be most efficiently targeted to reduce uncertainty.

Where probabilistic modelling is undertaken, results will be presented as expected costs and outcomes, with uncertainty represented using cost-effectiveness planes and/or cost-effectiveness acceptability curves/frontier (CEACs/CEAF).

1.6 Gap Analysis

Evidence gaps identified pertaining to the intermediate and final outcomes from the scope and those pertaining to the economic modelling will be summarised in tabular and narrative form. If appropriate, a ‘traffic light’ scheme will be used to highlight relative importance of the

gap. Key areas for evidence generation will be summarised in tabular form. Narrative text will also address missing clinical evidence for other parts of the scope, such as population, setting and comparators.

1.7 Handling the company submissions

Data received from the company will be appraised and, where consistent with the decision problem, will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Data provided (e.g. cost and resource use data) will be assessed against NICE's manual (2022),[6] reasonableness of assumptions made and appropriateness of the data used.

Any academic or commercial in confidence data taken from a company submission will be marked up as appropriate in the report.

1.8 Competing interests of authors

None.

1.9 References

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2. National Health Service (UK). Treatment - Agoraphobia 2022. Available from: https://www.nhs.uk/mental-health/conditions/agoraphobia/treatment/.

3. National Institute for Health and Care Excellence (NICE). Generalised anxiety disorder and panic disorder in adults: management. Clinical guideline [CG113] London: NICE; 2020. Available from: https://www.nice.org.uk/guidance/cg113.

4. National Institute for Health and Care Excellence (NICE). Virtual reality for treating agoraphobia and agoraphobic avoidance: early value assessment. In development [GID-HTE10016] London: NICE; 2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-hte10016.

5. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: University of York; 2009. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.

6. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Process and methods [PMG36] London: NICE; 2022. Available

from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.

7. Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation (Handbooks for Health Economic Evaluation) Oxford: Oxford University Press; 2006.

8. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. Value Health. 2022;25(1):3-9.

Appendix 1 Sample Search Strategy (Medline)

Ovid MEDLINE(R) ALL <1946 to March 23, 2023>

1 Agoraphobia/ 2670
2 agoraphobi*.tw. 3608
3 ((phobi* or anxi* or fear*) adj3 (crowd* or 'open spac*' or 'go* out' or 'leav* home' or 'leav* house')).tw. 89
4 1 or 2 or 3 4468
5 exp virtual reality/ 5395
6 Virtual Reality Exposure Therapy/ 862
7 Augmented Reality/ 1082
8 (VR or 'virtual realit*').tw. 20806
9 (haptic adj2 technolog*).tw. 136
10 (VRCBT or VR-CBT).tw. 19
11 ("automated therap*" or "VR therap*" or "VR cognitive therap*" or "virtual reality therap*" or "virtual reality exposure" or VRET or "virtual reality based exposure" or VRBET).tw. 616
12 ("extended realit*" or "augmented realit*" or "mixed realit*").tw. 4368
13 ('game change' or gamechange or 'oxford VR' or BehaVR or 'HTC Vive' or 'Meta Quest' or 'Pico Neo').af. 132
14 ('amelia vr' or 'amelia virtual care').af. 0
15 invirto.af. 0
16 ('xr therapeutics' or XRT).af. 1203
17 or/5-16 26862
18 4 and 17 54