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Medical technology consultation: GID-HTE10016 Virtual reality for treating agoraphobia and agoraphobic avoidance: early value assessment

Supporting documentation

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **Final post-consultation and 2nd committee meeting assessment report** – an independent report produced by an external assessment group (EAG) who have reviewed and critiqued the available evidence. (also available as a separate document to view/download)
2. **Final post-consultation and 2nd committee meeting assessment report appendix –** appendix to the independent report produced by an external assessment group (EAG)
3. **Final post-consultation and 2nd committee meeting assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
4. **Patient survey report** – patient commentary gathered by the NICE team on the technologies.
5. **Consultation comments and responses table** – a table of all the comments received during the public consultation period and the responses from the NICE team.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Virtual reality for treating agoraphobia and agoraphobic avoidance [GID-HTE10016]

External Assessment Group report

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Early Value Assessment Programme

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Number of attached appendices: 4

Purpose of the assessment report

The purpose of this External Assessment Group (EAG) report is to review the evidence currently available for included technologies and advise what further evidence should be collected to help inform decisions on whether the technologies should be widely adopted in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and the report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the early value assessment.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None.

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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Abbreviations

Term	Definition
A&E	Accident and emergency
Afc	Agenda for change
ASD	Autism spectrum disorder
BAI	Beck Anxiety Inventory
CBT	Cognitive behavioural therapy
CEA	Cost-effectiveness analysis
CE mark	*Conformité européenne* (European conformity) marking
CI	Confidence interval
CORE-OM	Clinical Outcomes in Routine Evaluation – Outcome Measure
CRD	Centre for Reviews and Dissemination
DP	Decision problem
DTAC	Digital Technology Assessment Criteria
EAG	External assessment group
EE	Economic evaluation
EQ-5D	EuroQoL-5 dimensions
EQ-5D-5L	EuroQoL-5 dimensions 5-level
EVA	Early value assessment
GAD-7	Generalised Anxiety Disorder Assessment 7
GP	General practitioner
HRQoL	Health-related quality of life
HRSD	Hamilton Rating Scale for Depression
HTA	Health technology assessment
IAPT	Improving Access to Psychological Therapies
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	Interquartile range
ITT	Intention to treat
MANCOVA	Multivariate analysis of covariance
MANOVA	Multivariate analysis of variance
MAUDE	Manufacturer and User Facility Device Experience

MCID	Minimally clinically important difference
MID	Minimally important difference
MeSH	Medical subject headings
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
N/A	Not applicable
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLM	National Library of Medicine
NR	Not reported
O-AS	Oxford Agoraphobic Avoidance Scale
O-BAT	Oxford Behavioural Avoidance Test
ONS	Office for National Statistics
OWSA	One-way sensitivity analysis
PenTAG	Peninsula Technology Assessment Group
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PW	People with
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
ReQoL	Recovering Quality of Life quality
RWE	Real world evidence
SA	Sensitivity analysis
SCM	Specialist Committee Member
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
TAU	Treatment as usual
UK	United Kingdom
UKCA	United Kingdom Conformity Assessed marking
VAS	Visual analogue scale
VR	Virtual reality

WHO	World Health Organization

1. EXECUTIVE SUMMARY

Quality and relevance of clinical evidence

The EAG considered that the clinical effectiveness for all technologies was uncertain, reflecting the relatively early stage of development of the interventions. No evidence was available for Invirto. For the other three technologies, Amelia Virtual Care, gameChangeVR and XR Therapeutics, clinical effectiveness evidence was limited. There was one key effectiveness study per technology. For XR Therapeutics, evidence was limited to one single arm study of eight people with autism spectrum disorder (ASD), which reached equivocal conclusions about effectiveness. For Amelia Virtual Care, the included single-arm study measured acceptance and adherence of the technology (called Psious at the time of the trial, but now called Amelia), but did not report any clinical outcomes. In the gameChangeVR RCT, there was some evidence of a benefit of gameChangeVR over treatment as usual in terms of agoraphobia symptoms. However, it should be noted that the magnitude and duration of benefit is uncertain, the treatment as usual comparator profile was not profiled precisely in published information, there was no evidence of benefit on wider secondary outcome measures, and the evidence comes only from one trial.

Adverse event data were only provided for one intervention, gameChangeVR, and these data came from an RCT, rather than real world safety observation.

Quality and relevance of economic evidence

The EAG identified one published economic evaluation of the cost-effectiveness of gameChangeVR+treatment as usual (TAU) vs TAU in people with psychosis and agoraphobia, conducted alongside the RCT. The EAG noted the results were highly sensitive to a small number (n=4) of participants in an inpatient setting. EAG's exploratory modelling of gameChangeVR suggests a high degree of uncertainty and whilst point estimates suggest it may not represent a cost-effective use of NHS resources when judged against the NICE reference case, the uncertainty is such that its being cost-effective cannot be ruled out at this time.

Evidence Gap Analysis

There was uncertainty surrounding the clinical effectiveness of all interventions. A number of evidence gaps were identified. These included 1) the differences in populations and

outcomes studied for each intervention, 2) the absence of any evidence for Invirto, economic evidence for XR Therapeutics, and clinical and economic evidence for Amelia 3) differences in comparators across trials, 4) published evidence not being available for all outcomes, 5) an absence of evidence on the durability of the effect of VR-based therapies, and 6) safety data only being available for gameChangeVR.

2. DECISION PROBLEM

Table 1 details the final scope issued by NICE for this EVA, defined per element of assessment. SCMs generally considered the scope to be well aligned to NHS practice.

Table 1: Summary scope of the assessment

Element of assessment	Final scope issued by NICE
Population	People aged 16 years and over with agoraphobia or agoraphobic avoidance
Subgroups	If the evidence allows the following subgroups will be considered: • 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 severe mental illness • high or severe agoraphobic avoidance
Interventions (proposed technologies)	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. Namely: • Amelia Virtual Care (Amelia Virtual Care) • gameChangeVR (Oxford VR) • Invirto (Invirto) • XR Therapeutics (XR Therapeutics) VR interventions would be offered in addition to standard care for co-occurring mental health conditions.
Comparator	Standard care which may include any combination of: • 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.
Healthcare setting	Outpatient clinics, inpatient settings or home-based care

Element of assessment	Final scope issued by NICE
Outcomes	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

	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration should include:
	• Costs of the standalone VR headsets
	• Costs of the technologies including license fees
	• Healthcare professional grade and time
	• Cost of other resource use (e.g. associated with managing anxiety, adverse events or complications):
	  ○ GP or mental health team appointments
	  ○ Healthcare professional training

Time horizon	The time horizon for estimating the clinical and economic value should be sufficiently long to reflect any differences in costs or outcomes.

Abbreviations: CBT, Cognitive Behavioural Therapy; EVA, Early Value Assessment; GP, General Practitioner; NICE, National Institute for Health and Care Excellence; SCM, Specialist Committee Member; VR, virtual reality

3. OVERVIEW OF THE TECHNOLOGY

3.1. Purpose of the medical technology

Agoraphobia is an anxiety disorder characterised by marked and excessive fear of being in situations where escape may be difficult or help may not be available[1,2]. This experience may be described in terms of feeling threatened or worried about leaving home or other place of safety. Agoraphobia involves fear and avoidance of places or situations that might cause panic and feelings of being trapped, helpless or embarrassed. It constitutes a form of anxious avoidance of everyday situations and may co-occur with other mental health conditions, such as panic disorder, depression, social anxiety and psychosis.

Given the high prevalence of mental health conditions and the importance of early intervention, improving and widening mental health services has been identified as a key priority for the NHS.[1] The most recent Adult Psychiatric Morbidity Survey reports that only one in three people with a common mental health condition accesses treatment.[3] Barriers to accessing face-to-face treatments such as individual cognitive behavioural therapy (CBT) include a shortage of trained healthcare professionals and limited clinical resources, while agoraphobia may further impact a person's ability to access mental health services and support and may lead to discontinuation, for example through difficulty tolerating exposure therapy. Agoraphobia may also often be untreated or undertreated when it co-occurs with other mental health conditions.

Virtual reality (VR)-based interventions may increase access to care by offering another treatment channel for people with agoraphobia or agoraphobic avoidance. VR is a simulated 3-dimensional environment with scenes and objects that people can explore and interact with, most typically using a VR headset. Alternatively, images can be projected onto a large hemispherical screen. This can create an immersive experience that is thought to trigger emotional responses similar to those in real-world situations. VR may be used as a tool in therapy sessions or as a vehicle to deliver a digital intervention with the support of a mental health worker, in particular exposure therapy. It can allow people to immerse themselves in real-world situations while being in the safety of their home or clinic. Virtual environments can be adjusted based on a person's needs and individual treatment plan. This could allow more gradual exposure to stressful situations, which may increase comfort and confidence in completing interventions.

Using VR as a treatment modality would support remote treatment delivery. This would allow some people to receive treatment at home and may address barriers to accessing treatment for those who cannot or prefer not to attend face-to-face treatment. This could facilitate faster access to symptom management. The scalable nature of VR-based interventions could allow mental health professionals to treat more people in less time and therefore use time and resources more efficiently compared with standard care interventions for agoraphobia and agoraphobic avoidance.

3.2. Product properties

This scope focuses on VR technologies for treating agoraphobia and agoraphobic avoidance that meet the following criteria:

- Can be used as a platform to treat agoraphobia and agoraphobic avoidance either as a digital intervention with the support of a mental health worker or as a tool in face-to-face therapy or teletherapy.
- Meet the standards within the digital technology assessment criteria (DTAC), including the criteria to have a European conformity (CE) or United Kingdom Conformity Assessed (UKCA) mark where required. Products may also be considered if they are actively working towards required CE or UKCA mark and meet all other standards within the DTAC.
- Are available for use in the NHS.

In total, four VR technologies for treating agoraphobia and/or agoraphobic avoidance were included in the scope. For the included technologies, the EAG noted that version changes may limit the generalisability of evidence. Furthermore, it should be noted that evidence evaluating the interventions did not always use the present brand names.

3.2.1. Amelia Virtual Care (Amelia Virtual Care)

Amelia Virtual Care is a VR platform designed to be used 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 Amelia's smartphone app. It also offers a homework feature with virtual mindfulness and relaxation sessions. Amelia helps therapists to facilitate the delivery of evidence-based treatment including gradual exposure, mindfulness-based cognitive therapy and desensitisation. Amelia has over 100 virtual environments that can be configured and personalised to a person's needs using a simple control panel.[4] Amelia was

previously called Psious. The company has confirmed that this was largely a re-branding exercise with no changes to the intervention content, though some changes had been made to environments and avatar options.

3.2.2. gameChangeVR (Oxford VR)

gameChangeVR was designed to treat agoraphobia and agoraphobic avoidance in people with psychosis. It delivers cognitive therapy within a VR environment and is compatible with a range of VR equipment that uses six degrees of freedom tracking (i.e the range of motion for objects within here dimensional space). 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 six 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 gameChangeVR in the real world. It may be used with outpatients in clinics or at home. The company suggested that it may also benefit people in inpatient settings. The EAG noted that the name of this technology has changed since the CE mark was issued. gameChangeVR was initially called Social Avoidance. The company request for information states that this name has not yet been updated on the CE mark, but this will be done on the next iteration of the Declaration of Conformity and Instructions for Use. The company advised that the latest version of the technology functions 'untethered'; that is to say, removing the need for a high specification desktop or laptop computer and allowing it to run on the latest stand-alone headset devices.

3.2.3. Invirto (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. No company reference list was provided, and the company did not respond to queries by NICE. No

evidence was identified by the EAG and therefore this technology was noted but not explored in detail.

3.2.4. XR Therapeutics (XR Therapeutics)

XR Therapeutics (XRT) offers a VR-based treatment platform to help reduce anxieties and treat phobias including agoraphobia. It was 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. The company said this is easy to install, operate and maintain. The company has advised that originally the technology used third-party hardware called the Blue Room, as referenced in Maskey et al.[5] However, XR Therapeutics has now developed the Immersive Studio, in-house hardware and software. The company states that the *"treatment is still based on the initial research, but we have significantly advanced the technology being used"* (Personal Communication, XR Therapeutics, April 2023).

3.3. Comparator

The comparator is standard care which may include guided self-help, CBT with exposure therapy, applied relaxation, antidepressants and/or simple contact and monitoring with services.

4. CLINICAL CONTEXT

The target population for this assessment is described in section 3.1.

4.1. Care pathway

The NHS recommends a stepped care approach for treating agoraphobia and any underlying panic disorder.[1] The first step involves recognition and accurate diagnosis, including identification of any comorbidities. The second step involves guided self-help. The third step involves more intensive treatments such as CBT or medication.

Psychological treatments for agoraphobia include self-help programmes and CBT with exposure therapy and is usually delivered in primary care or in local settings such as NHS Talking Therapies. However, agoraphobia can be treated in secondary care and inpatient settings, particularly due to co-occurring complex or severe mental health problems.

Treatment for agoraphobia and agoraphobic avoidance 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 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 generalised anxiety disorder and panic disorder in adults[6] recommends that people with moderate to severe panic disorder with or without agoraphobia should be offered CBT or an antidepressant. For those diagnosed with psychosis, the NICE clinical guideline[7] recommends oral antipsychotic medication along with psychological interventions including family intervention and individual CBT. SCM input advised that only a minority of people with psychosis receive the recommended treatment and may instead be offered antipsychotic medication and simple contact and monitoring with services.

One SCM noted that the care pathways outlined in the scope reflect routine practice well. Generally, it was noted that that there is no established care pathway for agoraphobia within a psychosis setting and that people with agoraphobia and psychosis may not necessarily be diagnosed with agoraphobia due to symptom overlap and a focus on treating psychosis symptoms as the primary diagnosis.

4.1.1. Current use of VR technologies to treat agoraphobia

The companies advised that their respective VR technologies are in current use within the NHS for agoraphobia or psychosis: Amelia Virtual Care (six NHS Trusts), gameChangeVR (two NHS Trusts on an investigational basis) and XR Therapeutics (four NHS Trusts). SCMs were not aware of VR technology use in routine NHS practice for agoraphobia.

It is anticipated that VR-based interventions[4] would be offered after clinical assessment and diagnosis and as an alternative or addition to standard care psychological interventions for agoraphobia and agoraphobic avoidance. VR could be delivered by a therapist as part of face-to-face therapy or teletherapy or used as a standalone intervention with the support of a mental health worker such as an assistant psychologist, peer support worker or therapist. The level of support provided may vary depending on the intervention and the person's need.

4.2. User issues and preferences

It is anticipated that VR technologies may increase treatment options and access to care. They may enable some people to receive treatment at home. This may be especially beneficial for people with agoraphobia or agoraphobic avoidance who have difficulty leaving their homes to access standard care. VR technologies may also help people to test their fear expectations in a setting where they feel safe. People may feel more comfortable completing behavioural experiments in VR and this could increase their confidence in performing these tasks in real-world settings. People may be more motivated to use and engage with VR if they have sufficient digital skills and prefer remote or digital interventions to face-to-face therapy.

However, it should be taken into consideration that some people may have a preference for face-to-face therapy and may choose not to use VR technology. There may be some concerns about the level of support provided and uncertainty around how treatment may be delivered. Lay SCM input noted that some may be disappointed if scenes in VR interventions are not photorealistic. The realism of a VR environment is important both in terms of how it influences the perception of the user[8] and how it impacts the intended outcomes of the VR experience.[9]

5. SPECIAL CONSIDERATIONS, INCLUDING ISSUES RELATED TO EQUALITY

A number of potential equality issues have been identified.

People using VR-based technologies at home would be provided with the VR device through their mental health service. However, some VR technologies require Wi-Fi to use the intervention or upload content. This could lead to challenges for those in rural areas with poor internet services or those who do not have internet access in their homes.

Additional support may be required for those with poor digital literacy or poor internet connectivity. Furthermore, people with visual or cognitive impairment, problems with manual dexterity, people with a learning disability or who are unable to read or understand health-related information, and people who cannot read English may need additional support to use the technologies, although the EAG is aware that software packages can be (and have been) adapted to overcome some of these issues. Some people would benefit from VR in languages other than English. In general, views of mental health problems and interventions may vary according to their ethnicity, religious or cultural background.

VR may not be suitable for use by people with photosensitive epilepsy, significant visual, auditory, or balance impairment, organic mental disorder, primary diagnosis of alcohol or substance disorder or personality disorder, significant learning disability, or active suicidal plans.[4] Some VR interventions may involve moving around the room or standing. This may be difficult for some people with physical disabilities or additional accessibility needs.

6. POTENTIAL IMPLEMENTATION ISSUES

The NICE adoption and implementation team consulted clinical experts and noted several potential implementation issues for VR technologies:

- Safety and comfort – including dizziness, the amount of space needed, wearing glasses.
- Patient selection – ensuring VR technologies are used for people with the target condition.
- Acceptability.

However, some software can be (and has been) adopted to overcome some of these difficulties. The EAG also notes that not all interventions require the use of VR headsets. Other issues relevant to this appraisal are outlined in the scope.

7. CLINICAL EVIDENCE SELECTION

7.1. Search strategy

Search strategies were based on those devised during the initial scoping searches by NICE Information Services with some amendments. The search strategies used relevant search terms, comprising a combination of indexed keywords (e.g., Medical Subject Headings, MeSH) and free-text terms appearing in the titles and/or abstracts of database records and were adapted according to the configuration of each database. No date, language or publication status (published, unpublished, in-press, and in-progress) limits were applied. Searches for clinical and cost-effectiveness were combined and carried out in one search strategy.

Following deduplication, a total of 318 records of potentially relevant evidence on clinical and/or cost effectiveness were retrieved. Databases searched were Medline (including Medline in Process), Embase, PsycInfo, Cochrane, INAHTA, CEA Registry and ScharrHUD. Additional trial registries searched were Clinicaltrials.gov (NLM) and ICTRP (WHO). The websites of the individual companies were searched; NICE and SIGN websites were searched for related guidelines; MAUDE and MHRA were searched for adverse events data; the company submission references were also scanned for additional references.

The search strategies are presented in Appendix A.

7.2. Study selection

The abstracts and titles of references retrieved by the searches were screened for relevance. Full paper copies of potentially relevant studies were obtained. The retrieved articles were assessed for inclusion against pre-specified inclusion/exclusion criteria. At each stage of screening, a minimum of 10% of records were independently screened by a second reviewer. Discrepancies were resolved by discussion, with involvement of a third reviewer, where necessary. All duplicate papers were excluded.

This assessment looked across a range of evidence types, including RCTs and real-world evidence, to inform clinical effectiveness.

The following study types were excluded:

- Animal models

- Pre-clinical and biological studies
- Narrative reviews, editorials, opinion pieces
- Meeting abstracts for studies where full-text papers were available. If studies were only available as meeting abstracts, inclusion depended on sufficient information being available to offer meaningful critique.
- Studies not available in the English language.

Eligible studies assessed a scoped intervention (Amelia Virtual Care, gameChangeVR, XR Therapeutics or Invirto) in a population of adults (16+) with agoraphobia or agoraphobic avoidance.

Studies were not excluded if the comparator did not match the scope or if the outcomes did not match the scope, provided the outcomes appeared reasonable and could offer useful information in the context of the appraisal. Studies conducted in other populations were not included, but a brief commentary on these indirectly relevant studies was provided. This did not include studies conducted exclusively in a paediatric population, as it was not considered that these would inform the present decision problem. In the event that studies investigated a closely related population, such as a study with a majority of adult participants but some paediatric participants, these could be included, depending on what other evidence was identified.

A PRISMA flow diagram is provided as Appendix B.

Data were extracted from included studies by one reviewer into a bespoke database and a sample of at least 10% was checked by another reviewer. Generalisability to NHS practice was considered in the interpretation of the findings.

Due to time and resource constraints associated with conducting an EVA, the EAG did not conduct formal risk of bias assessment of the included studies. Generally, RCTs could be considered more robust than other study types, but it depends on the details of how each study was conducted, and how well the trial setting reflects routine clinical practice in terms for example of eligible population and staff attention, which could affect generalisability. For example, adverse event data may be better collected via cohorts or other longitudinal study designs.

The EAG identified the key studies for detailed assessment for each technology, based on a preference for studies conducted within a UK setting and studies near the top of the hierarchy of evidence[10] (such as RCTs) where available and then assessed whatever outcome data were available within these key studies, supplementing this with additional data from other studies where it was considered appropriate.

8. CLINICAL EVIDENCE REVIEW

The EAG identified a total of nine publications, comprising four unique studies, that were relevant to the present decision problem. One included paper[11] was an economic analysis of an included study and is explored in more detail in section 10.1 of this report.

Table 2 presents a detailed overview of the study design and characteristics of each included study. No evidence was identified for Invirto.

Table 2: Included clinical effectiveness studies

References	Study name	Country	Method	Sample	Intervention	Comparator(s)	Outcomes
Amelia Virtual Care							
Gelabert and Giner, 2018[12]	NR	Spain (Catalonia)[a]	Single-arm study	51 adults over 18 with a diagnosis of agoraphobia or panic disorder with agoraphobia (only 42 were included in analysis)	Amelia Virtual Care[a] (conference abstract, so no further details about intervention delivery available)	None	Follow-up was 6 months • Number of intervention sessions needed • Therapeutic adherence • Patient satisfaction
gameChangeVR							
Altunkaya et al, 2022;[11] Bond et al, 2023;[13] Freeman et al, 2022a,b,c[14-16]	gameChangeVR trial.	UK	RCT, with embedded qualitative study and economic evaluation	346 people (aged 16 or older) with a clinical diagnosis of schizophrenia spectrum disorder or an affective diagnosis with psychotic symptoms, and who have self-reported difficulties in going outside due to anxiety	gameChangeVR (approximately 6 sessions – with some variation if needed – of 30 minutes each over 6 weeks)	Treatment as usual (no published details, but information provided in correspondence from Prof Freeman is discussed in text)	Follow-up in primary analysis paper 6 months Primary: • Agoraphobic avoidance (Oxford Agoraphobic Avoidance Scale; Oxford-Behavioural Avoidance Test). Secondary: • Agoraphobia (Agoraphobia Mobility Inventory-Avoidance-scale), • Suicidal ideation (Columbia Suicidal Severity Rating Scale)

References	Study name	Country	Method	Sample	Intervention	Comparator(s)	Outcomes
							• Paranoia (Revised Green et al Paranoid Thoughts Scale) • Paranoia worries (Paranoia Worries Questionnaire) • Depression (PHQ-9) • Activity levels (actigraphy over 7 days; time budget) • Quality of life (EQ-5D) • Recovery Quality of Life questionnaire; Questionnaire about the Process of Recovery) • Safety (serious adverse events; adverse event profile) • Participant satisfaction • Participant experiences with gameChangeVR • Economic outcomes (see Section 10.1)
Knight et al, 2021;[17] Lambe et al, 2020[18]	gameChangeVR project	UK	Person-centred design process	Clinical psychologists, programmers, animators, designers, product managers,	Development of gameChangeVR (this study profiles the intervention development process rather	None	• Multistakeholder perspectives to inform the development of gameChangeVR • User acceptability ratings

References	Study name	Country	Method	Sample	Intervention	Comparator(s)	Outcomes
				producers, writers, researchers, 3D artists, mental health advocates, and people with lived experience of psychosis	than assessing the effectiveness of its delivery)		
XR Therapeutics							
Maskey et al, 2019[5]	NR	UK	Single-arm study	8 adults (18-60) with autism who reported 'fears and phobias')	XR Therapeutics[a] (2 visits each comprising 2 sessions of 20-30 minute with a 15 minute break)	None	Follow-up was 6 months • Participation • Retention • Symptom change (Target Behaviors) • Anxiety (Beck Anxiety Inventory, Generalized Anxiety Disorder 7, self-reported ratings of confidence in managing target anxiety situation) • Depression (Patient Health Questionnaire – 9) • Quality of life (WHOQOL-BREF).

a = confirmed through correspondence with the company.

Abbreviations: BDI, Beck Depression Inventory; dCBT, Computerised Cognitive Behavioural Therapy; CES-D, Center for Epidemiologic Studies Depression Scale; CORE-OM, Clinical Outcomes in Routine Evaluation – Outcome Measure; GAD, Generalised Anxiety Disorder assessment; HRSD, Hamilton Rating Scale for Depression; IAPT, Improving

Access to Psychological Therapies; MADRS, Montgomery-Asberg Depression Rating Scale; PHQ, Patient Health Questionnaire; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Report; RCT, Randomised controlled trial; UK, United Kingdom; USA, United States.

8.1. Overview of methodologies of all included studies

All studies described in Table 2 had some methodological limitations or misalignment with the NICE decision problem for this appraisal.

8.2. Study design, intervention and comparator

There was a total of four unique included studies (two for gameChangeVR and one for each of Amelia and XR Therapeutics), published in nine papers. The included studies for gameChangeVR and XR Therapeutics were conducted in a UK setting, while the included study for Amelia was conducted in Spain. There was one RCT –for gameChangeVR.[15]

The comparator in the gameChangeVR trial[15] was treatment as usual, which was not described clearly in the papers or company submission, although resource use was measured in the companion economic evaluation.[11] Some information on treatment as usual was provided in the supplementary material but not signposted in the main paper. Treatment as usual differed between trusts and centres, so could not be considered consistent across participants. Correspondence from the lead author of the gameChange trial, Professor Daniel Freeman, clarified that in the treatment as usual arm 92% of participants were on antipsychotic medication, 58% were on an antidepressant, 85% were seeing a care co-ordinator (believed to mainly be monthly) and around two thirds (exact value not provided) were seeing a psychiatrist every few months. This study took place in a UK setting, but standard care as a comparator also has known limitations due to variability in routine practice between centres.

There was no comparative evidence for Amelia or XR Therapeutics.

> **Evidence gap**: No clinical effectiveness evidence was available for Amelia, and no RCT evidence was available for XR Therapeutics. Pivotal evidence for gameChangeVR was as adjunct to treatment as usual against treatment as usual alone and no details were provided about what this comprised in the main trial paper. However, this can be partially inferred from the companion economic evaluation and the lead author communicated some further details. Any future research involving a treatment as usual (TAU) arm needs careful definition of TAU.

8.3. Participants and setting

The key studies for gameChangeVR and XR Therapeutics were conducted in a UK setting. The evidence for Amelia was from a Spanish setting, which the EAG considered to be relatively comparable, although there are likely to be some differences in terms of how care is structured and delivered. Studies were generally conducted in an outpatient setting, although four participants in the gameChange trial were psychiatric inpatients and incurred particularly high costs in the model.

All included studies described participants who are broadly relevant to the decision problem. The evidence base for gameChangeVR was specifically in the context of schizophrenia spectrum disorder or psychosis, which aligned to a subgroup of interest in the NICE scope. The single-arm study by Gelabert and Giner (2018),[12] for Amelia considered participants with a primary diagnosis of agoraphobia or panic disorder with agoraphobia. The Maskey et al[5] study for XR therapeutics included only eight participants consisting of adults with autism who had various 'fears and phobias', only two of whom reported phobias related to agoraphobic symptoms (open spaces and crowded buses). This study therefore is only partially relevant for this decision problem.

> **Evidence gap**: Evidence for Amelia Virtual Care was only available in a Spanish setting. There was no evidence for XR therapeutics in a population with agoraphobia (only 2/8, 25%) of participants had fears related to those experienced by people with agoraphobia)
>
> **Generalisability gap**: Available evidence for gameChangeVR was exclusively in a psychosis setting. The available study for XR Therapeutics considered exclusively people with autistic spectrum disorders. However, this specific focus may also have a benefit, as the intervention specifically considers the needs of people with autism which might address health inequalities.

8.4. Outcomes

None of the included studies reported all outcomes included in the NICE scope, but all reported some outcomes of interest. The gameChangeVR project[17,18] and Gelabert et al for Amelia [12] focused on user experience and process outcomes. The gameChangeVR trial[15] and Maskey et al[5] studies presented clinical effectiveness

outcomes. Instruments used differed, but both studies presented measures of mood and social functioning or quality of life. The gameChangeVR trial reported measures of agoraphobia symptoms, while Maskey et al[5] assessed symptom change using target behaviours. Safety data were presented for the gameChangeVR trial, in terms of serious adverse events, but not for the other interventions.

The EAG noted that change with respect to validated thresholds for minimally clinically important difference (MCID) were not always reported in the trial publications, and those reported were not clearly cited or justified. The EAG was unable to identify published MCID thresholds in an agoraphobia population for the key outcome measures, and therefore the interpretation of clinical effectiveness outcomes is uncertain. The EAG asked SCMs for input on this matter. While the SCMs reported that a variety of measures were used in their clinical practice, no specific MCIDS were identified. However, one suggested a potential rule of thumb based on 0.5 standard deviations.

> **Evidence gap**: Evidence was not available for all scoped outcomes for all scoped interventions. Validated MCIDs may not be available for key outcome measures, and therefore change with respect to the MCID was not comprehensively assessed. No clinical outcomes were reported for Amelia.
>
> **Heterogeneity issue**: There was variation in which outcomes were assessed between studies and what instruments were used.

8.5. Quality of included studies

A RCT was available for just one of the three technologies (gameChangeVR). UK-based evidence was available for two technologies (gameChangeVR and XR Therapeutics). Evidence for Amelia was available from Spain, which may be relatively generalisable to a UK context, but there will be some differences to consider in terms of culture and health system operation. The company advised that most of the environments used in Amelia are language-free, meaning they contain ambient audio but do not have a specific script or audio guide. This may aid transferability between countries, although it is noted that the environments have not specifically been validated in different languages. It is important to note that the Amelia environments are not intended as treatment protocols, but rather as tools for therapist use based on clinical judgement.

In the principal evaluation of gameChangeVR,[15] it should be noted that there was a substantial pause in recruitment from 16 March 2020 to 14 September 2020. It is uncertain if this would have impacted upon sampling consistency. Moreover, due to face-to-face restrictions caused by COVID, a protocol amendment was necessitated to replace the original primary outcome measure the Oxford Behavioural Avoidance Test (O-BAT) with a previous secondary outcome measure the Oxford Agoraphobic Avoidance Scale (O-AS). In total, 19 participants had VR therapy curtailed due to Covid-19-related policy decisions and 8 participants in the VR group could not receive any therapy. Treatment was unaffected for 84% of participants. These circumstances may result in somewhat reduced generalisability compared to trials conducted at other times.

The Maskey et al[5] study for XR Therapeutics included only eight patients and was specifically conducted with a population of people with autism who had 'fears and phobias'. The generalisability of this evidence to a broader agoraphobia population is therefore restricted. Additionally, gameChangeVR is positioned for agoraphobia specifically in a psychosis context, which is a subgroup of the NICE scope, but may not generalise to the broader scoped population.

> **Methodological gap**: Studies for gameChange VR and XR Therapeutics assessed populations that were relevant to the NICE scope, but often did not match precisely to the full breath of the scoped population.

8.6. Results from the evidence base

The EAG summarises the results from the evidence base in this section, arranged by intervention as per the NICE scope. Detailed results for all eligible studies are presented in Appendix D.

8.6.1. Amelia Virtual Care

Evidence was available from one single-arm study of Amelia, conducted in a Spanish setting.

In the single-arm study by Gelabert and Giner (2018),[12] 98% of the 42 participants completed their course of psychotherapy within the previously established course of eight sessions. Two participants required two additional sessions of Amelia Virtual Care therapy beyond the protocol. The entire treatment protocol was completed by

82.4% of participants, with the main cause (55.6%) for non-completion being a lack of presence within the virtual environment and consequent perception of its usefulness. Presence relates to the extent participants can really feel like they are in the scenario being situated. On the Client Satisfaction Questionnaire-8,[19] 57% of participants indicated a high or very high presence, while 12% indicated a null or low sense of presence. Across categories, there was an average satisfaction rating of 68%.

Overall, while there is evidence that Amelia has fairly good adherence and patient satisfaction, there is no evidence as to whether Amelia produces clinical benefit over and above existing care.

8.6.2. gameChangeVR

Evidence was available from one person-centred design study of how gameChangeVR was developed (the gameChangeVR project)[17,18] and one RCT of gameChangeVR added on top of treatment as usual against treatment as usual alone[14-16] (not specifically defined, the gameChangeVR trial), with embedded qualitative[13] and economic[11] analyses – both conducted in a UK setting.

In the gameChangeVR project,[17,18] a series of six key scenarios were developed based on participant input and feasibility of designing a suitable VR environment. These were: café (request or order), waiting room (give personal information), pub (unexpected event/erratic behaviour), bus (trapped/shut in), food shop (find an item), and street (safe place to unknown). In user testing, the success criterion was pre-determined as 90% of users rating gameChangeVR as immersive, easy to use and engaging. This was achieved, with all six participants rating gameChangeVR accordingly.

In the gameChangeVR trial, qualitative analysis[13] showed that anxious avoidance was having a significant impact on participants' lives before the VR intervention, leaving some of them housebound and isolated. Overall, participants reported that using the intervention created an anxiety response that was useful for learning and practicing a different response while still within their safe environment. There was a need to balance the intensity of the anxiety response to a middle ground, so that the intervention was not boring (anxiety response too low) or that the intervention was not overly draining (anxiety response too high). The authors reported that the support

provided within the intervention meant that finding the right balance was *"usually"* possible (Bond et al, p.8). Those people who supplemented the intervention with activities to reinforce learning (e.g. writing notes, active reflection, discussions with care teams) generally had a better response to the intervention. Motivation to engage with the intervention, including undergoing the anxiety response within, was reported to be important. Those who were coping well with their condition had less motivation for this. Those who were struggling the most with agoraphobic avoidance expressed the greatest appreciation for, and gains from, gameChangeVR therapy.

Freeman et al[15] found statistically significant benefits of VR exposure therapy on agoraphobic avoidance (p=0.026) and distress (p=0.014) measured by O-AS and the Questionnaire about the Process of Recovery.[20] However, the EAG considered that the magnitude of effect on reported outcome measures was not particularly large; the authors reported that a difference of 1 point on the O-AS avoidance measure was considered clinically meaningful, though the difference between arms was <1. No minimally important difference (MID) for the O-AS distress was reported and the EAG was unable to identify this. However, the difference between arms (-4.33, 95%CI -7.78, -0.87) appeared small in comparison to the scale (0-80). There was no statistically significant difference between arms in participants' quality of life or other secondary outcome measures. The EAG also noted that numerical differences between treatment arms reduced between week 6 and week 26, suggesting that any benefit of gameChangeVR as compared to usual care was short-lived.

Consistent with the qualitative evidence suggesting that those with more severe symptoms may benefit more from gameChangeVR, Table 4 of the Freeman et al[15] publication shows that those with severe symptoms showed larger improvements on agoraphobic avoidance and distress symptoms as measured by the O-AS (SCM input noted that while there is no specific criteria for severe symptoms, it would be fairly straightforward to identify people with severe agoraphobia on a case by case basis). In this paper, average avoidance was a score of 0 on the O-AS, moderate avoidance 1-2, high avoidance 3-5 and severe avoidance 6-8. In the case of the O-AS avoidance, the benefit was >1 indicating that the difference was clinically meaningful according to this threshold. The benefit for distress was >10% of the scale and was considered to be more likely to be clinically meaningful for patients, pending a validated MID threshold. These differences were also reasonably stable between 6 and 26 weeks. In comparison, benefits for participants with average,

moderate or high severity symptoms were absent or more uncertain. Only O-AS subscales were reported separately according to baseline severity, and therefore it was unclear if this pattern of effects was present across other scoped outcomes. Freeman et al[16] found that participants with severe agoraphobia showed the greatest benefits from gameChangeVR therapy, exhibiting significant post-treatment improvements in agoraphobic avoidance, agoraphobic distress, ideas of reference, persecutory ideation, paranoia worries, recovery quality of life, and perceived recovery, but no significant improvements were found in depression, suicidal ideation, or health-related quality of life. Further data can be found in Table 3 of the publication.

Considering patient satisfaction, Freeman et al[14] found that 65.8% of patients were very satisfied with VR therapy, 30.8% were mostly satisfied, 2.5% were indifferent or mildly dissatisfied, and 0.8% of patients were quite dissatisfied. Difficulties concentrating in VR (see adverse events Section 9) were associated with slightly lower satisfaction. Safety data are presented in Section 9. An economic analysis was also conducted[11] and this is discussed in Chapter 13.

While gameChangeVR received high levels of patient satisfaction from participants, there was evidence that it was only beneficial for reducing symptoms of agoraphobia in participants with severe symptoms at baseline (as opposed to those with average, moderate or high symptom severity). However, more evidence is needed to determine whether this effect was consistent across other outcomes, such as quality of life. Furthermore, base case economic results for gameChange were highly influenced by four inpatient people with psychosis who incurred particularly high costs. This was not explored in the gameChange trial publications.

8.6.3. Invirto

No eligible evidence was identified for this technology.

8.6.4. XR Therapeutics

Evidence was available from one single-arm study [5] assessing eight adults with autism and ‘fears and phobias’ – conducted in a UK setting. This was the most relevant evidence available for this technology. There were no other adult studies for

this technology identified in this appraisal. There were two paediatric studies, which are discussed in Section 8.7

As this was a single-arm study, results can only show whether participants' scores improved over time and cannot show whether XR Therapeutics was more effective than standard care or whether any benefit of this technology remains following adjustment for confounding effects.

Retention and participation were achieved for all sessions. Members of an expert panel rated five out of eight participants as showing an improvement in their symptoms related to their phobia, however these participants did not include the two participants with phobias relevant to agoraphobia (open spaces and crowded buses), whose symptoms were reported to be "equivocally improved". This was a smaller potential improvement that allowed by the scale, which also included options for "normalised", "markedly improved", and "definitely improved". Two of the non-responders attributed their non-response to personal circumstances and routine changes respectively, while the third was making progress at the 6-month follow-up while not yet meeting response criteria. The sample did not show any benefit for general symptoms of anxiety (GAD-7 and BAI), depression (PHQ-9) or quality of life. Participants' self-reported confidence for managing their phobia appeared to improve between baseline and the end of session 4, though as with other outcomes, these data are challenging to interpret without a control arm. Across the sample, there was no difference in WHOQOL-BREF subscales following treatment, with the exception of a small improvement in the social subscale.

The company's reporting focused on statistical significance and the company attributed the absence of statistically significant benefit to the absence of specifically validated outcome measures for a population of people with autism. However, the EAG was not convinced by this explanation, given that the measures used (Table 2) have been widely used across populations, including people with autism.

8.7. Additional indirectly relevant evidence

In addition to the included studies, the EAG noted some additional indirectly relevant studies and studies that are outside of scope. These are listed with reasons for exclusion in Table 17 and Table 18, in Appendix C.[21-51]

The EAG considered that the most potentially relevant among these additional studies are Freeman et al[27] for gameChangeVR and Maskey et al[50] and Maskey et al[51] for XR Therapeutics. Freeman et al[27] randomised 30 people with persecutory delusions to receive either virtual reality exposure or virtual reality cognitive therapy. Compared to exposure, cognitive therapy led to reductions in delusion conviction (reduction 22.0%, P = 0.024, Cohen's d = 1.3) and real-world distress (reduction 19.6%, P = 0.020, Cohen's d = 0.8). Additional Maskey et al studies were conducted in a paediatric population. However, given the presence of only one adult study for this intervention, it was considered that this evidence may be of interest. These were both conducted in a population of young people (up to age 14) with autistic spectrum conditions who have fears and phobias. Maskey et al[52] reported a single blind RCT on a total of 35 young people from the North East of England compared to delayed treatment and found no statistically significant benefit on questionnaire outcomes, although a statistically significant improvement in Target Behaviours was found for the intervention group compared to the control group, from baseline to two months (U=67.5, p=0.021) and from baseline to six months post treatment (U=53.0, p=0.007), with six out of 16 participants counted as responders in the treatment group after six months compared to no participants in the control group. Maskey et al[51] reported a single-arm study of eight young people from the North East of England and found that four participants were classed as responders at 12 months, three were classed as non-responders and one participant was lost to follow up. An earlier paper by Maskey et al,[50] also in a paediatric population with autism, but delivering the intervention differently than the later work, found that among nine young people, four overcame their phobias, eight out of nine were classed as treatment responders, this was maintained at 12-16 months follow-up and there was no loss to follow up in this analysis.

9. ADVERSE EVENTS

Information on adverse events were only available for one intervention (gameChangeVR). MAUDE (U.S. Food and Drug Administration) and MHRA (UK Government alerts) searches did not retrieve any results.

Freeman et al[15] found that there was no statistically significant difference in the occurrence of serious adverse events between the gameChangeVR group (12 events in 8 patients) and the usual care alone group (eight events in seven patients, p=0.37). However, serious adverse events per participant were numerically higher in the gameChangeVR group and the EAG considers caution is required in interpreting the lack of statistical significance due to small sample size. A secondary analysis paper from this trial[14] presents a broader adverse event profile. The most common adverse events were thinking about what might be happening in the room (14.2%), lasting headache (8.3%), and the headset causing feelings of panic (7.4%). However, there was no assessment of VR-specific adverse events using a standard questionnaire, such as the Simulator Sickness Questionnaire[53] to assess cybersickness, as used by Pot-Kolder et al[54] in a study of a non-scoped VR technology. This secondary analysis profiled adverse events only in the VR arm and not in the treatment as usual arm.

> **Evidence gap**: Published safety information was only available for one intervention (gameChangeVR) investigated specifically in a psychosis context, and VR-specific adverse events were not assessed using a standard questionnaire. Moreover, safety data came only from an RCT, rather than real-world safety assessment.

10. ECONOMIC EVIDENCE

10.1. Published economic evidence

The search for economic evidence was conducted alongside the search for clinical evidence, detailed in Section 7.1. After screening, the only directly relevant study identified was Altunkaya et al (2022),[11] a within-trial cost-effectiveness analysis conducted alongside Freeman et al. 2022.[15] The objective of the evaluation was to estimate the maximum cost-effectiveness price for gameChangeVR given conventional willingness-to-pay thresholds for QALYs routinely used in the NHS.

A full critique of the clinical trial can be found in Section 8, above. Briefly, 346 participants with psychosis and symptoms of agoraphobia were randomised to gameChangeVR+TAU or TAU (174 intervention, 172 comparator), with six-month follow-up. The frequency of participants' HRQoL and use of health and social care was recorded at baseline, six weeks and six months.

Participants completed two types of health-related questionnaires, EQ-5D-5L and Recovering Quality of Life (ReQoL). From this, two sets of utility scores were generated and consequently two sets of QALYs also produced. QALYs were calculated from utilities using the area under the curve approach. GameChangeVR+TAU was associated with an incremental gain of +0.008 (-0.010 to 0.026) EQ-5D-based-QALYs (Table 3) and +0.003 (-0.011 to 0.017) ReQoL-based QALYs (Altunkaya et al 2022[11]) compared with TAU alone.

Costs were calculated from an NHS and personal social services perspective (as per the NICE reference case[55]), as well as a societal perspective. Health care services comprised GP contacts, contacts with psychiatrists, therapists and community mental health teams, hospitalisations, emergency department visits, outpatient appointments and paid help from NHS or social care services. Societal costs comprised criminal justice costs, private health care and carer time, but did not measure lost productivity from time-off-work. Criminal justice costs included police contacts, nights spent in a police cell or prison, psychiatric assessments whilst in custody and criminal or civil court appearances. Unit cost for paid care at home was based on the home care worker cost per hour reported on PSSRU 2019;[56] while the unit cost for unpaid care received from family and friends was based on minimum hourly wage in 2019.[57]

Overall, gameChangeVR was associated with a -£105 (-£1,135 to £924) difference in NHS & PSS costs (Table 4). These incremental costs excluded the cost of delivering gameChangeVR so were used to estimate the maximum cost that could be charged to yield an ICER below commonly accepted thresholds used by NICE and the NHS.

The EAG notes that the cost of VR headsets, training and intervention delivery was not included in the analysis, thus the maximum cost-effective prices represent the maximum per patient cost of delivering the entire intervention (software, headset, training, and intervention delivery), not just the licence cost for the software.

Taking an NHS and PSS perspective and using QALYs calculated using EQ-5D, the gameChangeVR intervention could cost up to £262 or £341 per person based on a £20,000 or £30,000 threshold for it to be cost-effective. When considering the intervention's impact on wider societal costs beyond the NHS and PSS perspective (which is beyond the scope of costs usually considered within NICE appraisals), the maximum cost-effective price was greater (Table 5).

Subgroup analyses were conducted stratifying participants by Oxford Agoraphobic Avoidance Scale, defined as (1) high or severe avoidance, (2) high or severe distress, (3) high or severe avoidance or distress, and (4) high or severe avoidance and distress. In each case the base case was the most pessimistic (i.e. the lowest maximum price). Table 5 reports the most optimistic subgroup by perspective based on a £20,000 per QALY threshold. From an NHS+PSS perspective in those with high or severe avoidance and distress, the maximum price yielding an ICER below £20,000 is £684 (£844 at £30,000/QALY). Full subgroup analyses are reported in Altunkaya et al. 2022.[11]

The EAG noted the lack of statistically significant differences in incremental costs and QALYs and that the base case results were disproportionately driven by four psychiatric inpatient participants (three randomised to gameChangeVR+TAU and one to TAU). Specifically, the point estimate difference in NHS+PSS costs between arms increased from -£105 to +£233, and incremental QALYs fell from 0.008 to 0.006, resulting in there being no positive price at which gameChangeVR was cost-effective in the general population with psychosis and agoraphobia from an NHS+PSS perspective. However, there were subgroups for which gameChangeVR had the potential to be cost-effective: subgroups 1 (high or severe avoidance) and 4 (high or severe avoidance and distress), and 3 (high or severe avoidance or distress)

at a £30,000 threshold only. The most optimistic scenario yielded a max price of £125 at a £20,000 threshold (or £324 at £30,000) (Table 5).

Table 3 Utilities and QALYs accrued (EQ-5D-based)

	gC+TAU (n=174), mean (SE)	TAU (n=172), mean (SE)	Adjusted mean difference (95% CI)
Baseline	0.538 (0.021)	0.545 (0.020)	N/A
6 weeks	0.608 (0.021)	0.588 (0.022)	0.026 (-0.023-0.075)
6 months	0.570 (0.023)	0.568 (0.022)	0.007 (-0.043 to 0.057)
QALYs @ 6m	0.293 (0.010)	0.288 (0.009)	0.008 (-0.010 to 0.026)

gC: gameChangeVR; TAU: treatment as usual; N/A: not applicable. Source: Tables 2&4, Altunkaya et al (2022) [11]

Table 4 Summary costs, gameChangeVR+TAU vs TAU

Category	gC+TAU (n=174), mean (SE)	TAU (n=172), mean (SE)	Adjusted mean difference (95% CI)
NHS+PSS	£2695 (£619)	£2194 (£515)	–£105 (–£1135 to £924)
Criminal Justice	£42 (£20)	£2 (£2)	£38 (–0 to 77)
Caregiving	£2839 (£400)	£4403 (£860)	–£1,576 (–£3432 to £280)
Other private	£58 (£15)	£135 (£30)	–£88 (–£149 to –£26)
Societal	£5634 (£763)	£6733 (£993)	–£1,731 (–£3886 to £424)

Source: Table 4, Altunkaya et al (2022) [11]

Table 5 Maximum cost-effective price for different WTP thresholds, base case and selected sub-group analyses (EQ-5D-based QALYs)

	Incremental QALYs (95% CI)	Incremental cost (95% CI)*	Max price @ £20,000 per QALY	Max price @ £30,000 per QALY
NHS & PSS perspective				
Base Case (n=174, 172)	0.008 (-0.010 to 0.026)	–£105 (–£1135 to £924)	£262	£341
High or severe avoidance and distress (n=72, 90)	0.016 (-0.012 to 0.044)	-£365 (-£2399 to £1670)	£684	£844
Base Case excluding 4 inpatient participants (n=171, 171)	0.006 (-0.012, 0.025)	£233 (-£417 to £883)	N/A*	N/A*
High or severe avoidance excluding 4 inpatient participants (n=88, 98)	0.020 (-0.005 to 0.045)	£274 (-£699 to £1248)	£125	£324

Societal perspective				
Base Case (n=174, 172)	0.008 (-0.010 to 0.026)	–£1731 (–£3886 to £424)	£1888	£1967
High or severe avoidance (n = 90, 99)	0.021 (-0.004 to 0.046)	-£2431 (-£6005 to £1142)	£2859	£3073
Base Case excluding 4 inpatient participants (n=171, 171)	0.006 (-0.012 to 0.025)	-£1315 (-£3314 to £683)	£1435	£1495
High or severe avoidance excluding 4 inpatient participants (n=88, 98)	0.020 (-0.005 to 0.045)	-£1911 (-£5195 to £1374)	£2310	£2509

**Societal perspective includes NHS+PSS plus criminal justice services, private health care and carer time. So: Tables 6 & S13, Altunkaya et al. 2022* [11]

In summary, the evidence suggests that from an NHS+PSS perspective, the maximum acceptable per-patient price for delivering the gameChangeVR intervention ranges from below zero (in the general population with psychosis and agoraphobia, excluding inpatient participants) to £844 (subgroup with high or severe avoidance and distress, including psychiatric inpatient participants). However, this range underestimates uncertainty as it is based on point estimates from scenario analyses, ignoring confidence intervals around each.

10.1.1. Indirect evidence for economic outcomes

The EAG screened for indirectly relevant studies, as described in Section 8.7. We found no studies that provided information indirectly relevant to cost-effectiveness of the interventions. The only study which had discussed the benefit and cost was Segal (2011).[24] However, the paper only considered the therapist's perception of benefit and costs using virtual reality delivered treatments. Hence, it does not provide information on actual economic value. The EAG therefore concluded that there is no indirectly relevant study in this area.

10.1.2. Learnings relating to model structure and key issues impacting cost-effectiveness

The Altunkaya et al paper[11] was the only economic study considered of direct relevance to the decision questions. The EAG therefore used this as a starting point to develop a decision model to explore several uncertainties, namely duration of effect (i.e. time to relapse) and the effect of subsequent rounds of treatment.

10.2. Conceptual modelling

The primary purpose of this analysis was to assess whether there is a plausible *prima facie* case for any of the VR interventions to be cost-effective, and if so, to identify evidence gaps to guide future data collection. Due to the high-level exploratory nature of the modelling, point estimate ICERs should be considered broadly indicative and not conclusive.

As no evidence was received from the manufacturer of Invirto (and no published evidence was identified by the EAG) and no clinical effectiveness evidence was available for Amelia, the EAG excluded these two technologies from further analysis. The two other interventions (gameChangeVR and XRT) were both trialled in different populations: gameChangeVR was trialled in people with psychosis and agoraphobia as an adjunct to TAU, and XRT is at an early stage of development but was explored in people with ASD and fears/phobias.

These therefore represent two different decision problems (DP):

1. What is the cost-effectiveness of gameChangeVR+TAU vs TAU in people with psychosis and agoraphobia? (DP1)

2. What is the cost-effectiveness of XRT vs TAU in people with ASD and agoraphobia? (DP2)

In DP2, in people with ASD, the EAG noted that the evidence base for XRT was very weak in the target population for this EVA (reflecting the early stage of development of its product). The EAG therefore excluded XRT from formal modelling and provided commentary on the available evidence and how it could be used in a future model to estimate the likely costs and outcomes associated with XR Therapeutics. Decision problem 1 is described below.

An early value assessment is reported using a decision analytic model for DP1, in people with psychosis and agoraphobia. The model drew from the one economic evaluation of relevance identified in the EAG's searches (gameChangeVR, Altunkaya et al. 2022[11]), complemented by evidence sourced from the literature and supplemented with expert opinion. The analysis should be regarded as exploratory, focusing on the uncertainties in the data, rather than as a definitive estimate of the cost-effectiveness of the interventions against relevant comparator(s).

Evidence Gap: Clarity on whether VR interventions are generalisable to more than the target patient groups observed in the included studies, and thus whether more than one of the interventions would be available to the same patient (although SCM input noted that such a situation is unlikely at the moment, given the limited availability of the interventions). If so, their relative cost-effectiveness must be compared to ensure the most efficient intervention is offered first. Direct head-to-head trials (rather than indirect statistical comparisons) are considered the least biased evidence source of comparative effectiveness.

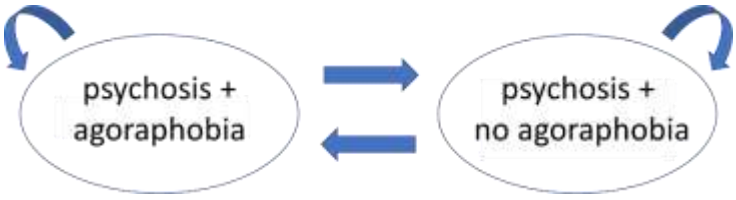
10.2.1. Population

The analysis is structured as a decision problem with a distinct population: people with psychosis and agoraphobia. There are no limitations by age or other subgroupings in the analysis.

10.2.2. Model structure

The model is a two-state state-transition model (Markov model). The states are psychosis+agoraphobia and psychosis alone.

Figure 1: Structure of state-transition model



Health states labelled according to decision problem 1. State names for decision problem 1 are people with psychosis+agoraphobia and psychosis+no agoraphobia.

The transition period for the model is six months and it is run for a period of five years. A six-month transition period was chosen to reflect the follow-up period of the most relevant source study (Altunkaya 2022[11]) as this enabled relatively easy translation of the data to the model. Five years were chosen as a reasonable time horizon over which to explore uncertainties in recurrence rates, and effectiveness of subsequent courses of therapy. (Note also Appendix F, supplied as a separate document.)

The choice of a state-transition model was driven purely by the need to explore uncertainties in longer term costs and effects of the different interventions. The key source study was a within-trial economic evaluation of gameChangeVR (Altunkaya 2022[11]). This presented costs accrued and health state utilities at six months (*inter alia*) by treatment arm. A state-transition model requires discrete health states to be defined, such as 'responder' and 'non-responder'. Data are not reported in such a manner in the source study.[11] Furthermore, doing so requires dichotomising patients according to either their absolute score on an outcome measure, or a minimum change in score. The cut-offs for these are essentially arbitrary, usually based on subjective clinical opinion as to what constitutes a meaningful change or difference in scores, and any categorisation results in loss of information (e.g. all patients with an outcome score above the cut-off are classed as responders no matter what their actual score).

To avoid such a dichotomy in this analysis, we assume all patients receiving VR therapy 'respond' at six months such that the mean per person utility changes according to the (adjusted) mean difference observed in the clinical trial for gameChangeVR (+0.007 SE approx. 0.013, Table 2, Altunkaya et al 2022[11]). This is the mean change in utility amongst all those who received the intervention. Therefore, 100% of patients transition from the 'agoraphobia' health state to the 'non-agoraphobia' health state in cycle 1. Subsequent cycles allowed the EAG to explore uncertainties around recurrence and effectiveness of second or more courses of VR therapy up to a time horizon of five years.

The model base case assumed those who relapse were offered additional rounds of therapy. Alternative assumptions were explored in scenario analysis.

Costs and outcomes accrued after the first year of analysis were discounted at 3.5% as recommended in the NICE manual.[55]

10.2.3. Interventions and Comparators

Definitions of intervention and comparators were driven by availability of source data. Participants were allocated to gameChangeVR+TAU compared with TAU. As described in section 8.2 above, TAU was not specifically defined and may have varied from centre to centre.

Evidence gap: What is TAU and how best should it be defined in any future studies?

Evidence gap: What is the cost-effectiveness of gameChangeVR in place of TAU rather than as adjunct?

10.3. Model Inputs

10.3.1. Clinical Parameters

Clinical parameters were drawn from the gameChangeVR RCT[15] and expert opinion.

10.3.1.1. Response

As described in section 10.2.2, the health state utility assigned to the response health state is derived from clinical trial results. This is the mean of all participants in the intervention arm of the study, and so includes all levels of response, from zero to 'maximum' or 'full'. For the purpose of the model, this utility difference is the driver of effect rather than a probability of response. We therefore assume a 100% probability of 'response' for all interventions.

Evidence gap: treatment effect estimates for XR and Amelia.

Evidence gap: (Optional) definitions of 'response', or 'partial' and 'complete' response according to an appropriate disease specific scale.

Evidence gap: Is there any difference in effect with who delivers the intervention(s)?

10.3.1.2. Relapse

No evidence was identified from the literature on relapse rates. The EAG consulted the manufacturers and clinical experts on plausible relapse rates.

Population with psychosis

The manufacturer of gameChangeVR stated that the mean outcome scores did not change from end of treatment to six months, and that a figure of 10% relapse at 12 months may be expected.

General population

Amelia does not recommend a specific protocol for treatment and the manufacturer stated that the relapse rate is likely to vary depending on the protocol used. Using Craske and Barlow's protocol (pp 24-29),[58] it might be expected that:

> *…between 80% and 100% of patients undergoing these treatments will be panic free at the end of treatment and maintain these gains for up to 2 years. These results reflect substantially more durability than medication treatments. Furthermore, between 50 and 80% of these patients reach a point of "high end state", meaning within normative realms of symptoms and functioning, and many of the remainder have only residual symptomatology.*

Population with ASD

XR therapeutics reported that in their initial studies on nine children with autism, eight improved and all improvements were maintained for 12 months. A study on eight adults with autism[52] classified five as responders, all maintained at six months. Finally, a feasibility crossover RCT of VR+CBT for specific phobias in young people with ASD found improvement to be maintained at six months (Maskey 2019[52]). In summary, according to the company, for those that showed improvements, they appeared to be maintained at six months, and there is some evidence of continued effect at 12 months. The company acknowledged that collected data to date cannot show that 100% of improvements would be maintained long term but stressed the desire to collect this evidence as part of any conditional approval by NICE.

Based on these subjective opinions, the EAG assumed a base case relapse rate of 25%, varied according to a uniform distribution between 0% and 50%.

> **Evidence gap**: relapse rates over the short-, medium- and long-term following treatment (over six to 24 months or longer).

10.3.1.3. Response from second and subsequent courses of therapy

There are no data on whether a participant will respond as well to a second course of therapy post relapse. We include the relative risk of response for second and subsequent rounds of treatment purely to explore scenarios, with the relative risk set at one in our base case.

10.3.2. Resource use and cost

Resource use and costs are calculated from an NHS and personal social services perspective (as per the NICE reference case). In addition, public sector (NHS & PSS plus criminal justice) and societal (defined as public sector plus time spent caring) costs are also calculated and reported for additional information as these were reported in Altunkaya et al. 2022.[11] All costs are adjusted to a 2021 price year.

10.3.2.1. Intervention costs

Intervention costs comprise licensing costs, therapist time (including delivery and training), and apportionment of capital cost of the VR headset. In the following the EAG describes the resource requirements for gameChange, before summarising quantities and costs included in the model.

gameChangeVR

gameChangeVR is recommended in those aged 16 and above and a course comprises six sessions over a period of six weeks, involving 30 mins of VR. In the RCT of gameChangeVR[15], a mental health worker (peer support worker, assistant psychologist or clinical psychologist) was in the room with the participant, but they were not required to have previous experience of cognitive therapy. The mental health workers had a half day training session in delivery of the VR therapy, and weekly supervision was provided to them during the clinical trial. In its submission, the company stated that training of the mental health worker comprises three 90-minute sessions (4.5hrs), which is provided by the company as part of the licence fee.

In a session with a patient, the mental health worker first explained the therapy concepts, assisted with donning the headset, and started the programme. They then set homework tasks for the participants to apply the lessons learned in VR to real life situations. These tasks were reviewed by the worker. Sessions were held in an NHS clinic or in the participant's own home.

In the EAG's base case, the intervention was assumed delivered by a Band 4 mental health worker, under the supervision of a Band 8c clinical psychologist (Table 7).

gameChangeVR states a cost of [redacted] per patient per course of therapy [redacted]

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Additional information from SCMs suggested that a full-time clinician is expected to have 14-16 clinical contacts per week. An assistant psychologist would expect to see three people per day if home based, and more if the patients were able to come to the clinic. The estimate of home visits is based on a 45-60 minute session, time to assemble and pack-up, travel time and note writing. SCMs also confirmed that staff with a wide range of skill levels and pay bands could deliver the intervention (most commonly people from bands 3-5, but sometimes higher).

Summary

Based on the descriptions above, the EAG estimated a course of treatment with gameChangeVR cost [redacted] (Table 6 and Table 7).

Table 6: Unit Costs

Item	Unit	Unit Cost	Source
Mental health worker	Hour	£33.00	AfC Band 4, equivalent to clinical psychology assistant practitioner (ch 17, and hourly cost from ch 10.1 PSSRU 2021
Clinical psychologist	Hour	£105.00	consultant clinical psychologist (Band 8c, Ch 9, PSSRU 2021)
VR headset cost	Headset	£300	Notional cost.
gameChangeVR Licence	per patient per course	[redacted]	gameChangeVR company Rfl.

Table 7: Intervention Resource Use

Item	Quantity	Total Cost
gameChangeVR *Per session*		
Mental health worker intervention delivery	1 hour	£33.00
Mental health worker weekly supervision	1hr MH worker+clinical psychologist, assuming 15 sessions pw per MH worker	£9.20

Training	4.5 hours with clinical psychologist and 6 MH workers in attendance, assuming training lasts 2 years before refresher required (eg due to staff turnover)	£0.17
VR Headset	One per MH worker conducting 15 sessions pw for 44 weeks/year, lasting 2 years	£0.64
Total		*£43.01*
Per course		
Per session costs above	Six sessions per course	£258.05
Licence cost		[redacted]
Total per course, gameChangeVR		[redacted]

10.3.2.2. Other health service use costs

Altunkaya et al.[11] reported a point estimate difference in routine health service use of -£105 (95%CI -£1135 to £924) per patient, equivalent to -£112.15 in GBP2021, with an approximate standard error of £280.50 (Table 8).

Evidence gap: Are there any differences in other health service contacts between patients receiving VR-based therapy vs TAU?

10.3.2.3. Criminal justice costs

Altunkaya et al[11] reported a (borderline statistically significant) increase in criminal justice costs associated with gameChangeVR vs TAU in the population with psychosis. The EAG noted the magnitude was small (mean, 95%CI: +£38, £0 to £77 per patient). Adjusted to 2021 prices this equates to £40.59, with an approximate standard error of £10.49 per patient (Table 8).

Evidence gap: Is the finding of increased criminal justice costs of note and in need of further investigation or is it spurious?

10.3.2.4. Other costs

Whilst outside the NICE reference case, the EAG considered that other cost elements including informal caregiving and lost productivity from time off work may be of note.

Altunkaya et al[11] reported an informal care cost difference of -£1576 (-£3432 to £280) per participant in patients receiving gameChangeVR compared with TAU. Adjusted to GBP2021 this equates to -£1683 with an approximate SE of £506 per patient (Table 8).

The EAG noted that there was no evidence on changes in employment or hours worked associated with gameChangeVR. This was excluded from the EAG's analysis but the evidence gap noted.

> **Evidence gap**: Is there a change in productivity / hours worked associated with successful treatment for agoraphobia in a population with psychosis?

Table 8: Incremental health service, criminal justice and carer costs associated with gameChangeVR vs TAU

Cost item	mean	SE	Distribution	Source/Notes
Incremental cost of NHS+PSS in pw psychosis vs pw psychosis+agoraphobia (NICE reference case cost perspective)	-£112.50	£280.50	Normal	Altunkaya et al. 2022[11] adjusted to 2021 prices using NHSCII[59]
Incremental cost of criminal justice services in pw psychosis vs pw psychosis+agoraphobia (non-reference case)	£40.59	£10.49	Normal	Altunkaya et al. 2022[11] adjusted to 2021 prices using NHSCII[59]
Incremental cost of time spent caring in pw psychosis vs pw psychosis+agoraphobia (non-reference case)	-£1683.28	£505.70	Normal	Altunkaya et al. 2022[11] adjusted to 2021 prices using NHSCI[59]I

10.3.3. Health State Utilities

Baseline health state utility was set to the weighted mean of baseline utility across both arms of the gameChangeVR study (Table 2, Altunkaya et al. 2022[11]). The increase in utility associated with treatment (representing the health state of people with psychosis without agoraphobia) was equal to the adjusted mean difference at six months (+0.007, 95%CI -0.043 to 0.057).

Table 9: Health State Utilities

DP	Health state	Utility, mean (SE)	Distribution	Source / Notes
1	People with psychosis and agoraphobia	0.541 (0.021)	B(319.08, 270.19)	Weighted mean of baseline utility, Altunkaya et al. 2022,[11] Table 2

1	Treatment effect (gameChangeVR)	+0.007 (0.013)	N(0.007,0.013)	Altunkaya et al. 2022,[11] Table 2. SE estimated from 95%CI
1	People with psychosis	0.548 (0.024)	-	Inferred from BL+treatment effect (previous two rows).

Evidence gap: Is EQ-5D sensitive to meaningful differences in HRQoL in people with agoraphobia (with and without psychosis)? Are disease specific scales (such as Beck Anxiety Inventory) with suitable mapping algorithms to health state utility suitable?

10.3.4. Model assumptions

A summary of the key assumptions in the decision modelling are in Table 10.

Table 10 Assumptions in exploratory modelling

1	gameChangeVR is delivered as per Freeman et al[15] as an adjunct to TAU rather than in place of TAU
3	The driver of effect in the model is change in utility following treatment rather than probability of response. Thus the 'probability of response' is 100% but the utility gain includes the values from all source study participants, as reflected in the standard deviation around mean utility difference.
4	The transition period of the model is 6 months, with a five year time horizon
6	Base case relapse rate is 25% per six months. Participants who relapse are offered repeat VR therapy
7	Repeat sessions are available when required and are as effective as the first session

10.4. Approach to Analysis

The EAG conducted a cost utility analysis estimating the incremental cost per incremental QALY gained from gameChangeVR compared with TAU in people with psychosis and agoraphobia. Analyses are conducted from the perspective of the NHS+PSS (NICE reference case). Only costs that differ between arms are measured and valued. Results for from a public sector and societal perspective are presented for information.

The EAG reports mean and SE costs and QALYs gained per patient in each arm, incremental cost-effectiveness ratios and probability of cost-effectiveness at £20,000 and £30,000 per QALY thresholds. Means and uncertainty distributions are generated from probabilistic analysis of 10,000 simulations, sampling from the distributions of input parameters specified in Table 8 and Table 9 above.

Additional sensitivity and scenarios were conducted as follows:

10.4.1. SA1: One-way sensitivity analysis, incremental utility gain from gameChangeVR

After excluding four psychiatric inpatient participants, Altunkaya et al.[11] reported no positive price at which gameChangeVR was cost-effective from an NHS+PSS perspective in the overall population. However, the analysis suggested there was the potential for the intervention to be cost-effective in those with 'high or severe avoidance'.[11] Whilst incremental QALYs in this subpopulation are reported (+0.020, 95%CI -0.005 to 0.0045 over six months, Table S13, Altunkaya et al. 2022[11]), incremental utility is not. Therefore, as a proxy for this subgroup, the EAG conducted a one-way sensitivity analysis on incremental utility to determine the minimum required for gameChangeVR to be cost-effective from an NHS+PSS perspective.

10.4.2. SA2: Cost of VR headset

The cost of VR headsets varies substantially. In its base case the EAG assumed a cost of £300, which is a representative cost of a self-contained VR headset in 2023, although high specification headsets retail for close to £1,000 each. The EAG conducted a one-way sensitivity analysis, varying the cost of a headset from £0 to £1,000.

10.4.3. SA3: Licence fees

License fees are a key cost input. The EAG therefore varied the fee for gameChangeVR to explore the impact on cost-effectiveness. Results are presented as point estimate ICERs as well as decision uncertainty (showing the probability of cost-effectiveness at £20,000 per QALY and £30,000 per QALY thresholds). The fees associated with a 50% probability of cost-effectiveness are identified.

10.4.4. SA4: Relapse rate

The EAG's base case assumed a 25% relapse rate per six months. This was varied between 0% and 100% in one-way sensitivity analysis.

10.4.5. SA5: Subsequent therapy availability

The EAG's base case assumed patients would get repeat therapy straightaway on relapse (i.e. within the same six month model cycle). The EAG explored a scenario where no repeat therapy was provided.

10.4.6. SA6: Subsequent therapy effectiveness

The EAG's base case assumed second and subsequent cycles of VR-based therapy were as effective as the first. The EAG conducted a one-way sensitivity analysis varying the effect of second and subsequent rounds of therapy from 0% to 100% of the effect of the first.

10.4.7. SA7: Two-way sensitivity analysis of licence fees versus relapse rate

This analysis explored the maximum cost-effective licence fees for the interventions as a function of the relapse rate.

10.4.8. SA8: Two-way sensitivity analysis of licence fees versus incremental utility from gameChangeVR

As a proxy for exploring the cost-effectiveness of gameChangeVR in severe subgroups, the EAG conducted a one-way analysis on utility gain. However, this analysis shows the cost-effectiveness of combinations of different licence fees against utility gain, so shows the maximum cost-effective licence fee as a function of the incremental gain in utility.

All sensitivity analyses were conducted probabilistically, holding the target parameter at a given value whilst running the PSA on all other values as described in Wilson 2021.[60]

10.5. Results from the economic modelling

10.5.1. Base Case Results

Base case results are reported in Table 11 below. VR therapy is an adjunct to standard care (TAU), costs reported are only those that differ between arms. Thus, the reported cost for TAU is zero.

Table 11: DP1 base case results

	Costs			QALYs				P(CE)	
Perspective	**gC+TAU**	**TAU**	**Inc.**	**gC+TAU**	**TAU**	**Inc.**	**ICER**	**£20k**	**£30k**
NHS+PSS	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26.3%	31.2%
Additional perspectives									
Public	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22.9%	27.5%
Societal	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99.0%	99.0%

Note QALYs vary by perspective due to Monte Carlo error

Whilst the point estimate ICER suggests that on average gameChangeVR is not cost-effective from an NHS+PSS perspective, the EAG base case suggests there is substantial decision uncertainty with around 25% to 30% probability of gameChangeVR being cost-effective from an NHS+PSS perspective at conventional thresholds of willingness to pay.

10.5.2. Scenario & Sensitivity Analyses

As previously stated, the point estimates from the decision modelling should be considered indicative only. The modelling does, however, provide a useful platform from which to explore a number of uncertainties. The results of the sensitivity analyses are presented below. Data from which figures are drawn are presented in Appendix E.

10.5.2.1. SA1: Incremental Utility gain

The gameChangeVR trial[15] observed a higher treatment effect in the more severe subgroup. As a proxy for conducting an economic analysis in patients with more

severe agoraphobia, the EAG explored the ICER as a function of the utility difference from relief of agoraphobia in people with psychosis. Under the base case assumptions of the decision model, a mean utility gain from relief of agoraphobia of at least [redacted] is required to achieve an ICER below £30,000 per QALY gained, and at least [redacted] to achieve an ICER below £20,000 per QALY (Figure 2). (Note also Appendix F, supplied as a separate document)

Figure 2 SA1: OWSA on utility gain from relief of agoraphobia in people with psychosis

Figure redacted.

10.5.2.2. SA2: Cost of VR headset

Whilst an important cost element, the per session cost of the VR headset is very low, therefore the ICER is mostly insensitive to changes in the purchase price of the VR headset within the range considered (Figure 3).

Figure 3 SA2: OWSA on cost of VR headset

Figure redacted.

10.5.2.3. SA3: Licence fees

The point estimate results are highly sensitive to the licence fee charged, varying between dominant to £140,000 per QALY. The magnitude of the sensitivity is driven by the licensing model:

[redacted] (Figure 4).

Figure 4 OWSA licence fee per user per course, gameChangeVR

Figure redacted.

10.5.2.4. SA4: Relapse rate

Relapse rate is entered in the model as a six-month probability. One-way sensitivity analysis suggests the ICER of gameChangeVR deteriorates as the relapse rate increases (Figure 5).

Figure 5 OWSA on relapse rate

Figure redacted.

10.5.2.5. SA5: Subsequent therapy availability

Under the assumed base case relapse rate (25% per six-months), where repeat sessions are not available, the ICER is correspondingly less favourable. This is due to incurring the cost of the initial therapy, but the benefit only being sustained for a relatively short period (Table 12).

Table 12 Scenario analysis on availability of repeat therapy sessions

Available	Inc £	Inc QALY	ICER
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]

10.5.2.6. SA6: Subsequent therapy effectiveness

As the relative effectiveness of subsequent therapy falls, the ICER deteriorates. This is because the same cost is incurred, but the relative benefit diminishes (Figure 6).

Figure 6 Relative Effectiveness of Subsequent Therapy

Figure redacted.

10.5.2.7. SA7: Two-way sensitivity analysis of licence fee vs relapse rate

As the six-month probability of relapse increases from zero, the maximum cost-effective licence fee declines accordingly. Figure 7 illustrates combinations of licence fee for gameChangeVR and probability of relapse associated with an ICER below £20,000 per QALY, between £20,000 and £30,000 and over £30,000.

Figure 7 Heatmap of licence fee vs 6m probability of relapse, gameChangeVR

Figure redacted.

10.5.2.8. SA8: Two-way sensitivity analysis of licence fee vs incremental utility

As the incremental utility associated with gameChangeVR increases, the licence fee associated with an ICER below £20,000 / QALY and below £30,000 increases (Figure 8).

Figure 8 Two-way sensitivity analysis, licence fee vs incremental utility, gameChangeVR

Figure redacted.

10.6. Commentary

10.6.1. gameChangeVR

gameChangeVR was the only intervention for which there was a published economic evaluation. Drawing directly on this (Section 10.1), the EAG noted that gameChangeVR was priced above that which would normally be considered cost-effective from an NHS+PSS perspective. Only by including broader societal costs (in particular, time spent caring) did the price point chosen by gameChangeVR become cost-effective.

Within-trial economic evaluations suffer from limitations including drawing only on one source of evidence of effect (the RCT on which they are based) and are limited in time horizon to the follow-up period of the study (six months in this case). The EAG therefore undertook some exploratory decision modelling to explore a number of scenarios and assumptions around relapse rate, effectiveness of repeat sessions, as well as assumed utility gains from relief of agoraphobia *inter alia* (described in section 10.4).

Under a base case assumption of 25% relapse every six months and assuming sustained effectiveness of repeat sessions, the ICER was [redacted], and thus is even less likely to represent an efficient use of NHS resources (Table 11). However, probabilistic analyses and one- and two-way sensitivity analyses suggested this finding was associated with substantial decision uncertainty and was highly sensitive to assumptions made in the model (section 10.5.2). In particular, two-way sensitivity analyses suggested there were scenarios under which combinations of licence fees and relapse rates and/or utility gains from relief of agoraphobia yield cost-

effectiveness estimates within that generally considered a good value for money investment by the NHS (that is, an ICER below £20,000 or £30,000). The EAG base case assumed gameChangeVR was delivered by a Band 4 mental health worker. If this is delivered by a higher band worker, then the ICER would be expected to increase further.

Bringing together the published economic evaluation of gameChangeVR conducted alongside the RCT and the decision modelling, the EAG notes that the within-trial evidence on cost-effectiveness (Altunkaya et al[11]) was largely driven by four participants who were inpatients, and that excluding these, in the population with psychosis and agoraphobia, gameChangeVR was unlikely to be cost-effective. However, subgroup analysis amongst those with high or severe avoidance suggested a licence cost of up to £324 would yield an ICER at or below £30,000 per QALY. [redacted]
However, the EAG's analysis projecting the six-month findings to five years suggested that uncertainty in relapse rates / sustainability of treatment effect, the availability or otherwise of repeat courses of therapy, and their relative effectiveness, did have the capacity to alter the ICER substantially and there were scenarios where the ICER of gameChangeVR could be within NICE's willingness to pay threshold.

10.6.2. Amelia

There are no data on the clinical effectiveness of Amelia. The EAG notes that the company licences their technology at a cost of [redacted] However, in the absence of any evidence it is impossible to draw conclusions on the plausibility of this, and more research is needed to confirm the appropriateness of the company's price.

10.6.3. XR Therapeutics

There are no data on the relative effectiveness of XR Therapeutics. The EAG notes that the company charges a price of [redacted]

[redacted]. In the absence of any evidence, it is impossible to draw conclusions on the plausibility of this, and more research is needed to confirm the appropriateness of the company's price.

11. INTERPRETATION OF THE EVIDENCE

11.1. Interpretation of the clinical and economic evidence

Following systematic searches, four unique clinical studies were identified, of which two were on gameChangeVR, one was on Amelia Virtual Care, and one on XR Therapeutics. RCT evidence was available for gameChangeVR. UK evidence was available for gameChangeVR and XR Therapeutics. All evidence on Amelia came from a Spanish setting; the EAG considered this to be fairly generalisable to a UK setting, with some limitations related to differences in culture and health system organisation. Evidence on gameChangeVR was specific to a population of schizophrenia spectrum disorder or psychosis, which was a relevant subgroup in the NICE scope.

In order to clarify how the scoped psychosis sub-group related to the studied population of psychosis or schizophrenia spectrum disorder in the gameChange trial, the EAG sought SCM input on how psychosis related to schizophrenia spectrum disorder. Advice was generally consistent but with different emphases. One SCM advised that *"psychosis is an umbrella term that encompasses conditions like schizophrenia"*. Another SCM advised that *"schizophrenia spectrum disorder refers to schizophrenia which is a psychotic disorder… Schizophrenia is a chronic mental health condition with distortion in thought and perception. Psychosis is when there is loss of touch with reality. Psychosis refers to symptoms that affect thought and perception. Psychosis is not a mental health diagnosis as such. Patients with schizophrenia experience psychosis."* One SCM emphasised that psychosis *"is a symptom-based description, usually referring to positive symptoms such as hearing voices, seeing visions or having unusual beliefs (commonly paranoia). People can be described as have symptoms of psychosis even if they do not have a formal diagnosis", while "schizophrenia spectrum disorder diagnosis refers to having a psychosis diagnosis, of which there are many subcategories."*

Available evidence for the psychosis sub-population equates solely and in full to the available evidence for gameChangeVR. Evidence on XR Therapeutics was specific to people with autism with 'fears and phobias'. This was considered relevant to the present decision problem, although not precisely aligned to the scope. Evidence was

not available for all scoped outcomes and safety data were only reported for gameChangeVR.

The EAG considered evidence for XR Therapeutics in the target population to be very limited. There was only one single-arm study of eight people with autism who had specific fears and phobias.[52] Evidence of a benefit was only found in just over half of participants (five out of eight), and neither participant with fears thematically related to agoraphobia (fear of open spaces and fear of crowded buses) showed any benefit. Simliarly, the only evidence for Amelia was a single-arm study, in which adherence and satisfaction was reported. While Amelia has fairly good adherence and patient satisfaction, no clinical outcomes were available in the scoped population, and hence there is no evidence with regards to its potential clinical benefit.

The evidence for gameChangeVR was suggestive of a small clinical benefit, however there was uncertainty as to its duration and how meaningful this benefit would be to participants. A subgroup analysis suggested that any clinical benefit was limited to those with very severe symptoms only, though limited data exploring outcomes by severity was reported. Moreover, there was no evidence of a benefit on a wider range of outcome measures. gameChangeVR was studied solely in a psychosis population, which is a subgroup of the scope. Effectiveness evidence was only available from one RCT and no further studies of any design.

The economic evidence for the three VR-based interventions is extremely limited. The EAG notes that gameChangeVR is priced at a point above that which would be considered cost-effective according to the NICE reference case (NHS+PSS perspective), but within that which would be considered value for money if a wider societal perspective is adopted (defined in Altunkaya 2022 as NHS+PSS, criminal justice and carer time costs). The EAG's exploratory modelling suggests the uncertainty is such that there are scenarios under which gameChangeVR may be cost-effective, for example in certain populations or with more optimistic interpretations of clinical effect estimates, but more evidence is required to confirm or refute this. Amelia is [redacted] while XR Therapeutics [redacted]

[redacted] Again, in the complete absence of randomised controlled evidence in the target population conclusions cannot be drawn as to either Ameila's or XR Therapeutic's cost-effectiveness.

11.2. Integration into the NHS

Information available to the EAG suggests that there is already some use of the scoped VR technologies within certain NHS trusts. Wider use would involve upscaling across more trusts. Potential challenges include ensuring sufficient appropriate staff resource and training to deliver such interventions. Furthermore, there are some challenges relating to access to digital technologies and service providers would have to consider supply of relevant equipment or signposting to relevant community resources, such as libraries, where equipment can be accessed, noting potential concerns regarding opening hours, access for patients who work during the day and are unable to leave the house, and confidentiality. When considering VR as a treatment option, it needs to be taken into account that there should be an alternative treatment modality for people for whom VR is unsuitable.

11.3. Evidence gap analysis

A summary of evidence gaps, pertaining to the intermediate and final outcomes from the scope, and those pertaining to decision modelling are summarised in Table 13. Evidence was focused around certain key outcomes and therefore there is limited information about certain additional scoped outcomes. A narrative assessment of evidence gaps in other methodological areas besides outcomes is presented within the clinical section of the report.

Table 13: Evidence Gap Analysis

Outcomes	Amelia Virtual Care	gameChangeVR	XR Therapeutics
Intermediate outcome: Patient choice and preferences	No studies **RED**	No studies **RED**	No studies **RED**
Intermediate outcome: Acceptability and satisfaction	One study **AMBER**	One study **AMBER**	One study **AMBER**
Intermediate outcome: Accessibility and digital access	No studies **RED**	No studies **RED**	No studies **RED**
Intermediate outcome: Intervention adherence and completion	One study **AMBER**	One study **AMBER**	One study **AMBER**
Intermediate outcome: Intervention-related adverse events	No studies **RED**	One study **AMBER**	No studies **RED**
Intermediate outcome: Device-related adverse events	No studies **RED**	One study **AMBER**	No studies **RED**
Clinical outcome: Change in agoraphobia symptoms	No studies **RED**	One study **AMBER**	One study, mixed results **AMBER**
Clinical outcome: Change in other psychological symptoms	No studies **RED**	One study, negative results **RED**	One study, negative results **RED**
Clinical outcome: Global functioning and work and social adjustment	No studies **RED**	No studies **RED**	No studies **RED**
Clinical outcome: Rates of recovery, time to recovery	No studies **RED**	No studies **RED**	No studies **RED**
Clinical outcome: Rates of relapse or deterioration, time to relapse or deterioration	No studies **RED**	No studies **RED**	No studies **RED**
Patient reported outcomes: Health-related quality of life	No studies **RED**	One study, negative results **RED**	One study, negative results **RED**
Patient reported outcomes: Recovering quality of life	No studies **RED**	One study, negative results **RED**	No studies **RED**
Patient reported outcomes: Patient experience	No studies **RED**	One study **AMBER**	No studies **RED**
Patient reported outcomes: Social contact	No studies **RED**	One study, negative result **RED**	No studies **RED**

Modelling and economic outcomes

Effectiveness evidence: Populations & comparative data	Each intervention has been trialled in very different populations (eg gameChangeVR in people with psychosis and agoraphobia, Amelia in people with agoraphobia with or without panic disorder, and XR Therapeutics in people with autism and 'fears and phobias'). It is unknown whether any of the interventions are interchangeable between different populations and thus require head to head comparison **RED**
Effectiveness evidence: Comparative data	There is no randomised evidence on the effectiveness of Amelia or XR Therapeutics in the target population. **RED**
Effectiveness evidence: Comparative data	There is no evidence on durability of treatment effect and/or relapse rates after more than six months follow-up. **RED**
Effectiveness evidence: Comparative data	There is no evidence on effect of second or subsequent courses of therapy. **RED**
Effectiveness evidence: Comparative data	Is there an impact on other health service use from VR-based therapies? **AMBER**
Effectiveness evidence: Generalisability	Is there any difference in effect between who delivers the interventions? **AMBER**
Costs: Criminal justice costs	Is the impact of gameChangeVR on criminal justice costs in people with psychosis of meaningful? **AMBER**
Costs: Lost productivity	Is there a case for including time off work within economic evaluations of agoraphobia (outside NICE reference case)? The evidence base contains no data on lost productivity. **RED**
HRQoL: Health state utilities	Evidence on health state utilities is currently very weak **RED**

11.4. Ongoing studies

Ongoing studies, identified either through company lists or EAG searches, are listed below in Table 14.

Amelia Virtual Care	gameChangeVR	Invirto
[redacted]	No ongoing trials	DRKS00027001.[61] Evaluation of "Invirto aftercare" for anxiety disorders: a pilot study.
[redacted]		DRKS00027585.[62] Evaluation of "Invirto Therapy" for people with panic disorder: a randomized-controlled trial
[redacted]		
[redacted]		
[redacted]		

Table 14. Ongoing studies

Amelia Virtual Care	gameChangeVR	Invirto	XR Therapeutics
[redacted]	No ongoing trials	DRKS00027001.[61] Evaluation of "Invirto aftercare" for anxiety disorders: a pilot study.	No ongoing trials – monitoring of real-world outcomes is being conducted
[redacted]		DRKS00027585.[62] Evaluation of "Invirto Therapy" for people with panic disorder: a randomized-controlled trial	
[redacted]			
[redacted]			
[redacted]			

11.5. Summary and conclusions of evidence gap analysis

There are a number of evidence gaps in respect of the clinical evidence base as it pertains to the decision problem. These in part drive key uncertainties within the economic analysis. Key gaps included:

Population gaps

- The populations studied differed for each intervention, precluding direct comparison. While the population for Amelia corresponded best to the breadth of the NICE scope for this appraisal, the population studied for gameChangeVR was restricted to schizophrenia spectrum disorder or psychosis (psychosis being a subgroup in the NICE scope), and the population studied for XR Therapeutics was restricted to people with autism.
- No UK evidence was available for Amelia Virtual Care. Differences in health system organisation and treatment pathways may limit generalisability of international evidence.

Intervention gaps

- There is limited evidence for all interventions.
- There is no evidence on Invirto and no clinical effectiveness evidence for Ameila in adults with agoraphobia.
- Evidence for the different interventions was not balanced across populations and outcomes.

Comparator gaps

- There is uncertainty about how closely comparators matched routine practice, especially with regard to treatment as usual.
- There is no evidence on the durability of the effect of VR-based therapies / relapse rates after more than six months follow-up.

Outcome gaps

- Published evidence was not available for some outcomes. There was also heterogeneity in how clinical measures are reported. No clinical outcomes were reported for Amelia.
- Safety data were only available for gameChangeVR.

Other considerations

- Whilst outside the NICE reference case, employment status / lost time at work may be a key element of importance in any economic analysis of treatments for agoraphobia. Lost productivity was not measured in either of the RCTs identified by the EAG.

Included studies mostly suffered from methodological limitations, and bias in effect estimates could not be ruled out as a result.

11.6. Key areas for evidence generation

The EAG presents several specific evidence generation recommendations in Table 15.

Table 15: Evidence generation recommendations

Research question	Recommended study design	Outcomes
1. Would clinical effectiveness of scoped interventions be shown with longer follow-up?	Cohort study in RWE setting with standard care as comparator	Key scoped outcomes
2. Are statistically significant differences in outcomes clinically meaningful?	Validation study of minimally clinically significant differences	Agoraphobia symptoms, and potentially other key measures
3. What is the durability of effect / relapse rate associated with VR-based therapies?	Longer term follow-up of RCTs	Disease-specific and generic HRQoL tools, repeat presentation for treatment
4. Is Amelia effective (particularly in a UK setting)?	An RCT or comparative RWE study in a UK setting	Key scoped outcomes

12. CONCLUSIONS

12.1. Conclusions from the clinical evidence

A total of four eligible unique studies were available for consideration. The EAG was aware of a small number of ongoing studies, though it is unknown whether any will enhance the evidence base within the present scope. RCT evidence was available only for gameChangeVR. UK evidence was available for gameChangeVR and XR Therapeutics.

There was only one key effectiveness study for XR Therapeutics and gameChangeVR, and none for Amelia. The EAG considered evidence for XR Therapeutics in the target population to be very limited – there was only one single-arm study of eight people with autism with specific fears and phobias.[5] Evidence of a benefit was only found in just over half of participants (five out of eight), and no benefit was apparent in those with fears thematically related to agoraphobia. The EAG noted some evidence of a benefit for gameChangeVR on symptoms of agoraphobia, however it was unclear whether this benefit would be clinically meaningful or would be durable. There was evidence that the intervention was only beneficial for those with very severe symptoms at baseline, but as few outcomes explored the effect of baseline severity, further evidence is needed to establish this. Furthermore, gameChangeVR was studied solely in a psychosis population, which is a subgroup of the scope only.

12.2. Conclusions from the economic evidence

At the price point chosen for gameChangeVR and drawing solely on the published within-trial analysis (Altunkaya et al[11]), it is unlikely to be considered cost-effective under NICE's reference case analysis. However, the Altunkaya et al[11] analysis was limited in duration to six months. The EAG's exploratory analysis suggests that coupled with a price reduction, there are scenarios where the ICER could be within NICE's conventional threshold, but there is a great deal of uncertainty, so it is not possible to declare gameChangeVR cost-effective or not.

There is too little evidence on Amelia or XR Therapeutics to draw any conclusions as to cost-effectiveness.

[redacted]

[redacted]

The key uncertainties are in 1) the effects of each of the interventions and 2) the duration of effect in those that do respond.

12.3. Summary of the combined clinical and economic sections

There was only one intervention for which RCT evidence is available. The EAG considered clinical effectiveness to be uncertain for all three technologies for which eligible evidence was available. The EAG did not consider there to be robust evidence for the clinical effectiveness of any scoped intervention. gameChangeVR, within the population studied, did show some evidence of potential benefit on agoraphobia symptoms, however there were considerable uncertainties about the interpretation and reliability of these findings.

The economic evidence suggests gameChangeVR is at best borderline cost-effective, but it is not strong enough to either rule it out or in as representing value for money. There is no evidence on which to draw any conclusions as to the cost-effectiveness of Amelia or XR Therapeutics, [redacted].

Key evidence requirements are: 1) in populations where more than one VR-based intervention may be indicated, 2) to determine the clinical effectiveness of Amelia 3) to determine the relative effectiveness of all interventions compared with each other, and relevant control in relevant populations, 4) to assess clinical effectiveness for all technologies using a longer follow-up period, and 5) to assess MCIDs for key outcome measures in an agoraphobia population.

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14. APPENDICES

Appendix A: Searches for clinical and cost effectiveness evidence

Table 16: Resources searched for clinical and cost effectiveness studies

Database/Resource	Host	Date Searched	Results
MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily	Ovid	28.3.23	54
Embase	Ovid	28.3.23	117
APA PsycINFO	Ovid	28.3.23	92
CDSR / CENTRAL	Cochrane Library: Wiley	29.3.23	122
INAHTA HTA database	https://database.inahta.org/	30.3.23	7
Company websites		29.3.23	13
Guidelines	SIGN/NICE	29.3.23	2
ClinicalTrials.gov	http://www.clinicaltrials.gov/	29.3.23	24
WHO ICTRP	https://trialsearch.who.int/	29.3.23	31
MHRA	https://www.gov.uk/drug-device-alerts	29.3.23	0
MAUDE	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm	29,3,23	0
ScharrHUD	https://www.scharrhud.org/	29.3.23	0
CEA Registry	https://cear.tuftsmedicalcenter.org/	29.3.23	2
Total records retrieved			464
Total records after deduplication			318

Ovid MEDLINE(R) ALL <1946 to March 27, 2023>

1 Agoraphobia/ 2670

2 agoraphobi*.tw. 3609

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 4469

5 exp virtual reality/ 5404

6 Virtual Reality Exposure Therapy/ 862

7 Augmented Reality/ 1085

8 (VR or 'virtual realit*').tw. 20841

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. 617

12 ("extended realit*" or "augmented realit*" or "mixed realit*").tw. 4379

13 ('game change' or gameChange or 'oxford VR' or BehaVR or 'HTC Vive' or 'Meta Quest' or 'Pico Neo').af. 134

14 ('amelia vr' or 'amelia virtual care').af. 0

15 invirto.af. 0

16 ('xr therapeutics' or XRT).af. 1203

17 or/5-16 26907

18 4 and 17 54

Embase <1974 to 2023 March 27>

1 exp Agoraphobia/ 6838

2 agoraphobi*.tw. 4781

3 ((phobi* or anxi* or fear*) adj3 (crowd* or 'open spac*' or 'go* out' or 'leav* home' or 'leav* house')).tw. 127

4 1 or 2 or 3 7795

5 exp virtual reality/ 25414

6 Virtual Reality Exposure Therapy/ 910

7 Augmented Reality/ 2082

8 (VR or 'virtual realit*').tw. 28766

9 (haptic adj2 technolog*).tw. 162

10 (VRCBT or VR-CBT).tw. 26

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. 817

12 ("extended realit*" or "augmented realit*" or "mixed realit*").tw. 5237

13 ('game change' or gameChange or 'oxford VR' or BehaVR or 'HTC Vive' or 'Meta Quest' or 'Pico Neo').af. 251

14 ('amelia vr' or 'amelia virtual care').af. 0

15 invirto.af. 1

16 ('xr therapeutics' or XRT).af. 2916

17 or/5-1647116

18 4 and 17 117

APA PsycInfo <1806 to March Week 3 2023>

1 exp Agoraphobia/ 2961

2 agoraphobi*.tw. 5508

3 ((phobi* or anxi* or fear*) adj3 (crowd* or 'open spac*' or 'go* out' or 'leav* home' or 'leav* house')).tw. 108

4 1 or 2 or 3 5617

5 exp virtual reality/ 11366

6 Virtual Reality Exposure Therapy/ 249

7 Augmented Reality/ 909

8 (VR or 'virtual realit*').tw. 10254

9 (haptic adj2 technolog*).tw. 48

10 (VRCBT or VR-CBT).tw. 15

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. 655

12 ("extended realit*" or "augmented realit*" or "mixed realit*").tw. 1612

13 ('game change' or gameChange or 'oxford VR' or BehaVR or 'HTC Vive' or 'Meta Quest' or 'Pico Neo').af. 532

14 ('amelia vr' or 'amelia virtual care').af. 0

15 invirto.af. 0

16 ('xr therapeutics' or XRT).af. 19

17 or/5-16 16048

18 4 and 17 92

Cochrane Library

#1 MeSH descriptor: [Agoraphobia] explode all trees 472

#2 agoraphobi* 1262

#3 ((phobi* or anxi* or fear*) NEAR/2 (crowd* or 'open spac*' or 'go* out' or 'leav* home' or 'leav* house')) 448

#4 #1 or #2 or #3 1692

#5 MeSH descriptor: [Virtual Reality] explode all trees 784

#6 MeSH descriptor: [Virtual Reality Exposure Therapy] explode all trees 267

#7 MeSH descriptor: [Augmented Reality] explode all trees 57

#8 (VR or 'virtual realit*') 8193

#9 (haptic adj2 technolog*) 7

#10 (VRCBT or VR-CBT) 27

#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) 8383

#12 ('extended realit*' or 'augmented realit*' or 'mixed realit*') 1225

#13 'extended realit*' 224

#14 ('game change' or gameChange or 'oxford VR' or BehaVR or 'HTC Vive' or 'Meta Quest' or 'Pico Neo') 1598

#15 ('amelia vr' or 'amelia virtual care') 1

#16 invirto 2

#17 ('xr therapeutics' or XRT) 355

#18 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 14741

#19 #4 and #18 142

[55 in CDSR and 67 in CENTRAL]

INAHTA

((((((((((agoraphobia)[mh]) OR (agoraphobi*)) OR (virtual reality)[mh])) OR ("virtual reality")) OR ("extended reality")) OR ("augmented reality")) OR ("mixed reality"))) OR ((gameChange OR amelia OR invirto or XR)))

ClinicalTrials.gov

Search string	Results
Agoraphobia/Virtual Reality/all studies	7
Agoraphobia/VR/all studies	3
GameChange/all studies	1
Oxford vr/all studies	8
Amelia virtual care/all studies	0
Invitro/all studies	1
Xr therapeutics/phobia/all studies	4

ICTRP – using basic search

Search string	Results
Agoraphobia and 'virtual reality'	9
Agoraphobia and VR	3
GameChange	4
'Oxford vr'	4
'Amelia virtual care'	0
Invitro	3
'xr therapeutics'	8

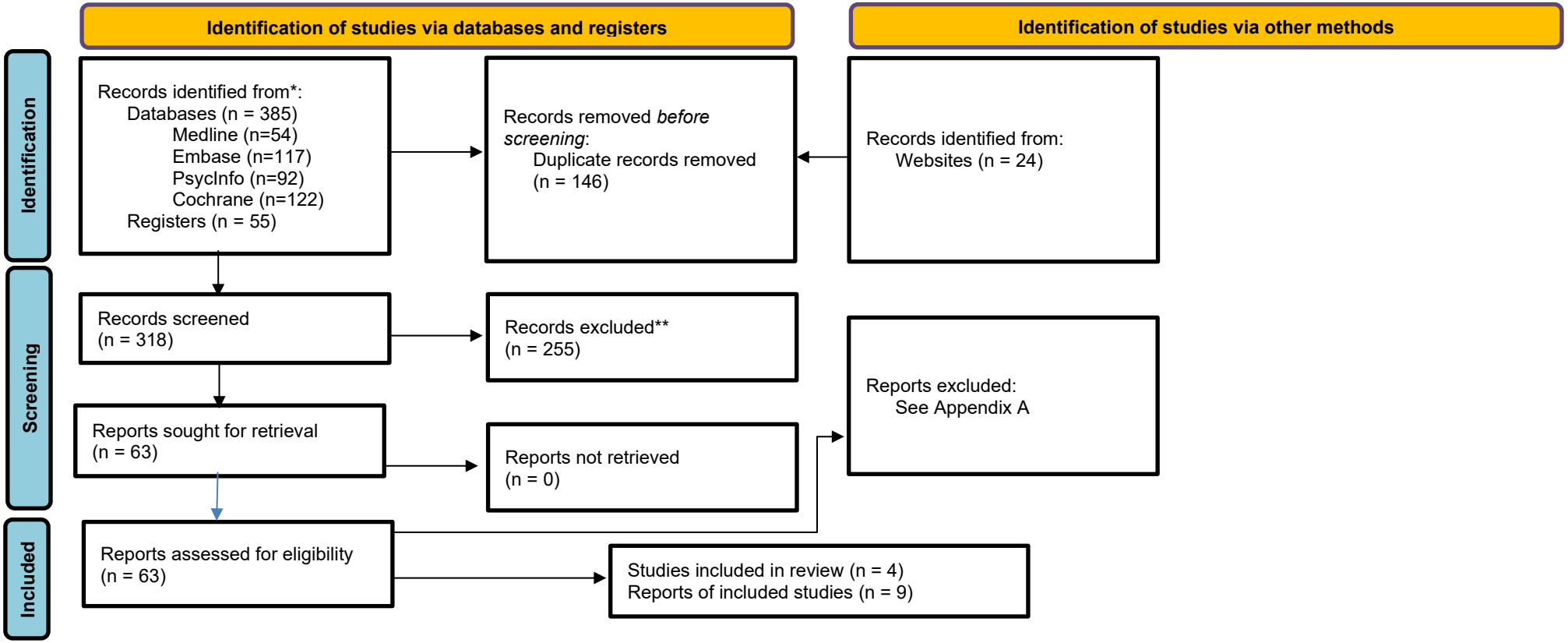
CEA Registry and ScharrHUD

agoraphobia or virtual reality or VR

NICE and SIGN

Agoraphobia or virtual reality or VR

Appendix B: PRISMA flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix C: List of excluded studies and studies awaiting assessment

Table 17. List of excluded full-text English-language publications studies from company lists, with reasons

Excluded study	Reason for exclusion
Amelia Virtual Care	
Adjorlu et al[36]	Population (paediatric)
Alsem et al[28]	Population (paediatric)
Bioulac et al[31]	Population (paediatric)
Botella et al[41]	Population (phobias)
Botella et al[40]	Population (post-traumatic stress disorder)
Dehghan et al[30]	Population (paediatric)
Garcia-Palacios et al[22]	Population (specific phobias)
Gerardi et al[42]	Population (post-traumatic stress disorder and other anxiety disorders)
Guillen et al[43]	Population (stress-related disorders)
Hua et al[33]	Population (paediatric)
Kelson et al[32]	Population (paediatric)
Kirkham & Batten[23]	Population (anxiety)
McCann et al[45]	Population (anxiety disorders)
Meyerbroker & Emmelkamp[44]	Population (anxiety disorders)
Modrego-Alarcon et al[21]	Population (students with stress)
Morina et al[46]	Population (specific phobias)
Opris et al[47]	Population (anxiety disorders)

Excluded study	Reason for exclusion
Powers & Emmelkamp[48]	Population (anxiety disorders)
Segal et al[24]	Population (broad psychological)
Segawa et al[39]	Population (addictive disorders)
Shah et al[25]	Population (mood disorders)
Servera et al[29]	Population (paediatric)
Snider et al[37]	Population (paediatric)
Tennant et al[35]	Population (paediatric)
Turner & Casey[49]	Population (broad psychological)
Wallach et al[38]	Population (public speaking anxiety)
Wong Sarver et al[34]	Population (paediatric)
GameChangeVR	
Brown et al[63]	Population (general psychiatric)
Freeman et al[27]	Population (persecutory delusions)
XR Therapeutics	
Maskey et al[52]	Population (paediatric)
Maskey et al[51]	Population (paediatric)

Table 18: List of excluded full-text publications from EAG search, with reasons

Excluded study	Reason for exclusion
ACTRN12609000959279[64]	Intervention
ACTRN12615000927527[65]	Intervention

Excluded study	Reason for exclusion
Andersen et al[66]	Intervention
Bentz et al[67]	Intervention
Botella et al[68]	Intervention
Botella et al[69]	Intervention
Canais et al[70]	Intervention
Carl et al[71]	Intervention
Castro et al[72]	Intervention
Chen et al[73]	Intervention
CN-00595152[74]	Intervention
DRKS00027001[61]	No results
DRKS00027585[62]	No results
Emmelkamp et al[75]	Intervention
Freeman et al[76]	Article type
Freitas et al[77]	Intervention
Gomez-Busto & Ortiz[78]	Intervention
ISRCTN10661970[79]	Intervention
ISRCTN12497310[80]	No results
ISRCTN12882676[81]	Intervention
ISRCTN17308399[82]	No results
Jang et al[83]	Intervention
KCT0007996[84]	Intervention
Krzystanek et al[85]	Intervention

Excluded study	Reason for exclusion
Ling et al[86]	Intervention
Lorenzo Gonzalez et al[87]	Intervention
Lundin et al[88]	Intervention
Malbos et al[89]	Intervention
Malbos et al[90]	Intervention
Manyande et al[91]	Population (paediatric)
Martin et al[92]	Intervention
Meyerbroeker et al[93]	Intervention
Meyerbroker et al[94]	Intervention
NCT00129610[95]	Intervention
NCT00734370[96]	Intervention
NCT03101332[97]	Intervention
NCT03845101[98]	Intervention
NCT03973541[99]	Intervention
NCT04695249[100]	Intervention
NCT05319509[101]	Population (students with anxiety)
NCT05510804[102]	Intervention
Pelissolo et al[103]	Intervention
Pitti et al[104]	Intervention
Pompoli et al[105]	Intervention
Pot-Kolder et al[54]	Intervention
Quero et al[106]	Intervention

Excluded study	Reason for exclusion
Vincelli et al[107]	Intervention
Vincelli et al[108]	Intervention
Vincelli et al[109]	Intervention
Vincelli et al[110]	Intervention
Wechsler et al[111]	Intervention
Wiebe et al[112]	Intervention

Appendix D. Additional study results

This table presents results for clinical effectiveness outcomes. Further details compared to the results presented in the main clinical section are provided where relevant. However, there has been a focus on making the results understandable rather than presenting all minutiae. Safety and economic outcomes are discussed in relevant report sections and not included in this table.

Table 19: Study results for clinical effectiveness

Papers	Study name	Results
Amelia Virtual Care		
Gelabert et al[12]	NR	98% of the 42 participants completed their course of psychotherapy within the previously established course of eight sessions. Two participants required 2 additional sessions of Amelia Virtual Care therapy beyond the protocol. The entire treatment protocol was completed by 82.4% of participants, with the main cause (55.6%) for non-completion being a lack of presence within the virtual environment and consequent perception of its usefulness. On the Client Satisfaction Questionnaire-8,[19] 57% of participants indicated a high or very high presence, while 12% indicated a null or low sense of presence. Across categories, there was an average satisfaction rating of 68%.
gameChangeVR		
Knight et al,[17] Lambe et al[18]	gameChangeVR project	A series of six key scenarios were developed based on participant input and feasibility of designing a suitable VR environment. These were: café (request or order), waiting room (give personal information), pub (unexpected event/erratic behaviour), bus (trapped/shut in), food shop (find an item), and street (safe place to unknown). In user testing, the success criterion was pre-determined as 90% of users rating gameChangeVR as immersive, easy to use and engaging. This was achieved, with all six participants rating gameChangeVR accordingly.
Altunkaya et al 2022,[11] Bond et al 2023,[13] Freeman et al 2022a,[14] Freeman et al 2022b,[15] Freeman et al 2022c[16]	gameChangeVR trial	Qualitative analysis showed that anxious avoidance was having a significant impact on participants' lives before the VR intervention, leaving some of them housebound and isolated. Those who were struggling the most with agoraphobic avoidance expressed the greatest appreciation for, and gains from, gameChangeVR therapy. Five key superordinate themes were identified: i) experience and cost of anxious avoidance without treatment, ii) reasons to try: curiosity and motivation for trying VR treatment, iii) a place to practice different or new

Papers	Study name	Results
		responses to anxiety, iv) the security of knowing VR scenarios are not real, despite experiencing an anxiety response, and can therefore be a safe place to learn and build confidence and v) taking learning from the VR intervention into the real world. There are no subordinate themes within themes 1 and 2. Subordinate themes within theme 3 are: a) an immersive experience, b) a chance to observe anxiety, and c) new ways of responding. Subordinate themes within theme 4 are: a) the sweet spot of safety and anxiety and b) calibrating for a personalised approach. Subordinate themes within theme 5 are: a) from training wheels to real-world practice and b) one thing to hold onto. Overall, participants reported that using the intervention created an anxiety response that was useful for learning and practicing a different response while still within their safe environment. There was a need to balance the intensity of the anxiety response to a middle ground, so that the intervention was not boring (anxiety response too low) or that the intervention was not overly draining (anxiety response too high). The authors reported that the support provided within the intervention meant that finding the right balance was “usually” possible (Bond et al, p.8). Those people who supplemented the intervention with activities to reinforce learning (e.g. writing notes, active reflection, discussions with care teams) generally had a better response to the intervention. Motivation to engage with the intervention, including undergoing the anxiety response within, was reported to be important. Those who were coping well with their condition had less motivation for this. In the primary quantitative analysis, Freeman et al[15] found that compared to the usual care alone group, participants in the VR therapy group had greater reductions in agoraphobic avoidance (p=0.026) and distress (p=0.014) at follow-up, measured by O-AS. Between-group differences were greater using the O-BAT, where data were available. No between-group differences were found for secondary outcome measures (excluding O-BAT, which was initially a primary outcome), except for recovery as assessed by the Questionnaire about the Process of Recovery.[20]. The difference in O-AS was statistically significant, but was small. A difference of -0.47 (scale 0-8) and 4.3 on a scale of 0-100. A difference of 0.47 is not going to hange the severity classification of avoidance as assessed by the scale (average 0, moderate 1, high 3, severe 6). Half (55%) of participants found a VR intervention appealing and described feeling intrigued by what it would be like.[13] In the secondary quantitative analyses, Freeman et al[14] found that 65.8% of patients were very satisfied with VR therapy, 30.8% were mostly satisfied, 2.5% were indifferent or mildly dissatisfied, and 0.8% of patients were quite dissatisfied. Difficulties concentrating in VR (see adverse events Section 9) were associated with slightly lower

Papers	Study name	Results
		satisfaction. Meanwhile, Freeman et al[16] found that participants with severe agoraphobia showed the greatest benefits from gameChangeVR VR therapy, exhibiting significant post-treatment improvements in agoraphobic avoidance, agoraphobic distress, ideas of reference, persecutory ideation, paranoia worries, recovery quality of life, and perceived recovery, but no significant improvements were found in depression, suicidal ideation, or health-related quality of life. Further data can be found in Table 3 of the publication.
XR Therapeutics		
Maskey et al[5]	NR	Retention and participation were achieved for all sessions. Five out of eight participants achieved improvement to symptoms related to target behaviours. Two of the non-responders attributed this to personal circumstances and routine changes respectively, while the third was making progress at the 6-month follow-up while not yet meeting response criteria. No consistent pattern of reliable or observable changes was found on any of the standardized questionnaire measures, relating to anxiety, depression and quality of life. There is selective presentation of numerical results in the company publication. Therefore, reporting only narrative results here prevents undue focus on highlighted values.

Appendix E: Data from Sensitivity Analyses

Data informing the figures reported in section 10.5.2 are reported in tables below.

Table:20 SA1: Incremental utility gain from gameChangeVR

Incremental utility	Inc £	Inc QALY	ICER
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table:21 SA2: Cost of VR Headset

	DP1 (gameChangeVR)		
£ of headset	Inc £	Inc QALY	ICER
0	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]

150	[redacted]	[redacted]	[redacted]
200	[redacted]	[redacted]	[redacted]
250	[redacted]	[redacted]	[redacted]
300	[redacted]	[redacted]	[redacted]
350	[redacted]	[redacted]	[redacted]
400	[redacted]	[redacted]	[redacted]
450	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]
550	[redacted]	[redacted]	[redacted]
600	[redacted]	[redacted]	[redacted]
650	[redacted]	[redacted]	[redacted]
700	[redacted]	[redacted]	[redacted]
750	[redacted]	[redacted]	[redacted]
800	[redacted]	[redacted]	[redacted]
850	[redacted]	[redacted]	[redacted]
900	[redacted]	[redacted]	[redacted]
950	[redacted]	[redacted]	[redacted]
1000	[redacted]	[redacted]	[redacted]

Table:22 SA3: Licence fees

DP1 (gameChangeVR)			
£ per person per course	**Inc £**	**Inc QALY**	**ICER**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table:23 SA4 Relapse Rate

	DP1 (gameChangeVR)		
P(relapse/6m)	**Inc £**	**Inc QALY**	**ICER**
0	[redacted]	[redacted]	[redacted]
0.05	[redacted]	[redacted]	[redacted]
0.1	[redacted]	[redacted]	[redacted]
0.15	[redacted]	[redacted]	[redacted]
0.2	[redacted]	[redacted]	[redacted]
0.25	[redacted]	[redacted]	[redacted]
0.3	[redacted]	[redacted]	[redacted]
0.35	[redacted]	[redacted]	[redacted]
0.4	[redacted]	[redacted]	[redacted]
0.45	[redacted]	[redacted]	[redacted]
0.5	[redacted]	[redacted]	[redacted]
0.55	[redacted]	[redacted]	[redacted]
0.6	[redacted]	[redacted]	[redacted]
0.65	[redacted]	[redacted]	[redacted]
0.7	[redacted]	[redacted]	[redacted]
0.75	[redacted]	[redacted]	[redacted]
0.8	[redacted]	[redacted]	[redacted]
0.85	[redacted]	[redacted]	[redacted]
0.9	[redacted]	[redacted]	[redacted]
0.95	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]

Table:24 SA6 Relative Effectiveness of Repeat Therapy

	DP1 (gameChangeVR)		
relative effectiveness	**Inc £**	**Inc QALY**	**ICER**
0	[redacted]	[redacted]	[redacted]
0.05	[redacted]	[redacted]	[redacted]
0.1	[redacted]	[redacted]	[redacted]
0.15	[redacted]	[redacted]	[redacted]
0.2	[redacted]	[redacted]	[redacted]
0.25	[redacted]	[redacted]	[redacted]
0.3	[redacted]	[redacted]	[redacted]
0.35	[redacted]	[redacted]	[redacted]
0.4	[redacted]	[redacted]	[redacted]
0.45	[redacted]	[redacted]	[redacted]
0.5	[redacted]	[redacted]	[redacted]
0.55	[redacted]	[redacted]	[redacted]
0.6	[redacted]	[redacted]	[redacted]
0.65	[redacted]	[redacted]	[redacted]
0.7	[redacted]	[redacted]	[redacted]
0.75	[redacted]	[redacted]	[redacted]
0.8	[redacted]	[redacted]	[redacted]
0.85	[redacted]	[redacted]	[redacted]
0.9	[redacted]	[redacted]	[redacted]
0.95	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]

Table: 25SA7: Heatmap of licence cost of gameChange vs probability of relapse

Table redacted.

Table: 26SA8: Heatmap of licence cost of gameChangeVR vs incremental utility

Table redacted.

Virtual reality for treating agoraphobia and agoraphobic avoidance [GID-HTE10016]

External Assessment Group report

Appendix F

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Early Value Assessment Programme

Produced by Peninsula Technology Assessment Group (PenTAG)
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Date completed 22/05/2023

Contains confidential information: Yes

Purpose of the assessment report

The purpose of this External Assessment Group (EAG) report is to review the evidence currently available for included technologies and advise what further evidence should be collected to help inform decisions on whether the technologies should be widely adopted in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and the report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the early value assessment.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None.

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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Abbreviations

Term	Definition
A&E	Accident and emergency
Afc	Agenda for change
ASD	Autism spectrum disorder
BAI	Beck Anxiety Inventory
CBT	Cognitive behavioural therapy
CEA	Cost-effectiveness analysis
CE mark	*Conformité européenne* (European conformity) marking
CI	Confidence interval
CORE-OM	Clinical Outcomes in Routine Evaluation – Outcome Measure
CRD	Centre for Reviews and Dissemination
DP	Decision problem
DTAC	Digital Technology Assessment Criteria
EAG	External assessment group
EE	Economic evaluation
EQ-5D	EuroQoL-5 dimensions
EQ-5D-5L	EuroQoL-5 dimensions 5-level
EVA	Early value assessment
GAD-7	Generalised Anxiety Disorder Assessment 7
GP	General practitioner
HRQoL	Health-related quality of life
HRSD	Hamilton Rating Scale for Depression
HTA	Health technology assessment
IAPT	Improving Access to Psychological Therapies
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	Interquartile range
ITT	Intention to treat
MANCOVA	Multivariate analysis of covariance
MANOVA	Multivariate analysis of variance
MAUDE	Manufacturer and User Facility Device Experience

MCID	Minimally clinically important difference
MID	Minimally important difference
MeSH	Medical subject headings
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
N/A	Not applicable
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLM	National Library of Medicine
NR	Not reported
O-AS	Oxford Agoraphobic Avoidance Scale
O-BAT	Oxford Behavioural Avoidance Test
ONS	Office for National Statistics
OWSA	One-way sensitivity analysis
PenTAG	Peninsula Technology Assessment Group
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PW	People with
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
ReQoL	Recovering Quality of Life quality
RWE	Real world evidence
SA	Sensitivity analysis
SCM	Specialist Committee Member
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
TAU	Treatment as usual
UK	United Kingdom
UKCA	United Kingdom Conformity Assessed marking
VAS	Visual analogue scale
VR	Virtual reality

WHO	World Health Organization

1. SUMMARY

The purpose of this appendix is to provide additional analyses which NICE considers may be useful for the appraisal committee.

Specifically, an analysis with a reduced time horizon (two years instead of five), and analyses representing more severe subgroups for DP1 (gameChange).

2. TWO-YEAR TIME HORIZON

Table 1 reproduces Table 11 from the main report, with the results of the two-year scenario added. Analyses are probabilistic based on 10,000 simulations.

The shorter time horizon leads to an increased ICER for DP1 (gameChange, deteriorating cost-effectiveness).

Table 1: Time horizon scenario analysis, DP1 (gameChange+TAU vs TAU)

Time horizon		Costs			QALYs				P(CE)	
	Perspective	**gC+TAU**	**TAU**	**Inc.**	**gC+TAU**	**TAU**	**Inc.**	**ICER**	**£20k**	**£30k**
5 years	NHS+PSS	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26.3%	31.2%
	Additional perspectives									
	Public	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22.9%	27.5%
	Societal	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99.0%	99.0%
2 years	NHS+PSS	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.8%	13.4%
	Additional perspectives									
	Public	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.7%	12.0%
	Societal	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	97.6%	97.6%

Note QALYs vary by perspective due to Monte Carlo error

3. SEVERE SUBGROUP ANALYSIS

In a series of post-hoc analyses, Freeman et al[1] reported outcomes including EQ-5D utilities at six weeks and six months follow-up for a number of subgroups. As the treatment effect appears to be greater in more severe subgroups, the EAG conducted analyses in those with high and severe avoidance.

The EAG noted a decline in utility difference at six months vs six weeks in the complete analysis (+0.026 to +0.007) and the high avoidance subgroup (+0.09 to +0.04), but the reverse in the severe subgroup (+0.01 to +0.05). This is somewhat counterintuitive and appeared to be valid (and not a typographical error). The EAG therefore conducted additional scenario analyses on DP1 (gameChange) assuming an incremental utility from gameChange of +0.04 (SE 0.05) and +0.05 (SE 0.0525).

Table 2 Health state utilities by subgroup

Subgroup	Adjusted difference, EQ5D utility at 6 weeks, mean (SE)	Adjusted difference, EQ5D utility at 6 months, mean (SE)	Source
All	+0.026 (0.013)	+0.007 (0.013)	Altunkaya et al. 2022[2]. imputed, adjusted analysis. Table 2. SE estimated from 95%CI
High avoidance	+0.09 (0.0475)	+0.04 (0.05)	Freeman et al. 2022c[1], SE estimated from 95%CI
Severe Avoidance	+0.01 (0.05)	+0.05 (0.0525)	Freeman et al. 2022c[1], SE estimated from 95%CI

Table 3 Severity subgroup scenario analysis, DP1 (gameChange+TAU vs TAU)

Subgroup		Costs			QALYs				P(CE)	
	Perspective	**gC+TAU**	**TAU**	**Inc.**	**gC+TAU**	**TAU**	**Inc.**	**ICER**	**£20k**	**£30k**
All	NHS+PSS	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26.3%	31.2%
	Additional perspectives									
	Public	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22.9%	27.5%
	Societal	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99.0%	99.0%
High avoidance	NHS+PSS	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57.1%	65.2%
	Additional perspectives									
	Public	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54.4%	62.3%
	Societal	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	98.7%	97.7%
Severe avoidance	NHS+PSS	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	63.1%	70.4%
	Additional perspectives									
	Public	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	60.7%	68.5%
	Societal	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99.0%	98.6%

4. CONCLUSION

A shorter time horizon is associated with a higher ICER. The appropriate time horizon for an economic evaluation is long enough to capture all differences in cost and outcomes being compared. Therefore, the shorter (two year) time horizon may yield an unduly pessimistic estimate of the cost-effectiveness of gameChange.

Point estimate ICERs of gameChange for the high and severe avoidance subgroups from an NHS & PSS perspective are within the range normally considered cost-effective by NICE. However, there is substantial uncertainty associated with this, and the EAG noted that in Freeman et al,[1] the point estimate incremental utility at six months' follow-up was substantially higher compared with the six-week value, when typically a tailing off of treatment effect over time would typically be expected. This requires further exploration to verify or refute.

5. REFERENCES

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health technology evaluation

Assessment report overview

Virtual reality for treating agoraphobia and agoraphobia avoidance: early value assessment

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the external assessment group (EAG) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the committee may wish to discuss. It should be read along with the external assessment report. The overview forms part of the information received by the medical technologies advisory committee when it develops its recommendations on the technologies.

Key issues for consideration by the committee are described in section 9, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is underlined and highlighted in either [redacted] (for academic in confidence information) or in [redacted] (for commercial in confidence information). Any depersonalised data in the submission document is underlined and highlighted in [redacted].

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Additional analyses carried out by EAG

1 The technology

This early value assessment (EVA) focuses on the use of virtual reality (VR) for treating agoraphobia and agoraphobic avoidance. VR is a simulated 3-dimensional environment with scenes and objects that people can explore, most typically using a VR headset. This creates an immersive experience that can trigger emotional responses like those in real-world situations. VR may be used as a tool in therapy sessions or as a digital intervention with the support of a mental health worker. It can help deliver techniques such as exposure therapy, which gradually increases a person's exposure to situations they fear and avoid. It allows people to immerse themselves in real-world situations while being in the safety of their home or clinic. Virtual environments can be adjusted based on a person's needs and individual treatment plan. This could allow more gradual exposure to stressful situations and increased comfort and confidence in completing interventions.

In total, 4 VR technologies are included in this assessment. Details on these technologies are provided in the topic scope and assessment report:

- Amelia Virtual Care (Amelia Virtual Care) for mental health disorders including agoraphobia. It is a software-only VR platform designed to be used by therapists as a tool to support treatment in clinics or at home.
- gameChangeVR (Oxford VR) for agoraphobic avoidance in people with schizophrenia spectrum disorders or affective disorders with psychotic symptoms. It is a software-only VR therapy delivered by an automated virtual therapist and supported by a mental health worker in clinic or at home. It is designed to be used as part of a treatment plan for psychosis.
- Invirto (Invirto) for anxiety disorders including agoraphobia. The company did not respond to requests for information and no evidence was identified. This technology was therefore noted but not assessed.
- XR Therapeutics (XR Therapeutics) for anxiety disorders including agoraphobia. It uses a fully immersive screen-based VR studio and is delivered in-person by a therapist in combination with CBT.

2 Proposed use of the technology

2.1 Disease or condition

Agoraphobia is an anxiety disorder characterised by marked and excessive fear of being in situations where escape may be difficult or help may not be available (World Health Organization (WHO) 2022). Some people may describe this experience as feeling threatened or worried about going out. It involves fear and avoidance of places or situations that might cause panic and feelings of being trapped, helpless or embarrassed. This anxious avoidance of everyday situations may occur with other mental health disorders including panic disorder, depression, social anxiety and psychosis. More information on agoraphobia is provided in the topic scope.

2.2 Patient group

The patient group for this assessment is people aged 16 years and over with agoraphobia or agoraphobic avoidance. This includes agoraphobia and agoraphobic avoidance that occurs with other common mental health problems or severe mental illness. This EVA includes a subpopulation of people with psychosis who have agoraphobia or agoraphobic avoidance but does not exclude any other co-occurring mental health conditions.

2.3 Unmet need and current management

The NHS recommends a stepped care approach for treating agoraphobia and any underlying panic disorder (NHS 2022). The first step involves recognition and diagnosis, including identifying any comorbidities. This is used to develop a treatment plan. This may involve lifestyle changes and self-help techniques to help relieve symptoms. People may also be offered guided self-help with therapist support. If needed or preferred, more intensive treatments should be offered. NICE's guideline on 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. Antidepressants may be offered if the disorder is long-standing or if the person has not benefited from or has declined psychological intervention.

People with psychosis who have agoraphobia or agoraphobic avoidance should also be treated in line with their treatment plan. NICE's guideline on psychosis and schizophrenia in adults states that people with psychosis should be offered oral antipsychotic medication and psychological interventions including family intervention and CBT. But experts advised that access to CBT is limited with people more likely to be offered antipsychotic medication and simple contact and monitoring with services.

The most recent Adult Psychiatric Morbidity Survey reports that only 1 in 3 people with a common mental health disorder accesses treatment (McManus et al. 2016). There may be considerable barriers to accessing treatment, including a shortage of trained mental health professionals and limited clinical resources. Agoraphobia may further impact a person's ability to access mental health services and support. Clinical experts advised that agoraphobia is often untreated or undertreated when it occurs with other mental health conditions because treatment tends to focus on the more severe or prominent disorder. Some people with agoraphobia or agoraphobic avoidance may also discontinue treatment because of difficulty tolerating techniques such as exposure therapy. VR may increase access to care by offering another treatment option for agoraphobia and agoraphobic avoidance.

2.4 Proposed management with new technology

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. VR may be delivered by a therapist as part of face-to-face therapy or teletherapy. Some technologies may also be used as a standalone intervention with the support of a mental health worker such as an assistant psychologist, peer support worker or therapist. VR could support the remote delivery of treatment which would allow some people to receive treatment at home. This could increase access to care for those who are unable or prefer not to attend face-to-face treatment.

The place in the care pathway may differ for agoraphobia and agoraphobic avoidance with or without other mental health disorders such as psychosis.

VR for treating agoraphobia and agoraphobic avoidance is not intended to replace treatments for other mental health disorders, such as antipsychotic medication. Treatment options should be discussed by healthcare professionals and patients and should consider clinical assessment and judgement, patient preferences and risk, and the level of support needed.

3 The decision problem

Details of the decision problem are described in the scope. No changes were made to the decision problem during the assessment.

4 The evidence

4.1 Summary of evidence of clinical benefit

The EAG found 4 studies with a total of 9 publications that were relevant to the decision problem (Table 1). The rationale for selecting these studies is outlined in section 7 of the assessment report.

Table 1. Studies included in the assessment

Technology	Publication and study design
Amelia Virtual Care	1 publication: • 1 single-arm study (poster) (Gelabert and Giner 2018)
gameChangeVR	7 publications: • 1 RCT (Freeman et al. 2022a) with embedded qualitative study (Bond et al. 2023, Freeman et al. 2022b) and economic evaluation (Altunkaya et al. 2022) • Secondary analysis of RCT (Freeman et al. 2022c) • Design process study (Knight et al. 2021, Lambe et al. 2020)
Invirto	No evidence found
XR Therapeutics	1 publication: • 1 single-arm feasibility study (Maskey et al. 2019)
Abbreviation: RCT: randomised controlled trial	

A summary of the clinical evidence is presented for each technology. More details can be found in Table 2 of this overview and section 8 of the assessment report.

Amelia Virtual Care. The relevant evidence included 1 single-arm study in adults with agoraphobia with or without panic disorder (Gelabert and Giner 2018). This showed that 82% of people completed the entire treatment protocol, with an average satisfaction rating of 68%. Overall, Amelia Virtual Care had fairly good adherence and patient satisfaction, but no clinical outcomes were reported.

gameChangeVR. Relevant clinical evidence included 1 RCT (Freeman et al. 2022a) with embedded qualitative studies (Bond et al. 2023, Freeman et al. 2022b) and secondary analysis (Freeman et al. 2022c). The RCT showed that gameChangeVR plus usual care was more effective than usual care alone in reducing agoraphobic avoidance and distress at 6 weeks, but benefits were not maintained at follow-up. There was no significant difference between groups in quality of life or other psychological symptoms except perceived recovery at 6 weeks. Post-hoc analysis showed that treatment benefits were only seen in people with high and severe agoraphobia at baseline based on the Oxford Agoraphobic Avoidance Scale (O-AS), with these benefits maintained at 26 weeks. The O-AS was developed by researchers at Oxford University who were also involved in the development of gameChangeVR. Experts advised that the O-AS is not routinely used in the NHS.

Secondary analysis (Freeman et al. 2022c) showed significant post-treatment improvements from gameChangeVR with usual care compared with usual care alone in people with severe agoraphobia, specifically in agoraphobic avoidance ($p<0.001$) and distress ($p=0.002$), symptoms of psychosis, recovering quality of life ($p=0.004$), and perceived recovery ($p=0.038$). Most people were mostly (31%) or very (69%) satisfied with gameChangeVR.

XR Therapeutics. Relevant evidence was only available from 1 single-arm feasibility study in autistic adults with fears and phobias (Maskey et al. 2019). This study had a small sample size of 8 people, of whom only 2 reported fears or phobias relevant to agoraphobia. Findings for these 2 people showed equivocal improvement in target behaviours and no benefit in general symptoms of anxiety, depression or quality of life.

Table 2. Details of studies included in the assessment report, grouped by technology

Study design	Participants & setting	Intervention & comparator	Key outcomes measures and results
Amelia Virtual Care (number of studies=1)			
Gelabert and Giner (2018) Single-arm study Location: Spain	51 adults with agoraphobia with or without panic disorder **Setting**: 7 adult mental health centres	**Intervention**: Amelia Virtual Care **Comparator**: None Follow-up: 6 months	**Therapeutic adherence** 42 people (82.4%) completed the treatment protocol. The main reason for non-completion was a lack of presence in the virtual environment, that is how much a person feels they are in the scenario or situation. **Number of sessions needed** 98% of people who completed the course did so within the prescribed 8 sessions, with 2 people needing an extra 2 sessions beyond the protocol. **Client Satisfaction Questionnaire-8** Average satisfaction rating was 68%. 57% of people reported high or very high presence, while 12% reported null or low presence.
gameChangeVR (number of studies=2)			
Freeman et al. (2022a) RCT Location: UK Related papers: • Altunkaya et al. (2022) • Bond et al. (2023) • Freeman et al. (2022b) • Freeman et al. (2022c)	346 people aged 16 years or older with schizophrenia spectrum psychosis or an affective diagnosis with psychotic symptoms who have difficulties going outside because of anxiety **Setting**: 9 NHS mental health trusts in England	**Intervention**: gameChangeVR with usual care, delivered in about 6 weekly sessions of 30 minutes each (n=174) **Comparator**: Usual care alone (n=172) Freeman et al. (2022a) stated "usual care was recorded using the Client Service Receipt Inventory, and usually comprised prescription of antipsychotic medications, regular visits from a community mental	131 people in the gameChangeVR arm had the least minimum dose of VR therapy (at least 3 sessions). Provision of VR therapy was affected by COVID-19 pandemic restrictions for 27 people. The effect of the pandemic on usual care was not reported. Most common components of usual care from baseline to 6 weeks [n (%)]: • antipsychotic: 155 (89%) in gameChangeVR group, 155 (90%) in comparator • antidepressant: 94 (54%) gameChangeVR, 94 (55%) comparator • anxiolytic: 12 (7%) gameChangeVR, 14 (8%) comparator • care coordinator meetings: 126 (72%) gameChangeVR, 124 (72%) comparator • psychiatrist meetings: 44 (25%) gameChangeVR, 52 (30%) comparator • counselling or therapy: 9 (5.2%) gameChangeVR, 14 (8.1%) comparator • GP meetings: 41 (24%) gameChangeVR, 49 (29%) comparator

		health worker and occasional outpatient appointments with a psychiatrist". Follow-up: 6 months	**Agoraphobic avoidance** Compared with usual care, gameChangeVR had a statistically significant reduction in agoraphobic avoidance (p=0.026) and distress (p=0.014) at 6 weeks. Differences between groups were not significant at follow-up. Post-hoc analysis showed people with severe and high agoraphobia at baseline were the only groups to benefit from gameChangeVR with benefits maintained at follow-up: • O-AS avoidance adjusted mean difference at 6 weeks: moderate 0.08, high -0.34, and severe -1.63 (p=0.014) • O-AS avoidance adjusted mean difference at 26 weeks: moderate 0.10, high 0.33, and severe -2.06 (p<0.001) Secondary analysis showed significant post-treatment improvements from gameChangeVR in people with severe agoraphobia compared with usual care alone: • O-AS avoidance adjusted mean difference: post-treatment -1.63 (p<0.001), follow-up -2.06 (p<0.001) • O-AS distress adjusted mean difference: post-treatment -10.5 (p=0.002), follow-up -12.97 (p=0.001) **Other psychological symptoms** People in the gameChangeVR group reported better recovery (Questionnaire about the Process of Recovery) at 6 weeks than usual care alone (p=0.004). There were no other statistically significant differences in secondary outcomes on psychological symptoms such as paranoia, depression (PHQ-9) and activity levels. **Quality of life** There was no statistically significant difference in quality of life between arms. Secondary analysis showed significant benefits from gameChangeVR compared with usual care alone on ReQoL-20 in people with severe agoraphobia (adjusted mean difference 6.90, 95% confidence interval 2.20 to 11.60; p=0.004). There was no significant difference on the EQ-5D between groups. **Participant experiences** People reported that using gameChangeVR created an anxiety response that was useful for learning and practicing a different response in a safe environment. It was important to be motivated to engage with the intervention and the anxiety response, with people who completed activities to reinforce learning having a better treatment

			response. People who had the most difficulty managing their agoraphobic avoidance were said to be more motivated and to benefit most from gameChangeVR. **Patient satisfaction** 68.5% of people were very satisfied with gameChangeVR, 30.8% were mostly satisfied and the remaining were mildly dissatisfied or quite dissatisfied. **Safety** There were 25 adverse events (12 serious) in the gameChangeVR group and 29 (8 serious) in usual care alone. 10 serious adverse events for gameChangeVR were rated as definitely not related to the intervention and 2 were probably not related.
Lambe et al. (2020) Design process study Location: UK Related paper: • Knight et al. (2021)	Stakeholders including mental health workers, designers and people with lived experience	**Intervention**: Development of gameChangeVR using a person-centred design process **Comparator**: None	**User acceptability ratings** All users (n=6) rated gameChangeVR as immersive, easy to use and engaging
XR Therapeutics (number of studies=1)			
Maskey et al. (2019) Single-arm feasibility study Location: UK	8 autistic adults with fears and phobias recruited from NHS adult autism diagnosis team and a local autism support network. Of these, 2 had phobias relevant to scope (open space and crowded buses) **Setting**: VR facility	**Intervention**: XR Therapeutics delivered in 2 visits, each comprising of 2 20-to-30-minute sessions **Comparator**: None Follow-up: 6 months	**Retention and participation** Achieved for all sessions. The role of the supporter was important and needed further exploration. Supporters reported needing more guidance about their role and how best to support the person to tackle their real-life anxiety target. **Target Situation Rating (professional rating scores ranging 0 to 9)** 5 out of 8 people were rated as showing an improvement in symptoms related to their phobia. This did not include the 2 people with phobias relevant to agoraphobia who were rated as 'equivocally improved' at post-treatment and follow-up. **Confidence in managing target anxiety situation** Confidence ratings increased pre-post treatment **Other symptoms** There was no pattern of reliable or observable changes on the GAD-7, BAI or PHQ-9. **Quality of life**

			There was an increase in the WHOQOL-BREF social subscales post-treatment (mean 41.7 pre- to 47.0 post) and follow-up (mean 51.0) but no other subscales.

Abbreviations: ACQ: Agoraphobic Cognition Questionnaire, AI: Agoraphobia Inventory, BAI: Beck Anxiety Inventory, BSQ: Body Sensations Questionnaire, EQ-5D: EuroQoL-5 dimensions, GAD-7: Generalised Anxiety Disorder-7, LSAS: Liebowitz Social Anxiety Scale, O-AS: Oxford Agoraphobic Avoidance Scale, O-BAT: Oxford Behavioural Avoidance Test, PHQ-9: Patient Health Questionnaire-9, RCT: randomised controlled trial, ReQoL: Recovering Quality of Life questionnaire, SUA: Subjective Units of Anxiety, WHOQOL-BREF: World Health Organization Quality of Life scale

The EAG made the following comments on the limitations and generalisability of the evidence base:

Population. Studies for gameChangeVR and XR Therapeutics were conducted in the UK, while the evidence for Amelia Virtual Care was from Spanish settings. This is likely to be comparable to the UK but there may be some differences in the delivery of care. All 3 technologies had study populations broadly relevant to the decision problem. Amelia Virtual Care had evidence in people with agoraphobia with or without panic disorder. gameChangeVR and XR Therapeutics focused on subgroups, specifically psychosis with agoraphobic avoidance and autism with fears and phobias, respectively. There was no evidence on XR Therapeutics in a population with agoraphobia. This limits the generalisability of the evidence to the broader scoped population.

Intervention. There was no evidence on Invirto and no relevant clinical effectiveness evidence on Amelia Virtual Care. There was limited relevant evidence on the clinical effectiveness of the 2 remaining technologies. This consisted of 1 RCT (gameChangeVR) and 1 single-arm study (XR Therapeutics).

Comparator. There are limitations with comparators for all technologies. There was no relevant comparative evidence on Amelia Virtual Care or XR Therapeutics. For gameChangeVR, there was only 1 comparative study which compared gameChangeVR plus usual care with usual care alone, but usual care varied across patients. The EAG considered that there are limitations to using treatment as usual as a comparator because of the variation in routine practice across centres.

Outcomes. All studies reported some outcomes of interest, but evidence was not available on all scoped outcomes for all technologies. gameChangeVR was the only technology with evidence on adverse events. There was variation in outcomes across studies and the instruments used.

In summary, the EAG considered the clinical effectiveness to be uncertain for all technologies. While there was some evidence of potential benefits on

agoraphobia symptoms for gameChangeVR, the EAG concluded that there were considerable uncertainties about the interpretation and reliability of these findings. More evidence is needed including evidence on the longer-term effects of all interventions.

4.2 Summary of economic evidence

The EAG identified 1 economic study (Altunkaya et al. 2022) that was relevant to the decision problem. This was a within-trial cost-effectiveness analysis of gameChangeVR conducted alongside the RCT (Freeman et al. 2022a). There was no economic evidence on any of the other technologies.

Altunkaya et al. (2022) aimed to estimate the maximum cost-effective price for gameChangeVR using the conventional willingness-to-pay thresholds. It reported incremental gain in utilities for gameChangeVR plus usual care of +0.008 (-0.010 to 0.026) QALYs (E5-5D) and +0.003 (-0.011 to 0.017) QALYs (ReQoL) compared with usual care alone. Using an NHS and personal social services (PSS) perspective and EQ-5D-based QALYs, the maximum cost-effective price for gameChangeVR was £262 or £341 per person based on a £20,000 or £30,000 threshold respectively. This increased to £682 (£20,000 per QALY) and £844 (£30,000 per QALY) for the subgroup of people with high or severe agoraphobic avoidance and distress.

The EAG noted that the base case results were disproportionately driven by 4 people in psychiatric inpatient settings. When these were removed, there was no positive price at which gameChangeVR was cost-effective in the general population of psychosis with agoraphobia from an NHS and PSS perspective. However, gameChangeVR had the potential to be cost-effective in subgroups with high or severe avoidance or distress. The most optimistic of these scenarios showed a max price of £125 at a £20,000 threshold or £324 at £30,000. The maximum cost-effective price of gameChangeVR was greater when considering the intervention's impact on wider societal costs but this is beyond the scope of this assessment.

4.2.1 Conceptual modelling

The EAG used Altunkaya et al. (2022) as a starting point to develop a decision model to explore uncertainties in the cost-effectiveness of the VR technologies, specifically the duration of the treatment effect and the effect of subsequent rounds of treatment. The primary purpose of the analysis was to assess the plausibility of the technologies being cost-effective and to identify evidence gaps for future evidence generation. The EAG advised that this modelling is exploratory and does not provide conclusive findings on the cost-effectiveness of the technologies compared with standard care.

The EAG developed a decision analytical model for gameChangeVR plus usual care compared with usual care alone in people with psychosis who have agoraphobic avoidance. The EAG excluded Amelia Virtual Care, XR Therapeutics and Invirto from the analysis because of the limited or lack of relevant clinical evidence.

The model was a 2-state Markov model transitioning between psychosis with agoraphobia and psychosis alone. The choice of a state-transition model was driven by the need to explore uncertainties in longer-term costs and effects of the different interventions. The model structure is outlined in section 10.2.2 and Figure 1 of the assessment report. The transition period was 6 months with a time horizon of 5 years. This reflected the follow-up periods in the evidence and aimed to provide a reasonable time horizon to explore uncertainties in relapse or recurrence (referred to as 'relapse rate') and effectiveness of subsequent courses of treatment. The EAG also conducted an additional analysis using a shorter time horizon of 2 years. This is outlined in Appendix B of this overview and supplementary Appendix F of the assessment report.

Markov models require discrete health states to be defined, such as 'responder' and 'non-responder'. The EAG noted that this is not reported in the evidence. It therefore assumed that everyone having VR therapy responded to treatment at 6 months with the mean per person utility changing in line with the adjusted mean difference reported in the evidence. The model

assumed that everyone transitioned from the 'agoraphobia' health state to the 'non-agoraphobia' health state in cycle 1. Subsequent cycles allowed the EAG to explore uncertainties around relapse rate and effectiveness of further courses of VR therapy. Key assumptions in the model are outlined in section 10.3.4 of the assessment report.

4.2.2 Model inputs

Clinical parameters

Clinical parameters were sourced from the evidence and expert advice. Intervention and comparators were based on the clinical trial. In Freeman et al. (2022a), gameChangeVR was delivered with usual care and compared with usual care alone. Response to treatment was driven by the health state utility derived from the findings of the clinical trial (Freeman et al. 2022a). The model used the utility difference between VR therapy and standard care as the driver of effect rather than a probability of response. The EAG assumed a base case relapse rate of 25% which was varied according to a uniform distribution between 0% and 50%. There was no evidence on the effectiveness of subsequent courses of VR therapy. The EAG included the relative risk of response for subsequent courses of treatment to explore scenarios. This was set at 1 in the base case.

Health state utilities

Baseline health state utility was set to the weighted mean baseline utility across both arms in the gameChangeVR trial (Altunkaya et al. 2022, Freeman et al. 2022a). The change in utility associated with VR therapy was equal to the adjusted mean difference between gameChangeVR plus usual care and usual care alone at 6 months (+0.007, 95% confidence interval -0.043 to 0.057).

Costs and resource use

The base case calculated costs and resource use from an NHS and PSS perspective. Costs and resource use in the model are presented in Table 3 and Table 4. These are the incremental costs and resources needed for

delivering gameChangeVR in addition to standard care. Costs of standard care are not presented because these were assumed to be the same in both arms. Intervention costs included licence costs, therapist time and apportionment of capital cost of the VR headset. The model also considered a point estimate difference in other health service costs between gameChangeVR plus usual care and usual care alone. This was -£112.15 (SE £280.50) per person based on findings in Altunkaya et al. (2022) adjusted to 2021 prices. More information on intervention costs is provided in section 10.3.2.1 of the assessment report.

In line with Altunkaya et al. (2022), the EAG also considered costs from a broader societal perspective as additional analyses. These included criminal justice costs and costs of informal caregiving (see sections 10.3.2.3 and 10.3.2.4 of the assessment). Cost modelling using a societal perspective is not detailed in this overview because it is outside the scope of this assessment.

Table 3. Unit costs

Item (unit)	Unit Cost	Source
Mental health worker (per hour)	£33.00	Band 4, equivalent to clinical psychology assistant practitioner (ch 17, and hourly cost from ch 10.1 PSSRU 2021)
Clinical psychologist (per hour)	£105.00	Consultant clinical psychologist (Band 8c, Ch 9, PSSRU 2021)
VR headset	£300	Notional cost
gameChangeVR licence (per person per course)	[redacted]	Company

Table 4. Intervention resource use

Item	Quantity	Total Cost
gameChangeVR (per session)		
Mental health worker intervention delivery	1 hour	£33.00
Mental health worker weekly supervision	1 hour with clinical psychologist, assuming mental health worker conducts 15 sessions per week	£9.20
Training	4.5 hours with clinical psychologist with 6 mental health workers in attendance, assuming training lasts 2 years before refresher required	£0.17

VR Headset	One per mental health worker conducting 15 sessions per week for 44 weeks/year, lasting 2 years	£0.64
Total per session		£43.01
gameChangeVR (per course)		
Per session costs	Six sessions per course	£258.05
Licence cost		[redacted]
Total per course		[redacted]

4.2.3 Approach to analysis

The EAG conducted a cost utility analysis estimating the incremental cost per incremental QALY gained from gameChangeVR plus usual care compared with usual care alone in people with psychosis who have agoraphobic avoidance. Analyses were conducted from an NHS and PSS perspective. Only costs that differed between arms were measured and valued. The EAG reported mean costs and QALYs gained per person in each arm, incremental cost-effectiveness ratios and probability of cost-effectiveness at £20,000 and £30,000 per QALY thresholds. Means and uncertainty distributions were generated from probabilistic sensitivity analysis of 10,000 simulations sampled from the distributions of input parameters. The EAG also conducted several probabilistic sensitivity analyses and scenarios which are outlined in sections 10.4.1 to 10.4.8 of the assessment report.

4.2.4 Results

The exploratory base case results are presented in Table 5. Point estimate ICER suggests that on average gameChangeVR is not cost-effective from an NHS and PSS perspective. But the EAG base case suggests there is substantial decision uncertainty with around 25% to 30% probability of gameChangeVR being cost-effective from an NHS and PSS perspective at conventional thresholds of willingness to pay. gameChangeVR may be cost-effective from a wider societal perspective, but this falls outside the scope of this assessment.

Table 5. gameChangeVR base case results

Costs			QALYs				P(CE)	
gC+TAU	TAU	Inc.	gC+TAU	TAU	Inc.	ICER	£20k	£30k
[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26.3%	31.2%
Abbreviations: gC: gameChangeVR, P(CE): probability of cost-effectiveness, QALYs: quality adjusted life years, TAU: treatment as usual								

Scenario and sensitivity analyses

The EAG considered that while the point estimates from the decision modelling were only indicative, the modelling provided a useful platform to explore several uncertainties:

Incremental utility gain. The minimum utility gain for gameChangeVR to achieve an ICER below the £30,000 threshold is [redacted] ([redacted] for an ICER below £20,000 per QALY). Additional analysis using utilities from high and severe agoraphobia subgroups found point estimate ICERs within the range considered to be cost-effective from an NHS and PSS perspective. More information is provided in Appendix B of this overview and Appendix F of the assessment report.

Licence fees. Results were highly sensitive to licence fees. The licence fee associated with a 50% probability of cost-effectiveness was about [redacted] at a £20,000 per QALY threshold or [redacted] at a £30,000 threshold.

Incremental utility versus licence fees. The maximum cost-effective licence fee for gameChangeVR increased as incremental utility increased. Two-way sensitivity analysis of gameChangeVR licence costs versus incremental utility can be found in section 10.5.2.8 and Table SA8 of the assessment report.

Cost of VR headset. The ICER was not sensitive to changes in the cost of the VR headset.

Relapse rate. One-way sensitivity analysis suggested the ICER of gameChangeVR deteriorates as the relapse rate increases. Under the base

case, gameChange was only cost-effective if relapse rates were less than [redacted] at a £30,000 per QALY threshold and less than [redacted] at the £20,000 threshold.

Relapse rate versus licence fees. The maximum cost-effective licence fee for gameChangeVR decreased as the probability of relapse increased. Two-way sensitivity analysis of gameChangeVR licence costs versus relapse rate can be found in section 10.5.2.7 and Table SA7 of the assessment report.

Effectiveness of subsequent therapy. The ICER deteriorates with a decline in the relative effectiveness of subsequent VR therapy. This is because the same cost is incurred with less relative benefit.

In summary, the EAG noted that gameChangeVR is priced above what would normally be considered cost-effective from an NHS and PSS perspective. But there is great uncertainty in the base case which was highly sensitive to the assumptions in the model. The EAG concluded that there are scenarios where gameChangeVR may be cost effective particularly in people with high and severe agoraphobia, but more evidence is needed.

The EAG did not model the possible cost-effectiveness of Amelia Virtual Care or XR Therapeutics because of their limited clinical evidence.

5 Ongoing research

The companies for gameChangeVR and XR Therapeutics said there were no ongoing trials, but XR Therapeutics are monitoring real-world outcomes. Amelia Virtual Care provided information marked as academic in confidence on 5 ongoing studies, but the populations are not in scope. The EAG also found 2 ongoing studies for Invirto which may be relevant when completed:

- Evaluation of "Invirto aftercare" for anxiety disorders: a pilot study (DRKS00027001)
- Evaluation of "Invirto Therapy" for people with panic disorder: a randomized-controlled trial (DRKS00027585)

6 Evidence gap analysis

The EAG presented a summary of the evidence gaps pertaining to outcomes from the scope (Table 6) and the decision modelling (Table 7). There was no published evidence on Invirto which is a noted evidence gap.

Table 6. Evidence gaps in outcomes from the scope

Outcomes	Amelia Virtual Care	gameChangeVR	XR Therapeutics
Intermediate outcomes			
Patient choice and preferences	No studies **RED**	No studies **RED**	No studies **RED**
Acceptability and satisfaction	One study **AMBER**	One study **AMBER**	One study **AMBER**
Accessibility and digital access	No studies **RED**	No studies **RED**	No studies **RED**
Intervention adherence and completion	One studies **AMBER**	One study **AMBER**	One study **AMBER**
Intervention-related adverse events	No studies **RED**	One study **AMBER**	No studies **RED**
Device-related adverse events	No studies **RED**	One study **AMBER**	No studies **RED**
Clinical outcome			
Change in agoraphobia symptoms	No studies **RED**	One study **AMBER**	One study, mixed results **AMBER**
Change in other psychological symptoms	No studies **RED**	One study, negative results **RED**	One study, negative results **RED**
Global functioning and work and social adjustment	No studies, **RED**	No studies **RED**	No studies **RED**
Rates of recovery, time to recovery	No studies **RED**	No studies **RED**	No studies **RED**
Rates of relapse or deterioration, time to relapse or deterioration	No studies **RED**	No studies **RED**	No studies **RED**
Patient reported outcomes			
Health-related quality of life	No studies **RED**	One study, negative results **RED**	One study, negative results **RED**

Outcomes	Amelia Virtual Care	gameChangeVR	XR Therapeutics
Recovering quality of life	No studies **RED**	One study, negative results **RED**	No studies **RED**
Patient experience	No studies **RED**	One study **AMBER**	No studies **RED**
Social contact	No studies **RED**	One study, negative result **RED**	No studies **RED**

Table 7. Evidence gaps in modelling and economic outcomes

Effectiveness evidence	
Populations and comparative data	Each intervention has been trialled in very different populations. It is unknown whether any of the interventions are interchangeable between different populations and thus require head-to-head comparison **RED**
Comparative data	There is no randomised evidence on the effectiveness of Amelia Virtual Care or XR Therapeutics. **RED**
Comparative data	There is no evidence on durability of treatment effect and/or relapse rates. **RED**
Comparative data	There is no evidence on effect of second or subsequent courses of therapy. **RED**
Comparative data	Is there an impact on other health service use from VR-based therapies? **AMBER**
Generalisability	Is there any difference in effect between who delivers the interventions? **AMBER**
Costs	
Criminal justice costs	Is the impact of gameChangeVR on criminal justice costs in people with psychosis of meaningful? **AMBER**
Lost productivity	Is there a case for including time off work within economic evaluations of agoraphobia (outside NICE reference case)? The evidence base contains no data on lost productivity. **RED**
Health related quality of life	
Health state utilities	Evidence on health state utilities is currently very weak **RED**

6.1 Summary and conclusions of evidence gap analysis

The EAG identified several evidence gaps in the clinical evidence base. These in part drive key uncertainties in the economic analysis:

Population gaps. The populations studied for each intervention differed. The clinical evidence for XR Therapeutics included 2 people with phobias that the EAG considered to be relevant to agoraphobia. But there was no evidence in adults with agoraphobia. There was no UK evidence for Amelia Virtual Care which may limit the generalisability of findings to the NHS.

Intervention gaps. There is limited evidence for all interventions. There was no evidence on Invirto, no relevant clinical effectiveness evidence for Amelia Virtual Care, and no comparative evidence on XR Therapeutics.

Comparator gaps. There is uncertainty about how closely comparators match routine practice in the NHS, especially for treatment as usual (usual care).

Outcome gaps. Published evidence was not available for some outcomes. There was also heterogeneity in how clinical measures were reported. It was unclear whether some statistically significant differences in outcomes were clinically meaningful. There was no evidence on the durability of the effect (relapse rates) of VR therapies for any of the technologies. Clinical evidence on safety outcomes (adverse effects) were only available for gameChangeVR.

Decision modelling. Evidence gaps for the economic modelling are mostly related to the limited clinical evidence, quality of life outcomes, utilities and relapse rates. Whilst outside the reference case, employment status and lost time at work may be an important factor to consider in economic analysis of treatments for agoraphobia. This was not measured in any of the studies.

7 Equalities considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular

protected characteristics and others. Several potential equality issues and considerations in using VR for treating agoraphobia have been identified:

- Some VR technologies need Wi-Fi to use the intervention or to upload content. Additional support and resources may be needed for people who are unfamiliar with digital technologies or do not have access to the internet.
- People with visual or cognitive impairment, problems with manual dexterity, a learning disability or who are unable to read or understand health-related information (including people who cannot read English) may need additional support to use VR. Some people would benefit from VR in languages other than English. XR Therapeutics has adapted its intervention for autistic people and people with learning disabilities. The company said its VR studio is also accessible for people with physical disabilities, including people using wheelchairs.
- VR may not be suitable for use by people with photosensitive epilepsy; significant visual, auditory, or balance impairment; organic mental disorder; primary diagnosis of alcohol or substance disorder or personality disorder; significant learning disability; or active suicidal plans. Some VR interventions may involve moving around the room or standing. This may be difficult for some people with physical disabilities or additional accessibility needs.
- People's ethnicity, religious or cultural background may affect their views of mental health problems and interventions. Healthcare professionals should discuss the language and cultural content of VR with patients before use.
- People facing social inequality and disadvantage, discrimination and exclusion are at higher risk of mental health problems. Agoraphobia and agoraphobic avoidance can significantly affect people's daily living. Under the Equality Act 2010, a person has a disability if they have a physical or mental impairment that has a substantial and long-term effect on their ability to do typical day-to-day activities.

Age, disability, race and religion or belief are protected characteristics under the Equality Act (2010).

8 Implementation

Some of the scoped technologies are already used in the NHS. The EAG reported that wider use would involve upscaling across more trusts. Potential challenges with integration into the NHS included having enough staff resources and training to deliver the interventions. There may also be challenges with access to the technologies and equipment particularly for people who work during the day or are unable to leave home. NHS trusts would also have to purchase and maintain VR headsets when used for the delivery of VR therapy as these are not usually provided by the companies.

NICE's adoption and implementation team spoke with clinical experts who had experience of VR for treating agoraphobia and agoraphobic avoidance. Some implementation considerations may not apply to all technologies. Key considerations raised in the adoption of these technologies include:

Safety and comfort. Potential safety considerations based on the clinical evidence on VR therapy delivered via headsets includes concerns with possible side effects such as dizziness and motion sickness. This may be less of a concern with more recent versions of devices. There were also concerns with the space needed to use VR and issues with bumping into things in the room. Experts advised that a couple of metres is enough to use these technologies. Other considerations are whether the headset is comfortable to wear over glasses or use if the person's eyes are sensitive to glare. If people have any discomfort or concerns with using VR, they can remove the headset or leave the immersive setting.

Patient selection. Some VR therapies may be used as a standalone intervention if there is appropriate and careful patient selection. gameChangeVR includes a virtual coach that guides the person through treatment. Interventions have been found to work best with a mental health worker who helps with patient engagement. VR may not be suitable for

everyone. Healthcare professionals and patients should discuss treatment options before use.

Acceptability. Preliminary implementation work and input from people with lived experience showed good acceptability of using VR for agoraphobia and agoraphobic avoidance. People reported good immersive quality of the technologies and were motivated to try the interventions because they wanted a solution to their difficulties. Anecdotal reports suggested some people have quick progress and symptom improvement including increase in real-world activities. Experts suggested that people with more severe symptoms may have greater response to treatment. Healthcare professionals may initially be a little hesitant to using VR but demonstrations, training and support can help.

9 Issues for consideration by the committee

9.1 Unmet need

Only 1 in 3 people with a common mental health disorder accesses treatment. This may be even lower for people with agoraphobia who may have increased challenges getting the treatment and support they need. These may include:

- underdiagnosis or undertreatment of agoraphobia or agoraphobic avoidance when presenting with more severe or prominent mental health disorders such as psychosis
- difficulty leaving home to access treatment
- difficulty completing treatments such as in vivo exposure
- limited clinical resources which means people may not be offered NICE recommended treatments such as CBT but may instead receive drug treatments and simple contact with services and monitoring.

VR therapy may increase access to care by offering another treatment option. It could support the remote delivery of treatment which would allow some people to receive treatment at home. This could increase access to care for those who are unable or prefer not to attend face-to-face treatment.

9.2 Population

Evidence on the effectiveness of each technology was in different populations. Relevant evidence on XR Therapeutics was in autistic adults with fears and phobias. XR Therapeutics is indicated for use in a broader population of agoraphobia. The committee may wish to consider the generalisability of the evidence to this population.

The evidence for gameChangeVR showed benefits in reducing agoraphobic avoidance in people with severe agoraphobia at baseline. This aligns with anecdotal reports from clinical experts that people with the greatest difficulty in managing their agoraphobia or agoraphobic avoidance may be more motivated to use VR therapy and may see the greatest benefits.

9.3 Care pathway

There was limited evidence comparing gameChangeVR plus usual care compared with usual care alone. But there was no comparative evidence on the other technologies. There was also no evidence on other possible uses of these technologies, such as the remote use of Amelia Virtual Care as part of teletherapy for people who may be unable to attend face-to-face sessions. There was also no evidence on the use of gameChangeVR as a standalone therapy with asynchronous remote support. The committee may wish to consider the generalisability of the evidence across treatment settings and how variation in treatment delivery may affect outcomes.

9.4 Clinical evidence

There is limited evidence on all technologies. The relevant clinical evidence consists of 4 studies including 1 RCT for gameChangeVR which suggests some benefits in improving symptoms of agoraphobia. But the EAG advised that there were substantial uncertainties.

For gameChangeVR, key uncertainties were:

- the lack of a treatment effect in the broader population of psychosis with agoraphobic avoidance, suggesting benefits may be limited to people with more severe symptoms at baseline
- the long-term benefits of gameChangeVR compared with usual care
- the lack of benefit on EQ-5D-based quality of life outcomes.

For Amelia Virtual Care, key uncertainties were the lack of relevant clinical effectiveness or comparative evidence. For XR Therapeutics, key uncertainties were the lack of evidence in adults with agoraphobia and the limited evidence on clinical effectiveness in adults.

9.5 Economic evidence

The economic modelling is exploratory and should not be used as a definitive result of cost-effectiveness. Findings were highly sensitive to the assumptions in the model, including incremental utility from the limited clinical evidence.

Because of the limited evidence, economic modelling was only done on gameChangeVR. The exploratory base case suggested that based on the clinical evidence, licence costs and assumed relapse rates, gameChangeVR would not be a cost-effective treatment for the overall population from an NHS and PSS perspective. The cost-effectiveness of gameChangeVR was driven by the licence fees, utility and relapse rates. The EAG noted that gameChangeVR was

[redacted]

The committee may wish to consider if it is possible to mitigate the degree of uncertainty in the cost modelling to increase probability of cost-effectiveness.

9.6 Key gap analysis conclusions

There is no evidence on Invirto and limited evidence on the other 3 technologies. The EAG did not identify any ongoing studies that would address the evidence gaps in line with the decision problem but noted that some technologies may be collecting real-world outcomes.

10 Authors

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NICE Medical Technologies Evaluation Programme

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11 Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report

- Barnish MS, Lovell A, Robinson S, et al. Virtual reality for treating agoraphobia and agoraphobic avoidance [GID-HTE10016]: external assessment group report. May 2023.

A list of registered stakeholders and expert adviser Specialist Committee Members can be found in the published project documents.

B Companies of technologies included in the final scope:

- Amelia Virtual Care
- Invirto
- Oxford VR
- XR Therapeutics

C Related NICE guidance

- Mental health problems in people with learning disabilities: prevention, assessment and management (2016) NICE guideline 54
- Psychosis and schizophrenia in adults: prevention and management (2014) NICE clinical guideline 178. Last updated 1 March 2014.
- Common mental health problems: identification and pathways to care (2011) NICE clinical guideline 123
- Generalised anxiety disorder and panic disorder in adults: management (2011) NICE clinical guideline 113. Last updated 15 June 2020

D References

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World Health Organisation (WHO) (2023) International Classification of Diseases, Eleventh Revision (ICD-11)

12 Appendix B: Additional analyses carried out by the EAG

The EAG conducted additional analyses after submitting the assessment report exploring (1) a reduced time horizon of 2 years and (2) scenario analysis with more severe subgroups for gameChangeVR. This is reported in supplementary Appendix F of the assessment report.

12.1 Time horizon scenario analysis

The EAG conducted a scenario analysis using a 2-year time horizon. At a 2-year time horizon, gameChangeVR was found to be less cost-effective than the base case (Table 8).

Table 8. Time horizon scenario analysis

Time horizon	Costs			QALYs				P(CE)	
	gC+TAU	TAU	Inc.	gC+TAU	TAU	Inc.	ICER	£20k	£30k
5 years	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26.3%	31.2%
2 years	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.8%	13.4%

12.2 Severe subgroup scenario analysis

The EAG conducted a scenario analysis using utility differences for high and severe agoraphobia subgroups from Freeman et al. (2022c). The change in utility associated with VR therapy at 6 months was +0.04 (SE 0.05) for high agoraphobic avoidance and +0.05 (SE 0.053) for severe avoidance. Results of this analysis are presented in Table 9. It shows that point estimate ICERs for the high and severe avoidance subgroups from an NHS and PSS perspective are within the range normally considered cost-effective by NICE. But the EAG advised that there is substantial uncertainty associated with this. For the severe agoraphobia subgroup, Freeman et al. (2022c) reported the point estimate incremental utility at 6-months follow-up was higher than 6-weeks post-treatment. The EAG considered that a tailing off of treatment effect over time would typically be expected and concluded that further exploration is needed.

Table 9. Severity subgroup scenario analysis

Group	Costs			QALYs				P(CE)	
	gC+TAU	TAU	Inc.	gC+TAU	TAU	Inc.	ICER	£20k	£30k
All	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26.3%	31.2%
High	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57.1%	65.2%
Severe	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	63.1%	70.4%

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health technology evaluation

Patient survey report

Virtual reality technologies for treating agoraphobia or agoraphobia avoidance

In May 2023, NICE's public involvement programme posted an online survey seeking the views of people with agoraphobia or agoraphobic avoidance. In total, 10 people with agoraphobia symptoms and a representative of a patient organisation responded to the survey. None of the responders had used VR for treating agoraphobia or agoraphobic avoidance.

1. Experiences of agoraphobia

People described the significant impact of agoraphobia symptoms on their life. This included low quality of life, feeling excluded, feeling trapped inside or housebound, and difficulty travelling on public transport:

"Struggled to leave the house, even going onto the back garden caused a panic attack. For about 6 months. Even when improving I planned my routes if I was walking so that I could sit and rest because I thought I would faint." [R6]

"For a long time I generally had trouble in crowded environments, in cities, loud places etc., but I could mostly manage. Over time I struggled more, first it began during my first year of university. I would commute on a regular basis but I would experience panic when being in certain places: tunnel vision, racing heart, headaches, being out of breath and so on. But mostly it was in that one scenario, commuting in the mornings, other than that, travelling to and from university was fine. I didn't seek any help at that time as I was mostly managing, even though it could have been helpful at that time. However, during the pandemic things changed a lot, and it enabled a way for me to do the same work but at home, which was easy for me as I felt the most comfortable at home. I didn't have a routine of going out often, so I would only leave the house if I had to at that point. It was easy for the first few months but over time, stress built up and circumstances got more difficult. That lead to me experiencing more panic attacks outside, leading to move avoidance behaviour. Retreating more and more into the more predictable house environment. A year after the start of the pandemic I was housebound and would even panic when people would knock on the door. I refused to meet with people outside if I could, and

I struggled to fulfil responsibilities if they occurred outside of the home. Even being at home stopped being comfortable, as I grew less and less tolerant towards more of everything that was going on." [R8]

"Feel excluded - like everyone is enjoying the freedom of life except me. Everyday at work is a challenge, for example big face to face meetings make it worse. Feel exhausted by the weekend so undertaking CBT or "pushing myself" in my leisure time, means I'm even more exhausted and spend most of my week in a state of panic." [R11]

"Was trapped in my flat for about 5 years. I could just access the corner shop (only a few yards away). Any GP, Dentist, DSS appointments I needed help from 3rd party to take me. As well as agoraphobia, not going out, socialising or outside contact almost non-existent so depression and other phobic experiences came to fruition and escalated, making existence horrendous." [R12]

"Anxiety before going out. Debilitating panic when using public transport or in scenarios where escape not swiftly possible." [R15]

2. Standard care for agoraphobia

Overall, 7 of 11 people had treatment and support for agoraphobia. Of these, all had talking therapy and medication and 6 used some form of self-help.

2.1 Talking therapies

Most people who had talking therapy had cognitive behavioural therapy (CBT). One person had support from community psychiatric nurses and an occupational therapist while another had online counselling. CBT ranged from 8 to 12 weekly sessions to 7 years. Some people said talking therapy helped their agoraphobia, but others found it difficult to complete with little benefit. At least one person paid to attend private sessions because they had difficulty getting help through the NHS:

"CBT for 8 weeks, once a week. Hard work but it did help a lot." [R11]

"Support from CPN and Occ Therapist to work on problems associated with agoraphobia and associated anxiety. Some of this help lasted months, other times just a few sessions. The therapy did not appear to help very much as I was fine whilst out with the therapist but back alone or with others, nothing much changed. Made matters worse as I became more convinced nothing would help and I would be stuck like this for life." [R12]

"I started online therapy last year, specifically counselling. I had done something like this before via my university, but it was short (only 4 weeks, one session per week)

and it wasn't too significant. I funded the therapy privately, as getting help through the public healthcare system was challenging (many phone calls, invalidating and abrasive staff). I used an online therapy provider that matched me with a therapist. I was reluctant to try it, but the therapist was great and we worked on many aspects of my situation. I was more closed off at the beginning but managed to open up about other areas in my life over time and I believe it was a key part of my successes last year in recovering. Having that relationship you could fall back on and talk about the challenges I was facing at that time was incredibly valuable." [R8]

"CBT face to face 12x really upsetting delving into past trauma" [R15]

2.2 Drug treatments

Prescribed medication included citalopram, propranolol and diazepam. People generally said that drug treatments helped with their agoraphobia, but some had side effects including vivid dreams, difficulty sleeping and dependency:

"Citalopram for anxiety, still on it. Propranolol for anxiety to be taken at periods of high anxiety as needed." [R6]

"I was prescribed propanolol (10mg) from my GP, which is helpful and I do continue to take it while in more challenging situations, like travelling. While much of the help from my GP wasn't so useful, I did find that propanolol helped a little bit so that was beneficial to me. I had also taken diazepam when I took my first flight last year, which was successful at making me calm, but wasn't something that would really help me long term so I only used it that one time." [R8]

"10mg - 20mg citilopram. They also helped but side effects weren't pleasant. The vivid dreams means night time isn't always relaxing." [R11]

"To try and control my anxiety which hopefully would enable me to work on issues such as agoraphobia, I was given diazepam. I used this medicine for about 3 years. I soon became addicted to it and any benefit it first had soon wore off. Side effects became worse and I felt in a worse state than before ever taking them. Other meds such as beta blockers, prozac etc were tried but side effects were awful so stopped very soon after they were prescribed." [R12]

2.3 Self-help

Some people used self-help to manage their agoraphobia, including self-help books and online resources such as support sites or YouTube. Benefits included seeing others with similar difficulties and what worked for them:

"Researching what had worked for other people via 'legit' sites e.g. NHS, official support sites." [R6]

“Some self help books. Again very good and actually was good to know I wasn't the only person feeling this way.” [R11]

“I would read and watch articles on Youtube etc about relaxation, cbt therapy, dealing with depression and anxiety etc. Agoraphobia information and help was not easily available or it did not seem to relate to my specific problems. It did help in some ways in making me think about situations in different ways but overall any progress has been minimal.” [R12]

2.4 Overall benefits of standard care

For some, standard care helped their symptoms of agoraphobia. One person reported that they “Rarely feel them now” [R6] while another said:

“I've got a lot better since then, and now I can do things like fly, commute and go on walks outside, to name a few. My tolerance is still somewhat limited and things like commuting require a fair amount of planning. Some circumstances continue to make me more uncomfortable than others, such as sunlight, higher temperatures, loudness, crowds. I would still find walking in some parts of the city to be highly uncomfortable and potentially lead to panic, so I still work with it to some extent, planning my routes such that I can tolerate them and a bit less so about how practical they are. I can do many more things, but being in these situations tends to make exhausted. Therefore, I try to plan around it if I can, giving myself enough space between certain outings or meetings so that I have enough time to rest and prepare myself for the next situation. For example, this academic year I attended university physically once a week on average, so that I could rest enough to be able to work from home as well. Agoraphobic symptoms still make social meetings difficult if they're not online, as I can attend one off meetings but consistency is difficult, like on a daily or biweekly basis for example. I tend to meet less people as a result, and struggle with social connections especially, but I think I have symptoms of social anxiety too which may be more significant in that case.” [R8]

Others reported continued difficulties with agoraphobia symptoms which meant they tended to prepare and plan for situations and events such as leaving home or talking public transport. This had a significant effect on their quality of life and overall mental wellbeing:

“I have a safety net of an area I feel usually comfortable in. If I try pushing those bounderies then I really begin to suffer mentally. This has meant I have never been able to go on holiday, never visit other cities or places. Sometimes living in just my area is enough but other times depression sinks in knowing I am a prisoner and unable to travel with friends etc. Having experienced this for over 30 years it leaves me bitter, depressed and worthless.” [R12]

“Highly restricting on all aspects of life. A lifetime prison sentence with the irony that I am both jailor and prisoner. Low self esteem and periods of deep depression and profound despair.” [R15]

3. Virtual reality (VR) for treating agoraphobia

No one who completed the survey had used VR for agoraphobia. Six of 8 people said they would consider using VR for agoraphobia while 2 were not sure. Overall, 4 of 11 people said they would prefer VR, 2 preferred standard care and 5 people had no preference. People who were interested in using VR said they would “try anything” to improve their agoraphobia and thought VR could provide a helpful treatment option for some:

“I think the preferred treatment should always be that which is a) most clinically effective, and b) based on the patient's choice...I believe the use of virtual reality provides a safe way for agoraphobic people to become used to everyday situations, from the comfort of a safe and secure environment. I have experience using VR technology (I own a Metaquest headset) and it is extremely immersive. I think the application of VR technology for the treatment of agoraphobia is a fantastic endeavour.” [R5]

“It might help you to access outside in a safe space to control your anxiety and build up to going out.” [R6]

“Just talking about a problem is fine in some ways, understanding what is happening in your body etc. but dealing with it in reality is totally different and I never felt any empathy for the distress I go through. A new idea and approach, such as virtual reality, might be a new way forward and suit people who have not found much success with other therapies. With agoraphobia being such a life destroying thing, a new way to address it would be more than welcome.” [R12]

“Both as I think the VR will highly compliment other forms of treatment” [R11]

“Standard Care has proved to be almost ineffective with me over many years of attempting to try this over and over. I am totally resolved to just living with my problem for the rest of my life as medication, CBT etc has only worked to a small degree. Something completely new and unheard of may be a chance to at least improve on how my life is.” [R12]

“Available expertise with panic attack/ agoraphobia treatment in my experience is very limited. General anxiety or specific phobia easier to treat. Ask for help on panic attack treatment, exposure therapy etc and there's few specialist resources.” [R15]

4. Potential barriers to accessing VR for agoraphobia

Most people (8 of 11) thought there were barriers to accessing VR for treating agoraphobia, including digital literacy and access to technology, geographical inaccessibility to treatment and lack of familiarity with the technology:

“Older people may be less willing to adopt VR technologies - lack of exposure to VR technologies, lack of trust in its efficacy. VR may not be useful for people who suffer from motion sickness - can be an issue even when using VR for relatively short periods of time. Due to the potential cost, it is likely that people living in lower-income areas may be less likely to be offered this treatment. May not be appropriate for those suffering from extreme cases of agoraphobia - too immersive, a slower more graded approach may be preferred.” [R5]

“Less digitally experienced, people on low or fixed incomes, postcode lottery if it is available on the NHS.” [R6]

“Remote or those in rural areas. Those that struggle to access care or secure a diagnosis. People with complex emotional needs often have their needs overlooked as well” [R10]

“Like myself, this is a treatment that until today is unheard of so I can see many people being wary or unconvinced that it could be any help. Barriers may include which part of the country you live in, how accessible this is locally and is it NHS or privately available. Other barriers would be from people unfamiliar with technology but I believe this must have improved drastically over the past decade.” [R12]

“The poor and elderly who may not afford internet connection or be afraid of the technology” [R15]s

National Institute for Health and Care Excellence

Medical technologies evaluation programme

Virtual reality technologies for treating agoraphobia or agoraphobic avoidance: early value assessment

Consultation comments table

There were 47 consultation comments from 3 groups:

- 12 comments from 1 company
- 7 comments from 2 healthcare professionals
- 28 comments from NHS England

The following themes have been identified:

- Recommendations: comments 1 to 7
- Unmet need: comments 8 to 17
- Potential risks: comments 18 to 19
- Current and proposed management: comments 20 to 27
- Clinical evidence: comments 28 to 41
- Cost and resource use: comments 42 to 46
- Equality considerations: comment 47

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
Recommendations (n=7)					
1	2	NHS England	Has all of the relevant evidence been taken into account?	Without further significant investment for further RCTs, any potential benefits of this technology will be lost and patients will be left with limited treatment. The evaluation of evidence does not seem to take this into account. It would be helpful if the recommondation allowed the products to be used contingently whilst further RCTs are done. The current recommendation that they can not be used in the NHS means that likely the companies will no longer have any investment, and therefore this innovation will no longer be available for patients.	Thank you for your comment. Following committee discussion on the consultation comments, section 1 of the guidance has been updated to a partial recommendation for use of gameChangeVR to treat severe agoraphobic avoidance in people with psychosis while more evidence is generated. The committee considered that more evidence is needed for the remaining technologies and indications for use as outlined in section 1.4. Recommendations for use in research are not intended to stop innovative technologies being available to patients. But access to these technologies should be through company or research funding (non-core NHS funding). Section 1.5 has been added to the guidance to make this clearer.
2	2	NHS England	Are the recommendations sound and a suitable basis for guidance to the NHS?	The recommendations are not a suitable basis for guidance to the NHS, as they will effectively stop VR being available for patients. As stated in other comments, this will leave many patients without care as the alternative treatments are not readily available to patients.	Thank you for your comment. Please see response to comment 1.
3	5	Healthcare professional	Are the recommendations sound and a suitable basis for guidance to the NHS?	Yes	Thank you for your comment.
4	6	Company	Are the recommendations sound and a suitable basis for guidance to the NHS?	Given that the data has not been interpreted appropriately we do not believe that the recommendations are sound. The gameChange product is safe and clinically efficacious in the groups that it was designed for (high and severe agoraphobia). If the purpose of the EVA is to	Thank you for your comment. The external assessment group (EAG) advised that only around half of the population in the clinical trial (Freeman et al. 2022) included people with high and severe agoraphobia. The committee considered that the

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
				provide early access for patients to therapies that will be beneficial and improve quality of life, this recommendation does not do that.	evidence showed potential benefits of gameChangeVR in people with psychosis who have severe agoraphobic avoidance, particularly given the limited access to other psychological interventions. Following committee discussion on the consultation comments, section 1 of the guidance has been updated to a partial recommendation for use of gameChangeVR to treat severe agoraphobic avoidance in people with psychosis while more evidence is generated. Please also see response to comment 1.
5	1	NHS England	1.2 “Overall, more evidence is needed on the benefits of VR technologies, including benefits in more severe agoraphobia and agoraphobic avoidance whether people are more likely to continue treatment with virtual reality how using VR technologies may affect clinical and system outcomes.”	It would be helpful if this could be gathered as "practice based evidence". This would allow patients who have no access to alternative treatments to benefit from the VR technology, whilst it is developed and improved. Without further significant investment for further RCTs, any potential benefits of this technology will be lost and patients will also lose out in the interim.	Thank you for your comment. Please see response to comment 1.
6	2	NHS England	3.19	As above, in practice patients are not accessing standard care, so the outcome of this recommendation will mean less patients are able to access any care.	Thank you for your comment. Following committee discussion on the consultation comments, section 1 of the guidance has been updated to a partial recommendation for use of gameChangeVR

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
					to treat severe agoraphobic avoidance in people with psychosis while more evidence is generated. The committee carefully considered the unmet need, the clinical evidence and advice from the clinical and patient experts. It acknowledged that access to psychological interventions such as cognitive behavioural therapy (CBT) for psychosis varies and is very limited for some people. The committee concluded that the clinical evidence showed potential benefits of gameChangeVR for treating severe agoraphobic avoidance in people with psychosis, particularly given the limited access to psychological interventions in community mental health services. The committee considered that more evidence is needed for the remaining technologies and indications for use as outlined in section 1.4. Recommendations for use in research are not intended to stop innovative technologies being available to patients. But access to these technologies should be through company or research funding (non-core NHS funding). Section 1.5 has been added to the guidance to make this clearer.
7	3	NHS England (NHS Talking Therapies teams)	3.20 “The committee concluded that further research was needed on all VR technologies before they could be recommended for routine use in the NHS”	I think it could be clearer whether this means that VR should not be used while further evidence is generated. It seems to me that there is little evidence to suggest that it is unhelpful but more needs to be done to shape evaluations so that clearer information about HOW VR can be used effectively, as part of standard treatment, is needed.	Thank you for your comment. Please see response to comment 1.

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
Unmet need (n=10 comments)					
8	1	NHS England	Has the unmet need been appropriately considered, including any additional needs for specific subgroups?	The unmet need does not seem to have been considered adequately. Only a very small minority of patients with Severe Mental Illness including psychosis can access to a NICE recommended psychological therapy (Provisional data from the Mental Health Service Data Set suggests this may be less than 1% of community mental health patients in England). Although there is a national NHSE programme of work to address this gap, progress is slow due to significant workforce pressures and training requirements - plus high training costs. This means that the majority of patients who could benefit from psychological therapies, have poorer outcomes than they could/should. It is unlikely this will be resolved over the next few years. There is a moral imperative to address this. GameChange VR could could improve the outcomes of some of these patients who have no access to an evidence based treatment at present and are often isolated and unable to access wider support.	Thank you for your comment. Please see response to comment 6. Potential benefits of VR technologies in addressing the unmet need have been added to section 1 (text box) and sections 3.1 and 3.2 of this guidance.
9	2	NHS England	Has the unmet need been appropriately considered, including any additional needs for specific subgroups?	The unmet need has not been considered adequately. Only a very small minority of patients with Severe Mental Illness including psychosis can access a NICE recommended psychological therapy (Provisional data from the Mental Health Service Data Set suggests this may be less than 1% of community mental health patients in England). The technologies could could improve the outcomes of some of these patients who have no access to an evidence based treatment at present and are often isolated and unable to access wider support.	Thank you for your comment. Please see response to comment 8.

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
10	5	Healthcare professional	Has the unmet need been appropriately considered, including any additional needs for specific subgroups?	Yes	Thank you for your comment.
11	6	Company	Has the unmet need been appropriately considered, including any additional needs for specific subgroups?	Yes	Thank you for your comment.
12	1	NHS England		My role within NHS England is as a national clinical advisor focused on a programme of work aimed at improving access to NICE recommended psychological therapies for people with severe mental health problems. My expertise is on this topic and therefore my comments relate specifically to gameChange VR since this is aimed at meeting an unmet need for patients presenting with psychosis and agoraphobia. I endorse the comments made by the specialist committee members, however, the extent of the paucity of access to NICE recommended therapy within standard care in services is not explicit. At present only a very small minority of patients with psychosis outside of early intervention in psychosis services have access to NICE recommended treatments i.e. CBT for Psychosis (CBTp) and Family Interventions. Although there are known problems with the data quality, provisional data collected via the national Mental Health Service	Thank you for your comment. Please see response to comment 8.

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
				Data Set suggests that less than 1% of patients with SMI are receiving 2 or more sessions of any NICE recommended therapy. Data suggests that less than 600 community mental health patients in England had 2+ sessions of CBTp over a 12 month period. In other words there is an extreme unmet need. Most patients are not offered any choice of evidence based treatment other than medication. A national CBTp training programme has been commissioned to attempt to address this significant shortage, however it will take years to grow the therapist workforce. It takes 2 years to train a CBTp therapist and with the current workforce shortage only limited staff are able to be released to train. Training costs (including access to clinical supervision and time off work to train) are high. Without access to effective treatments people with psychosis and agoraphobia are often isolated in their own homes, unable to access supplementary support or employment. Despite the "limited evidence", gameChange VR could address some of this unmet need and have a significant impact on the lives of some of the 95%+ patients who have no access to NICE recommended psychological therapy and little chance of every getting this.	
13	2	NHS England		Despite NICE recommendations that everyone with psychosis should have access to CBT, those patients outside of Early Intervention in Psychosis services (EIP) have extremely limited access to CBT (<1%) to help them with problems including agoraphobia. T	Thank you for your comment. Please see response to comment 8.

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
14	4	Healthcare professional		I have delivered gameChange as a peer support worker both in the RCT (during the pandemic) and currently on the Greater Manchester Mental Health NHS Foundation Trust (GMMH) implementation study. I realise you still need more research conducted to confirm feasibility of VR technology, but I just wanted to share some of my observations: Many service users have benefited from this technology within GMMH. There are not many interventions available to individuals, especially within Community Mental Health Teams and it has been life changing for some individuals. We will hopefully still be able to continue to support people to leave the house with gameChange, for many there are just no other options.	Thank you for your comment. The committee values the input of healthcare professionals in guidance development. Following committee discussion on the consultation comments, section 1 of the guidance has been updated to a partial recommendation for use of gameChangeVR to treat severe agoraphobic avoidance in people with psychosis while more evidence is generated. The committee carefully considered the unmet need, the clinical evidence and advice from the clinical and patient experts. It acknowledged that access to psychological interventions such as CBT for psychosis varies and is very limited for some people. The committee concluded that the clinical evidence showed potential benefits of gameChangeVR for treating severe agoraphobic avoidance in people with psychosis, particularly given the limited access to psychological interventions in community mental health services.
15	1	NHS England	1.2 “Additional analysis of the gameChangeVR trial suggests that it only has potential benefits for people with psychosis and more severe agoraphobia. But this needs confirming.”	Despite NICE recommendations that everyone with psychosis should have access to CBT, those patients outside of Early Intervention in Psychosis services (EIP) have extremely limited access to CBT (<1%) to help them with problems including agoraphobia. This represents a significant unmet need and means this group are often unable to leave their homes to access other support including employment support. It also leads to severe isolation which contributes to longer term health problems.	Thank you for your comment. Please see response to comment 8.
16	1	NHS England	2.4 “Clinical experts advised that access to CBT is limited,	Provisional data collected by NHS England suggests that less than 1% of patients with severe mental health problems outside of Early Intervention in Psychosis services (EIP) are	Thank you for your comment. Please see response to comment 8.

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
			so people are more likely to be offered antipsychotic medication with simple contact and monitoring from their mental health service."	accessing CBT. There is a national programme working to address this shortage, however due to workforce pressures and the time it takes to train a therapist - there will be an unmet need for several years. GameChange could provide an alternative treatment option for some where there is no alternative offer.	
17	2	NHS England	3.1	This section does not accurately take into account the level of unmet need in this area. A small minority of patients with psychosis outside of early intervention in psychosis services have access to NICE recommended treatments i.e. CBT for Psychosis (CBTp) and Family Interventions. Provisional data collected via the national Mental Health Service Data Set suggests that less than 1% of patients with SMI are receiving 2 or more sessions of any NICE recommended therapy. Data suggests that less than 600 community mental health patients in England had 2+ sessions of CBTp over a 12 month period. Most patients are not offered any choice of evidence based treatment other than medication, therefore it is integral that if there are suitable alternatives, these are made available.	Thank you for your comment. Sections 3.1 and 3.2 of the guidance have been amended to better capture this unmet need. Please also see response to comment 8.
Potential risks (n=2 comments)					
18	5	Healthcare professional	Has all of the relevant evidence been taken into account?	Yes, especially the side effects of virtual reality. Bouchard et al 2017 and Davis et al 2015 consider cyber sickness within a virtual environment and subjectivity. I cannot see in the assessment report whether side effects are further impacted if medications were already being used and nausea was already present prior to VR treatment	Thank you for your comment. The committee carefully considered the evidence on adverse events related to the use of virtual reality and VR technologies. The published evidence on the included VR technologies did not report the potential adverse events mentioned in your comment. The clinical experts advised that it was unusual for people to report adverse events other than perhaps being dizzy. The

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
				Bouchard, S., Dumoulin, S., Robillard, G., Guitard, T., Klinger, E., Forget, H., Loranger, C., Roucaut, F. (2017) 'Virtual reality compared with in vivo exposure in the treatment of social anxiety disorder: a three-arm randomised controlled trial' The British Journal of Psychiatry [online] Available at: https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/virtual-reality-compared-with-in-vivo-exposure-in-the-treatment-of-social-anxiety-disorder-a-threearm-randomised-controlled-trial/D541B09E2FF234FA82A7001AB44E3989 (Accessed 19th July 2019) Davis, S., Nesbitt., K., Nalivaiko, E. (2015) 'Comparing the onset of cybersickness using the Oculus Rift and two virtual rollercoasters', Proceedings of the 11th Australian Conference on Interactive Entertainment [online] Available at: http://crpit.scem.westernsydney.edu.au/confpapers/CRPITV167Davis.pdf (Accessed 19th August 2019)	committee concluded that VR technologies seemed safe to use with clinical assessment, healthcare professional support and monitoring. But more research is needed on adverse effects as outlined in section 1.6.
19	5	Healthcare professional	Has all of the evidence on any population subgroups, such as more severe agoraphobia, been taken into account and reasonably interpreted?	Evidence doesn't appear to have risk assessment of suicide and anxiety disorders as all patients receiving psychiatric treatment in any method should have a risk assessment. Unclear whether VR exacerbates risk of suicide in initial stages (like some antidepressents), or whether there is no additional risk of suicide using this method. I am mindful of the NCISH report for anxiety and suicide figures: https://documents.manchester.ac.uk/display.aspx?DocID=66829	Thank you for your comment. The protocol for this assessment included consideration of any adverse effects of the technology, and any data for rates of suicide or self-harm reported in included studies would have been relevant for consideration within this outcome. The EAG advised that it was not aware of any data for the risk of suicide or self-harm in the included studies. The EAG considered that further evidence is needed to determine whether outcomes such as suicide or self-harm may be associated with VR technology.

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
Current and proposed management (n=8 comments)					
20	2	NHS England		NHS Talking Therapies services are not open to patients with complex needs.	Thank you for your comment. Section 2.3 has been amended to make the care pathway clearer, specifically separating the pathway for agoraphobia without complex or severe mental health conditions from agoraphobia and agoraphobic avoidance in people with psychosis. It reads: "*Agoraphobia with co-occurring complex or severe mental health conditions would not be treated in primary care or NHS Talking Therapies for anxiety and depression services, but most likely in community mental health services or inpatient services."*
21	3	NHS England (NHS Talking Therapies teams)	2.1 "Virtual reality may be used as a tool in therapy sessions or as a standalone intervention with the support of a mental health professional."	What is the difference between these two treatment protocols? Which approach is this assessment looking at? I don't think it's clear enough what approach to using VR this analysis is assessing and it doesn't seem fair to assume that because VR does not work if used in certain ways, it should also not be used in other ways. I would predict that, when used by appropriately trained clinicians as part of a structured evidence-based treatment protocol, it achieves much better outcomes than when it's used as a 'stand alone' tool, for example, but this document doesn't differentiate.	Thank you for your comment. Section 2.1 and 2.2 of the guidance have been amended to make these 2 uses cases clearer. It reads: "*Some VR technologies are designed to be used by a qualified therapist* as a tool in therapy sessions *to support the delivery of face-to-face or remote cognitive behavioural therapy (CBT). Other VR technologies are designed to be* a standalone digital intervention *that can be used* with the support of a *wider range of* mental health professionals...NICE has assessed 2 VR technologies for treating agoraphobia *(Amelia Virtual Care and XR Therapeutics)* and *1 VR technology for treating* agoraphobic avoidance *in people with psychosis (gameChangeVR). The assessment included VR technologies that are designed to be used as tools in therapy sessions and VR technologies that are standalone digital interventions*." All technologies in the assessment are delivered with the support of a mental health professional. Section 2.2 has been amended to include more information in the

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
					technology descriptions. Additional details can also be found in the final scope on the NICE website.
22	3	NHS England (NHS Talking Therapies teams)	2.3 "This is used to develop a treatment plan that may involve lifestyle changes and unguided"	use of unguided self-help should not be delivered by NHS Talking therapies services - all therapy for agoraphobia should be delivered by or with direct support from a trained clinician. It may well be that in this context, treatment which includes use of VR achieves better outcomes than what it would as a stand-alone treatment. I'm unclear how VR could ever be used without the support of a therapist to be honest as it doesn't sound like the technology itself provides any of the clinical explanation for doing the behavioural experiments/exposure exercises or any psychoeducation around agoraphobia - it's not clear from this report.	Thank you for your comment. Section 2.3 of the draft guidance was not specific to the treatment of agoraphobia in NHS Talking Therapies services. This has been amended to make the care pathway clearer, specifically separating the pathway for agoraphobia without complex or severe mental health conditions from agoraphobia and agoraphobic avoidance in people with psychosis. Section 2.3 has also been amended to state that the treatment of agoraphobia without complex or severe mental health conditions is usually delivered in primary care or NHS Talking Therapies for anxiety and depression services. Mention of unguided self-help has been removed from this section.
23	1	NHS England	2.6	Only medication is available for the vast majority of patients with psychosis. There is no choice/alternative.	Thank you for your comment. This is outlined in Section 2.4 of the guidance.
24	2	NHS England	2.6	Only medication is available for the vast majority of patients with psychosis.	Thank you for your comment. Please see response to comment 23.
25	3	NHS England (NHS Talking Therapies teams)	2.6	Given the broad scope for this EVA, is the comparator matched to the severity of the agoraphobia and the setting for the treatment (e.g. NHS Talking Therapies vs CMHT?)	Thank you for your comment. Section 2.6 has been amended to state the comparators more clearly for agoraphobia, and agoraphobic avoidance in people with psychosis. It reads: "The comparator *for Amelia Virtual Care and XR Therapeutics* is standard care for agoraphobia, *and for gameChangeVR* it is standard care for agoraphobic avoidance in people with psychosis. This may vary depending on a person's individual needs and preferences, comorbidities *and the treatment setting*. *Standard care treatments for agoraphobia without complex or severe mental health conditions may include*

#	Consultee ID	Group	Section	Comments [sic]	NICE response (including changes made to MTCD, if applicable)
					guided self-help, CBT or antidepressants. *Standard care treatments for agoraphobic avoidance in people with psychosis may include CBT, antidepressants or monitoring from community mental health services. Clinical experts advised that VR technologies for treating agoraphobic avoidance in people with psychosis would not be offered instead of antipsychotic medication. So, this was not a comparator in this assessment.*
26	1	NHS England	3.2 "One clinical expert recalled the challenges of treating agoraphobia in Improving Access to Psychological Therapies services (now named NHS Talking Therapies for anxiety and depression) because some people did not come to sessions. They considered it may be more helpful to offer VR therapy in both primary and secondary care to increase access to treatment both in clinics and people's homes."	NHS Talking Therapies services are not open to patients with complex needs or those who require a multi-disciplinary approach. It is very unlikely that a patient with psychosis would be accepted by this service (and they wouldn't be able to access this anyway if they couldn't leave their home).	Thank you for your comment. This early value assessment was not limited to people with psychosis or complex needs. Section 3.1 describes the experiences of a clinical expert who previously worked in Improving Access to Psychological Therapies services (now NHS Talking Therapies for anxiety and depression) treating agoraphobia without psychosis.

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27	3	NHS England (NHS Talking Therapies teams)	3.17 “hey suggested that options for self-referral would further increase access to treatment for people who are less likely to engage with mental health services.”	I don't understand how this could work since delivery of treatment relies upon the use of the VR being explained and supported by a clinician.	Thank you for your comment. Clinical experts advised that access to VR technologies is usually via healthcare professional referral. But they have facilitated self-referral by advertising the service so people can call in and ask to be seen. VR technologies would be offered after clinical assessment and should be delivered with the support of a mental health professional as outlined in section 1 of the guidance.
Clinical evidence (n=14 comments)					
28	1	NHS England	Has all of the relevant evidence been taken into account?	The impact of GameChange on personal recovery as an outcome appears to have been down-played. Personal recovery as a construct, represents the 5 factors that mental health service users identify as those most important to their wellbeing (Connectedness, Hope, a positive Identity, Meaning in their lives, Empowerment or "CHIME"). As such NHSE have selected ReQoL, the outcome measure used in the GameChange trial to measure recovery, to be introduced as the standard patient reported outcome measure within community mental health services across England.	Thank you for your comment. The EAG responded that scores from the Questionnaire about the Process of Recovery were reported as a secondary outcome in the gameChange trial (reported in Freeman et al.) and were fully reported in the EAG report and used in the EAG’s economic analysis. The results for this outcome have not been downplayed – there was no difference between arms in ReQOL scores at 6- or 26- weeks following treatment for the overall population. There is therefore no evidence that gameChangeVR has an impact on personal recovery over and above treatment as usual. The clinical experts did not comment on ReQoL vs EQ-5D or personal recovery as an outcome in clinical practice.
29	6	Company	Has all of the relevant evidence been taken into account?	Yes, but the interpretation is flawed in many ways. We outline that below	Thank you for your comment.
30	1	NHS England	Are the summaries of clinical and cost effectiveness reasonable	Regarding GameChange VR, the balance of evidence/benefits seems to be based on a notion that there is an alternative more or equally effective, NICE recommended psychological treatment	Thank you for your comment. Please see response to comment 6.

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			interpretations of the evidence?	available for most patients with psychosis and agoraphobia. This is not the case.	
31	6	Company	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	No and we directly comment on areas in the document which is incorrect interpretations of the data.	Thank you for your comment.
32	6	Company	Has all of the evidence on any population subgroups, such as more severe agoraphobia, been taken into account and reasonably interpreted?	No. The Lancet paper shows that the effect of gameChange is moderated by the severity of agoraphobia or avoidance. It has a moderate to large effect size in those with high or severe agoraphobia. This is not reasonably interpreted given that the interpretation in the draft suggests that there is no clear evidence that the intervention drives the change when that is precisely what has been published.	Thank you for your comment. The EAG report highlighted the larger effect size on participants with high or severe agoraphobia at baseline, both in the clinical and economic findings. This is also noted in the draft guidance. However, the results in the severe population are for two outcomes only and are based on a post hoc trial analysis. The EAG was also uncertain whether this group represents a clinically differentiated group in NHS clinical practice. The EAG considered that it is therefore reasonable for the guidance to note that further evidence is needed to support this finding.
33	6	Company	1.2 “But it is not clear whether these benefits are because of the VR technology or the standard care used.”	This is completely incorrect. It was the entire point of the RCT design and we clearly show the effect is because of the intervention. Negative data would not be publishable in The Lancet. Standard care was the same in both arms of the gameChange trial, hence the treatment difference is directly ascribable to the intervention. Furthermore, the gC trial and publication included a mediation analysis, which is also published in the Lancet paper. This is not mentioned in the reporting at all as far as I can see. It clearly shows the hypothesised mechanisms underlying gameChange do contribute to explaining statistically the treatment effect. This helps substantiate the treatment effect.	Thank you for your comment. The EAG considered that the mediation analysis does not necessarily provide support for VR technology driving benefit in outcomes. The mediation analysis reported in the publication explores potential mechanisms in the change in primary outcomes; i.e. they explored whether changes in specific cognitions and behaviour (threat cognitions, defence behaviours, safety beliefs) explained any change in the outcome. The analyses show that two of the mechanisms accounted for a portion of change in the outcomes at 6 weeks but the effect was not statistically significant at 26 weeks.

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					The EAG considered that in their response, the company are making the assumption that changes in these mediators can only be due to the VR technology and not to standard of care. Treatment as usual in the trial included medication, regular appointments with a care coordinator, appointments with psychiatrists and social workers, psychological therapy, and non-pharmacological interventions. The EAG considered it plausible that standard of care options may affect cognitions and behaviour in a way that influences the trial outcomes. As stated in the EAG report, there was no meaningful difference in outcomes between the trial arms for the full population. Overall, the EAG considered the statement in the draft guidance to be correct, in that it's not clear whether change in the outcomes is being driven by the VR technology or the standard of care.
34	6	Company	1.2 "Additional analysis of the gameChangeVR trial suggests that it only has potential benefits for people with psychosis and more severe agoraphobia. But this needs confirming."	We mentioned this multiple times across the process – THIS IS the group that the intervention was primarily designed for. People who were largely housebound and avoided most of the situations were the right fit for gameChange and could practise going back into these situations and we show that we have significant and medium to large effect sizes in these groups.	Thank you for your comment. Please see response to comment 4. The EAG advised that the analyses in the severe population were conducted as part of a post hoc analysis. As stated in the trial publication, Freeman et al.: "In the post-hoc analysis of the outcome effects on the primary outcome measure by severity of agoraphobic avoidance and distress, treatment benefits with VR therapy were only seen in the groups with severe and high agoraphobia at baseline". A very limited evidence base is provided in those participants with severe agoraphobia at baseline, who constituted approximately half of the trial sample only. Further evidence is needed to determine the reliability of the findings in the severe group.
35	6	Company	3.5 "The committee considered that	We disagree that there is limited evidence. gameChange was tested in a very rigorous evaluation with 346 patients with psychosis. This is	Thank you for your comment.

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			there was limited evidence supporting the clinical effectiveness of VR technologies for treating agoraphobia and agoraphobic avoidance."	one of the most substantial trials in mental health research, was pre-registered, and conducted to very high standard. There were planned moderation and mediation tests to understand the intervention and we show the clinical effects were mediated through the mechanisms we hypothesized.	The EAG report considered that the clinical effectiveness evidence for the 3 VR technologies included in the assessment was limited because there was one key study per technology. The EAG noted that the availability of an RCT with 346 participants with psychosis is notable. However, people with psychosis and agoraphobia represent only a subset of the population treated for agoraphobia in the NHS. Furthermore, evidence for a meaningful benefit of gameChangeVR was only evident for the severe population, which as discussed in response to earlier points was restricted to a post hoc analysis in two outcomes. The EAG considered that further evidence for the clinical effectiveness of gameChangeVR in those with severe symptoms is also needed.
36	1	NHS England	3.6 "There was also no statistically significant difference in quality of life or other psychological symptoms except perceived recovery at 6 weeks. Post-hoc analysis showed that treatment benefits were only seen in people with high and severe agoraphobia at baseline with these benefits maintained at 6 months."	Personal recovery is the outcome that the majority of service users/patients identify as one of, if not the most important outcome to them. It is therefore a highly important finding. NHS England have selected ReQoL, the Patient Reported Outcome Measure (PROM) of recovery used in gameChange, to measure the effectiveness of all community mental health services in England. This measure was selected by a committee including people with lived experience, based on their views that 'personal recovery' should be the primary outcome services should be focused upon.	Thank you for your comment. Please see response to comment 28.

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37	6	Company	3.6 “Post-hoc analysis showed that treatment benefits were only seen in people with high and severe agoraphobia at baseline with these benefits maintained at 6 months.”	There was a planned moderation analysis. This showed higher levels of threat cognitions (i.e. fears) was a large moderator of outcomes. We simply took this finding into an easily understandable grouping of avoidance. gC really designed for the housebound and that group showed the changes.	Thank you for your comment. The EAG responded that the authors of the original Freeman et al. trial report that “We also performed post-hoc moderation analyses testing whether age, gender, and severity of agoraphobic avoidance and distress at baseline affected treatment response.” No change to the guidance has been made.
38	3	NHS England (NHS Talking Therapies teams)	3.19 “So, the committee was unsure whether virtual reality was the driver of the effect or whether the effect was primarily or exclusively because of standard care.”	This point seems very important	Thank you for your comment.
39	6	Company	3.19 “Comparators: there was uncertainty about how closely comparators matched routine practice in the NHS. Amelia Virtual Care and gameChangeVR were delivered in addition to standard care and compared	This is also incorrect. gameChange collected data on standard care and it was exactly what would be expected in the NHS. the gameCHnage trial was run under standard NHS care delivery and hence standard of care was not only quite clear to define, but was also the comparator. Standard of care was also the same in both arms of the trial, throughout the trial, so it WOULD NOT explain effects.	Thank you for your comment. The statement on uncertainty related to across all trials of the class of technology under consideration, not just gameChange. For clarity, this section has been amended to read: “Comparators: more research is needed on the clinical effectiveness of VR therapy compared with standard care in the NHS”. Please also see response to comment 33.

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			with standard care alone, but standard care differed across trials. So, the committee was unsure whether virtual reality was the driver of the effect or whether the effect was primarily or exclusively because of standard care."		
40	6	Company	3.19 "there was uncertainty about how closely comparators matched routine practice in the NHS."	This is also incorrect, as published in great detail in supplementary materials in the Lancet Psychiatry paper. We detailed routine practice at the NHS which was used as standard of care in the gameChange trial. This was also fed back to the external assessment group ahead of the last meeting yet this remains in the report.	Thank you for your comment. This statement in the draft guidance refers to the evidence base across all technologies and populations considered. The EAG understood that standard care for people with agoraphobia varies across the population and across NHS services. For clarity, this section has been amended to read: "Comparators: more research is needed on the clinical effectiveness of VR therapy compared with standard care in the NHS".
41	6	Company	3.20 "Research should include well-designed and adequately powered studies with appropriate comparators in the NHS."	the gameChange trial was appropriately powered for those with high and severe avoidance. It also used NHS standard of care as the comparator.	Thank you for your comment. Section 3.20 in the draft guidance related to research on agoraphobia as a whole, not just in gameChangeVR. This section has been removed from the final guidance to reflect subsequent updates to the early value assessment guidance template.
Cost and resource use (n=5 comments)					

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42	5	Healthcare professional	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	Yes, in virtuo (VR) spaces for gradual exposure to the avoided stimuli (eg public spaces, planes, perceived fearful stimuli) are cheaper than initial physical exposure which may require multiple professionals in the home, travel costs, time resources etc for patient engagement in the initial stages, although equally personalised software is expensive as each patient has individualised needs. Not every patient will have the same symptoms of panic/fear so personalised VR treatment may also be costly as you are creating many different situations.	Thank you for your comment. The committee considered the evidence and the EAG's exploratory economic modelling and concluded that while the cost effectiveness of VR technologies for treating agoraphobia is uncertain, gameChangeVR may be cost effective in people with psychosis who have severe agoraphobic avoidance. But more evidence is needed to confirm this.
43	1	NHS England	1.2 "but gameChangeVR may be cost effective in people with psychosis and more severe agoraphobia."	It does not seem that staff training costs were factored into the modelling. At present in order to increase availability of CBT for Psychosis (CBTp) NHS England fund the two year training at a cost of approx 20K per person. GameChange VR can be delivered by staff without this level of training which saves the associated training costs. It also offers increased capacity to access therapy without the delay of training a new cohort of CBTp therapists.	Thank you for your comment. The EAG has advised that training costs were as reported in Alkuntaya and as described in the EAG report. Wider costs of NHS staff training were outside the decision problem. The reason being is that CBT therapists (in this NHS funded course) are being trained to help treat a wide range of conditions (they are not being specifically trained for agoraphobia). Costs in EAG analyses relate to all costs involved in the treatment of agoraphobia (in the standard of care arm this is the NHS staff time per session with the patient), not NHS sunk costs.
44	1	NHS England	2.2 "The intervention is delivered by an automated virtual therapist and is supported by a mental health professional"	The alternative/standard form of delivery is via a trained CBTp therapist (paid at band 7 or above) who requires 2 years of training. There is a very limited supply of trained CBTp therapists in England at present. GameChange VR provides a fast-track supply route to allow more patients to access and potentially benefit from therapy.	Thank you for your comment. The potential resource benefits around the lower grade of healthcare professional to deliver gameChangeVR is described in sections 1 (text box) and 3.12 of the guidance.
45	1	NHS England	3.10	It is unclear if the two-year training costs associated with standard care (CBTp) have been taken into	Thank you for your comment.

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			"The EAG advised that more evidence is needed to confirm these findings. The committee concluded that limitations and uncertainties in the clinical evidence created limitations and uncertainties in the economic model. Further research on clinical and cost effectiveness is needed."	account in the economic analysis. This is currently commissioned by NHSE at a cost of approx 20K per person.	Please see response to comment 43.
46	3	NHS England (NHS Talking Therapies teams)	3.11 "Training was half a day and staff were said to have quickly acquired th"	to note that in NHS Talking Therapies services, treatment would need to be delivered by appropriately trained NHS TTad clinicians.	Thank you for your comment. This statement refers to training to use gameChangeVR, not practitioner or therapist training to work in NHS Talking Therapies services. This has been amended: "*They advised that the staff* training *on how to use and support the delivery of gameChangeVR took* half a day and that staff quickly learnt the skills needed for implementation."
Equality considerations (n=1 comment)					
47	5	Healthcare professional	Are there any equality issues that need special consideration and are not covered in the medical technology	Autism and sensory difficulties when using VR- I could only see one study that discussed this topic, more would be helpful	Thank you for your comment. The committee carefully considered equality issues and considerations for this topic. It concluded that more evidence was needed on using VR technologies in different patient groups. This has been added to sections 1.6 and 3.20 of the guidance.

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			consultation document?		

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