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

External Assessment Group report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Early Value Assessment Programme

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Date completed 22/05/2023

Contains confidential information: Yes

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.

Acknowledgements

The EAG acknowledges the administrative support of Sue Whiffin and Jenny Lowe (both PenTAG) and Specialist Committee Member (SCM) input from Robert Dudley (Gateshead Early Intervention in Psychosis service, CNTW Foundation Trust), Rhema Immanuel (East London and North East London NHS Foundation Trust) and Elizabeth Murphy (Greater

Manchester Mental Health NHS Foundation Trust (GMMH NHS)). We also thank Prof Sam Vine (University of Exeter) for input on VR-based technology.

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.

Contents

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 pivotal trial was a Spanish randomised controlled trial (RCT) in an agoraphobia population in which participants on CBT and participants on Amelia+CBT both performed better than participants on drug therapy alone. However, generally, participants on Amelia+CBT were not significantly superior in their performance than participants on CBT. The EAG noted that CBT and drug therapy were co-administered in the Amelia arm and therefore this raises doubts as to whether the beneficial effect in the Amelia arm may be being driven by CBT rather than Amelia. 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 and Amelia suggest a high degree of uncertainty and whilst point estimates suggest the therapies may not represent a cost-effective use of NHS resources when judged against the NICE reference case, the uncertainty is such that their 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 UK evidence for Amelia Virtual Care, 3) the absence of any evidence for Invirto and economic evidence for XR Therapeutics, 4) differences in comparators across trials, 5) published evidence not being available for all outcomes, 6) an absence of evidence on the durability of the effect of VR-based therapies, and 7) 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 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 ten publications, comprising five 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
Castro et al, 2014[13]	NR	Spain (Canary Islands)	RCT	80 adults with long-term (5 years +) agoraphobia	Amelia Virtual Care[a] + cognitive behavioural therapy + paroxetine (20-30 mg daily) or venlafaxine (37.5-75 mg daily). 11 individual clinical sessions of 30-45 minutes	Waiting list (drug treatment); Cognitive behavioural therapy + paroxetine or venlafaxine. 11 individual clinical sessions of 30-45 minutes	Follow-up was 6 months • Agoraphobia (Agoraphobic Cognition Questionnaire) • Body sensations (Body Sensations Questionnaire) • Anxiety (Beck Anxiety Inventory • Subjective Units of Anxiety) • Social function (Behavioral Avoidance Test, Liebowitz Social Anxiety Scale) • Dropout.
gameChangeVR							

References	Study name	Country	Method	Sample	Intervention	Comparator(s)	Outcomes
Altunkaya et al, 2022;[11] Bond et al, 2023;[14] Freeman et al, 2022a,b,c[15-17]	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) • 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;

References	Study name	Country	Method	Sample	Intervention	Comparator(s)	Outcomes
							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;[18] Lambe et al, 2020[19]	gameChangeVR project	UK	Person-centred design process	Clinical psychologists, programmers, animators, designers, product managers, producers, writers, researchers, 3D artists, mental health advocates, and people with lived experience of psychosis	Development of gameChangeVR (this study profiles the intervention development process rather than assessing the effectiveness of its delivery)	None	• Multistakeholder perspectives to inform the development of gameChangeVR • User acceptability ratings
XR Therapeutics							
Maskey et al, 2019[5]	NR	UK	Single-arm study	8 adults (18-60) with autism who	XR Therapeutics[a] (2 visits each	None	Follow-up was 6 months • Participation

References	Study name	Country	Method	Sample	Intervention	Comparator(s)	Outcomes
				reported 'fears and phobias')	comprising 2 sessions of 20-30 minute with a 15 minute break)		• 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 five unique included studies (two for Amelia, two for gameChangeVR and one for XR Therapeutics), published in ten papers. The included studies for gameChangeVR and XR Therapeutics were conducted in a UK setting, while the included studies for Amelia were conducted in Spain. There were two RCTs – one for Amelia[13] and one for gameChangeVR.[16]

The comparator in the gameChangeVR trial[16] 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 were two comparator arms in Castro et al[13] for Amelia. One was CBT plus either paroxetine or venlafaxine. The other was waiting list control for CBT, i.e. receiving drug treatment only, in the form of paroxetine or venlafaxine. It should be noted that participants in the intervention arm of this study also received CBT plus paroxetine or venlafaxine.

There was no comparative evidence for XR Therapeutics.

> **Evidence gap**: 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. Amelia was co-administered with CBT and drug therapy, which means in the comparison of Amelia and CBT, it is unclear whether Amelia or CBT is driving the effect vs drug therapy alone.

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 key Castro et al[13] trial for Amelia considered participants with specifically long-term agoraphobia (at least five years' duration). 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: The pivotal trial for Amelia Virtual Care considered exclusively participants with long-term agoraphobia. 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[18,19] and Gelabert et al for Amelia [12] focused on user experience and process outcomes. The gameChangeVR trial,[16] Castro et al[13] and Maskey et al[5] all presented clinical effectiveness outcomes. Instruments used differed, but all three studies presented measures of mood and social functioning or quality of life. The gameChangeVR trial and Castro et al[13] for Amelia both 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.
>
> **Heterogeneity issue**: There was variation in which outcomes were assessed between studies and what instruments were used.

8.5. Quality of included studies

RCTs were available for two of the three technologies (Amelia and 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,[16] 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 pivotal Castro et al[13] RCT for Amelia was restricted to participants with long-term agoraphobia (five years or longer), which restricts generalisability to the broader population seen in routine clinical practice. SCM input suggested that generally longer duration of psychosis would be associated with poorer outcomes, although there will be exceptions. 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 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 RCT[13] comparing Amelia Virtual Care in combination with in-person CBT+paroxetine or venlafaxine, with 1) CBT+paroxetine or venlafaxine and 2) waiting list (which comprised paroxetine or venlafaxine). There was also one single-arm study of Amelia. Both were conducted in a Spanish setting. Castro et al[13] included only people with long-term agoraphobia of more than five years duration.

In the RCT by Castro et al, the dropout rate was 37.5% at post-treatment across groups. Most dropouts occurred before the exposure sessions started, principally due to schedule problems or a perceived lack of novelty compared to other treatments. There was a statistically significant difference between groups in dropout rates pre-treatment ($X^2 = 5.83$, $p<0.05$) but not at follow up ($X^2 = 1.76$, $p>0.05$).

Dropout rates were highest in the CBT only group (53.33%), second in the drug only group 35.3% and lowest in the group who received Amelia Virtual Care virtual reality therapy (23.3%). This may suggest that treatment adherence on Amelia is likely to be better than for the other treatments, or as differences had already emerged before the exposure sessions, it could instead suggest increased interest in using VR. However, it should still be noted that nearly a quarter of participants receiving Amelia dropped out. This may reflect general difficulties experienced by people with agoraphobia across interventions.

The publication reported that both the Amelia+CBT and CBT groups resulted in statistically significant improvements from baseline for agoraphobic cognitions, physical sensations associated with anxiety, general anxiety, and cognitive and overt behaviour related to agoraphobia when the person was alone as compared to drug treatment alone. However, there was no statistically significant difference in outcomes between the Amelia+CBT and CBT arms. There was no difference between Amelia+CBT and CBT in agoraphobic cognitions, physical sensations associated with anxiety and general anxiety, though numerical differences were

noted in agoraphobic symptoms when accompanied and alone, and social anxiety. The EAG were unclear if these differences were clinically meaningful.

The study authors suggested that a 50% change in symptoms could be clinically meaningful to participants, though no evidence was presented to support this. This is a proportionate rather than absolute reduction. SCM input suggested that 50% would likely be seen as a clinically meaningful reduction, although it was an ambitious target to expect for psychological interventions and smaller reductions may be clinically meaningful. No group showed a 50% decrease from baseline in agoraphobic cognitions and physical sensations when experiencing anxiety, though participants receiving Amelia+CBT showed a 50% decrease in agoraphobia and social anxiety symptoms. Those receiving CBT alone showed a 50% reduction from baseline in general anxiety symptoms, but not in other measured outcomes. No outcomes decreased by 50% in the drug only arm. As data for a 50% reduction in outcomes were incompletely presented in the publication text, this prevented full scrutiny by the EAG.

The advantages for the Amelia+CBT and CBT arms over drug therapy were relatively modest, although the absence of an MCID for specific scales makes it difficult to interpret how important these differences were. For example, for the Agoraphobia Cognition Questionnaire, pre-treatment scores were mean (SD) 38.07 (9.46) for CBT, 37.30 (7.63) for Amelia and 32.30 (9.46) for drug; post-treatment scores were 25.50 (8.67) for CBT, 28.72 (7.28) for Amelia+CBT and 30.15 (8.33) for drug; and follow-up scores were 28.00 (10.90) for CBT, 24.57 (9.27) for Amelia+CBT (and not assessed for drug treatment alone). Total scores on this scale can range from 0 to 40 with higher scores indicating greater severity of agoraphobia.

No change scores were reported for the Agoraphobia Cognition Questionnaire. The EAG has calculated these from the information in Table 1 of the Castro et al[13] paper, although it should be noted that there is no measure of uncertainty available for these scores and that they are not adjusted for baseline factors. As such, they should be interpreted with caution. Pre- and post-treatment are the time points available for all three treatment arms. The absolute changes (pre minus post) were for 8.58 Amelia+CBT, 12.57 for CBT and 2.15 for drug treatment alone. Therefore, for this particular outcome, improvement on CBT alone was numerically superior than

Amelia+CBT, while both were considerably superior to drug therapy alone. It cannot be ruled out that this effect is driven primary or exclusively by CBT.

Overall, the findings of Castro et al[13] showed that Amelia and CBT were both superior to drug therapy alone on certain key measures, although it was unclear how clinically meaningful these differences were. However, outcomes on Amelia and CBT tended not to be statistically significantly different from each other. Scores were also numerically similar, suggesting no meaningful difference in effectiveness between the CBT and Amelia arms. It should be noted that Amelia was co-administered with CBT and drug therapy and compared with 1) CBT and drug therapy and 2) drug therapy alone. As such, it cannot be ruled out that the benefit in the Amelia group is instead being driven by CBT.

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,[20] 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, it is unclear whether Amelia does produce clinical benefit over and above existing care. [18,19] Amelia was primarily positioned to improve adherence when co-administered with CBT and be equally clinically effective to CBT alone. No protocol for the Amelia trials was provided or could be identified. The primary outcome measure was not clearly defined. However, the presentation of results in the trial publication is not consistent with adherence being the primary outcome measure.

While participants in the Amelia arm in the Castro et al[13] paper had numerically better scores at follow-up than CBT alone, it was unclear whether this was clinically meaningful and this was based on very small numbers, 14 in the Amelia arm and 9 in the CBT arm, without data available from the drug comparison arm at this time point.

Furthermore, the timing of the observed effect on dropout rates, with the difference being seen before the initiation of exposure therapy, means that the company's claimed benefit on drop out may actually reflect greater interest in VR instead.

8.6.2. gameChangeVR

Evidence was available from one person-centred design study of how gameChangeVR was developed (the gameChangeVR project)[18,19] and one RCT of gameChangeVR added on top of treatment as usual against treatment as usual alone[15-17] (not specifically defined, the gameChangeVR trial), with embedded qualitative[14] and economic[11] analyses – both conducted in a UK setting.

In the gameChangeVR project,[18,19] 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[14] 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[16] 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.[21] 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[16] 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[17] 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[15] 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 18 and Table 19, in Appendix C.[22-52]

The EAG considered that the most potentially relevant among these additional studies are Freeman et al[28] for gameChangeVR and Maskey et al[51] and Maskey et al[52] for XR Therapeutics. Freeman et al[28] 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[53] 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[52] 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,[51] 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[16] 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[15] 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[54] to assess cybersickness, as used by Pot-Kolder et al[55] 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.[16] 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[56]), 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;[57] while the unit cost for unpaid care received from family and friends was based on minimum hourly wage in 2019.[58]

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).[25] 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), the EAG excluded this from further analysis. The three other interventions (Amelia, gameChangeVR and XRT) were all trialled in different populations: gameChangeVR was trialled in people with psychosis and agoraphobia as an adjunct to TAU; XRT is at an early stage of development but was explored in people with ASD and fears/phobias; and Amelia was trialled in a population with (primary) agoraphobia of long duration (5 years+) as an adjunct to face-to-face CBT.

These therefore represent three 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 Amelia+CBT vs CBT alone in people with primary agoraphobia? (DP2)
3. What is the cost-effectiveness of XRT vs TAU in people with ASD and agoraphobia? (DP3)

In DP3, 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 problems 1 and 2 are described below.

An early value assessment is reported using two identical decision analytic models that differ in terms of the population considered: (DP1) people with psychosis and agoraphobia and (DP2) general population with agoraphobia. The model drew from the one economic evaluation of relevance identified in the EAG's searches

(gameChangeVR, Altunkaya et al. 2022[11]), the RCT of Amelia,[13] with the remaining 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 RCTs 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.

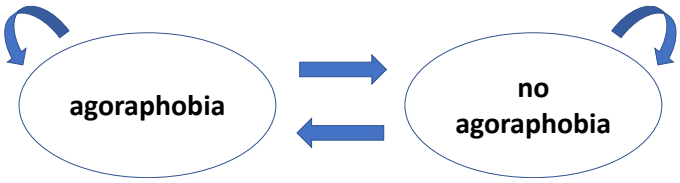
10.2.1. Population

The analysis is structured into two decision problems with two distinct populations: DP1: people with psychosis and agoraphobia and DP2: people with agoraphobia alone. 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). In the analysis in DP1 (psychosis and agoraphobia), the states are psychosis+agoraphobia and psychosis alone. In DP2, these are agoraphobia and no agoraphobia (Figure 1).

Figure 1: Structure of state-transition model



Health states labelled according to decision problem 2. 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]) and an equivalent change for Amelia inferred from change in BAI score (mean -0.005, SE 0.027, see Section 10.3.3 below for details). 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.

We apply the same principle to the analysis of Amelia.

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.[56]

10.2.3. Interventions and Comparators

The EAG presents two decision analyses:

DP1: comparing gameChangeVR+TAU vs TAU for agoraphobia in people with psychosis.

DP2: comparing Amelia+CBT vs CBT for agoraphobia in the general population.

Definitions of intervention and comparators were driven by availability of source data. For gameChangeVR, 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.

For Amelia, the source study was a three-arm RCT of Amelia+CBT, CBT alone and drug therapy. The EAG understands Amelia is marketed as a tool to assist with various psychological therapies rather than as a stand-alone course of therapy. This is reflected in the study design where the effect of Amelia without adjunct CBT was not evaluated. Furthermore, data at six-months follow-up were not collected for the drug therapy arm. Thus, the interventions and comparators for the general population analysis are Amelia+CBT compared with CBT alone.

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?

Evidence gap: Is Amelia amenable to remote use to help treat agoraphobia, and if so, what is its cost-effectiveness compared with remotely delivered CBT without Amelia (or versus other appropriate comparators)?

10.3. Model Inputs

10.3.1. Clinical Parameters

Clinical parameters were drawn from the gameChangeVR RCT,[16] the Amelia RCT[13] 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.

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),[59] 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[53] 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[53]). 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

In DP1, 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. In DP2, the perspective is limited to NHS+PSS alone. Cost categories described below are intervention costs, routine care cost, criminal justice costs and lost productivity.

10.3.2.1. Intervention costs

Intervention costs comprise licensing costs for each of the VR applications, 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 each intervention, 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[16], 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].

Amelia

Amelia is designed to be used under the guidance of a therapist or remotely with a smartphone app. The manufacturer does not prescribe a specific protocol for use of their product, so for the purpose of this analysis we assume Amelia is used as an adjunct to face-to-face CBT as per the Castro et al. RCT.[13]

The company evidence submission states that the company provides training to professionals in a group with other professionals, and the 'onboarding phase' lasts two months. Training is divided into two sessions, one focusing on technical onboarding (use of the VR headset and associated apps), and the other on clinical onboarding covering elements such as introducing VR to patients, cybersickness and specific interventions the platform offers (e.g. exposure, cognitive restructuring and relaxation/mindfulness). A practice session is incorporated into the training.

Amelia is available as [redacted]. The EAG considers the most relevant to be [redacted]. The VR hardware costs [redacted] (Pico VR).

Specialist Committee Member Comments

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], and for Amelia [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.
Amelia Licence	per centre per month	[redacted]	Amelia 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]
Amelia *Per session*		
Licence (professional plus homework)	Assuming used for 60 sessions per month	[redacted]
VR Headset	One per MH worker conducting 15 sessions pw for 44 weeks/year, lasting 2 years	£0.64
Training	4.5 hours per clinical psychologist, assume lasts 2 years, 15 sessions pw, 44 weeks/year	£0.36
Total per session		[redacted]
Total per course, Amelia	Assuming six sessions	[redacted]

10.3.2.2. Other health service use costs

gameChangeVR

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).

Amelia

No data were available on other health service costs in population (2). The EAG noted the uncertainty but did not include any difference in other health service costs in its analysis, and that this may have underestimated uncertainty in the cost-effectiveness of Amelia.

> **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 either gameChangeVR or Amelia. 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 either the general population or the 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[60]
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[60]
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[60]I

10.3.3. Health State Utilities

For DP1 (people with psychosis and agoraphobia), 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).

For DP2 (general population with agoraphobia), health state utilities were based on a crude conversion of Beck Anxiety Inventory scores (as reported in Castro et al. 2014), following a method reported by Freed et al[61] converting Beck Depression Inventory (BDI) scores. This equates a maximum BDI score of 63 to a published utility for untreated depression of 0.3 and a BDI score of 0 to a utility of 0.9, defined in Revicki and Wood as "depression in remission, not in treatment", with a linear

interpolation of scores in between the two extremes.[62] For example, a BDI score of 31.5 is assigned a utility of 0.6.

The EAG identified a study reporting EQ5D utilities for generalised anxiety disorder.[63] Although based on Spanish preference weights, the EAG considered this to be the most appropriate study as it focused on anxiety, and thus was the most suitable to map between EQ5D and BAI. This reported a health state utility for severe anxiety of 0.53 and for no or minimal anxiety of 0.84. These were equated to the maximum and minimum scores on the BAI of 63 and 0 respectively, with an assumed (inverse) linear relationship between the two. Thus, a BAI of 31.5 equates to a health state utility of 0.685.

BAI was chosen as the source of utilities for pragmatic purposes as it is commonly used in psychological disorders and a previously used cross-walk to health state utility exists, although it suffers from severe methodological limitations (specifically it assumes a linear relationship between BAI and utility).

The weighted mean baseline (pre-treatment) BAI score across all three treatment groups in Castro et al. was 31.49 (SE 1.41) equating to a utility of 0.685 (SE 0.007). Castro et al did not report adjusted change in BAI, stating that it was not statistically significant. Crude calculation of the difference in the change in BAI score from baseline to six-month follow-up between VR+CBT and CBT alone was -0.99 (SE 5.41 (favouring CBT alone), equating to a utility difference of -0.005 (SE 0.027) (Table 9).

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).
2	People with agoraphobia	0.685 (0.007)	B(3051.07, 1402.57)	Weighted mean of 3 arms of Castro et al. 2014,[13] Table 1
2	Treatment effect	-0.005 (0.027)	N(-0.005, 0.027)	Crude estimation from unadjusted reported data in Castro et al. 2014,[13] Table 1

2	People without agoraphobia	0.680 (0.028)	-	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[16] as an adjunct to TAU rather than in place of TAU
2	Amelia is delivered as per Castro et al. as an adjunct to face-to-face CBT rather than in place of CBT.
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
5	Health state utilities for DP2 (Amelia) are based on a crude transformation from BAI score.
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 (DP1) gameChangeVR compared with TAU in people with psychosis and agoraphobia, and (DP2) from Amelia compared with TAU in people with primary 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 DP1 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 (DP1) and from Amelia (DP2)

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.

The point estimate utility change from Amelia was negative, albeit with a wide confidence interval. The EAG therefore explored the ICER of Amelia in DP2 as a function of the utility gain from relief of agoraphobia.

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 on DP1 and DP2, 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 and Amelia 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 (DP1 and DP2).

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 (DP1 and DP2).

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 (DP1 and DP2).

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 (DP1 and DP2).

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 (DP1).

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 (DP1).

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.[64]

10.5. Results from the economic modelling

10.5.1. Base Case Results

10.5.1.1. DP1: gameChangeVR vs TAU in people with psychosis and agoraphobia

Base case results are reported in Table 11 and Table 12 below. As in both cases VR therapy is an adjunct to standard care (TAU for gameChangeVR and CBT for Amelia), costs reported are only those that differ between arms. Thus, the reported cost for TAU and CBT 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

10.5.1.2. DP2: Amelia+CBT vs CBT in people with agoraphobia

Table 12: DP2 base case results

	Costs			QALYs				P(CE)	
Perspective	**A+CBT**	**CBT**	**Inc.**	**A+CBT**	**CBT**	**Inc.**	**ICER**	**£20k**	**£30k**
NHS+PSS	[redacted]	£0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41.0%	41.6%

Whilst point estimate ICERs suggest that on average the interventions are 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 and 42% probability of Amelia 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 from gameChangeVR (DP1) and Amelia (DP2)

The gameChangeVR trial[16] 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.

In DP2, the minimum utility gain from relief of agoraphobia required for Amelia to be cost-effective is less than [redacted] (Figure 3).

Figure 3 SA1: OWSA on utility gain from relief of agoraphobia in general population (w/o psychosis)

Figure redacted.

10.5.2.2. SA2: Cost of VR headset (DP1 & DP2)

Whilst an important cost element, the per session cost of the VR headset is very low, therefore the ICERs of DP1 (gameChangeVR) and DP2 (Amelia) are mostly insensitive to changes in the purchase price of the VR headset within the range considered (Figure 4).

Figure 4 SA2: OWSA on cost of VR headset

Figure redacted.

10.5.2.3. SA3: Licence fees

In both decision problems, point estimate results are sensitive to the licence fee charged. In DP1 (gameChangeVR) results are highly sensitive, varying between dominant to £140,000 per QALY but much less so in DP2 (Amelia), varying between -£900 to -£8500 per QALY (in all cases Amelia is dominated by TAU). The magnitude of the sensitivity is driven by the different licensing models:

[redacted]. There is no licence fee associated with a 50% probability of cost-effectiveness for Amelia. This is driven by point estimate incremental utility being negative. Overall decision uncertainty is approximately 40% to 45% (Figure 6).

Figure 5 OWSA licence fee per user per course, gameChangeVR

Figure redacted.

Figure 6 OWSA licence fee per centre per month, Amelia

Figure redacted.

10.5.2.4. SA4: Relapse rate (DP1 & DP2)

Relapse rate is entered in the model as a six-month probability. One-way sensitivity analysis suggests the ICERs of both gameChangeVR (DP1) and Amelia (DP2) deteriorate as the relapse rate increases (Figure 7).

Figure 7 OWSA on relapse rate

Figure redacted.

10.5.2.5. SA5: Subsequent therapy availability (DP1 & DP2)

Under the assumed base case relapse rate (25% per six-months), where repeat sessions are not available, the ICERs are 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 13).

Table 13 Scenario analysis on availability of repeat therapy sessions

	DP1			DP2		
Available	**Inc £**	**Inc QALY**	**ICER**	**Inc £**	**Inc QALY**	**ICER**
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.5.2.6. SA6: Subsequent therapy effectiveness (DP1 & DP2)

As the relative effectiveness of subsequent therapy falls, the ICERs in both decision problems deteriorate. This is because the same cost is incurred, but the relative benefit diminishes (Figure 8).

Figure 8 Relative Effectiveness of Subsequent Therapy

Figure redacted.

10.5.2.7. SA7: Two-way sensitivity analysis of licence fee vs relapse rate (DP1 & DP2)

As the six-month probability of relapse increases from zero, the maximum cost-effective licence fee declines accordingly. Figure 9 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 9 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, DP1 (gameChangeVR)

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 10).

Figure 10 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

The point estimate treatment effect of Amelia was approximately zero, but with very wide confidence intervals. However, the cost of adding Amelia into a course of CBT was commensurately low. Whilst our base case suggests CBT alone dominates Amelia+CBT, there was an over 40% probability that the ICER could be below £20,000 or £30,000 per QALY. A key element of uncertainty was the transformation of BAI into health state utility. In the clinical trial[13] this showed virtually no effect of Amelia over and above CBT.

10.6.2.1. XR Therapeutics

There are no data on the relative effectiveness of XR Therapeutics. The EAG notes that the company charges a price of [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, five unique clinical studies were identified, of which two were on Amelia Virtual Care, two on gameChangeVR and one on XR Therapeutics. RCT evidence was available for Amelia and 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. Available evidence on Amelia was most closely aligned to the breadth of the NICE scope on agoraphobia. 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. For RCT

evidence, most but not all comparator groups were 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.[53] 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. The EAG noted evidence from an RCT[13] suggesting that Amelia in combination with CBT was more effective than drug therapy alone. However, the EAG also noted that Amelia was not significantly more effective than CBT, and so there was considerable uncertainty in the EAG's perspective whether it was Amelia or CBT that was driving the clinical benefit. As such, the EAG considered the evidence for the clinical effectiveness of Amelia to be limited. Furthermore, the EAG noted that lower dropout for Amelia was observed before exposure sessions. The company cited an advantage in terms of treatment adherence in its marketing materials. However, the data are also interpretable in terms of greater interest in VR treatment rather than a benefit in terms of adherence, although we also noted that participants in the Amelia arm had numerically better scores at follow-up than CBT alone.

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.

Point estimate results for Amelia+CBT vs CBT alone are negative (lower utility and higher cost), but with very large standard errors, thus more evidence is required to establish a reliable estimate of cost-effectiveness.

XR Therapeutics

[redacted]. Again, in the complete absence of randomised controlled evidence in the target population conclusions cannot be drawn as to its 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 14. 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 14: 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	Two studies **GREEN**	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	One study **AMBER**	One study **AMBER**	One study, mixed results **AMBER**
Clinical outcome: Change in other psychological symptoms	One study **AMBER**	One study, negative results **RED**	One study, negative results **RED**
Clinical outcome: Global functioning and work and social adjustment	One study, negative results **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**

Outcomes	Amelia Virtual Care	gameChangeVR	XR Therapeutics
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 of at least 5 years' duration). 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 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 15.

Amelia Virtual Care	gameChangeVR	Invirto
[redacted]	No ongoing trials	DRKS00027001.[65] Evaluation of "Invirto aftercare" for anxiety disorders: a pilot study.
[redacted]		DRKS00027585.[66] Evaluation of "Invirto Therapy" for people with panic disorder: a randomized-controlled trial
[redacted]		
[redacted]		
[redacted]		

Table 15. Ongoing studies

Amelia Virtual Care	gameChangeVR	Invirto	XR Therapeutics
[redacted]	No ongoing trials	DRKS00027001.[65] Evaluation of "Invirto aftercare" for anxiety disorders: a pilot study.	No ongoing trials – monitoring of real-world outcomes is being conducted
[redacted]		DRKS00027585.[66] 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 randomised evidence on XR Therapeutics 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.
- The comparators were not common across trials – indeed in Castro et al[13] the comparators CBT and drug therapy were both also administered in the intervention arm.

- 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.
- 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 16.

Table 16: 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 in a UK setting?	Further RCT or comparative RWE study in a UK setting	Key scoped outcomes

12. CONCLUSIONS

12.1. Conclusions from the clinical evidence

A total of five 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 for Amelia Virtual Care and gameChangeVR. UK evidence was available for gameChangeVR and XR Therapeutics.

There was only one key effectiveness study for each technology. 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 evidence from an RCT[13] suggesting Amelia in combination with CBT was more effective than drug therapy alone. However, the EAG also noted that Amelia was not significantly more effective than CBT, which meant that there was considerable uncertainty in the EAG's perspective of whether it was Amelia or CBT that was driving the clinical benefit. As such, the EAG considered evidence of clinical benefit for Amelia to be limited. 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.

Likewise, point estimates of cost-effectiveness for Amelia as an adjunct to CBT tend towards the negative, but again data are too limited to draw definitive conclusions.

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

[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 are two interventions for which RCT evidence is available. All technologies only have one key effectiveness study. 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. Amelia and gameChangeVR, within the populations 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 and Amelia are at best borderline cost-effective, but it is not strong enough to either rule them out or in as representing value for money interventions. There is no evidence on which to draw any conclusions as to the cost-effectiveness of XR Therapeutics,

[redacted]

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

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14. APPENDICES

Appendix A: Searches for clinical and cost effectiveness evidence

Table 17: 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

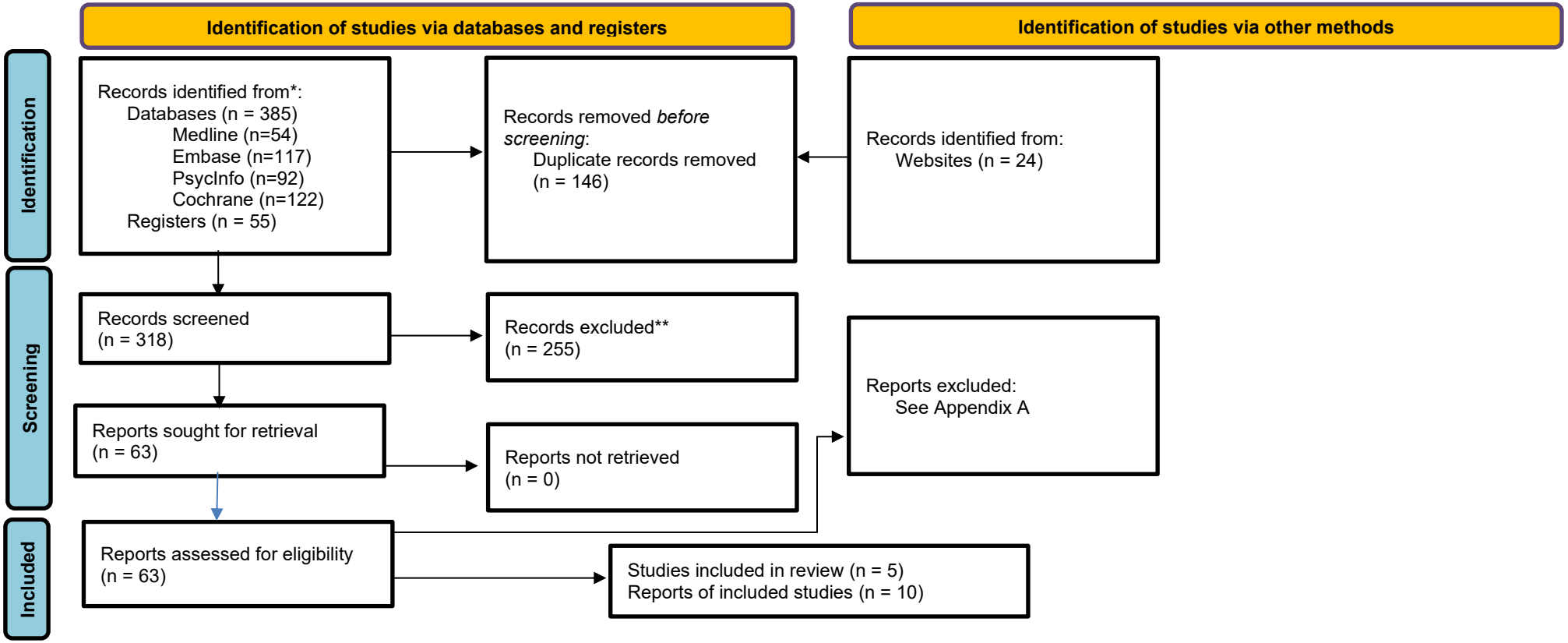
CEA Registry and ScharrHUD

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 18. 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[37]	Population (paediatric)
Alsem et al[29]	Population (paediatric)
Bioulac et al[32]	Population (paediatric)
Botella et al[42]	Population (phobias)
Botella et al[41]	Population (post-traumatic stress disorder)
Dehghan et al[31]	Population (paediatric)
Garcia-Palacios et al[23]	Population (specific phobias)
Gerardi et al[43]	Population (post-traumatic stress disorder and other anxiety disorders)
Guillen et al[44]	Population (stress-related disorders)
Hua et al[34]	Population (paediatric)
Kelson et al[33]	Population (paediatric)
Kirkham & Batten[24]	Population (anxiety)
McCann et al[46]	Population (anxiety disorders)
Meyerbroker & Emmelkamp[45]	Population (anxiety disorders)
Modrego-Alarcon et al[22]	Population (students with stress)
Morina et al[47]	Population (specific phobias)
Opris et al[48]	Population (anxiety disorders)

Excluded study	Reason for exclusion
Powers & Emmelkamp[49]	Population (anxiety disorders)
Segal et al[25]	Population (broad psychological)
Segawa et al[40]	Population (addictive disorders)
Shah et al[26]	Population (mood disorders)
Servera et al[30]	Population (paediatric)
Snider et al[38]	Population (paediatric)
Tennant et al[36]	Population (paediatric)
Turner & Casey[50]	Population (broad psychological)
Wallach et al[39]	Population (public speaking anxiety)
Wong Sarver et al[35]	Population (paediatric)
GameChangeVR	
Brown et al[67]	Population (general psychiatric)
Freeman et al[28]	Population (persecutory delusions)
XR Therapeutics	
Maskey et al[53]	Population (paediatric)
Maskey et al[52]	Population (paediatric)

Table 19: List of excluded full-text publications from EAG search, with reasons

Excluded study	Reason for exclusion
ACTRN12609000959279[68]	Intervention
ACTRN1261500092752[69]	Intervention

Excluded study	Reason for exclusion
Andersen et al[70]	Intervention
Bentz et al[71]	Intervention
Botella et al[72]	Intervention
Botella et al[73]	Intervention
Canais et al[74]	Intervention
Carl et al[75]	Intervention
Chen et al[76]	Intervention
CN-00595152[77]	Intervention
DRKS00027001[65]	No results
DRKS00027585[66]	No results
Emmelkamp et al[78]	Intervention
Freeman et al[79]	Article type
Freitas et al[80]	Intervention
Gomez-Busto & Ortiz[81]	Intervention
ISRCTN10661970[82]	Intervention
ISRCTN12497310[83]	No results
ISRCTN12882676[84]	Intervention
ISRCTN17308399[85]	No results
Jang et al[86]	Intervention
KCT0007996[87]	Intervention
Krzystanek et al[88]	Intervention
Ling et al[89]	Intervention

Excluded study	Reason for exclusion
Lorenzo Gonzalez et al[90]	Intervention
Lundin et al[91]	Intervention
Malbos et al[92]	Intervention
Malbos et al[93]	Intervention
Manyande et al[94]	Population (paediatric)
Martin et al[95]	Intervention
Meyerbroeker et al[96]	Intervention
Meyerbroker et al[97]	Intervention
NCT00129610[98]	Intervention
NCT00734370[99]	Intervention
NCT03101332[100]	Intervention
NCT03845101[101]	Intervention
NCT03973541[102]	Intervention
NCT04695249[103]	Intervention
NCT05319509[104]	Population (students with anxiety)
NCT05510804[105]	Intervention
Pelissolo et al[106]	Intervention
Pitti et al[107]	Intervention
Pompoli et al[108]	Intervention
Pot-Kolder et al[55]	Intervention
Quero et al[109]	Intervention
Vincelli et al[110]	Intervention

Excluded study	Reason for exclusion
Vincelli et al[111]	Intervention
Vincelli et al[112]	Intervention
Vincelli et al[113]	Intervention
Wechsler et al[114]	Intervention
Wiebe et al[115]	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 20: 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,[20] 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%.
Castro et al[13]	NR	Drop out across treatments 37.5%. Most dropouts occurred before treatment. Principal reasons were schedule problems or perceived lack of treatment novelty. There was a statistically significant difference between groups in dropout rates pre-treatment ($X^2 = 5.83$, $p<0.05$) but not at follow up ($X^2 = 1.76$, $p>0.05$). Correcting a presumed decimal point error, the group-specific drop out rates were 53.33% in the CBT group, 35.3% in the drug only group and 23.33% in the Amelia group (co-administered with CBT and drug). In a MANCOVA model, a statistically significant effect was found for the treatment * time (pre-treatment vs post-treatment) interaction (Wilks' Lamba = 0.42, F= 1.93, p=0.02). There was a significant effect of treatment on agoraphobic cognitions (F=5.21, p=0.01), body sensations (F=5.63, p<0.05 (reported as p =0.00)), general anxiety (F=3.45, p=0.04), cognitive and overt behaviours related to agoraphobia when the patient was alone (F=5.14, p=0.01) and cognitive and overt behaviours when the patient was accompanied (F=4.96, p=0.01). Amelia and CBT groups performed better than the drug group.

Papers	Study name	Results
		While statistically significant, between group differences were of moderate magnitude. For example, on the Agoraphobia Cognition Questionnaire, pre-treatment scores were M(SD) 38.07 (9.46) for CBT, 37.30 (7.63) for Amelia and 32.30 (9.46) for drug; post-treatment scores were 25.50 (8.67) for CBT, 28.72 (7.28) for Amelia and 30.15 (8.33) for drug; and follow-up scores were 28.00 (10.90) for CBT, 24.57 (9.27) for Amelia, and not assessed for drug. Further data can be found in Table 1 of the publication. In a further MANOVA model, also including the follow-up time point, which was not available for the drug group, there was no significant treatment effect. In the univariate model, there was only an effect of treatment on cognitive and overt behaviours when the patient was alone (F=3.97, p=0.27), in favour of Amelia. There was a significant time effect on Subjective Units of Anxiety (F=3.21, p=0.01), but no significant interaction with treatment group. Amelia patients spent more time in scenarios in the Behavioural Avoidance Test and had lower self-perceived anxiety (p=0.02). There were no other statistically significant differences between treatment groups in standardised assessments. Results generally showed CBT and Amelia to be superior across outcomes than drug therapy alone. However, it should be noted that the CBT and Amelia arms were generally not significantly different in outcomes. Since Amelia was co-administered with CBT and drugs, it cannot be ruled out that the benefit in the Amelia arm could be driven by CBT.
gameChangeVR		
Knight et al,[18] Lambe et al[19]	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,[14] Freeman et al 2022a,[15] Freeman et al 2022b,[16] Freeman et al 2022c[17]	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 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

Papers	Study name	Results
		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[16] 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.[21]. 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.[14] In the secondary quantitative analyses, Freeman et al[15] 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. Meanwhile, Freeman et al[17] found that participants with severe agoraphobia showed the greatest benefits from gameChangeVR VR therapy, exhibiting significant post-

Papers	Study name	Results
		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:21 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:22 SA1: Incremental utility gain from Amelia

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:23 SA2: Cost of VR Headset

	DP1 (gameChangeVR)			DP2 (Amelia)		
£ of headset	**Inc £**	**Inc QALY**	**ICER**	**Inc £**	**Inc QALY**	**ICER**
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
250	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
350	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
400	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
450	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
550	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
600	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
650	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
700	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
750	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

800	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
850	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
900	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
950	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table:24 SA3: Licence fees

DP1 (gameChangeVR)				DP2 (Amelia)			
£ per person per course	**Inc £**	**Inc QALY**	**ICER**	**£ per month**	**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]
[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]
[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:25 SA4 Relapse Rate

	DP1 (gameChangeVR)			DP2 (Amelia)		
P(relapse/6m)	**Inc £**	**Inc QALY**	**ICER**	**Inc £**	**Inc QALY**	**ICER**
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.05	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table:26 SA6 Relative Effectiveness of Repeat Therapy

	DP1 (gameChangeVR)			DP2 (Amelia)		
relative effectiveness	**Inc £**	**Inc QALY**	**ICER**	**Inc £**	**Inc QALY**	**ICER**
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.05	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

0.35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table: 27SA7: Heatmap of licence cost of gameChange vs probability of relapse

Table redacted.

Table: 28SA8: Heatmap of licence cost of gameChangeVR vs incremental utility

Table redacted.